USING NEAR INFRARED SPECTROSCOPY (NIRS) TO EXAMINE DORSOLATERAL PREFRONTAL ACTIVATION PATTERNS DURING WORKING MEMORY TASKS IN INDIVIDUALS DIAGNOSED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER

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Abstract

Neuroimaging in Attention Deficit Hyperactivity Disorder (ADHD) has consistently shown a profile of under-activation in the frontal lobes. However, studies examining frontal lobe activation in ADHD rarely control for working memory ability. We divided adult ADHD participants and age- and gender-matched controls into two groups, based on digits backward performance (good working memory, poor working memory) and compared their dorsolateral prefrontal cortex oxygenation during performance of an inhibition task (Stroop) and a working memory task (auditory N-back), using 2-channel Near Infrared Spectroscopy (NIRS). There were no effects of diagnostic group or working memory ability on Stroop performance or on dorsolateral prefrontal cortex activation during the Stroop task. There was no main effect for diagnosis on behavioral performance on the 2-back task ($p = 0.64$), but there was a main effect of working memory skill ($p = 0.009$); individuals with poorer working memory ability did worse on the 2-back, regardless of diagnosis. NIRS analysis showed that individuals with ADHD activated significantly less on the 2-back than controls, regardless of working memory ability ($p = 0.05$). Exploratory analyses showed that individuals with ADHD with poor working memory activated significantly less ($p = 0.05$) than controls with poor working memory, while ADHD and controls with good working memory did not differ from one another ($p = 0.60$). Results suggest a possible interaction between working memory ability and a diagnosis of ADHD, and emphasize the importance of examining pre-existent ability in studies measuring brain activation.
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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a behavioral disorder, usually diagnosed in childhood, which persists throughout an individual’s entire life. It is the most prevalent childhood disorder, with diagnosis occurring in 3-7% of all school age children. It is more common in boys than in girls, but this may be due to the difficulties faced by psychologists interpreting the current diagnostic criteria for ADHD, or because hyperactive and impulsive phenotypes in girls may be less pronounced than those in boys (Gomez, Harvey, Quick, Sharer & Harris, 1999). ADHD is marked by impairment in areas of executive function, impulsivity, and hyperactivity.

As children with ADHD grow up, ADHD symptoms that existed in childhood often persist, albeit with a shift in manifestation. In follow-up studies of children who were previously diagnosed in childhood with ADHD, the prevalence of symptoms overall appears to diminish, although this is theorized to be the result of shortcomings on the part of the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV), where symptom descriptions appropriate for children are no longer applicable for adults (Faraone, Biederman & Mick, 2005). Symptoms tend to persist consistently into adolescence, with 70-80% of adolescents (previously diagnosed with ADHD) exhibiting symptoms and still meeting diagnostic criteria for ADHD. These factors change in adulthood, however, with a lower percentage of adults reporting symptoms of ADHD (60%), and fewer meeting strict diagnostic criteria (Ingram, Hechtman &
Morgenstern, 1999). However, even in adults with ADHD who present with “fewer” symptoms than in childhood, those existent symptoms are still more prevalent than is seen in adults without the diagnosis. ADHD can be operationally defined as a persistent and developmentally inappropriate display of the above listed symptoms. In addition, the symptoms that continue remain impairing to functioning. This impairment of function is a key diagnostic criteria for any disorder, and thus merits the investigation of ADHD as it manifests in adolescence and adulthood.

ADHD as a present and functionally impairing disorder must therefore be examined not only in children, but in adolescents and adults. Untreated, ADHD can lead to severely limiting social, scholastic, and personal difficulties. In adolescence, for example, ADHD has been associated with increased use of alcohol and illegal drugs, as well as with poor academic performance and social skills (Brasset-Harknett & Butler, 2007; Salmeron, 2008). College students with ADHD tend to have lower mean GPA’s, greater rates of academic probation, and higher dropout rates relative to college students without the disorder (Frazier, Youngstrom, Glutting & Watkins, 2007). The existence of these risk behaviors makes it a relevant disorder to study in both children and young adults. The better our ability to identify the specific phenotype (the cognitive, neurological, neurochemical, and genetic characteristics of a disorder) of ADHD, the better our ability to treat and help those affected.

