An fNIRS Study of the Effects of Medication on Cognitive Functioning and Cerebral Hemodynamics in Adults with Attention-Deficit/Hyperactivity Disorder

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Abstract

An fNIRS study of the effects of medication on cognitive functioning and cerebral hemodynamics in adults with Attention-Deficit Hyperactivity Disorder

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Background: Current research indicates clear distinctions between the general population and individuals diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD), specifically in cognitive processes and physiological brain activity. Stimulant medications have been shown to improve and, in some cases, normalize dysfunction in both these areas. The majority of extant brain imaging literature has included functional magnetic resonance imaging (fMRI) in tandem with neuropsychological tests to explore these relationships. However, functional near-infrared spectroscopy (fNIRS) is a promising neuroimaging technology that offers some unique features including portability, ecological validity, and the ability to detect brain activity via concentrations of oxygenated and deoxygenated blood. Very few studies have used fNIRS as a tool to investigate the impact of medication on adults with ADHD, both in their cognitive functioning and brain hemodynamics. However, there is evidence that this technology may—in addition to providing novel information about cognitive and physiological functioning—actually be better suited to evaluating the ADHD population.

Objectives: The present study sought to: 1) compare differences in cognition (using neuropsychological tests) and neurophysiology (using fNIRS) between adults with ADHD (when unmedicated) and age-, gender-, and education-matched healthy control (HC) adults, and 2) compare differences in cognition and neurophysiology between medicated and unmedicated states in adults with ADHD. Ultimately, the goal was to

investigate the potential application of fNIRS as an assessment tool for both diagnostic (of the physiological underpinnings of the disorder) and monitoring (of the effectiveness of cognition-improving medications) purposes.

Participants: Nine individuals aged 18-25 diagnosed with ADHD and nine age-, gender-, and education-matched healthy control participants (HCs).

Method: All participants completed two testing sessions. HCs completed both sessions under normal conditions whereas ADHD participants completed one testing session while medicated and the other while unmedicated. Cognitive testing focused on working memory, a domain relevant to ADHD. Testing included 1) a two-subtest WAIS-IV; 2) a Sternberg delayed recognition task (a test of working memory); and 3) a visual n-back task (another working memory test). The latter two tasks were completed while participants were connected to a continuous wave fNIRS system to record cerebral hemodynamic activity during working memory performance. Demographic variables, confirmation of diagnosistic status, medications, and recent daily activities regarding caffeine, alcohol, tobacco, and other behaviors that could impact fNIRS data were recorded.

Results: Cognitively, while healthy controls performed better on working memory tasks than ADHD participants, and ADHD participants generally performed better when medicated than unmedicated, neither comparison reached significance. Physiologically, there were no significant differences in PFC activation between the HC and ADHD groups, nor between medicated and unmedicated states within the ADHD group.

Conclusions: The findings of this study mirror previous findings of the cognitive effects of medication in ADHD. Not surprisingly, individuals with ADHD performed working

memory tasks less accurately and more slowly than controls and the intake of stimulant medication led to an improvement in performance that reached levels similar to healthy individuals. By contrast, the medication-induced working memory improvements among adults with ADHD were not reflected in corresponding physiological changes measured by fNIRS. The lack of significant findings in this study may be due to low statistical power, though alternative explanations are also explored. Nonetheless, before fNIRS can contribute to clinical diagnosis and treatment of ADHD, more research is needed to establish its clinical application.

1. INTRODUCTION

Current research indicates that there are clear distinctions between the general population and individuals diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD), with respect to cognitive processes and physiological brain activity. Additionally, stimulant medications have been shown to improve functioning in both of these areas for individuals diagnosed with ADHD. The majority of brain imaging literature has included functional magnetic resonance imaging (fMRI) in tandem with neuropsychological tests to examine these areas. However, functional near-infrared spectroscopy (fNIRS) is another neuroimaging technology that offers some unique features including portability, ecological validity, and the ability to detect brain activity via concentrations of oxygenated and deoxygenated blood. To date, very few studies have used fNIRS as a tool to investigate the combined cognitive and physiological differences between individuals with ADHD and their healthy counterparts, or the impact medication has on adults with ADHD both in their cognitive functioning and brain hemodynamics. Results from existing neuroimaging studies that have investigated these variables (together or separately) have been limited in various ways, including small sample sizes, limited use of neuropsychological tests (i.e., using only one measure to gain an understanding about a large functional domain), and susceptibility to the hyperactive movement common among individuals with ADHD. In contrast, fNIRS may be better suited for evaluating this population, as it provides a valid measure of frontal lobe activity (which is central to the cognitive dysfunction in ADHD), is robust during movement (another issue for those diagnosed with the disorder), and can provide novel information about cognitive and physiological functioning in ADHD, specifically

concerning blood flow. There were two aims to the present study: Aim 1 sought to examine the differences in cognitive performance and cerebral physiology between healthy control (HC) adults and adults with ADHD (when unmedicated). Aim 2 sought to examine the differences in cognitive performance and cerebral physiology between medicated and unmedicated states in adults with ADHD.

1.1 Attention Deficit Hyperactivity Disorder

While the majority of research in ADHD has focused on children, there is a growing body of literature examining adults. ADHD is a neurodevelopmental behavioral disorder characterized by age-inappropriate symptoms of inattention, hyperactivity, and impulsivity (American Psychiatric Association [APA], 1994, 2000). These symptoms must be observed early in life (before age 7), pervasive across situations, and chronic. With a prevalence rate of 3-9.5% (APA, 1994; Froehlich et al., 2007; Centers for Disease Control and Prevention [CDC], 2010), ADHD is the most frequently diagnosed psychological disorder in school-aged children. Sixty-five percent of cases persist into adulthood (Barkley, Fischer, Smallish, & Fletcher, 2002; Biederman et al., 2006), resulting in an estimated prevalence rate of 4% among the adult population that is affected with the disorder (Faraone & Biederman, 2005; Kessler et al., 2006). Various studies have found that children, adolescents, and adults diagnosed with the disorder exhibit similar clinical features including inattention and distractibility, as well as disruptions in both academic and occupational domains (Biederman, Mick, & Faraone, 2000; Hechtman, 1992; Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1993; Spencer, Biederman, & Mick, 2007; Taylor, Chadwick, Heptinstall, & Danckaerts, 1996); similar

findings in brain abnormalities have also been suggested, as described below (Seidman, Valera, & Bush, 2004).

1.1.1 Neural Correlates of ADHD

Structural and functional neuroimaging studies have consistently found a variety of structures and networks to be implicated in ADHD. A compilation of evidence suggests that when the clinical features carry into adulthood, so too do the structural and functional deviations (Cubillo, Halari, Smith, Taylor, & Rubia, 2012). Specific abnormalities are discussed below.

1.1.1.1 Structural Neural Correlates

Multiple studies have indicated that decreased volumes of specific brain structures and reduced cortical thickness occur in individuals with ADHD. Most notably, abnormalities have been found in: overall cortical gray matter, fronto-striatal structures (lateral prefrontal and dorsal cingulate cortices, caudate, and putamen), medial frontal regions (rostral anterior cingulate cortex and supplementary motor area), and the temporo-occipito-parietal junction (Bush et al., 2005; Cubillo & Rubia, 2010). Presumably, these structural differences translate into the cognitive differences observed among individuals with ADHD, as there are unique relationships between areas of the brain and cognitive functioning. In terms of the fronto-striatal structures, the dorsolateral and ventrolateral prefrontal cortices (DLPFC and VLPFC, respectively) are believed to play a role in an array of domains including vigilance, attention (selecting, dividing, and shifting), working memory, planning, and other executive functions (Bush et al., 2005; Duncan & Owen 2000; Posner & Peterson 1990). Additionally, the VLPFC has been linked to behavioral inhibition. The dorsal anterior cingulate cortex is thought to be

associated with motivation, complex cognitive processing, response selection and inhibition, target detection and error detection, and performance monitoring. Especially relevant to functioning in ADHD is the fact that there is evidence to suggest that this area also has a role in modulating reward-based decision making.

Moreover, the medial frontal regions have been implicated in response selection and initiation behaviors. Thus, the deviations from normality in these structures as well as their connections with striatal, cerebellar, and parieto-temporal areas likely contribute to the observed deficits in the above behaviors in the adult ADHD population (Cubillo & Rubia, 2010).

1.1.1.2 Functional Neural Correlates

Consistent with structural evidence that grossly implicates dysfunction of the frontal lobes in ADHD, multiple neuroimaging (fMRI and PET) meta-analyses and reviews have reported corresponding functional abnormalities in the frontal lobe (Aron & Poldrack, 2005; Bush et al., 2005; Cubillo & Rubia, 2010; Dickstein, Bannon, Castellanos, & Milham, 2006; Paloyelis, Mehta, Kuntsi, & Asherson, 2007). Specifically, hypoactivity in the anterior cingulate, dorsolateral prefrontal, and inferior prefrontal cortices has been most commonly reported. In their review, Cubillo & Rubia (2010) concluded that reduced activation occurs during tasks targeting motor inhibition (e.g., Go/No-go), attention and interference inhibition (e.g., Color-Word Stroop, Simon or Eriksen Flanker tasks), and working memory (e.g., digit span, n-back).

Similarly, fNIRS studies with adult and child/adolescent participants of cognitive function in ADHD have consistently reported a lower level of activation (i.e., reduced levels of oxygenated blood in the brain) during various cognitive tasks including the

Go/No-Go, Stroop, n-back, and verbal fluency tests (Ehlis, Bahne, Jacob, Herrmann, & Fallgatter, 2008; Inoue et al., 2012; Kobel et al., 2009; Negoro et al., 2010; Schecklmann et al., 2009). Only one child study using fNIRS found that ADHD participants exhibited an increase in oxygenated hemoglobin (HbO_2) and cerebral blood volume (CBV) during a cognitive task (Weber, Lutschg, & Fahnenstich, 2005); however this task (trail making) focused on attentional abilities whereas others have focused more on working memory and executive functioning, and this could explain the discrepancy. In sum, current research suggests that both structural and functional abnormalities occur particularly in frontal cortical areas and are consistent with the cognitive dysfunction observed in individuals with ADHD, findings which the present study is designed to build on.

1.1.2 Neuropsychological Profile of ADHD

While a majority of ADHD research to date has been carried out with children and adolescents, the field has recognized the importance of gaining a better grasp of the disorder in adults in order to improve understanding of the disorder throughout the lifespan. This can be seen in the growth of literature specifically reporting on adult ADHD. Much of this research has found that many symptoms and difficulties found in children are also seen in adults, with neuropsychological dysfunction a consistent feature of adults with ADHD (Faraone et al., 2000; Woods, Lovejoy, & Ball, 2002).

Various reviews and meta-analyses have reported that, similar to children, adults with ADHD experience deficits in multiple domains of function, the most prominent impairments consistently occurring in speed of complex information processing, attention and executive functions (e.g., tasks of verbal fluency, inhibition, and set shifting), and

working memory (Boonstra, Oosterlaan, Sergeat, & Buitelaar, 2005; Cubillo et al., 2012; Hervey, Epstein, & Curry, 2004; Woods et al., 2002).

Other studies have investigated common complaints related to cognitive and neuropsychological functioning in adults with ADHD. Time-related issues appear to be prominent, particularly problems meeting deadlines, completing tasks, and planning (Riccio et al., 2005). A review of the literature by Davidson (2008) revealed that the most commonly reported complaints among adults with ADHD are problems with procrastination, frustration, poor motivation, insomnia, and time-management difficulties.

1.1.3 Pharmacology: Effects of Medication on Individuals with ADHD

1.1.3.1 Effects of Medication on Cognition

Various types of medication exist for the treatment of symptoms associated with ADHD. Stimulants such as Methylphenidate (MPH) have been shown to be the most effective—and therefore most prescribed—class of medications (Greenhill et al., 2002; Safer & Malever, 2000). Stimulants such as MPH function via a mechanism that impacts two specific neurotransmitters: dopamine (DA) and norepinephrine (NE; Volkow et al., 2004). Specifically, MPH increases extracellular levels of DA and NE by blocking their respective transporters. Because DA and NE are responsible for reducing the firing rate of background neurons that can distract an individual from the task at hand, it is theorized that MPH functions by increasing DA and NE, which helps decrease background noise in the service of improving cognitive function.

In their review of the literature, Swanson, Baler, and Volkow (2011) reported that stimulant medications led to improvements in an array of cognitive functions ranging from those that incorporated executive functioning (e.g., inhibition, working memory,

strategy formation, planning, and set-shifting) to those that did not (e.g., complex reaction time, spatial recognition memory reaction time, and delayed matching-to-sample). Other single studies with adults have reported similar findings regarding cognitive improvement: Biederman et al. (2008) found that MPH improves performance on sustained attention and verbal learning tasks; Agay, Yechiam, Carmel, and Levkovitz (2010) found better digit-span test scores among medicated individuals; and Topaloglu et al. (2008) found that medicated ADHD participants' reaction times during executive control tasks were more similar (i.e., shorter)—though not identical—to healthy controls'.

Taken together, these findings suggest that stimulant medications successfully enhance cognitive functioning in individuals with ADHD. The present study capitalized on this evidence and we anticipated that the same findings would be observed when comparing medicated and unmedicated conditions among adults with ADHD. Additionally, the present study targeted the links between the cognitive deficits associated with adult ADHD and specific PFC neuroanatomy. Subsequently, we anticipated neurophysiological differences between the medicated and unmedicated ADHD groups, as well as between the healthy control and the unmedicated ADHD groups, discussed in more detail below.

1.1.3.2 Effects of Medication on Brain Physiology

A variety of findings have been described for imaging studies with both children and adults regarding the effects of stimulant medications on brain activity and hemodynamics. Both PET and fMRI studies utilizing working memory and executive functioning tasks have found contrasting results. While some have found decreases in

regional cerebral blood flow (rCBF) or regional cerebral blood volume (rCBV) in the prefrontal cortex (PFC) during tasks (Mehta et al., 2000; Schweitzer et al., 2004; Szobot et al., 2003; Weber, Lutschg, & Fahnenstich, 2007), others have found increases in PFC rCBF (Schweitzer et al., 2003) or PFC activation (Bush et al., 2008; Epstein, et al., 2007; Kim, J. Lee, Cho, & D. Lee, 2001; Rubia et al., 2009; Rubia, Halari, Christakou, & Taylor, 2009; Shafritz, Marchione, Gore, Shaywitz, & Shaywitz, 2004; Vaidya et al., 1998; Wong & Stevens, 2012).

Far less fNIRS research has been conducted, yet a conflict still exists. Topaloglu et al. (2008) observed patterns of decreased oxyhemoglobin (HbO_2) levels in MPH medicated adults (compared to their unmedicated selves) during a measure of attention, response inhibition, and cognitive flexibility, which they attributed to vasoconstriction. By contrast, Monden et al. (2012) observed a significant increase in HbO_2 during a Go/No Go task after intake of MPH by children.

The discrepancies among this literature could be due to various reasons, including imaging techniques, sample sizes, sample characteristics (e.g., adult vs. child; ADHD subtype), task type and difficulty, and medication regimens. Also, many of the studies only utilized one cognitive task, another factor that could have limited their findings. The present study aimed to address these limitations and contribute to the literature focused on adults in this area as well as provide some clarification on existing findings.

1.2 Functional Near-Infrared Spectroscopy

Providing visual information regarding the structure and function of the brain, neuroimaging is on the cutting edge of neuroscience research with a broad range of techniques available for different purposes. First described by Chance et al. (1993, 1998),

one of these techniques is functional near-infrared spectroscopy (fNIRS). fNIRS is a developing, noninvasive neuroimaging technology that utilizes the near infrared region of the electromagnetic spectrum (approximately 700-1000 nm) to detect brain activity via concentrations of oxygenated and deoxygenated blood.

Like fMRI, fNIRS detects neural responses by monitoring the hemodynamic response induced by cognitive tasks. Performance on cognitive tasks requires energy, which causes an increase in metabolic demand. Subsequently, this brings about a hemodynamic response, which can be seen as the increase in various components including: total cerebral blood flow (tCBF), regional cerebral blood flow (rCBF), regional cerebral blood volume (rCBV), and regional cerebral blood oxygenation (rCBO; Roy & Sherrington, 1890). Changes in these physiological variables are detected by the fNIRS system.

This imaging technology is distinct from fMRI in that it utilizes the ratio of the optical properties of oxygenated hemoglobin (oxy-Hb; HbO_2) and deoxygenated hemoglobin (deoxy-Hb; HHb), rather than their paramagnetic properties (as fMRI does). More specifically, fNIRS is based on the property that light in the near-infrared range can pass through skin, bone, and other tissues relatively easily and takes advantage of the distinct absorption characteristics of HbO_2 and HHb in the near-infrared spectrum to determine tissue oxygenation during cognitive activation (Izzetoglu et al., 2005; Villringer, 1997). Once the headpiece is in place, near-infrared light is emitted from one light source, penetrates the outer cortical layers, and is captured again by a detector. The wavelengths of light that were reflected and absorbed during the process are then conveyed to the data acquisition computer, which identifies concentration changes in

HbO_2 and HHb. In sum, fNIRS can record changes in brain activation and activity (Jobsis, 1977).