Under the DSM-IV, ADHD is categorized into three subtypes: “predominantly inattentive,” “predominantly hyperactive,” and “combined.” Many psychologists feel that these subtypes are insufficient, and projected changes in the DSM-V reflect these
sentiments, separating the subtypes into distinct disorders (Baeyerns, Roeyers & Vande Walle, 2006; Finn, 2009; Graetz, Sawyer, Hazell, Arney & Baghurst, 2001). Considering subtypes, however, can provide insights as we examine the existing literature. Many studies neglect this issue, and the possibility of this neglect confounding their research is very relevant. Subtypes have existed as a means for psychologists and psychiatrists to separate what they view as distinct features of a disorder in order to determine what is wrong, and how best to treat an individual. Subtypes indicate that “not all ADHD was made equal” and therefore are necessary factors in any investigation examining the causes and presentation of ADHD (Carlson, Shin & Booth, 1999).

As individuals diagnosed with ADHD grow up, the presentation of symptoms and subtypes changes. In children, ADHD typically manifests as the combined subtype, where the child expresses both hyperactive and inattentive symptoms with equal, or almost equal frequency. This is reflected in our stereotypical expectations of the “child with ADHD” versus those we have for an “adult with ADHD.” Most people, when presented with the idea of a child with ADHD, think of a bouncing-off-the-walls, speedy-talking, disruptive, and poorly focused child. In adults, however, ADHD symptoms shift towards a predominantly inattentive subtype, with over 90% of adults endorsing inattentive symptoms (Millstein, Wilens, Biederman & Spencer, 1997). When adults flippantly use the excuse, “I’m just so ADD!” they are usually referring to their inability to pay attention to what they are doing. This longitudinal trend toward inattentive symptoms is also supported by research. When symptoms in
adults versus those in children are examined, there is a higher prevalence of inattentive symptoms relative to hyperactive/impulsive symptoms among adults than among children (Kessler, Adler, Barkley, Biederman & Conners, 2006). Some researchers theorize that the trend toward inattentive symptoms is a result of an insufficient definition of ADHD. They suggest that the DSM-IV is currently unable to accurately reflect those struggles that might pertain to ADHD in adulthood (Faraone, Biederman & Mick, 2005).

Attention-deficit/hyperactivity disorder has been recognized as an “abnormal” set of behaviors since the time of the early Greeks. In the 1970’s, the first editions of the DSM labeled ADHD as “hyperkinesis,” or excessive movement of the body. Today, ADHD is understood as the compilation of a heterogeneous set of specific cognitive (working memory, response inhibition, etc), and behavioral (inattention, hyperactivity) factors (Braset-Harknet et al., 2007). Studies base their inquiries into the nature of ADHD on structural, behavioral, environmental and genetic viewpoints, and today we think that the disorder is caused by overlaps in all of these areas (Goldstein, 2009). Theories of ADHD examine aspects of its effects on cognitive control – whether those individuals diagnosed with ADHD have the ability to choose and perform actions that are situationally appropriate. Some inclusive theories have been developed to try and address many aspects of cognitive control (such as decision-making and attentional selection) at once. These theories suggest that there may be some inherent ability lacking in individuals with ADHD, such as their ability to set inhibitory “markers,” disabling them from controlling their own behavior, or their
ability to self-regulate based on a failure to evaluate past experience (Brasset-Harknett et al., 2007).

Two of the most widely studied aspects of cognitive control are response inhibition and working memory. Response inhibition concerns whether an individual is able to override a pre-programmed response, such as the pushing of a button. One of the most widely used response inhibition tasks is the “go/no-go” task. In this task, an individual is “trained” to have a certain response (the pushing of a button) to a specific stimulus (such as a green light). Eventually, the “go” signals are interrupted by a “no-go” signal. The amount of time it takes the individual performing the task to inhibit their pattern of pushing the button is known as the “reaction time.” The longer the reaction time, and the more mistakes an individual makes (pushing the button when he or she isn’t supposed to) are indicative of the individual’s ability to inhibit his or her responses (Alderson, Rapport, Sarver & Kofler, 2008).

Working memory, one of the other widely studied cognitive aspects of ADHD, is classically defined as our ability to simultaneously process, manipulate, and store information in order to undertake complex cognitive tasks, such as learning and reasoning (Baddeley, 1992; Martinussen, Hayde, Hogg-Johnson & Tannock, 2005). Working memory allows us to manage short term memory, including the constant influx of visual, verbal and spatial information. Although working memory tasks do not necessarily involve the choosing of situation-appropriate behaviors, many of the things working memory tasks ask a participant to do involve aspects of cognitive control. For example, in the N-back, a classic working memory task, an individual is
asked to watch or listen to a slow stream of information on a computer screen (usually letters), and indicate when the current stimulus (letter) matches one that was presented either one, two, or three letters back. Every time this occurs, the individual is to press a specific button. The greater the number back the task is asking the individual to remember (the greater the N), the greater the working memory load. The task requires that the individual pay attention and hold relevant information in their current thoughts, but also that he or she override the obvious response to the stimulus (simply pressing the button) and instead respond to a stimulus that occurred one or more trials ago (Durston, Zeeuw & Staal, 2008).

The “go/no-go” and N-back tasks are intrinsically linked by their cognitive processes. They both involve choosing one thing over the other, holding relevant rules or directions in working memory, and disallowing the participant from being “trigger-happy,” forcing him or her to wait and evaluate which behavior is appropriate given the situation. Thus, inhibition and working memory tasks are both excellent windows into the amalgam of symptoms and cognitive profiles individuals with ADHD present, and using tasks reflecting both cognitive processes in combination with neuroimaging technology can be an invaluable tool for finding the specific pathophysiology of the disorder. As ADHD gains attention across the world, research into these and other cognitive aspects of the disorder becomes increasingly necessary and poignant.

An increase in public attention to ADHD has led to a marked increase in the amount of self-referred adults claiming the need for a diagnosis of ADHD. Many individuals seek treatment for symptoms they view to be characteristic of ADHD,
having been introduced to the disorder through media, family, or academia. Unfortunately, this often leads to a self-report bias, wherein the diagnostician does not have sufficient evidence from supplementary sources to prove or disprove the patient’s claim of a disorder (Mannuzza, Klein, Klein, Bessler & Shrout, 2002). Finding phenotypes that delineate the progression and distinct structural and cognitive features associated with this disorder will help to address the issue of diagnosis, but will also elucidate the specific pathophysiology associated with the progression of the disorder, in hopes of better treatment options for those affected.

Many roads have been taken to understand ADHD, and some of the most revealing have been those that combine research in a variety of fields. For example, while neuroscience helps reveal what structural differences exist in the brain concurrent with cognitive disabilities, genetic findings support models of ADHD that are heritable and that have clear relationships with structural and functional abnormalities. Although cognitive concepts such as working memory and selective attention are essential characteristics of ADHD, and tasks that examine them lend insight to the nature of the disorder, their qualities alone cannot account for the vast range of symptoms presented across individuals diagnosed with ADHD. An inherently heterogeneous disorder, time must be spent examining genetic and neurological bases for the disorder.

One way that researchers have suggested to accomplish this synthesis is through the use of endophenotypes (Castellanos & Tannock, 2002; Doyle et al., 2005). Endophenotypes are multi-systemic models of disorders, bridging the areas of
neuroscience, genetics, and psychological evaluation, such as executive functioning profiles. They operate on the assumption that ADHD is relatively heritable, with twin studies showing rates of concordance between 60-90%, and that ADHD has a neurological basis that results in psychological manifestations (Durston et al., 2008; Todd et al., 2005). This heritability is seen not only in structural imaging studies, but also in functional neuroimaging and neuropsychological test performance.