1.2.1 Instrumentation

There are many commercially available fNIRS systems with different hardware setups that are being used in various settings (Strangman, Boas, & Sutton, 2002). Currently, there are three specific types of systems: time-resolved (TR), frequency-domain (FD), and continuous wave (CW), each having its own unique set of advantages and disadvantages. Both the TR and FD systems use lasers as light sources and measure changes or shifts in the phase and amplitude of the light as it passes through cortical tissue. Ultimately, these systems provide a more precise quantification of fNIR signals. CW systems use either continuous or a slow-pulsed light as the light source and measure the attenuation of amplitude of the incident light as it travels through cortical tissue. Due to having less sophisticated detectors, CW systems provide slightly less information regarding timing of changes. However the benefit of CW systems is that the hardware is more compact and inexpensive, and therefore more useable for a larger variety of applications. The fact that they do not need to employ lasers (although they have this capability) also increases the safety of the CW system. Lastly, within the above systems, there are two additional options in terms of setup. While some use a cap that covers the entire scalp, others use a sensory pad that is placed on the forehead, focusing solely on frontal cortical activity.

The Drexel system is a CW-fNIRS system that has been successfully used in a range of studies measuring brain activity during various cognitive tasks (Arenth, Ricker, & Schultheis, 2007; Ayaz et al., 2012; Irani, Platek, Bunce, Ruocco, & Chute, 2007;

Merzagora, Schultheis, Onaral, & Izzetoglu, 2011). It is comprised of three main components: a flexible headpiece, a control box, and a computer. The headpiece holds the fNIRS light sources/emitters and detectors/sensors; there are 4 light sources and 10 light detectors that, together, provide 16 channels for analysis. The sources and detectors are separated by 2.5 cm, which allows the near-infrared light to penetrate to a depth of approximately 1.25 cm. The control box and computer function together in data acquisition.

1.3 Advantages of fNIRS Over Current Methods for Studying Brain Activity in ADHD

fMRI has been used in an array of studies assessing prefrontal functioning in ADHD. However, various technicalities associated with the technology hinder its use and prevent it from being the ideal imaging method for use with this population. By contrast, fNIRS has a variety of advantages over fMRI. Such advantages include the following:

- *Scanner Apparatus/Environment:* fMRI involves a large apparatus for scanning and requires that individuals lie as still as possible inside of a loud and confined environment. Conversely, fNIRS is a compact, less restrictive, and quieter system. Not only does this allow individuals to be tested in a more relaxed, ecologically valid environment but provides flexibility and the opportunity for bedside use in both clinical and research settings (Ehlis et al., 2008; Villringer, Plancka, Hock, Schleinkoferc, & Dirnagla, 1993). Additionally, its compact size makes it more portable and employable in a larger range of settings.
- *Scanning Time:* fMRI requires a relatively long scanning time. This poses a problem when testing individuals diagnosed with ADHD, as symptoms such as distractibility, impulsivity, and hyperactivity can make it difficult for them to

endure the length of a long testing session (Schecklmann, et al., 2008). fNIRS surpasses this barrier by requiring much less time for measurement.

- *Motion Susceptibility:* fMRI—and similar functional imaging techniques—are limited in that they are very sensitive to body movement. This can be exceptionally problematic when testing individuals diagnosed with ADHD, who are more prone to be distracted and/or hyperactive and unable to remain still during scanning (Ehlis et al., 2008). Even small movements can lead to motion artifacts in the obtained neurological scans, reducing accuracy of those scans (Monden et al., 2012). By contrast, fNIRS is more robust to movement and motion artifacts, which allows more flexibility for testing in naturalistic settings that involve movement, when necessary (Ehlis et al., 2008). This technology has even been employed with success in studies where body movement has been a factor (Herrmann, Ehlis, & Fallgatter, 2004; Herrmann, Plichta, Ehlis, & Fallgatter, 2005; Hock et al., 1997; Matsuo, Kato, Fukuda, & Kato, 2000; Matsuo et al., 2003; Shinba et al., 2004; Suto, Fukuda, Ito, Uehara, & Mikuni, 2004; as cited in Monden et al., 2012).
- *Expense:* fNIRS is a more affordable system than other technologies. This, in turn, makes it a more accessible system to researchers.
- *Unique Capabilities:* While fMRI only detects changes in HHb, fNIRS is able to detect changes in both HHb and HbO_2 (and the ratio between them) as well as cytochrome aa_3, an enzyme of the respiration chain (Fallgatter, Ehlis, Wagener, Michel, & Herrmann, 2004; Obrig & Villringer, 2003; Strangman et al., 2002).

This not only allows fNIRS to provide additional information but also provides a unique signal and view of the hemodynamics of the brain.

Additionally, as previously discussed, both neuroanatomical anomalies and neurocognitive deficits in ADHD occur largely within the PFC and nearby structures. Therefore, fNIRS is an ideal assessment tool given the nature of the neuronanatomy associated with the disorder, as it is currently able to penetrate cortical areas to measure activity.

1.4 Present Study

In summary, while the current literature has touched on the individual aspects central to the current study, none have combined these aspects into a single study. Moreover, there are limiting factors involved in previous studies that were improved upon in the present design. Such factors include limited use of neuropsychological tests (i.e., using only one measure to gain an understanding about a large functional domain), and use of neuroimaging technologies (mainly fMRI and PET) susceptible to hyperactive movements that commonly occur in the ADHD population. In contrast, fNIRS may actually be better suited to evaluating this population, as it provides a good measure of frontal lobe activity (which is central to the cognitive dysfunction in ADHD), is robust to movement (another issue for those diagnosed with the disorder), and can gather novel information about cognitive and physiological functioning in ADHD (specifically concerning the blood flow). Thus, the present study was designed to address some of the above gaps that still remain in the literature. **Aim 1 of the present study sought to examine the differences in cognition and cerebral physiology between healthy control (HC) adults and unmedicated adults with ADHD.** If fNIRS can identify

differences in prefrontal neural activity commensurate with differences in cognitive functioning between healthy and clinical samples, this would lend support for the application of fNIRS in the clinical assessment of physiological underpinnings of neurocognitive disorders.

Additionally, although the current literature includes a considerable amount of research assessing cognitive functioning in adults who are medicated for treatment of ADHD, only one thus far has used fNIRS to measure brain activity during cognitive tasks under both medicated and unmedicated states. Further, a clear understanding of the effect of stimulant medication on brain physiology in adults with ADHD is also missing from the present literature (and even literature for this in children and adolescents is limited). Although studies have examined the effect that medication has on cognitive tasks, very few have combined this with the physiology involved. **Aim 2 of the present study sought to examine the differences in cognition and cerebral physiology between medicated and unmedicated states in adults with ADHD.** The present study examined functioning at the cognitive and physiological levels, as well as any correlations that existed between these levels.

Formal Statement Of Proposed Study Aims

Aim 1. To examine the differences in cognition and cerebral physiology between healthy control (HC) adults and adults with ADHD (when unmedicated).

Hypothesis 1: HC adults will perform significantly better on cognitive tasks than adults with ADHD (when unmedicated).

Hypothesis 2: When completing cognitive tasks, unmedicated ADHD adults will show lower levels of activation (i.e., lower levels of blood oxygenation) than HCs.

Hypothesis 3: Hemodynamic activity, as detected by fNIRS, will be correlated with cognitive performance.

Aim 2. To examine the differences in cognition and cerebral physiology between medicated and unmedicated states in adults with ADHD.

Hypothesis 4: ADHD adults will perform significantly better on cognitive tasks when medicated (i.e., they have taken their prescribed dosage of stimulant medication) than when unmedicated.

Hypothesis 5: When completing cognitive tasks, ADHD adults will show higher levels of activation (i.e., higher levels of blood oxygenation) when they are medicated than when unmedicated.

Hypothesis 6: Hemodynamic activity, as detected by fNIRS, will be correlated with cognitive performance.

2. METHOD

2.1 Participants

This study included 18 participants, ages 18-25 (M = 20.28, SD = 2.02), recruited from Drexel University and the Philadelphia area.

2.1.1 ADHD Adults

Participants with ADHD included nine adults, ages 18-25 years (M = 20.33, SD = 2.29), who were diagnosed with ADHD by a psychologist or medical doctor and who had an established treatment regimen of at least one month with ADHD medication. ADHD diagnostic status was assessed with the Barkley Adult ADHD Rating Scale-IV (BAARS-IV; Barkley, 2011). ADHD diagnosis was based on meeting DSM-IV-TR (APA, 2000)

criteria, as surveyed by the BAARS-IV, followed by confirmation of the diagnosis from the participant's prescribing physician.

2.1.2 Age-, Gender-, and Education-matched Healthy Adults

Participants in this group included nine adults, each within 2 years of the chronological age of a participant with ADHD and also matched on gender and education level. The age range of this group was very similar to that of the ADHD group (range = 18-24 years, M = 20.22 years, SD = 1.86).

2.2 Measures

All study participants completed all of the following measures.

2.2.1 ADHD Screen

Participants were assessed with the following validated ADHD screen in order to determine ADHD diagnostic status:

- *Barkley Adult ADHD Rating Scale-IV (BAARS-IV)*: The BAARS-IV (Barkley, 2011) is a screening tool for adults with ADHD (ages 18-89 years) that provides self-assessment of symptoms and their impact on domains of daily function across two time periods: current and childhood. It is based on DSM-IV-TR (APA, 2000) diagnostic criteria and takes approximately 5-7 minutes to complete. Further, it is normed by age group and retrospective report (i.e., presence of symptoms in childhood), thus providing a reliable measure of meeting a diagnosis of ADHD in adults.
- Participants with a positive screen were further evaluated by a follow-up confirmation of diagnosis with their prescribing doctor.

2.2.2 Intelligence

Participants were assessed with the following IQ measure to gather information about their fundamental ability and what could be expected of their performance on the cognitive tasks.

- *Wechsler Adult Intelligence Scale—Fourth Edition (WAIS–IV)*: The two-subtest version of the WAIS-IV (Wechsler, 2011) consists of Vocabulary and Block Design subtests and takes approximately 25-30 minutes to administer. With high reliability, this short form correlates well with the Full Scale IQ and provides a valid estimate of IQ.

2.2.3 Cognitive Tasks

This study aimed to examine within-subject and between-group differences in adults without and with ADHD (under medicated and unmedicated states), on measures of cognitive performance, namely on measures of working memory. Thus, we selected the Sternberg Delayed Recognition Task (Sternberg, 1966) and a visual n-back task, two tests commonly used to assess these functions (Sternberg, 1966). One benefit of using these tasks is that they are common to previous imaging studies with ADHD samples. Another benefit of using these tasks is that they are known to engage and activate the PFC (Manoach et al., 1997; Molteni, Butti, Bianchi, & Reni, 2008; Narayanan et al., 2005; Owen, McMillan, Laird, & Bullmore, 2005), a cortical area in which fNIRS is fully capable of measuring activity. The following cognitive tests were administered to each participant while connected to the fNIRS apparatus.

2.2.3.1 N-Back Task

The n-back is a task that has been widely used to assess working memory (Owen et al., 2005). More specifically, the n-back involves three load conditions in which stimuli are single, upper-case consonants presented in pseudo-random sequence on a computer monitor. Participants were asked to view the computer screen and press a specified button with their dominant hand for any stimulus that is a repeat of the same letter presented "n" positions ago (with "n" equal to 0-, 1-, and 2-positions ago). Thus, for the 0-back condition, participants were asked to press a button as soon as the stimulus target letter (e.g., "X") appeared on the screen. In the 1-back condition, participants were instructed to press a button as soon as they identified any stimulus matching the letter presented immediately before it (i.e., the target was one presentation back). For example, participants would press a button when they saw an "M" immediately following another "M." In the 2-back condition, participants were instructed to press a button as soon as they identified any stimulus matching a letter shown two presentations back. For example, participants would press a button when they saw an "M" that appeared two presentations after a previous "M." Participants were instructed not to press any buttons when a nontarget stimulus letter was presented.

In this study, participants were provided with on-screen instructions (7.5 second duration) regarding the task condition (0-, 1-, or 2-back) to be performed at the start of each block. Each block was comprised of 20 stimuli total (6 targets and 14 nontargets). Stimulus duration was 0.5 seconds, interstimulus delay was 2.5 seconds, and each block was followed by a 10 second rest period. The experiment protocol included five presentations each comprised of a randomized order of one 0-back block, one 1-back

block, and one 2-back block. Thus, each participant viewed a total of 15 blocks, ultimately comprised of three 0-back, three 1-back, and three 2-back blocks total (see Figure 1). Total test duration was approximately 20-25 minutes.

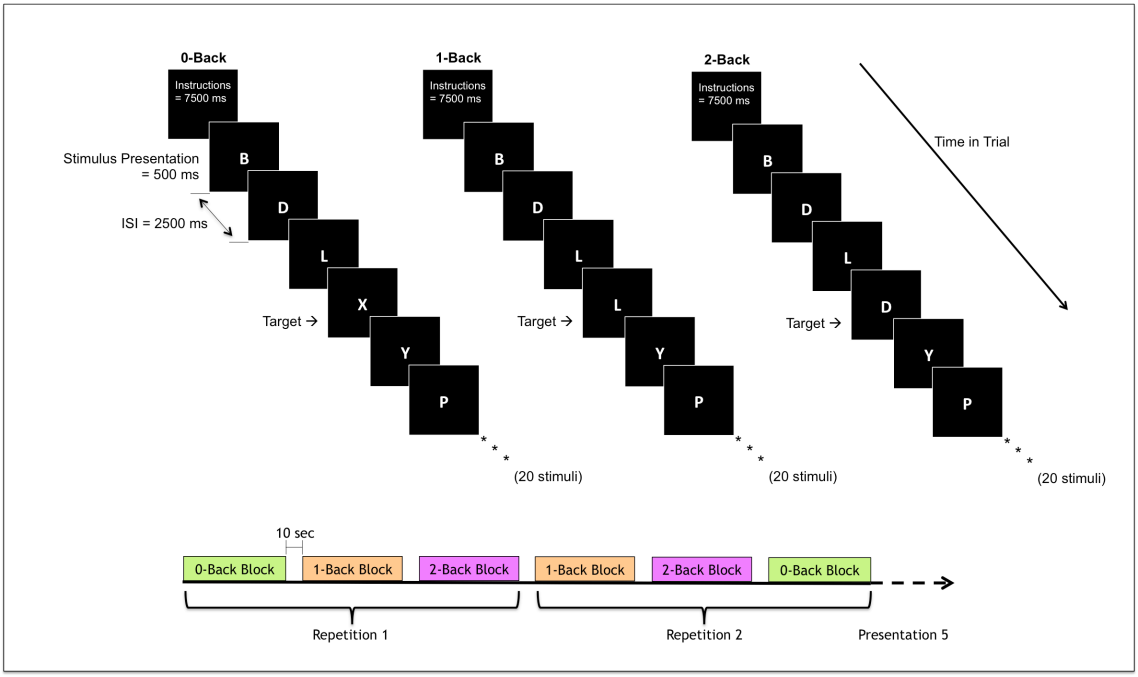

Figure 1. N-back Protocol
In the visual n-back task three conditions were used to incrementally vary the working memory load from zero items (0-back condition) to two items (2-back condition). Each of the three conditions was presented five times total, in a randomized order.

2.2.3.2 Sternberg Delayed Recognition Task

The Sternberg Working Memory Task (Sternberg, 1966) is a brief (i.e., approximately 15-20 minutes) task that has been widely used to assess working memory because it incorporates processes critical to working memory: simultaneous storage and processing of information (Baddeley, 1986). In this task, participants were shown a stimulus set comprised of a series of consonants on a computer screen. The task required

participants to maintain the stimulus set in memory while differentiating target letters from foils based on the probe that is presented after a brief delay (Figure 1). The task is designed to capture performance across three memory loads of increasing difficulty (i.e., 2-letter, 4-letter, and 6-letter stimulus sets). Reponses were made by having participants press one pre-specified button when the probe was part of the original stimulus set (i.e., when it was a target) and a different pre-specified button when the probe was not part of the original stimulus set (i.e., when it was a foil); the dominant hand was used for all manual responses.

At the outset of this task, participants were provided with visual instructions (of unlimited duration) about the task to be performed. Participants viewed a total of 54 trials comprised of a randomized presentation of 18 2-letter stimulus sets, 18 4-letter stimulus sets, and 18 6-letter stimulus sets across and within participants. Each trial consisted of a 2-second blank screen, followed by a 4-second stimulus set presentation, 0.5-second rest period, and 1-second probe presentation (see Figure 2).

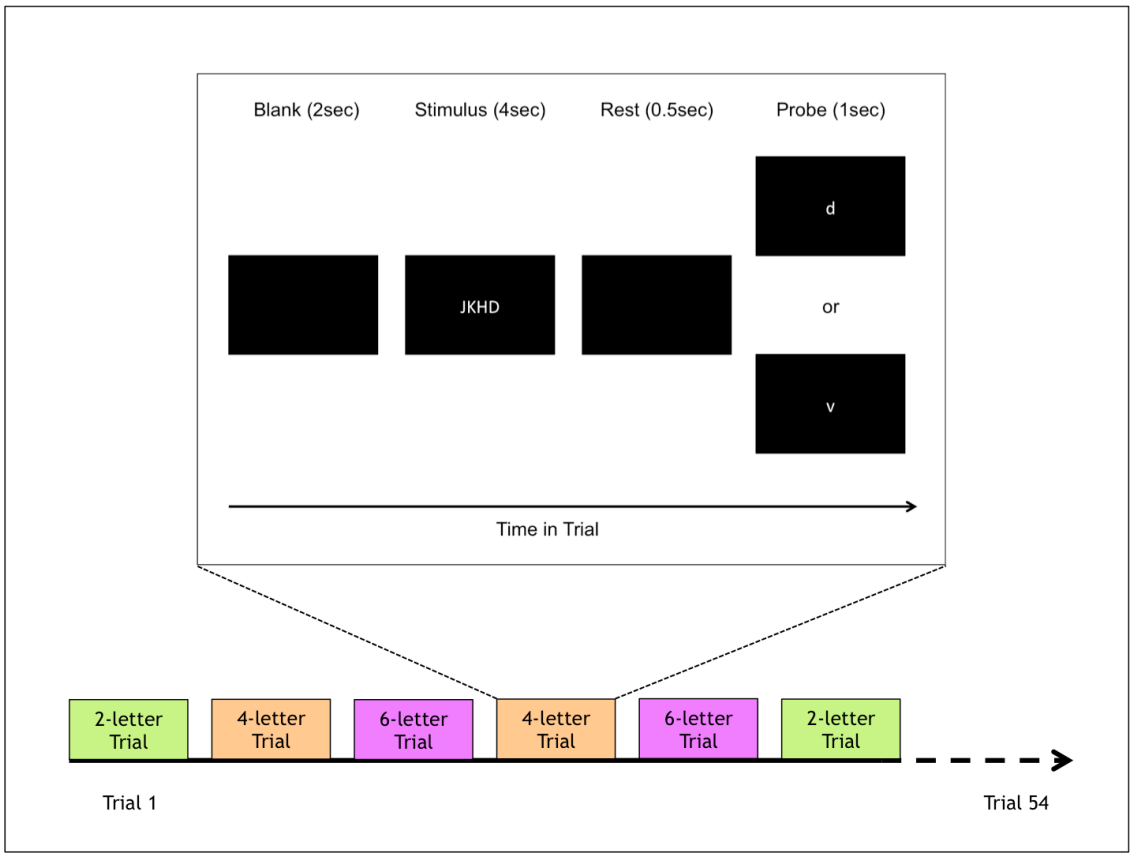

Figure 2. Sternberg Protocol
In the Sternberg delayed recognition task, three conditions were used to incrementally vary the working memory load (i.e., a 2-letter, 4-letter, and 6-letter stimulus sets). Each of the three stimulus sets was repeated 18 times, in a randomized order. The figure lays out an example of a trial with the 4-letter stimulus set.

Performance on both the Sternberg and N-back tasks is measured in terms of reaction time (to target stimuli) and accuracy (% correct for both target and non-target stimuli). These measures are significant to PFC function, as both reflect information processing during working memory tasks; presumably, the faster and more accurately one completes a task, the better the integrity of the PFC. Thus, for both tasks it is expected that higher accuracy and lower reaction times will reflect better working memory performance and, hence, better PFC function.

2.3 fNIRS Instrumentation and Data Acquisition

2.3.1 Instrumentation

This study used a continuous wave fNIRS system to monitor PFC activity of participants (as described in Ayaz et al., 2012). Chance et al. (1998, 1993) first described this system and it has since been further developed at Drexel University (Philadelphia, PA), manufactured and supplied by fNIR Devices LLC (Potomac, MD; www.fnirdevices.com). The system is comprised of three main components: a flexible headpiece (sensor pad), which holds light sources and detectors; a control box for hardware management; and a computer that runs the data acquisition (Figure 3).

Figure 3. fNIRS System Components
The components of the fNIRS system include: a flexible headpiece with light sources and detectors, control box, and computer system, as shown above (image from Ayaz et al., 2012).

The positioning of light source and detectors on the sensor pad create a total of 16 active optodes (channels) that are used to monitor neural activity specific to the dorsal and inferior frontal cortices of the brain (Ayaz et al., 2006; Ayaz et al., 2012; Izzetoglu et al., 2005). Each source emitted light at two different wavelengths in the near-infrared spectrum (i.e., 730 and 850 nm) and measures of emerging light intensity were obtained for each optode; sampling rate was 2 Hz. Changes in light absorption, as measured by fNIRS at each of the two wavelengths, were converted to changes in concentration of oxyhemoglobin (HbO_2) and deoxyhemoglobin (HHb). COBI Studio software (Drexel University) was used for data acquisition and visualization (Ayaz et al., 2011).

2.3.2 Data Acquisition and Processing

For each participant, raw fNIR data from each of the 16 optodes was filtered to eliminate physiologically irrelevant data (e.g., respiration and heart pulsation effects) and equipment noise, as previously described (Ayaz, Izzetoglu, Shewokis, & Onaral, 2010; Izzetoglu et al., 2005). Each participant's data was checked for any potential saturation (when light intensity at the detector was higher than the analog-to-digital converter limit), coupling problems (hair trapped between optodes) and motion artifact contamination by means of visual inspection and a coefficient of variation based assessment signal quality assessment (Ayaz, Izzetoglu, Shewokis, & Onaral, 2010). Using time synchronization markers, fNIR data segments for rest periods and task periods (5 repetitions per participant for n-back task, 18 trials for the Sternberg task) were extracted. Average oxygenation changes for each optode were calculated using the modified Beer-Lambert Law (Obrig & Villringer, 2003; Villringer & Chance, 1997) for task periods with respect to baseline rest periods preceding each task (Ayaz, 2010). For each repetition/trial of the

given working memory task, oxygenation change (HbO_2 – HbR) data for each optode was averaged according to the task workload (n-back: 0-,1-, and 2-back; Sternberg: 2-, 4-, and 6-letter) and was used as the dependent measure similar to previous reported studies (Ayaz, Shewokis, Bunce, Schultheis, & Onaral, 2009; Ayaz et al., 2012; Ayaz, Willems, et al., 2010; Izzetoglu et al., 2011; Izzetoglu, Bunce, Onaral, Pourrezaei, & Chance, 2004). Subsequently, to obtain the average oxygenation changes for the DLPFC, data from optodes 3-6 and 11-14 were averaged for each participant and used for comparison purposes.

2.4 Procedure

A summary of the study design and flow can be seen in Figure 4.

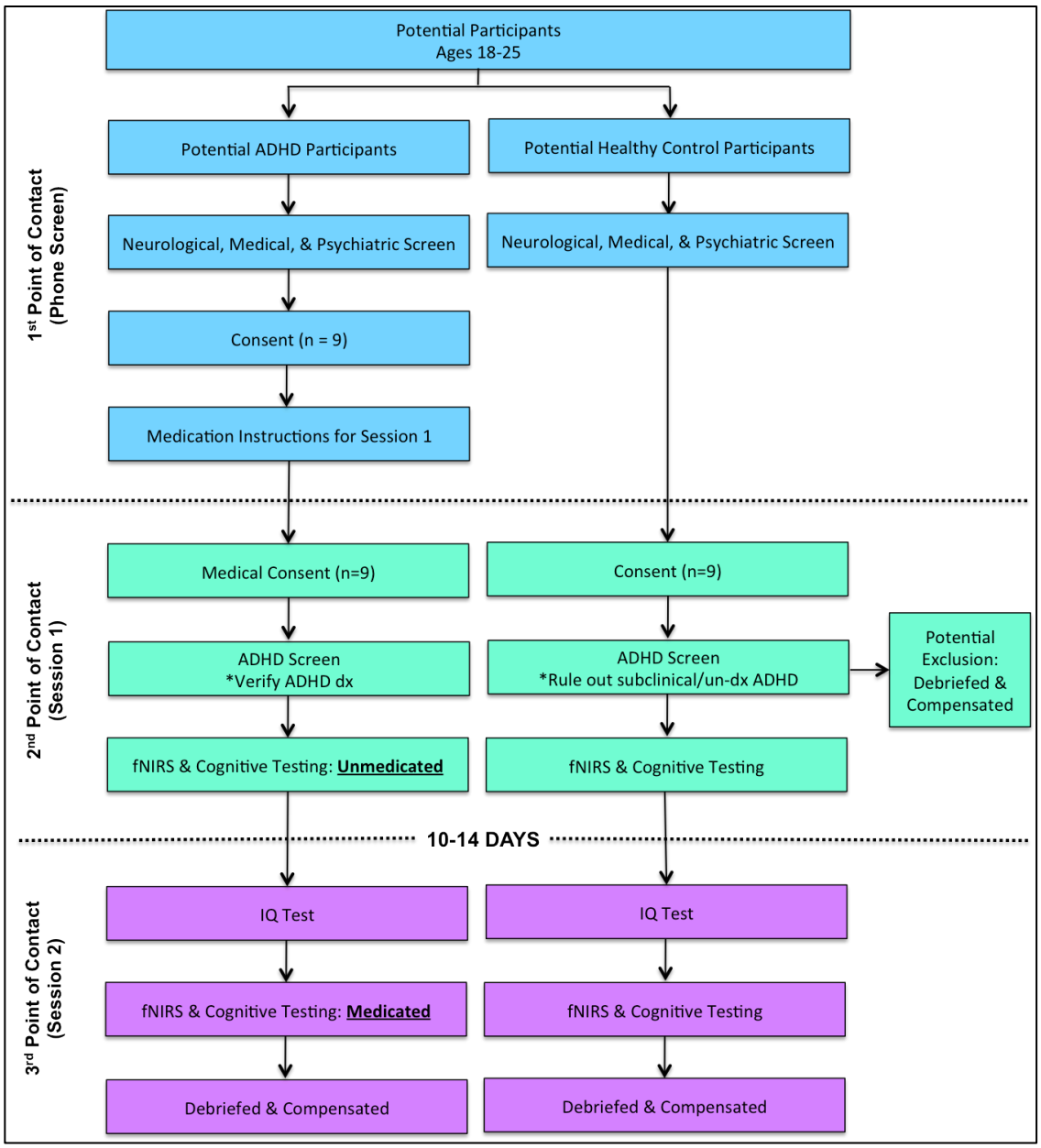

Figure 4. Study Design

The study included two groups: adults with ADHD and healthy controls. Each group proceeded through the study in a similar fashion, albeit steps surrounding consent and medication washout for the ADHD group.

2.4.1 Overview

Participants were recruited through flyers posted throughout Drexel University's campus and the surrounding Philadelphia community. Participants were tested at Drexel University and told that they could change their mind about participating at any time. All participants were compensated for participation with either extra credit (for undergraduate students) or $10 (for individuals from the community).

Because of some procedural nuances that differ between ADHD and HC participants, separate procedures are described below, as they relate to each group.

2.4.2 Procedure for ADHD Participants

ADHD participants completed two testing sessions, both occurring at Drexel University: the first while unmedicated and the second while medicated. This part of the procedure was not counterbalanced for a combination of methodological reasons. First, the BAARS-IV needed to be completed in the first testing session in order to appropriately classify ADHD and HC participants. Second, we wanted to get an accurate measure of intellectual ability without the hindrance of cognitive dysfunction and so the WAIS-IV needed to be completed during the medicated testing session. Third, to prevent fatigue during testing, we wanted both study sessions to be roughly equal in length and therefore the BAARS-IV (and other intake questionnaires) and WAIS-IV needed to be completed in separate sessions, requiring the unmedicated/BAARS-IV/intake session to always be completed first and the medicated/WAIS-IV session to be second. However, measures were taken to prevent practice effects when comparing medicated to unmedicated states within the ADHD group—and ensure that any differences in performance or cerebral physiology were due to medication effects only—including

randomizing the presentation of experimental stimuli for the cognitive tasks both within and across participants, as well as incorporating a 10-14 day gap between testing sessions. The following describes the procedures involved with this group in more detail.

To determine eligibility, all potential participants underwent a phone screen interview prior to enrollment in the study. Using a prepared script, questions were asked to ensure that neurological, medical, psychiatric, and other exclusion criteria were not met. Eligible individuals were invited to join the study and informed consent was obtained from all potential participants. Consent process took place over the phone, as the ADHD participants were required to understand and agree to the procedures for cessation of medication prior to their arrival to the first testing session, which was completed while unmedicated.

Participants were then scheduled for the first session of the study. They were instructed to not take their medication for at least 24 hours prior to the testing session to allow the effects of the stimulant to wear off, thus providing a good measure of the individual's unmedicated performance. All participants were also asked to refrain from other substances known to have an effect on regional cerebral blood flow (e.g., caffeine intake, alcohol intake, and exercise) for at least 24 hours prior to their testing session to prevent the effects these factors can have on fNIRS data (Laurienti et al., 2002; Levin et al., 1998).

Upon arrival to the first testing session, ADHD participants underwent the BAARS-IV (Barkley, 2011) ADHD screen to confirm ADHD diagnosis. Medical consent was also obtained in order to verify the diagnosis with the participant's prescribing doctor following the testing session. Regarding medication regimen, information pertaining to

medication type, dosage, and frequency of intake was carefully recorded. After having completed the above, participants then proceeded to the testing.

During testing, participants were familiarized with—and connected to—the fNIRS system for the completion of the cognitive tasks. A visual n-back task and the Sternberg delayed recognition task were then explained and administered individually. Each task included a practice session in order to ensure that the participant understood the given task and was proficient in it before completing the experimental session. Experimental stimuli for both tasks were randomized across trials.

The second testing session, (occurring 10-14 days after the first and approximately the same time of day) was completed while ADHD participants were medicated. During this session, participants first completed the two-subtest WAIS-IV and were then re-familiarized with—and connected to—the fNIRS system for the completion of the cognitive tasks (n-back and Sternberg tasks).

2.4.3 Procedure for Healthy Control Participants

Healthy control (HC) participants followed a very similar procedural flow as the ADHD group. Eligibility was determined by the same phone screen interview prior to being enrolled in the study and eligible individuals were invited to participant in the study. All potential participants were asked to refrain from substances known to have an effect on brain activity (e.g., caffeine intake, alcohol intake, and exercise) for at least 24 hours prior to their testing session.

Informed consent was obtained from potential participants upon their arrival for the first testing session but prior to participating in the testing session. Those who met criteria for inclusion in the study and completed informed consent were assessed with the

BAARS-IV (Barkley, 2011) ADHD screen to ensure that they did not meet criteria for ADHD. HC participants then proceeded to the testing session, which proceeded in the same manner as described in the ADHD participant procedure (i.e., HC participants completed the cognitive tasks while being connected to the fNIRS system).

Like the ADHD group, during the second session, participants first completed the two-subtest WAIS-IV. Then, participants were re-familiarized with—and connected to—the fNIRS system for the completion of the cognitive tasks (n-back and Sternberg tasks).

3. RESULTS

Two sets of analyses were completed for each variable of interest: 1) unmedicated ADHD participants compared to matched HC participants (only session 1 data for each group were used in these analyses), and 2) unmedicated ADHD participants compared to themselves when medicated. Session 2 data for the HC group was only used for the purpose of checking for practice/fatigue effects across working memory tasks.

3.1 Participant Demographics

Demographic characteristics of the study participants are provided in Table 1. The two groups did not differ significantly with respect to age ($t(16) = 0.11, p = 0.91$) or education ($t(16) = -0.74, p = 0.47$), as tested by independent samples *t*-tests. Group differences were also nonsignificant in performance on the WAIS-IV Vocabulary subtest ($t(16) = 0.31, p = 0.76$), WAIS-IV Block Design subtest ($t(16) = 0.12, p = 0.91$) or WAIS-IV FSIQ estimation ($t(16) = 0.22, p = 0.83$), suggesting that any differences noted between the HC and unmedicated ADHD groups on cognitive tests could not be attributed to differences in educational level and/or general intellectual ability.

Table 1. Participant Demographics

Study participants were comprised of nine ADHD participants and nine age-, gender-, and education-matched control participants. Participants were tested with a 2-subtest WAIS-IV to estimate FSIQ. The table reports the mean (*M*) and standard deviation (*SD*).

	ADHD	HC
	M ± SD	*M ± SD*
Number of Participants	9	9
Education	14.67 ± 1.87	14.11 ± 1.27
Age	20.33 ± 2.29	20.22 ± 1.86
WAIS-IV Vocabulary	13.44 ± 3.01	13.11 ± 1.27
WAIS-IV Block Design	10.78 ± 3.53	10.56 ± 4.33
WAIS-IV Estimated FSIQ	112.33 ± 16.78	110.67 ± 15.06

3.2 Cognitive Performance

Performance of the participants on the n-back and Sternberg tasks was evaluated in terms of accuracy and reaction time. For the n-back task, accuracy was calculated as the correct click ratio (d'), which was determined in the following way:

$$d' = \textit{percent correct responses} - \textit{percent incorrect responses}$$

$$d' = \left(\frac{click\ to\ targets}{all\ possible\ targets} * 100\right) - \left(\frac{click\ to\ nontargets}{all\ possible\ nontargets} * 100\right)$$

For the Sternberg task, accuracy was calculated as the percentage of probes correctly identified. For both tasks, reaction time was measured by how long (in milliseconds) it took for the participant to respond to a target stimulus or probe, depending on the task.

Potential practice effects on the n-back and Sternberg tasks were evaluated with data collected across testing sessions in the HC group. Contrasts of working memory performance between the first and second testing sessions revealed significant main effects of load on the performance measures of both the n-back (accuracy: $F(2, 16) = 25.78, p < 0.001$; target reaction time: $F(2, 16) = .506, p < 0.05$) and Sternberg (accuracy: $F(2, 16) = 5.52, p < 0.05$; reaction time: $F(1.24, 9.89) = 29.85, p < 0.001$, Greenhouse-

Geisser correction applied) tasks, but no significant differences in cognitive parameters between sessions (n-back accuracy: $F(1, 8) = 1.55, p = 0.249$; n-back target reaction time: $F(1, 8) = 4.49, p = 0.07$; Sternberg accuracy: $F(1, 8) = 0.54, p = 0.48$; Sternberg reaction time: $F(1, 8) = 0.03, p = 0.86$). Thus, results suggest there were no effects of prior exposure on later performance of these working memory variables in the context of this study.

3.2.1 N-back Performance

Accuracy

For effects between the HC and unmedicated ADHD groups, accuracy (d') was analyzed utilizing a 2 x 3 ANOVA (group: HC, unmedicated ADHD; load: 0-back, 1-back, 2-back) with repeated measures on load. The main effect of load ($F(2, 32) = 43.07$, $p < 0.001$) reached significance, but no effect of group ($F(1, 16) = 1.26, p = 0.28$) or of a load by group interaction was observed ($F(2, 32) = 0.48, p = 0.63$). The effect of load was such that participants were less accurate as task difficulty increased (participants were significantly less accurate on the 1-back compared to the 0-back condition, the 2-back compared to the 1-back, and the 2-back compared to the 0-back).

For effects comparing medicated to unmedicated states within the ADHD group, accuracy (d') was analyzed utilizing a 2 x 3 ANOVA (medication: on, off; load: 0-back, 1-back, 2-back) with repeated measures on both factors. Similar to between group analyses, the main effect of load ($F(2, 16) = 23.27, p < 0.001$) reached significance, but no effect of medication ($F(1, 8) = 0.13, p = 0.29$) or of a load by medication interaction was observed ($F(2, 16) = 1.34, p = 0.34$). The effect of load was such that, irrespective of medication condition, participants were significantly less accurate on the 1-back

compared to the 0-back condition and on the 2-back compared to the 0-back; there was no difference in performance between the 1- and 2-back conditions. Figure 5 presents the n-back accuracy data for both of these sets of comparisons.

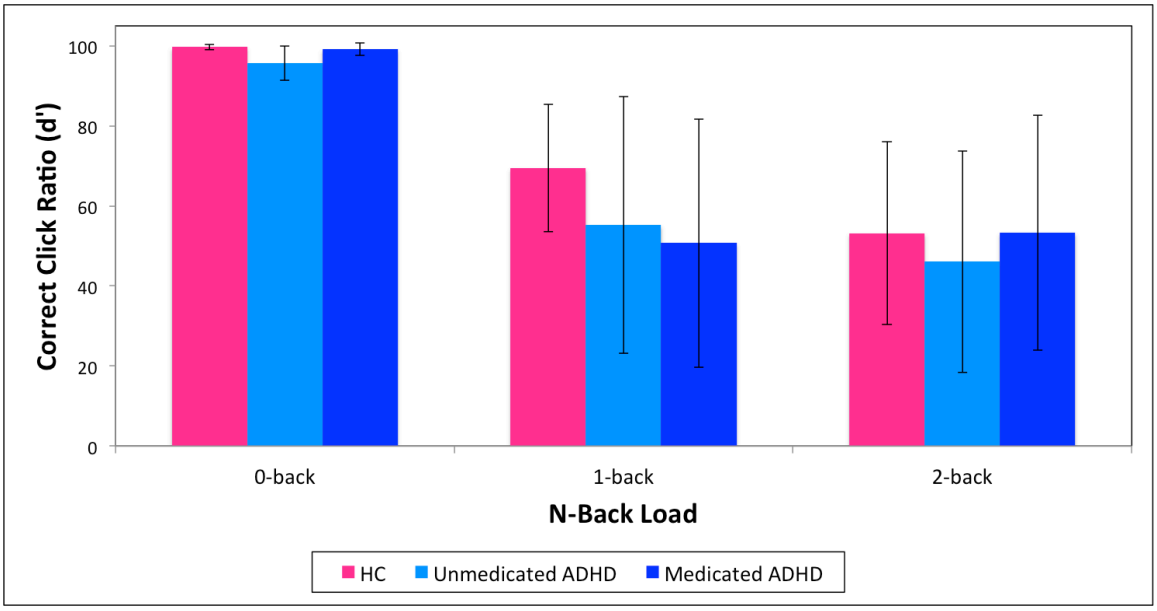

Figure 5. Accuracy on the N-back Task
Correct response ratio (d') for HC participants and for ADHD participants on and off medication, at 3 n-back loads: 0-back, 1-back, and 2-back. This figure represents 2 sets of analyses: 1) comparison of HC and unmedicated ADHD adults and 2) comparison of unmediated and medicated states within ADHD adults. In comparing HC and unmedicated ADHD groups, there was a significant main effect of load but not of group, and there was no load by group interaction. In comparing on and off medication within the ADHD group, there was also significant main effect of load but not of medication state, and there was no load by medication interaction.

Reaction Time

Target reaction time was analyzed between the HC and unmedicated ADHD groups using a 2 x 3 ANOVA (group: HC, unmedicated ADHD; load: 0-back, 1-back, 2-back) with repeated measures on load. The same parameter was analyzed between medicated and unmedicated states within the ADHD group using a 2 x 3 ANOVA

(medication: on, off; load: 0-back, 1-back, 2-back) with repeated measures on both factors. Comparisons showed main effects of load in both the HC vs. unmedicated ADHD ($F(1.07, 8.55) = 9.71, p < 0.05$, Greenhouse-Geisser correction applied) and ADHD on vs. off medication ($F(1.04, 16.60) = 6.75, p < 0.05$, Greenhouse-Geisser correction applied) analyses. Participants were slower to respond on the 1-back compared to the 0-back condition and on the 2-back compared to the 0-back, regardless of group membership or medication condition within the ADHD group. There were no main effects of group ($F(1, 16) = 0.08, p = 0.79$) or medication ($F(1, 8) = 0.08, p = 0.79$), nor interactions in either set of comparisons (HC vs. unmedicated ADHD: $F(1, 16) = 2.70, p = 0.12$; unmedicated ADHD vs. medicated ADHD: $F(2, 16) = 0.34, p = 0.71$). Figure 6 presents the n-back target reaction time data for both sets of analyses.

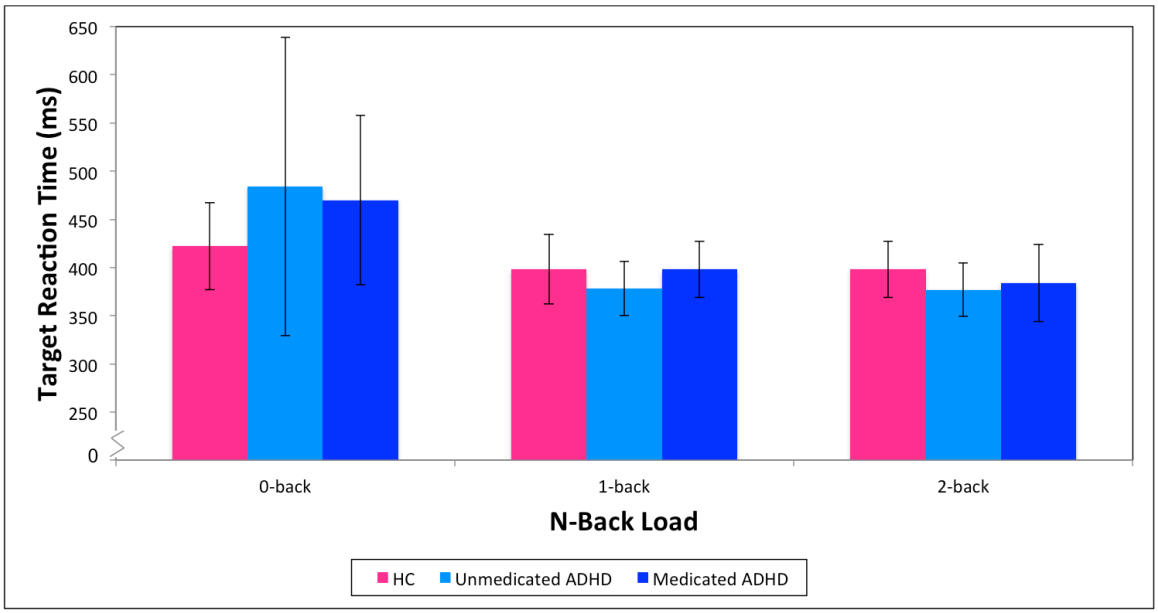

Figure 6. Target Reaction Time on the N-back Task
Target reaction time (ms) for HC participants and for ADHD participants on and off medication, at 3 n-back loads: 0-back, 1-back, and 2-back. This figure represents 2 sets of analyses: 1) comparison of HC and unmedicated ADHD adults and 2) comparison of unmediated and medicated states within ADHD adults. In comparing HC and unmedicated ADHD groups, there was a significant main effect of load but not of group, and there was no load by group interaction. In comparing on and off medication within the ADHD group, there was also a significant main effect of load but not of medication condition, and there was no load by medication interaction.

3.2.2 Sternberg Delayed Recognition Performance

Accuracy

HC and unmedicated ADHD comparisons of accuracy were completed using a 2 x 3 ANOVA (group: HC, unmedicated ADHD; load: 2-letter, 4-letter, 6-letter) with repeated measures on load. Results revealed a main effect of load ($F(2, 32) = 5.72, p < 0.01$) but not group ($F(1, 16) = 0.56, p = 0.47$). However, there was a significant load by group interaction ($F(2, 32) = 3.69, p < 0.05$). An analysis of simple main effects of this interaction was nonsignificant for differences in accuracy between on and off medication performance at each Sternberg level; this is likely due to lack of power associated with

the small sample size. Simple pairwise comparisons (independent samples *t*-tests) were completed to further investigate medication differences but were nonsignificant (2-letter: $t(16) = -1.75, p = 0.10$; 4-letter: $t(16) = -1.64, p = 0.12$; 6-letter: $t(16) = 1.14, p = 0.27$).

Sternberg accuracy between unmedicated and medicated states within the ADHD group were compared using a 2 x 3 ANOVA (medication: on, off; load: 2-letter, 4-letter, 6-letter) with repeated measures on both factors. No significant main effects of load ($F(2, 16) = 3.36, p = 0.06$) or medication condition ($F(1, 8) = 2.29, p = 0.17$) were detected in the ADHD on and off medication analysis and there was no load by medication condition interaction ($F(2, 16) = 2.14, p = 0.15$). Figure 7 presents the Sternberg accuracy cognitive data.

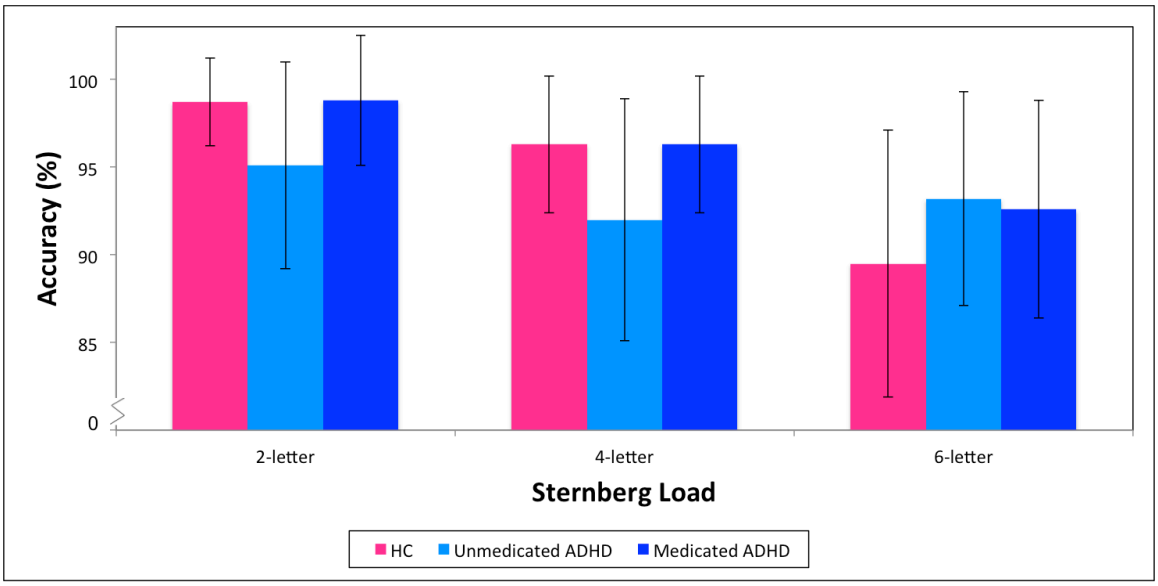

Figure 7. Accuracy on the Sternberg Delayed Recognition Task
Accuracy (% correct) for HC participants and for ADHD participants on and off medication, at 3 Sternberg loads: 2-letter, 4-letter, and 6-letter. This figure represents 2 sets of analyses: 1) comparison of HC and unmedicated ADHD adults and 2) comparison of unmediated and medicated states within ADHD adults. In comparing HC and unmedicated ADHD groups, there was a significant main effect of load but not of group, and there was a load by group interaction. In comparing on and off medication states within the ADHD group, there were no significant main effects of load or medication condition and there was no load by medication interaction.

Reaction Time

HC and unmedicated ADHD groups were compared via a 2 x 3 ANOVA (group: HC, unmedicated ADHD; load: 2-letter, 4-letter, 6-letter) with repeated measures on load. There was a significant main effect of load ($F(2, 32) = 20.22, p < 0.001$) but not of group ($F(1, 16) = 1.06, p = 0.32$) and no interaction was present ($F(2, 32) = 0.66, p = 0.52$). The effect of load was due to increased reaction times with increasing difficulty.

The ADHD group (on vs. off medication comparison) was analyzed via a 2 x 3 ANOVA (group: unmedicated, medicated; load: 2-letter, 4-letter, 6-letter) with repeated measures on load. This revealed a main effect of load ($F(2, 16) = 19.16, p < 0.001$) but

not medication condition ($F(1, 8) = 0.36, p = 0.56$). However, there was a load by medication interaction ($F(2, 16) = 7.10, p < 0.05$). Simple main effects analysis of the interaction yielded no significant difference in reaction time between medication status at each Sternberg load; power may have been insufficient. Supplemental paired *t*-tests were also nonsignificant (2-letter: $t(8) = 1.27, p = 0.24$; 4-letter: $t(8) = 1.46, p = 0.18$; 6-letter: $t(8) = -0.60, p = 0.57$). Figure 8 presents the Sternberg reaction time data based on cognitive performance.

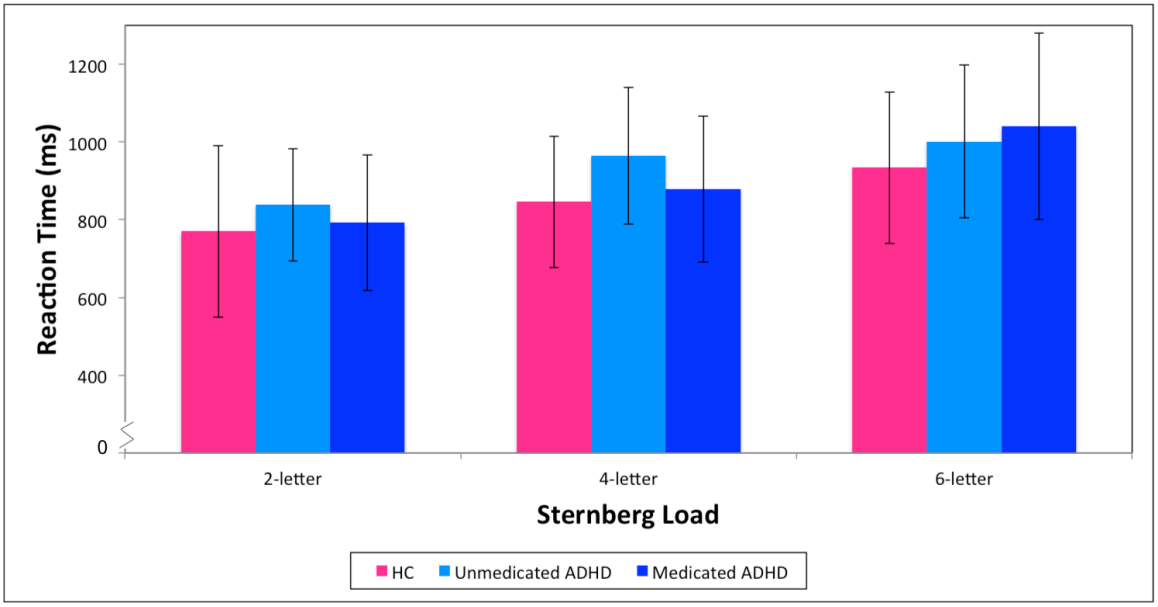

Figure 8. Reaction Time on the Sternberg Delayed Recognition Task
Reaction time (ms) for HC participants and for ADHD participants on and off medication, at 3 Sternberg loads: 2-letter, 4-letter, and 6-letter. In comparing HC and unmedicated ADHD groups, there was a significant main effect of load but not of group, and there was no load by group interaction. This figure represents 2 sets of analyses: 1) comparison of HC and unmedicated ADHD adults and 2) comparison of unmediated and medicated states within ADHD adults. In comparing on and off medication status within the ADHD group, there was also a significant main effect of load but not of medication condition, and there was a load by medication interaction.

3.2.2 Summary of Cognitive Findings

Table 2 summarizes all cognitive findings within the current study.

Table 2. Summary of Cognitive Findings

Results from all cognitive comparisons are reported below. Comparisons are listed in the far left column, followed by findings for each group analysis.

Comparison	Test	Cognitive Parameter	Task Load Performance			Summary
			Low	Med	High	
Unmedicated ADHD vs. HC	N-Back	Accuracy	ADHD < HC	ADHD < HC	ADHD < HC	Across loads, ADHD showed poorer accuracy than HC.
		Target Reaction Time	ADHD < HC	ADHD > HC	ADHD > HC	Across loads, ADHD showed quicker target RT than HC, except on 0-back.
	Sternberg	Accuracy	ADHD < HC	ADHD < HC	ADHD > HC	ADHD showed poorer accuracy than HC, except on the 6-letter.
		Reaction Time	ADHD < HC	ADHD < HC	ADHD < HC	Across loads, ADHD showed poorer RT than HC.
Unmedicated vs. Medicated ADHD	N-Back	Accuracy	Med > Unmed	Med < Unmed	Med > Unmed	Medicated ADHD showed better accuracy than unmedicated, except on 1-back.
		Target Reaction Time	Med > Unmed	Med < Unmed	Med < Unmed	Across loads, medicated ADHD showed slower target RT than unmedicated, except on 0-back.
	Sternberg	Accuracy	Med > Unmed	Med > Unmed	Med < Unmed	Medicated ADHD showed better accuracy than unmedicated, except on 6-letter.
		Reaction Time	Med > Unmed	Med > Unmed	Med < Unmed	Medicated ADHD showed better RT than unmedicated, except on 6-letter.

Note: Task load grouping differs by test. N-back: Low=0-back; Med=1-back; High=2-back. Sternberg: Low=2-letter; Med=4-letter; High=6-letter. Symbols represent performance, e.g., ADHD < HC signifies ADHD group performance on a task is poorer than the HC group.

3.3 Physiological Data

Baseline-corrected values of oxygenation changes (HbO_2 – HbR; measured in micromolars) during the cognitive tasks were compared between the unmedicated ADHD and HC group using repeated measures 2 x 3 ANOVAs. It was not expected that there would be differences in lateralization of oxygenation changes and separate preliminary analyses of this parameter in left and right hemispheres confirmed this. Thus, oxygenation changes in left (optodes 3-6) and right (optodes 11-14) DLPFC regions were combined in the analysis of fNIRS data recorded during performance of each cognitive task.

3.3.1 N-back fNIRS Data

A comparison between n-back task-related oxygenation changes in the HC and unmedicated ADHD groups showed no significant main effect of load ($F(1.27, 20.35) = 0.81, p = 0.41$, Greenhouse-Geisser correction applied) or of group ($F(1, 16) = 0.58, p = 0.46$), nor was there a significant load by group interaction ($F(2, 32) = 1.36, p = 0.27$).

Comparison between n-back task-related oxygenation changes in the medicated and unmedicated states within the ADHD group revealed significant main effects of load ($F(2, 14) = 5.87, p < 0.05$) but not medication condition ($F(1, 7) = 0.41, p = 0.54$), and there was no load by medication condition interaction ($F(1.04, 7.30) = 3.15, p = 0.12$, Greenhouse-Geisser correction applied). The effect of load was such that, irrespective of medication condition, participants' blood oxygenation levels were significantly lower during the 1-back compared to the 0-back condition and on the 2-back compared to the 0-back; there was no difference in performance between the 1- and 2-back conditions.

Figure 9 depicts the hemodynamic changes for each group during cognitive performance on each n-back condition.

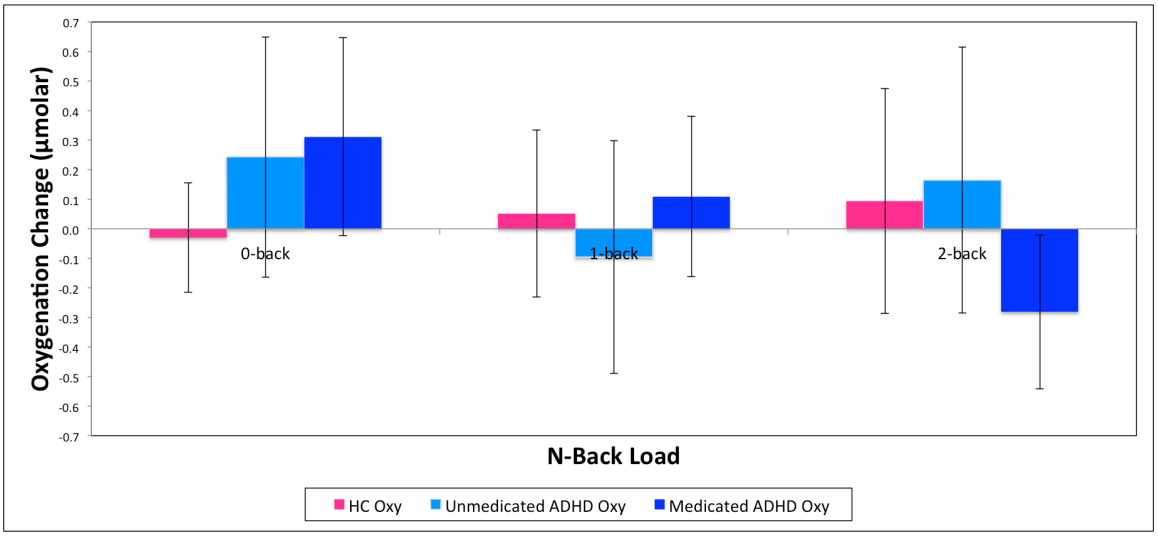

Figure 9. Hemodynamic Response During the N-Back Task
Oxygenation changes elicited in the DLPFC by the 0-back, 1-back, and 2-back load conditions of the n-back task. This figure represents 2 sets of analyses: 1) comparison of HC and unmedicated ADHD adults and 2) comparison of unmediated and medicated states within ADHD adults. In comparing HC and unmedicated ADHD groups, there were no significant main effects of load or group, and there was no load by group interaction. In comparing medication status within the ADHD group, there was a significant main effect of load but not of medication condition, and there was no load by medication condition interaction. Note: Medicated ADHD averages do not include 1 participant's values (no data available).

3.3.2 Sternberg Delayed Recognition fNIRS Data

Comparison between Sternberg task-related oxygenation changes in the medicated and unmedicated states within the ADHD group revealed no significant main effects of load ($F(2, 12) = 0.67, p = 0.53$) or medication condition ($F(1, 6) = 0.95, p = 0.37$), and no load by medication condition interaction ($F(2, 12) = 3.94, p = 0.05$).

As with the n-back, comparison between Sternberg task-related oxygenation changes in the HC and unmedicated ADHD groups showed no significant main effects of load ($F(1, 15) = 0.38, p = 0.69$) or group ($F(1, 16) = 0.62, p = 0.44$), nor a significant load by group interaction ($F(2, 30) = 0.92, p = 0.41$). Figure 10 depicts the hemodynamic changes for each group during cognitive performance across Sternberg loads.

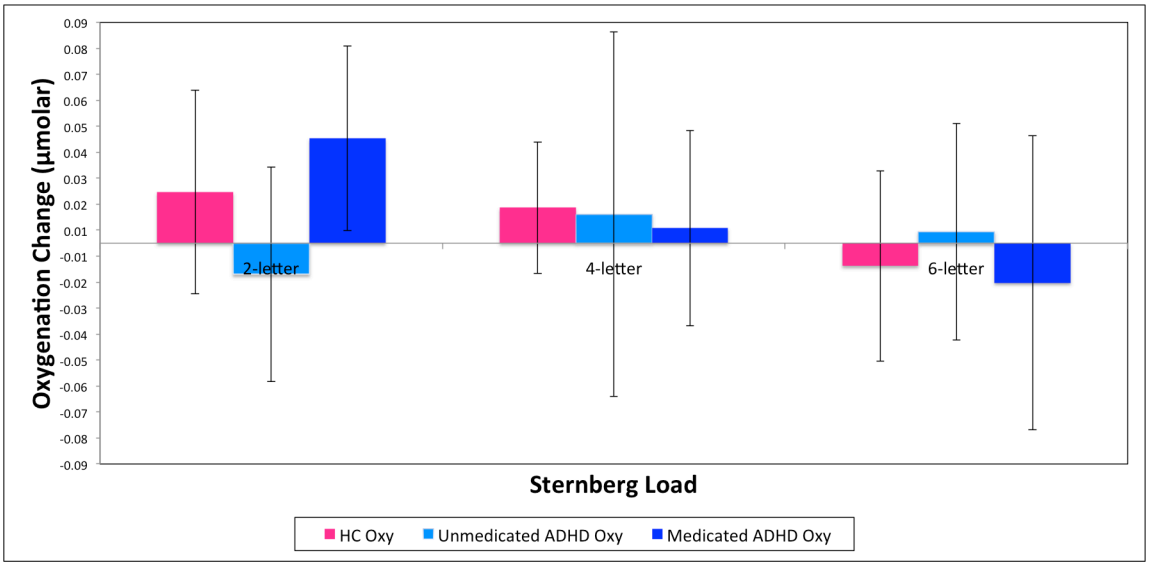

Figure 10. Hemodynamic Response During the Sternberg Delayed Recognition Task Oxygenation changes in the DLPFC elicited by the retrieval trials of the 2-letter, 4-letter, and 6-letter load conditions of the Sternberg delayed recognition task. This figure represents 2 sets of analyses: 1) comparison of HC and unmedicated ADHD adults and 2) comparison of unmediated and medicated states within ADHD adults. In comparing HC and unmedicated ADHD groups, there were no significant main effects of load or group and there was no load by group interaction. In comparing on vs. off medication in the ADHD group, there were no significant main effects of load or medication condition and there was no load by group interaction. Note: Medicated ADHD averages do not include values for 2 participants and unmedicated ADHD averages do not include 1 participant's values (no data available).

3.4 Correlational Results

The relationship between changes in cognitive performance (accuracy and response time) and the theoretically expected changes in hemodynamic response (oxygenation) on both the n-back and Sternberg tasks was directly investigated by means of parametric correlations (Pearson's r) and performed separately for the HC, ADHD-unmedicated, and ADHD-medicated groups. No significant relationships were found (see Tables 3A-C). Given the known limitations with fNIRS and the small sample size, it is not surprising that there are non-findings in the correlational data at this point.

Table 3. Correlations Between Cognitive and Hemodynamic Variables
Pearson's r and *p* values reported for each correlational analysis for HC (A), unmedicated ADHD (B), and medicated ADHD (C) groups. Correlations were assessed between the hemodynamic response (change in oxygenation) and performance variables (accuracy and reaction time) during cognitive tasks. All results were nonsignificant.

(A) HC Group

			Change in Oxygenation (μM)	
Test	**Variable**	**Load**	**r**	***p***
N-back	Accuracy	0	0.32	0.40
		1	-0.05	0.89
		2	0.09	0.82
	Target Reaction Time	0	-0.07	0.86
		1	0.27	0.49
		2	0.12	0.76
Sternberg	Accuracy	2	0.09	0.83
		4	0.19	0.63
		6	0.02	0.97
	Reaction Time	2	-0.20	0.60
		4	0.08	0.84
		6	-0.62	0.08

Note: Degrees of freedom = 7

(B) Unmedicated ADHD Group

			Change in Oxygenation (μM)	
Test	**Variable**	**Load**	**r**	***p***
N-back	Accuracy	0	-0.04	0.93
		1	0.51	0.16
		2	-0.39	-.30
	Target Reaction Time	0	-0.28	0.46
		1	-0.28	0.46
		2	0.54	0.13
Sternberg	Accuracy	2	0.33	0.42
		4	0.17	0.68
		6	-0.07	0.86
	Reaction Time	2	-0.69	0.06
		4	-0.05	0.90
		6	-0.33	0.42

Note: N-back Degrees of freedom = 7; Sternberg Degrees of freedom = 6

(C) Medicated ADHD Group

			Change in Oxygenation (μM)	
Test	**Variable**	**Load**	**r**	***p***
N-back	Accuracy	0	-0.56	0.15
		1	-0.05	0.91
		2	-0.02	0.97
	Target Reaction Time	0	0.05	0.91
		1	-0.06	0.88
		2	-0.13	0.76
Sternberg	Accuracy	2	0.32	0.48
		4	0.39	0.38
		6	-0.38	0.40
	Reaction Time	2	-0.51	0.25
		4	0.63	0.13
		6	0.04	0.93

Note: N-back Degrees of freedom = 6; Sternberg Degrees of freedom = 6

4. DISCUSSION

4.1 Findings and Implications

The aims of this study were to examine within-subject and between-group differences in cognitive performance and cerebral physiology (measured with fNIRS) among adults with ADHD compared to healthy controls and compared to themselves when on versus off medication during working memory tasks. Although some previous research has separately examined cognitive and physiological differences between healthy and ADHD groups, and other research has examined the effect that medication has on cognitive task performance in ADHD, very few have combined the cognitive aspects with the physiology involved, particularly with the use of fNIRS. Additionally, there still remain uncertainties about the impact of stimulant medications on physiological changes in the ADHD brain, which we set out to investigate in this study.

While few statistically significant differences were noted within and between these groups, several important trends in the data are worth noting. For instance, with respect to cognitive performance, results unsurprisingly revealed that unmedicated ADHD adults performed most poorly, with the medicated ADHD adults performing better but yet not as well as healthy control participants. Further, this study showed that the same adults with ADHD demonstrated some degree of improvement on aspects of working memory when they completed these same tasks while medicated. The improvements noted for the medicated adults with ADHD resembled an overall level of working memory ability comparable to healthy control participants such that medicated ADHD adults demonstrated reaction times and accuracy rates on par with those demonstrated by healthy controls. Together, these findings suggest that stimulant

medications improve working memory-related cognitive functions and are consistent with improvements demonstrated in other studies (e.g., Agay et al., 2010; Biederman et al., 2008; Topaloglu et al., 2008; Swanson et al., 2011).

With respect to physiological states in the PFC during working memory tasks, trends revealed that hemodynamic changes in the PFC within and across tasks were quite variable, dependent upon the group. In general, unmedicated ADHD adults demonstrated the greatest degree of variation in oxygenation changes in many task loads (i.e., larger range of values), compared to both themselves when medicated and the control group. This supported our predictions regarding the cognitive performance expectations for each group; that is, without medication, the ADHD brain functions less efficiently than the healthy brain, showing improvement when medicated. Outside of this trend, physiological changes did not correspond to changes in cognitive performance across groups, as originally expected; however, there was still an observable positive effect of medication on cognitive functioning, as seen in the cognitive data. Thus, this may be indicative of other possible mechanisms by which stimulant medications act that have yet to be addressed in the ADHD literature.

4.1.1 Cognitive Performance

The cognitive tasks included in this study were designed to measure specific aspects of working memory and ultimately provided insight into a performance profile of strengths and weaknesses demonstrated by unmedicated adults with ADHD as compared to themselves when medicated as well as to healthy controls. Generally speaking, there was a great deal of variability and inconsistency within and across parameters of working memory, resulting in a lack of significant findings for group comparisons. However, this

study was not without significant results. Though not central to the aims of this study, task load consistently impacted both accuracy and reaction time performance in all groups, in agreement with the literature (e.g., Ayaz et al., 2012; Cairo, Liddle, Woodward, & Ngan, 2004; Miller, Price, Okun, Montijo, & Bowers, 2009; Sternberg, 1969). Thus, the cognitive tasks sufficiently challenged participants as they were designed to do, and as expected, results showed that regardless of clinical diagnosis or medication status, increased task demands hinder working memory performance.

Of note, there were a few paradoxical conditions that resulted in surprising findings for within- and between-group comparisons. First, accuracy on the 1-back load of the n-back task showed that ADHD performance dropped slightly when medicated. Second, reaction time results across the entire n-back task were quite unexpected: all groups showed a general decrease in reaction time with increasing task load and ADHD participants exhibited longer reaction times when medicated compared to when they were unmedicated. This may, in part, be explained by anticipatory response mechanisms, particularly for the ADHD group, as has been demonstrated in previous work (Perchet, Revol, Fourneret, Mauguière, & Garcia-Larrea, 2001). Lastly, both accuracy and reaction time in the 6-letter load of the Sternberg revealed unexpected results regarding group performance: ADHD participants performed better than controls and ADHD participants performed better when unmedicated than medicated. It should be noted that the reason for these unexpected results could not be identified by review/analysis of data acquisition procedures.

Despite the nonsignificant, complicated, and somewhat paradoxical cognitive findings mentioned above, meaningful patterns in working memory functioning still

emerged. Working memory performance was measured via accuracy and reaction time, both reflecting cognitive ability and processing speed in this functional domain. Specifically, accurate information processing takes time and effort and therefore, the faster and more accurately one is able to complete a task, the greater the cognitive strength of one's PFC (Luce, 1986; Sternberg, 1969; Townsend & Ashby, 1983). General trends across these parameters suggest that adults diagnosed with ADHD struggle with storage and retrieval aspects of working memory, yet respond favorably to stimulant medications that are designed to promote function more similar to healthy peers. Moreover, when unmedicated, adults with ADHD tend to demonstrate slower (and hence poorer) processing speed during working memory tasks compared to their healthy counterparts, similar to other adult ADHD studies (Biederman et al., 2008; Topaloglu, et al., 2008).

The deficits described above are not unique to the adult ADHD population. Similar neuropsychological deficits in working memory and other cognitive domains have been identified across the lifespan (as reviewed in Swanson, et al., 2011). Although it has a lifetime trajectory, ADHD is typically conceptualized as a neurodevelopmental disorder beginning in childhood and examinations of its etiology have indicated that development of the cortical surface is delayed in the PFC in children with ADHD (Shaw et al., 2007; Shaw et al., 2012). This has led to a model of the disorder characterized by an early delay in brain development (particularly in frontal gray matter), rather than an overall or more sustained alteration in frontal lobe development, as the leading factor producing ADHD symptoms. Studies expanding these findings into adulthood do not yet exist, but it is possible that these early delays produce long-lasting cortical abnormalities

that are then seen in adulthood as cognitive deficits, which would be consistent with the pattern of cognitive results observed in this study.

It has already been well established that, even in the healthy brain, the frontal lobes demonstrate a protracted pattern of development compared to other neural regions, and continue to develop into the third decade of life (e.g., Durston et al., 2001; Romine & Reynolds, 2005; Sowell, Thompson, Tessner, & Toga, 2001). These neuroanatomical, neurophysiological, and neurochemical changes correlate with the emergence of the capacity to acquire the skills necessary for higher cognition (Grattan & Eslinger, 1991). Combining this with the model of delayed frontal gray matter development in ADHD, it is possible that the ADHD brain is at an even greater disadvantage in its development across the lifespan and perhaps the frontal lobes remain more anatomically variable and underdeveloped into adulthood compared to healthy individuals, further hindering the working memory skills among those with the disorder.

Fortunately, intake of stimulant medication has repeatedly been shown to improve working memory performance in the ADHD population, and this was demonstrated in the current study as well. Specifically, performance in both accuracy and reaction time parameters in the medicated ADHD group not only improved from their unmedicated state, but also resembled the performance level of healthy controls, aligning with previous work in the field (Kobel et al., 2009). Thus, the positive impact of medication is clear from a cognitive perspective; however, the specific mechanism(s) by which it acts and the neurophysiological effects it has remains unclear.

4.1.2 PFC Activation

From a blood flow perspective, patterns of cerebral activation were inconsistent during both working memory tasks. Oxygenation changes in the PFC across tasks were quite variable, dependent upon the group and load, with no detectable trends of statistical significance; this was especially true of the ADHD group. Importantly, the HC group displayed some notable trends. A positive relationship between increasing workload and oxygenation in the DLPFC was observed during the n-back task (in agreement with both fNIRS and fMRI studies of healthy individuals; e.g., Braver et al., 1997; Ayaz et al., 2012; Izzetoglu et al., 2005) and there was a negative relationship observed between increasing workload and oxygenation in the DLPFC during the Sternberg task. Thus, inconsistencies in the ADHD findings may speak to the inefficient functionality of the ADHD brain during working memory tasks (as described above). Furthermore, the unmedicated ADHD group generally demonstrated greater variability across tasks compared to the other groups, and variation within each of the groups themselves at each load level was notable. For example, the average change in oxygenation during the 4-letter Sternberg for the unmedicated ADHD group ranged from -0.0779 to 0.1571 μM while the HC group and medicated ADHD group ranged from -.0293 to 0.0388 μM and -0.0353 to 0.0576 μM, respectively. Given the inconsistent findings in the literature concerning predictable changes in brain activation and the hemodynamic response (as described in sections 1.1.1.2 and 1.1.3.2), the variability we found is not surprising. Some studies have reported reduced levels of oxygenated blood during various cognitive tasks including those in the adult ADHD brain compared to the healthy brain (e.g., Ehlis et al., 2008; Schecklmann et al., 2009). However, these studies employed a different fNIRS

system (ETG-4000, full head setup) and differences were identified in regions our system was incapable of measuring. Beyond this, the literature remains impoverished and those studies that do exist continue to find contradictory results. Additionally, conflicting findings of oxygenation changes under the influence of medication have also been reported (see Monden et al., 2012 and Topaloglu et al., 2008). To further complicate the literature, null group findings similar to those in this study have been found in prior work (Kobel et al., 2009; Schecklmann et al., 2010). For instance, Kobel et al. (2009) found that intake of Methylphenidate (MPH) led to a clear improvement on a behavioral level but this effect was not reflected in corresponding changes in functional brain organization.

Although there is no one explanation for these findings, additional suggestions can be made for the interpretation of the pattern of results. One possibility rests on the currently accepted way of conceptualizing of the brain as a collection of interconnected networks, rather than on a one-to-one correspondence between brain structure and cognition. Although there is compelling evidence suggesting that frontostriatal dysfunction may be central to the pathophysiology of ADHD, neuroimaging findings point to distributed neural substrates, and there is now substantial evidence of structural and functional alterations in regions outside the frontostriatal circuitry in ADHD (Cherkasova & Hechtman, 2009). Imaging research has not only identified differences in PFC activation during cognitive tasks, but also in more posterior cortical regions including the parietal cortex, occipital lobe, and cerebellum (e.g., Hale, Bookheimer, McGough, Phillips, & McCracken, 2007; Kobel et al., 2008; Schweitzer at al., 2000; Silk et al., 2005; Valera, Faraone, Biederman, Poldrack, & Seidman, 2005; Vance et al., 2007;

Wolf et al., 2008). It is possible that the biggest (and therefore more easily detectable) physiological differences occur within posterior regions that were not captured in this study. Having only investigated one part of the network implicated in ADHD, we may have overlooked a larger process at work. This is not to say that there are no physiological differences that occur in the PFC, simply that any differences were not large enough to be detected within the current sample. Although we can only speculate at this point, the current data, viewed in the context of the broader literature, suggests this as one strong possibility.

Additionally, the theory of cognitive reserve (Barnett, Salmond, Jones, & Sahakian, 2006) may help further explain our unexpected fNIRS findings. Sumowski and colleagues (2010) cited various studies that have consistently indicated intellectual enrichment (estimated with education or vocabulary knowledge) as a protective factor against cognitive impairment in other clinical populations including Alzheimer's disease (Stern, Alexander, Prohovnik, & Mayeux, 1992; Alexander et al., 1997; Bennett et al., 2003; Stern, 2006; Roe et al., 2008), stroke (Elkins et al., 2006), and multiple sclerosis (MS; Sumowski, Chiaravalloti, & DeLuca, 2009; Sumowski, Chiaravalloti, Wylie, & DeLuca). Intellectual enrichment ultimately enhances expression of the cognitive reserve network, which in turn reduces the negative impact of neuropathology on cognition (i.e., individuals with greater expression of the cognitive reserve network can withstand more severe brain disease before exhibiting cognition similar to patients with lesser network expression). Furthermore, in their study, Sumowski, Wylie, DeLuca, and Chiaravalloti (2010) conducted a similar working memory protocol to that of the present study and found that, while reaction time was unrelated to intellectual enrichment in the MS

population, intellectual enrichment was negatively associated with prefrontal recruitment, indicating that patients with lesser enrichment required more cerebral resources to perform the same cognitive task as patients with greater enrichment. In the present study, participants ranged from having 13-18 years of education. Due to the enhanced level of intellectual enrichment associated with an education at this level, it may be possible that the ADHD individuals possessed as much cognitive reserve as their healthy counterparts and therefore did not exhibit drastically different patterns of hemodynamic change (i.e., recruiting additional oxygen) during the cognitively demanding tasks.

However, ADHD has largely been conceptualized as a neurodevelopmental disorder, and this may prevent an affected individual from necessarily having the ability to develop strong neuronal/synaptic density—and therefore a cognitive reserve—throughout development. Thus, cognitive reserve may not be acting alone. An accumulating body of literature has indicated that early brain development is highly responsive to environmental influences (Halperin & Healy, 2011), and that there exists a relationship between exposure to environmental factors during neurodevelopment and occurrence of ADHD-like symptomatology (Pamplona, Pandolfo, Savoldi, Prediger, & Takahashi, 2009). Additionally, making modifications to the familial environment (e.g., partaking in cognitive training programs and social play groups for skill strengthening) has been suggested as a possible preventive strategy to ADHD. Such resources have been widely available for the present generation of individuals who are now young adults with the disorder (first reported by Cameron & Robinson in 1980), and—though not recorded—the participants in the current study may have been involved in similar

intervention programs as children and adolescents, aiding in the development of their cognitive reserve.

Although some have argued that fNIRS has better temporal resolution than fMRI (Strangman, Culver, Thompson, & Boas, 2002), there are still limitations with its ability to directly capture cognitive responses (such as reaction times) in milliseconds; for such fast responses, EEG must be considered. For instance, fNIRS allows for the acquisition of an indirect hemodynamic response associated with the neural response underlying a cognitive task, rather than the immediate neural response itself. The signal measured by fNIRS, the hemodynamic response function (HRF), is a metabolic—and thus indirect and slow—correlate of neural activity. Peak response latencies are in the order of several seconds following stimulus onset, with a plateau of several seconds (depending on stimulus duration), and a slow return to baseline over 5-10 seconds or longer (Gervain et al., 2011). Within the context of the current literature surrounding hemodynamic latency in fNIRS, our study provides an additional factor that should be taken into consideration when using fNIRS to investigate hemodynamic changes during cognitive tasks: the task designs themselves. In both the n-back and Sternberg protocols, stimuli are presented so closely to one another that each evoked response is overlapped with the prior and following ones. Thus, in the present study, overlapping responses may have further complicated the intrinsic time delay of fNIRS measurement. That is, the neural activation we intended to measure may have occurred between the time neural processing was initiated with stimulus onset and the time its metabolic correlate was recorded by the fNIRS system.

A second weakness of using HRF is highlighted by/in the work of Huppert and colleagues (2006) who have posited that there exists a large degree of inter-subject variance in response time-to-peak, which was observed in the present study. Diurnal effects on brain activity have also been noted. Brinckman et al. (2012) observed variation both within and across healthy participants completing typical daily activities (e.g., reading) across the span of a day (i.e., 8 hours). They concluded that individuals experience different peaks and valleys of blood flow that change according to the time of day, and the timing of these peaks and valleys can vary substantially between individuals. Although participants in the current study completed both testing sessions at approximately the same time of day, the inconsistent hemodynamic results may be a reflection of diurnal variation across the sample, produced by different participants being tested at different times from one another. Thus, our data demonstrate support for the argument of physiologically based inter-subject differences as well as diurnal differences in the hemodynamic response, which could ultimately impact the interpretation of group comparisons.

Ultimately, unanswered questions remain in the literature concerning the dynamics of the HRF in fNIRS. Currently, no such study exists that directly relates cognitive and hemodynamic responses in a mathematical fashion. Many studies acknowledge this shortcoming (e.g., Gervain et al., 2011; Huppert, Hoge, Diamond, Franceschini, & Boas, 2006) but have yet to develop a strategy to resolve the issue. Progress is being made to determine more precisely when the HRF peaks, but individual differences and differences across brain systems remain. Efforts have been made toward investigating and proposing methods for better standardizing the analysis of

hemodynamic changes using fNIRS (e.g., Schroeter et al., 2004), but the literature still lacks a definitive solution.

4.2 Limitations

A few limitations should be noted for a full understanding of the current findings. Similar to previous imaging studies with this population, the primary limitation of this study is the small sample size. Recruitment of ADHD adults was more difficult than anticipated and complicated by the fact that potential ADHD participants were excluded if they had been prescribed to take their medication only on an "as needed" basis. The rationale for the use of this stringent exclusion criterion was to 1) increase the probability of a reliable ADHD diagnosis, and 2) ensure that ADHD individuals included in the study had a steady regimen of stimulant medication (and therefore were accustomed to the daily benefits of it) that would lead to detectable cognitive and physiological changes during the washout period. Ultimately, however, this criterion may have limited the statistical power of results (by reducing sample size) and any null results should be interpreted with caution. Despite this important limitation, there is still evidence that supports meaningful and expected data trends in previous literature, as discussed above.

The validity of ADHD diagnostic status is another possible limitation to the findings in this study. Because our diagnostic procedures for identifying the ADHD sample versus the healthy control sample relied primarily on self-report, participants who screened positive for ADHD may not have had a true diagnosis of the disorder. Follow-up was completed with each ADHD participant's prescribing doctor in order to obtain collateral diagnostic information; however, the gold standard procedure for arriving at a clinical diagnosis of ADHD in a physician's office also relies only on patient self-report.

Additionally, participants with different ADHD subtypes and comorbidities were included in the study, increasing the heterogeneity of the ADHD group. Comorbidity of diagnoses such as anxiety, depression, and specific learning disability are very common with ADHD (Jensen, Martin, & Cantwell, 1997) and recruiting a patient sample diagnosed with ADHD alone would be difficult as this rarely occurs. Further, such a diagnostically "pure" group would not have been representative of the clinical disorder in the general population. Concerning subtypes, prior research has shown that the impact of stimulant medication does not differ based on diagnostic subtypes (Barkley, DuPaul & McMurraym, 1991) and therefore the heterogeneity resulting from the inclusion of different subtypes should not have impacted results. On the other hand, it is possible that other factors within the ADHD sample influenced heterogeneity and, subsequently, our results. For instance, the disorder has been previously described as neuropsychologically heterogeneous (Sonuga-Barke, 2005; Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2008) such that it cannot be easily diagnosed by means of assessing deficits in executive function or working memory. In addition to neuropsychological heterogeneity, there may be physiological heterogeneity to consider. Multiple neurological pathways—particularly compensatory pathways—might lead to similar cognitive outcomes. Thus, individuals may differ in the physiological underpinnings of the disorder, yet still exhibit the same degree of cognitive ability or disability, consequently making it difficult to identify a specific dysfunctional network that applies to all affected individuals.

4.3 Future Research

Aforementioned explanations for a lack of group and medication effects in the present study, coupled with similar problems noted in previous work, highlights the

difficulties inherent in conducting imaging research with the adult ADHD population. As a result, further research is required to better elucidate which specific components and/or processes of working memory are impaired in ADHD and which factors contribute to and modulate working memory function the most (ADHD subtype, cortical region, medication, age, gender). Having a clearer grasp of these factors could produce a more targeted approach to measuring specified areas of deficit, rather than continuing to take the more global approach to understanding PFC functioning in ADHD.

To this end, future controlled studies should aim to parse out the above factors as best as possible. For example, studies involving a larger cohort, and comparing participants with ADHD only (if possible) to participants with ADHD and comorbid disorders (e.g. depression, anxiety) is warranted. Additionally, despite the fact that the literature to this point indicates no major functional differences in working memory between ADHD subtypes, including an analysis of differences between ADHD subgroups may also be informative with much larger samples.

Another direction for future research would be to include a control task that targets an area of functioning known not to be negatively impacted in ADHD (e.g., language). This would be useful in comparing imaging data (i.e., how brain activity looks during a task participants are able to successfully complete compared to a task they struggle with) and ultimately strengthen future analyses and help identify how brain physiology is altered in ADHD. Additionally, outside of examining pharmacological interventions, investigating the effect of a neuropsychological treatment (e.g., a cognitive training program) on cognitive functioning in ADHD could be informative in determining if other treatments similarly affect (or lack an effect on) cognitive

functioning in this population.

Lastly, this study is only one of a handful that have begun to explore the potential application of fNIRS to clinical populations. Relative to other neuroimaging technologies, fNIRS is still a new and developing technology. In order to better validate the utility of fNIRS and its output, future studies comparing measurements of fNIRS with a presently accepted approach (such as fMRI) on the same individuals completing the same task should be conducted. fNIRS measurement has the potential to be a powerful and useful tool for evaluation of neuropsychological disorders including ADHD; however there are still gaps in the technology that need to be filled before moving to the clinic.

List of References

American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Association, 2000.

Agay, N., Yechiam, E., Carmel, Z., & Levkovitz, Y. (2010). Non-specific effects of methylphenidate (Ritalin) on cognitive ability and decision-making of ADHD and healthy adults. *Psychopharmacology (Berl), 210*(4), 511-519.

Alexander, G.E, Furey, M.L., Grady, C.L., Pietrini, P., Brady, D.R., Mentis, M.J., & Schapiro, M.B. (1997). Association of premorbid intellectual function with cerebral metabolism in Alzheimer's disease: implications for the cognitive reserve hypothesis. *Am J Psychiat, 154*(2), 165-172.

Arenth, P.M., Ricker, J.H., & Schultheis, M.T. (2007). Applications of functional near-infrared spectroscopy (fNIRS) to Neurorehabilitation of cognitive disabilities. *Clin Neuropsychol, 21*(1), 38-57.

Aron, A.R., & Poldrack, R.A. (2005). The cognitive neuroscience of response inhibition: Relevance for genetic research in attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57*(11), 1285-1292.

Ayaz, H. (2010). Functional Near Infrared Spectroscopy Based Brain Computer Interface. School of Biomedical Engineering, Science & Health Systems. PhD Thesis Drexel University, Philadelphia, PA, p. 214.

Ayaz, H., Izzetoglu, M., Platek, S. M., Bunce, S., Izzetoglu, K., Pourrezaei, K., & Onaral, B. (2006). Registering fNIR data to brain surface image using MRI templates. *Conf Proc IEEE Eng Med Biol Soc*, 2671-2674.

Ayaz, H., Izzetoglu, M., Shewokis, P.A., & Onaral, B. (2010). Sliding-window motion artifact rejection for functional near-infrared spectroscopy. *Conf Proc IEEE Eng Med Biol Soc*, 6567-6570.

Ayaz, H., Shewokis, P., Bunce, S., Schultheis, M., & Onaral, B. (2009). Assessment of Cognitive Neural Correlates for a Functional Near Infrared-Based Brain Computer Interface System. In D. Schmorrow (Ed.), *Foundations of Augmented Cognition. Neuroergonomics and Operational Neuroscience* (pp. 699-708).

Ayaz, H., Shewokis, P.A., Bunce, S., Izzetoglu, K., Willems, B., & Onaral, B. (2012). Optical brain monitoring for operator training and mental workload assessment. *NeuroImage, 59*(1), 36-47.

Ayaz, H., Shewokis, P.A., Curtin, A., Izzetoglu, M., Izzetoglu, K., & Onaral, B. (2011). Using MazeSuite and Functional Near Infrared Spectroscopy to study learning in spatial navigation. *J Vis Exp, 56*, e3443.

Ayaz, H., Willems, B., Bunce, B., Shewokis, P. A., Izzetoglu, K., Hah, S., . . . Onaral, B. (2010). Cognitive Workload Assessment of Air Traffic Controllers Using Optical Brain Imaging Sensors. In T. Marek, W. Karwowski & V. Rice (Eds.), *Advances in Understanding Human Performance: Neuroergonomics, Human Factors Design, and Special Populations* (pp. 21-31): CRC Press Taylor & Francis Group.

Baddeley, A. (1986). *Working memory*. Oxford, England: Clarendon Press.

Barkley, R.A., DuPaul G.J., & McMurraym M.B. (1991). Attention deficit disorder with and without hyperactivity: clinical response to three dose levels of methylphenidate. *Pediatrics, 87*(4), 519-31.

Barkley, R.A., Fischer, M., Smallish, L., & Fletcher, K. (2002). The persistence of attention-deficit/hyperactivity disorder into young adulthood as a function of reporting source and definition of disorder. *Journal of Abnormal Psychology, 111*(2), 279-289.

Barkley, R.A. (2011). Barkley Adult ADHD Rating Scale-IV (BAARS-IV). New York, NY: Guilford Press.

Barnett, J.H., Salmond, C.H., Jones, P.B., & Sahakian, B.J. (2006). Cognitive reserve in neuropsychiatry. *Psychol Med, 36*(8), 1053-1064.

Bennett, D.A., Wilson, R.S., Schneider, J.A., Evans, D.A., Mendes de Leon, C.F., Arnold, S.E., … Bienias, J.L. (2003). Education modifies the relation of AD pathology to level of cognitive function in older persons. *Neurology, 60*(12), 1909-1915.

Biederman, J., Mick, E., & Faraone, S.V. (2000). Age-dependent decline of ADHD symptoms revisited: impact of remission, definition, and symptom subtype. *Am J Psychiatry, 157*(5), 816-818.

Biederman. J., Monuteaux, M.C., Mick, E., Spencer, T., Wilens, T.E., Silva, J.M., . . . Faraone, S.V. (2006). Young adult outcome of attention deficit hyperactivity disorder: A controlled 10-year follow-up study. *Psychological Medicine, 36*(2), 167-179.

Biederman, J., Seidman, L.J., Petty, C.R., Fried, R., Doyle, A.E., Cohen, D.R., . . . Faraone, S.V. (2008). Effects of stimulant medication on neuropsychological functioning in young adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry, 69*(7), 1150-1156.

Boonstra, A.M., Oosterlaan, J., Sergeat, J.A., & Buitelaar, J.K. (2005). Executive functioning in adult ADHD: a meta-analytic review. *Psychological Medicine, 35*(8), 1097-1108.

Braver, T.S., Cohen, J.D., Nystrom, L.E., Jonides, J., Smith, E.E., & Noll, D.C. (1997). A parametric study of prefrontal cortex involvement in human working memory. *NeuroImage, 5*(1), 49-62.

Brinckman, D., Schultheis, M.T., Ehrhart, L. Weisser, V., Medaglia, J., & Merzagora, A. (2012, November). *Demonstration of Diurnal Patterns of Brain Activity Using fNIRS*. Poster presented at the Conference of the National Academy of Neuropsychology, Nashville, TN.

Bush, G., Spencer, T.J., Holmes, J., Shin, L.M., Valera, E.M., Seidman, L.J., . . . Biederman, J. (2008). Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task. *Arch Gen Psychiatry, 65*(1), 102-114.

Bush, G., Valera, E.M., & Seidman, L.J. (2005). Functional Neuroimaging of Attention-Deficit/Hyperactivity Disorder: A Review and Suggested Future Directions. *Biol Psychiatry, 57*(11), 1273-1284.

Cairo, T.A., Liddle, P.F., Woodward, T.S., & Ngan, E.T. (2004). The influence of working memory load on phase specific patterns of cortical activity. *Brain Res Cogn Brain Res, 21*(3), 377-387.

Cameron, M.I., & Robinson, V.M. (1980). Effects of cognitive training on academic and on-task behavior of hyperactive children. *J Abnorm Child Psychol, 8*(3), 405-419.

Centers for Disease Control and Prevention (CDC). (2010, November 12). Increasing Prevalence of Parent-Reported Attention-Deficit/Hyperactivity Disorder Among Children - United States, 2003 and 2007. *Morbidity and Mortality Weekly Report (MMWR), 59*(44), 1439-1443. Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5944a3.htm

Chance, B., Anday, E., Nioka, S., Zhou, S., Hong, L., Worden, K., . . . Thomas, R. (1998). A novel method for fast imaging of brain function, non-invasively, with light. *Optics Express, 2*(10), 411-423.

Chance, B., Zhuang, Z, UnAh, C., Alter, C., & Lipton, L. (1993). Cognition-activated low-frequency modulation of light absorption in human brain. *Proc Natl Acad Sci USA, 90*(8), 3770–3774.

Cherkasova, M.V., & Hechtman, L. (2009). Neuroimaging in attention-deficit hyperactivity disorder: beyond the frontostriatal circuitry. *Can J Psychiatry, 54*(10), 651-664.

Cubillo, A., Halari, R., Smith, A., Taylor, E., & Rubia, K. (2012). A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with Attention-Deficit/Hyperactivity Disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. *Cortex, 48*(2), 194-215.

Cubillo, A., & Rubia, K. (2010). Structural and functional brain imaging in adult Attention deficit hyperactivity disorder (ADHD): A review. *Expert Reviews of Neurotherapeutics, 10*(4), 603-620.

Davidson, M.A. (2008). Literature Review: ADHD in Adults : A Review of the Literature. *Journal of Attention Disorders, 11*(6), 628-641.

Dickstein, S.G., Bannon, K., Castellanos, F.X., & Milham, M.P. (2006). The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. *J Child Psychol Psychiatry, 47*(10), 1051-1062.

Duncan, J., & Owen, A.M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci, 23*(10), 475-483.

Durston, S., Hilleke, E., Hulshoff, P., Casey, B.J., Giedd, J.N., Buttlelaar, J.K., & VanEngeland, H. (2001). Anatomical MRI of the developing human brain: What have we learned? *Journal of the American Academy of Child and Adolescent Psychiatry*, *40*(9), 1012-1020.

Ehlis, A.,C., Bahne, C.G., Jacob, C.P., Herrmann, M.J., & Fallgatter, A.J. (2008). Reduced lateral prefrontal activation in adult patients with attention-deficit/hyperactivity disorder (ADHD) during a working memory task: A functional near-infrared spectroscopy (fNIRS) study. *Journal of pediatric research, 42*(13), 1060-1067.

Elkins, J.S., Longstreth, W.T., Monolio, T.A., Newman, A.B., Bhadelia, R.A., & Johnson, S.C. (2006). Education and the cognitive decline associated with MRI-defined brain infarct. *Neurology, 67*(3), 435-440.

Epstein, J.N., Casey, B.J., Tonev, S.T., Davidson, M.C., Reiss, A.L., Garrett, A., . . . Spicer, J. (2007). ADHD and medication-related brain activation effects in concordantly affected parent-child dyads with ADHD. *J Child Psychol Psychiatry, 48*(9), 899-913.

Fallgatter, A.J., Ehlis, A., Wagener, A., Michel, T., & Herrmann, M.J. (2004). Nah-Infrarot-Spektroskopie in der Psychiatrie [Near-infrared spectroscopy in psychiatry]. *Nervenarzt, 75*(9), 911-916.

Faraone, S.V., & Biederman, J. (2005) What is the prevalence of adult ADHD? Results of a population screen of 966 adults. *Journal of Attention Disorders, 9*(2), 384-391.

Faraone, S.V., Biederman, J., Spencer, T., Wilens, T., Seidman, L.J., Mick, E., & Doyle, A.E. (2000). Attention-deficit/hyperactivity disorder in adults: an overview. *Biol Psychiatry, 48*(1), 9-20.

Froehlich TE, Lanphear BP, Epstein JN, Barbaresi WJ, Katusic SK, & Kahn RS. (2007). Prevalence, recognition, and treatment of attention-deficit/hyperactivity disorder in a national sample of US children. *Archives of pediatrics and adolescent medicine, 161*(9), 857-864.

Gervain, J., Mehler, J., Werker, J.F., Nelson, C.A., Csibra, C., Lloyd-Fox, S., . . . Aslin, R.N. (2011). Near-Infrared Spectroscopy: A Report from the McDonnell Infant Methodology Consortium. *Developmental Cognitive Neuroscience, 1*(1), 22-46.

Grattan, L.M., & Eslinger, P. J. (1991). Frontal lobe damage in children and adults: A comparative review. *Developmental Neuropsychology, 7*(3), 283-326.

Greenhill, L., Beyer, D., Finkleson, J., Shaffer, D., Biederman, J., Conners, C., . . . Volkow, N. (2002). Guidelines and algorithms for the use of methylphenidate in children with Attention-Deficit/ Hyperactivity Disorder. *Journal of Attention Disorders, 6*(Supp1), s89-s100.

Hale, T.S., Bookheimer, S., McGough, J.J., Phillips, J.M., & McCracken, J.T. (2007). Atypical brain activation during simple and complex levels of processing in adult ADHD: an fMRI study. *Journal of Attention Disorders, 11*(2), 125-140.

Halperin, J.M., & Healey, D.M. (2011). The influences of environmental enrichment, cognitive enhancement, and physical exercise on brain development: can we alter the developmental trajectory of ADHD? *Neurosci Biobehav Rev, 35*(3), 621-634.

Hechtman, L. (1992). Long-term outcome in attention-deficit/hyperactivity disorder. *Psychiatr Clin North Am, 1,* 553-565.

Herrmann, M.J., Ehlis, A.C., & Fallgatter, A.J. (2004). Bilaterally reduced frontal activation during a verbal fluency task in depressed patients as measured by near-infrared spectroscopy. *J Neuropsychiatry Clin Neurosci, 16*(2), 170-175.

Herrmann, M.J., Plichta, M.M., Ehlis, A.C., & Fallgatter, A.J. (2005). Optical topography during a Go- NoGo task assessed with multi-channel near-infrared spectroscopy. *Behav Brain Res, 160*(1), 135-140.

Hervey, A., Epstein, J.N., & Curry, J.F. (2004). Neuropsychology of Adults With Attention-Deficit/Hyperactivity Disorder: A Meta-Analytic Review. *Neuropsychology, 18*(3), 485-503.

Hock, C., Villringer, K., Muller-Spahn, F., Wenzel, R., Heekeren, H., Schuh-Hofer S., . . . Villringer, A. (1997). Decrease in parietal cerebral hemoglobin oxygenation during performance of a verbal fluency task in patients with Alzheimer's disease monitored by means of near-infrared spectroscopy (NIRS) - correlation with simultaneous rCBF-PET measurements. *Brain Res, 755*(2), 293-303.

Huppert, T.J., Hoge, R.D., Diamond, S.G., Franceschini, M.A., & Boas, D.A. (2006). A temporal comparison of BOLD, ASL, and NIRS hemodynamic responses to motor stimuli in adult humans. *Neuroimage, 29*(2), 368-382.

Inoue, Y., Sakihara, K., Gunji, A., Ozawa, H., Kimiya, S., Shinoda, H., . . . Inagaki, M. (2012). Reduced prefrontal hemodynamic response in children with ADHD during the Go/NoGo task: a NIRS study. *Neuroreport, 23*(2), 55-60.

Irani, F., Platek, S.M., Bunce, S., Ruocco, A.C., & Chute, D. (2007). Functional near infrared spectroscopy (fNIRS): an emerging neuroimaging technology with important applications for the study of brain disorders. *Clin Neuropsychol, 21*(1), 9-37.

Izzetoglu, K., Ayaz, H., Merzagora, A., Izzetoglu, M., Shewokis, P. A., Bunce, S. C., . . . Onaral, B. (2011). The evolution of field deployable fNIR spectroscopy from bench to clinical settings. *Journal of Innovative Optical Health Sciences, 4*(3), 1-12.

Izzetoglu, K., Bunce, S., Onaral, B., Pourrezaei, K., & Chance, B. (2004). Functional optical brain imaging using near-infrared during cognitive tasks. *International Journal of Human Computer Interaction 17*(2), 211-227.

Izzetoglu, M., Izzetoglu, K., Bunce, S., Ayaz, H., Devaraj, A., Onaral, B., & Pourrezaei, K. (2005). Functional near-infrared neuroimaging. *IEEE Trans Neural Syst Rehabil Eng, 13*(2), 153-159.

Jensen, P.S., Martin, D., & Cantwell, D.P. (1997). Comorbidity in ADHD: implications for research, practice, and DSM-V. *J Am Acad Child Adolesc Psychiatry, 36*(8), 1065-1079.

Jobsis, F.F. (1997). Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science 198*(4323), 1264-1267.

Kessler, R.C., Adler, L., Barkley, R., Biederman, J., Conners, C.K., Demler, O., . . . Zaslavsky, A.M. (2006). The prevalence and correlates of adult ADHD in the

United States: Results from the National Comorbidity Survey Replication. *American Journal of Psychiatry, 163*(4), 716-723.

Kim, B.N., Lee, J.S., Cho, S.C., & Lee, D.S. (2001). Methylphenidate increased regional cerebral blood flow in subjects with attention deficit/hyperactivity disorder. *Yonsei Med J, 42*(1), 19-29.

Kobel, M., Bechtel, N., Weber, P., Specht, K., Klarhofer, M., Scheffler, K., . . . Penner, I.K. (2009). Effects of methylphenidate on working memory functioning in children with attention deficit/hyperactivity disorder. *Eur J Paediatr Neurol, 13*(6), 516-523.

Laurienti, P.J., Field, A.S., Burdette, J.H., Maldjian, J.A., Yen, Y.F., & Moody, D.M. (2002). Dietary caffeine consumption modulates fMRI measures. *Neuroimage 17*(2), 751-757.

Luce, R.D. (1986). *Response Times.* New York: Oxford University Press.

Manoach, D.S., Schlaug, G., Siewert, B., Darby, D.G., Bly, B.M., Benfield, A., . . . Warach, S. (1997). Prefrontal cortex fMRI signal changes are correlated with working memory load. *Neuroreport, 8*(2), 545-549.

Levin, J.M., Ross, M.H., Mendelson, J.H., Kaufman, M.J., Lange, N., Maas, . . . Renshaw, P.F. (1998). Reduction in BOLD fMRI response to primary visual stimulation following alcohol ingestion. *Psychiatry Res. 82*(3), 135-146.

Mannuzza, S., Klein, R.G., Bessler, A., Malloy, P., & LaPadula, M. (1993). Adult outcome of hyperactive boys: educational achievement, occupational rank, and psychiatric status. *Arch Gen Psychiatry, 50*(7), 565–76.

Matsuo, K., Kato, T., Fukuda, M., & Kato, N. (2000). Alteration of hemoglobin oxygenation in the frontal region in elderly depressed patients as measured by near-infrared spectroscopy. *J Neuropsychiatry Clin Neurosci, 12*(4), 465-471.

Matsuo, K., Taneichi, K., Matsumoto, A., Ohtani, T., Yamasue, H., Sakano, Y., . . . Kato, T. (2003). Hypoactivation of the prefrontal cortex during verbal fluency test in PTSD: a near-infrared spectroscopy study. *Psychiatry Res, 124*(1), 1-10.

Mehta, M.A., Owen, A.M., Sahakian, B.J., Mavaddat, N., Pickard, J.D., & Robbins, T.W. (2000). Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. *J Neurosci, 20*(6), RC65.

Merzagora, A.C., Schultheis, M.T., Onaral, B., & Izzetoglu, M. (2011). fNIR-based assessment of attention impairments after traumatic brain injury. *Journal of Innovative Optical Health Sciences, 4*(3), 251-260.

Merzagora, A.C. (2010). *Functional near infrared spectroscopy in the multimodal assessment of working memory impairments following traumatic brain injury*. (Doctoral dissertation). Retrieved from iDEA: Drexel E-repository and Archives. (http://hdl.handle.net/1860/3318)

Miller, K.M., Price, C.C., Okun, M.S., Montijo, H., & Bowers, D. (2009). Is the n-back task a valid neuropsychological measure for assessing working memory? *Arch Clin Neuropsychol, 24*(7), 711-717.

Molteni, E., Butti, M., Bianchi, A.M., & Reni, G. (2008). Activation of the prefrontal cortex during a visual n-back working memory task with varying memory load: A near infrared spectroscopy study. *Conf Proc IEEE Eng Med Biol Soc*. 4024-7.

Monden, Y., Dan, H., Nagashima, M., Dan, I., Kyutoku, Y., Okamoto, M., . . . Watanabe, E. (2012). Clinically-oriented monitoring of acute effects of methylphenidate on cerebral hemodynamics in ADHD children using fNIRS. Clinical *Neurophysiology 123*(6), 1147-1157.

Narayanan, N.S., Prabhakaran, V., Bunge, S.A., Christoff, K., Fine, E.M., & Gabrieli, J.D.E. (2005). The Role of the Prefrontal Cortex in the Maintenance of Verbal Working Memory. *Neuropsychology, 19*(2), 223-232.

Negoro, H., Sawada, M., Iida, J., Ota, T., Tanaka, S., & Kishimoto, T. (2010). Prefrontal dysfunction in attention-deficit/hyperactivity disorder as measured by near-infrared spectroscopy. *Child Psychiatry Hum Dev, 41*(2),193-203.

Obrig, H., & Villringer, A. (2003). Beyond the visible – imaging the human brain with light. *Journal of Cerebral Blood Flow and Metabolism, 23*(1), 1-18.

Owen, A.M., McMillan, K.M., Laird, A.R., & Bullmore, E. (2005). N-Back Working Memory Paradigm: A Meta-Analysis of Normative Functional Neuroimaging Studies. *Human Brain Mapping, 25*(1), 46-59.

Paloyelis, Y., Mehta, M.A., Kuntsi, J., & Asherson, P. (2007). Functional MRI in ADHD: a systematic literature review. *Expert Rev Neurother, 7*(10), 1337-1356.

Pamplona, F.A., Pandolfo, P., Savoldi, R., Prediger, R.D., & Takahashi, R.N. (2009). Environmental enrichment improves cognitive deficits in Spontaneously Hypertensive Rats (SHR): relevance for Attention Deficit/Hyperactivity Disorder (ADHD). *Prog Neuropsychopharmacol Biol Psychiatry, 33*(7), 1153-1160.

Perchet, C., Revol, O., Fourneret, P., Mauguière, F., & Garcia-Larrea, L. (2001). Attention shifts and anticipatory mechanisms in hyperactive children: an ERP study using the Posner paradigm. *Biol Psychiatry, 50*(1), 44-57.

Posner, M.I., & Petersen, S.E. (1990). The attention system of the human brain. *Annu Rev Neurosci 13*, 25-42.

Riccio, C.A., Wolfe, M., Davis, B., Romine, C., George, C., & Lee, D. (2005). Attention-Deficit/Hyperactivity Disorder: manifestation in adulthood. *Arch Clin Neuropsychol, 20*(2), 249-269.

Roe, C.M., Mintun, M.A., D'Angelo, G., Xiong, C., Grant, E.A., & Morris, J.C. (2008). Alzheimer disease and cognitive reserve: variation of education effect with carbon 11 labeled Pittsburgh compound B uptake. *Arch Neurol, 65*(11), 1467-1471.

Roy, C., & Sherrington, C. (1890). On the regulation of the blood supply of the brain. *Journal of Physiology (London), 11*(1-2), 85-108.

Rubia, K., Halari, R., Cubillo, A., Mohammad, A.M., Brammer, M., & Taylor, E. (2009). Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naive children with ADHD during a rewarded continuous performance task. *Neuropharmacology 57*(7-8), 640-652.

Rubia, K., Halari, R., Christakou, A., & Taylor, E. (2009). Impulsiveness as a timing disturbance: Neurocognitive abnormalities in attention-deficit hyper- activity disorder during temporal processes and normalization with methylphenidate. *Philos Trans R Soc Lond B Biol Sci 364*(1525), 1919-1931.

Safer, D.J. & Malever, M. (2000). Stimulant treatment in Maryland public schools. *Pediatrics, 106*(3), 533-539.

Schecklmann, M., Ehlis, A.C., Plichta, M.M., Romanos, J., Heine, M., Boreatti-Hummer, A., . . . Fallgatter, A.J. (2009). Diminished prefrontal oxygenation with normal and above-average verbal fluency performance in adult ADHD. *Journal of Psychiatric Research 43*(2), 98-106.

Schroeter, M.L., Bucheler, M.M., Muller, K., Uludag, K., Obrig, H., Lohmann, G., … von Cramon, D.Y. (2004). Towards a standard analysis for functional near-infrared imaging. *Neuroimage, 21*(1), 283-290.

Schweitzer, J.B., Faber, T.L., Grafton, S.T., Tune, L.E., Hoffman, J.M., & Kilts, C.D. (2000). Alterations in the functional anatomy of working memory in adult attention deficit hyperactivity disorder. *The American Journal of Psychiatry, 157*(2), 278-280.

Schweitzer, J.B., Lee, D.O., Hanford, R.B., Tagamets, M.A., Hoffman, J.M., Grafton, S.T., & Kilts, C.D. (2003). A positron emission tomography study of methylphenidate in adults with ADHD: alterations in resting blood flow and predicting treatment response. *Neuropsychopharmacology, 28*(5), 967-73.

Schweitzer, J.B., Lee, D.O., Hanford, R.B., Zink, C.F., Ely, T.D., Tagamets, M.A., . . . Kilts, C.D. (2004). Effect of methylphenidate on executive functioning in adults with attention-deficit/hyperactivity disorder: normalization of behavior but not related brain activity. *Biol Psychiatry, 56*(8), 597-606.

Seidman, L.J., Valera, E.M., & Bush, G. (2004). Brain function and structure in adults with attention-deficit/hyperactivity disorder. *Psychiatr Clin North Am, 27*(2), 323-47.

Shafritz, K.M., Marchione, K.E., Gore, J.C., Shaywitz, S.E., & Shaywitz, B.A. (2004). The effects of methylphenidate on neural systems of attention in attention deficit hyperactivity disorder. *Am J Psychiatry 161*(11), 1990-1997.

Shaw, P., Eckstrand, K., Sharp. W., Blumenthal. J., Lerch, J.P., Greenstein, D., . . . Rapoport J.L. (2007). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc Natl Acad Sci USA, 104*(49), 19649-19654.

Shaw, P., Malek, M., Watson, B., Sharp, W., Evans, A., & Greenstein, D. (2012). Development of cortical surface area and gyrification in attention-deficit/hyperactivity disorder. *Biol Psychiatry, 72*(3), 191-197.

Shinba, T., Nagano, M., Kariya, N., Ogawa, K., Shinozaki, T., Shimosato, S., . . . Hoshi, Y. (2004). Near- infrared spectroscopy analysis of frontal lobe dysfunction in schizophrenia. *Biol Psychiatry, 55*(2), 154-164.

Silk, T., Vance, A., Rinehart, N., Egan, G., O'Boyle, M., Bradshaw, J.L., & Cunnington, R. (2005). Fronto-parietal activation in attention-deficit hyperactivity disorder, combined type: functional magnetic resonance imaging study. *British Journal of Psychiatry, 187*, 282-283.

Sonuga-Barke, E.J. (2005). Causal models of attention-deficit/ hyperactivity disorder: from common simple deficits to multiple developmental pathways. *Biol Psychiatry, 57*(11), 1231-1238.

Sonuga-Barke, E.J., Sergeant, J.A., Nigg, J., & Willcutt, E. (2008). Executive dysfunction and delay aversion in attention deficit hyperactivity disorder: nosologic and diagnostic implications. *Child Adolesc Psychiatr Clin N Am, 17*(2), 367-384.

Sowell, E.R., Thompson, P.M., Tessner, K.D., & Toga, A.W. (2001). Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: Inverse relationships during postadolescent brain maturation. *J Neurosci, 21*(22), 8819-8829.

Spencer, T., Biederman, J., & Mick, E. (2007). Attention-deficit/hyperactivity disorder: Diagnosis, lifespan, comorbidities, and neurobiology. *Ambulatory Pediatrics, 7*(1), 73-81.

Sternberg, S. (1966). High-speed scanning in human memory. *Science, 153*(3736), 652-654.

Sternberg, S. (1969). The discovery of processing stages: Extension of Donders' method. In W. G. Koster (ed.), *Attention and Performance II*. Amsterdam: North-Holland.

Strangman, G., Boas, D.A., & Sutton, J.P. (2002). Non-invasive neuroimaging using near-infrared light. *Biological Psychiatry, 52*(7), 679-693.

Strangman, G., Culver, J.P., Thompson, J.H., & Boas, D.A. (2002). A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. *NeuroImage, 17*(2), 719-731.

Stern, Y. (2006). Cognitive reserve and Alzheimer disease. *Alz Dis Assoc Dis, 20*(3 Suppl 2), S69-S74.

Stern, Y., Alexander, G.E., Prohovnik, I., & Mayeux, R. (1992). Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. *Ann Neurol, 32*(3), 371-375.

Sumowski, J.F., Chiaravalloti, N., & DeLuca, J. (2009). Cognitive reserve protects against cognitive dysfunction in multiple sclerosis. *J Clin Exp Neuropsyc, 31*(8), 913-926.

Sumowski, J.F., Chiaravalloti, N., Wylie, G.R., & DeLuca, J. (2009). Cognitive reserve moderates the negative effect of brain atrophy on cognitive efficiency in multiple sclerosis. *J Int Neuropsych Soc, 15*(4), 606-612.

Sumowski, J.F., Wylie, G.R., DeLuca, J., & Chiaravalloti, N. (2010). Intellectual enrichment is linked to cerebral efficiency in multiple sclerosis: functional magnetic resonance imaging evidence for cognitive reserve. *Brain, 133*(2), 362-374.

Suto, T., Fukuda, M., Ito, M., Uehara, T., & Mikuni, M. (2004). Multichannel near-infrared spectroscopy in depression and schizophrenia: cognitive brain activation study. *Biol Psychiatry 55*(5), 501-511.

Swanson, J., Baler, R.D., & Volkow, N.D. (2011). Understanding the effects of stimulant medications on cognition in individuals with attention-deficit hyperactivity disorder: a decade of progress. *Neuropsychopharmacology, 36*(1), 207-226.

Szobot, C.M., Ketzer, C., Cunha, R.D., Parente, M.A., Langleben, D.D., Acton, P.D., . . . Rohde, L.A. (2003). The acute effect of methylphenidate on cerebral blood flow in boys with attention-deficit/hyperactivity disorder. *Eur J Nucl Med Mol Imaging, 30*(3), 423-426.

Taylor, E., Chadwick, O., Heptinstall, E., & Danckaerts, M. (1996). Hyperactivity and conduct problems as risk factors for adolescent development. *Journal of the American Academy of Child and Adolescent Psychiatry, 35*(9), 1213-1226.

Topaloglu, N., Kara, E., Karahan, E., Erdogan, S.B., Serap, S., Oner, O., . . . Akin, A. (2008). The effect of methylphenidate on brain hemodynamics of attention-deficit hyperactivity disorder measured by functional near infrared spectroscopy. Front. Hum. Neurosci. Conference Abstract: 10th International Conference on Cognitive Neuroscience.

Townsend, J.T., & Ashby, F.G. (1983). *Stochastic modeling of elementary psychological processes*. London: Cambridge.

Vaidya, C.J., Austin, G., Kirkorian, G., Ridlehuber, H.W., Desmond, J.E., Glover, G.H., & Gabrieli, J.D. (1998). Selective effects of methylphenidate in attention deficit hyperactivity disorder: A functional magnetic resonance study. *Proc Natl Acad Sci USA, 95*(24), 14494-14499.

Valera, E.M., Faraone, S.V., Biederman, J., Poldrack, R.A., & Seidman, L.J. (2005). Functional neuroanatomy of working memory in adults with attention-deficit/ hyperactivity disorder. *Biological Psychiatry, 57*(5), 439-447.

Vance, A., Silk, T.J., Casey, M., Rinehart, N.J., Bradshaw, J.L., Bellgrove, M.A., & Cunnington R. (2007). Right parietal dysfunction in children with attention deficit hyperactivity disorder, combined type: a functional MRI study. *Molecular Psychiatry, 12*(9), 826-832.

Villringer, A. (1997). Functional neuroimaging. Optical approaches. *Adv Exp Med Biol, 413*, 1-18.

Villringer, A., & Chance, B. (1997). Non-invasive optical spectroscopy and imaging of human brain function. *Trends Neurosci, 20*(10), 435-442.

Villringer, A., Plancka, J., Hock, C., Schleinkoferc, L., & Dirnagla, U. (1993). Near infrared spectroscopy (NIRS): A new tool to study hemodynamic changes during activation of brain function in human adults. *Neuroscience Letters, 154*(1-2), 101-104.

Volkow, N., Wang, G., Fowler, J.S., Telang, F., Maynard, L., Logan, J., . . . Swanson, J.M. (2004). Evidence that methylphenidate enhances the saliency of a

mathematical task by increasing dopamine in the human brain. *Am J Psychiatry 161*(7), 1173-1180.

Weber, P., Lutschg, J., & Fahnenstich, H. (2005). Cerebral hemodynamic changes in response to an executive function task in children with attention-deficit hyperactivity disorder measured by near-infrared spectroscopy. *Journal of Developmental and Behavioral Pediatrics 26*(2), 105-111.

Weber, P., Lutschg, J., & Fahnenstich, H. (2007). Methylphenidate-induced changes in cerebral hemodynamics measured by functional near-infrared spectroscopy. *J Child Neurol, 22*(7), 812-817.

Wechsler, D. (2011). *Wechsler Abbreviated Scale of Intelligence—Second Edition (WAIS-IV)*. Bloomington, MN: Pearson.

Wilens, T.E., Biederman, J., & Spencer, T.J. (2002). Attention deficit/hyperactivity disorder across the lifespan. *Annu Rev Med, 53*, 113-131.

Wilens, T.E., Faraone, S.V., & Biederman, J. (2004). Attention-deficit/hyperactivity disorder in adults. *JAMA, 292*(5), 619-623.

Wolf, R.C., Plichta, M.M., Sambataro, F., Fallgatter, A.J., Jacob, C., Lesch, K.P., . . . Vasic N. (2008). Regional brain activation changes and abnormal functional connectivity of the ventrolateral prefrontal cortex during working memory processing in adults with attention-deficit/hyperactivity disorder. *Human Brain Mapping, 30*(7), 2252-2266.

Wong, C.G., & Stevens, M.C. (2012). The effects of stimulant medication on working memory functional connectivity in attention-deficit/hyperactivity disorder. *Biol Psychiatry, 71*(5), 458-466.

Woods, S.P., Lovejoy, D.W., & Ball, J.D. (2002). Neuropsychological Characteristics of Adults with ADHD: A Comprehensive Review of Initial Studies. *The Clinical Neuropsychologist, 16*(1), 12-34.