The “neurological basis” of ADHD is a concept that surrounds the use of neuroimaging techniques such as functional magnetic resonance imaging (fMRI) to find the structural and functional “roots” of ADHD in the brain. When using neuroimaging techniques, it is important to clarify the terms “over-” or “under-” activation. In functional neuroimaging, principles of blood flow in the brain are used to determine “activation.” The assumption is that, when a brain area is more active, it receives greater blood flow. This results in changes in blood oxygenation levels, an effect that can be reliably measured in the frontal lobes of the brain using techniques such as fMRI or NIRS. In many neuroimaging studies, individuals with ADHD have shown under-activation (meaning they exhibit lower activation than controls) on tasks of cognitive control, including both inhibition and working memory measures.

The neurological basis of ADHD is often investigated after the fact; usually, a pattern of cognition seen in the disorder is discovered first, and the structural correlates to that process are evaluated later. An example of this is the theory of deficient error-awareness processing in individuals diagnosed with ADHD, which states that individuals with ADHD cannot self-correct, and are thus at a learning
disadvantage. From this theory, and using knowledge of brain behavior relationships from studies of acquired brain damage, researchers have identified several neurological areas of weakness in individuals with ADHD, including some of the same reward structures that are dysfunctional in individuals who are addicted to drugs. These structures are collectively known as the ventral striatum, and their “reward center” is known as the nucleus accumbens. These structures are associated with the neurotransmitter dopamine, which has also been implicated in the development, genetics, and progression of ADHD. Dopamine is a major neurotransmitter involved in reward-processing and motor control. The nucleus accumbens and the ventral striatum have been shown to be underactive in adults with ADHD during the anticipation of reward, and overactive in adults with ADHD after the receipt of a reward, which may help explain the tendency people with ADHD have towards immediate gratification. The ventral striatum has also been implicated in conjunction with structures such as the orbitofrontal cortex and the dorsolateral and ventrolateral prefrontal cortices, structures that are also known to be critical for working memory (See Figure 1).

The combination of neuropsychological theories, neuroimaging and genetics can lead to a more holistic view of ADHD, one that encourages the bridging of disciplines. Using endophenotypes is an example of how this bridge might be forged. Encouraging the use of a multi-systemic approach to the understanding of ADHD leads to greater reliability and accuracy in diagnosis, as well as confidence in treatment choices for clinicians. ADHD is not confined to a single area of interest, and
its symptoms reflect that heterogeneity. The theory behind endophenotypes – that a thorough understanding from the viewpoint of many disciplines and areas is necessary in the research and treatment of ADHD – is in line with the multi-faceted way in which ADHD presents itself. With this in mind, researchers and clinicians alike are encouraged to attend to ADHD in a variety of ways, delving into areas of cognition, neurology, behavior, and genetics. What follows is a brief review of the major components of ADHD endophenotype research and ways in which they relate to one another.

**Cognitive Deficits**

Many adults report symptoms of inattention and impulsivity at times. We all experience moments where we say things we wish we wouldn’t have, or feel like we can’t pay attention, no matter how hard we try. These cognitive abilities fluctuate normally within individuals. It is when these cognitive functions are chronically impaired, and an individual experiences an inability to function normally in his or her day-to-day life, that the problem deserves clinical attention. In ADHD, these cognitive skills are deficient in such a way that their absence becomes functionally harmful for the individual.

In research, and in the discussion of ADHD, these “cognitive abilities” are collectively known as executive functions. Executive functions are defined as those cognitive processes that allow us to successfully attain a future goal (Willcutt, Doyle,
Nigg, Faraone & Pennington, 2005). Executive functions include concepts such as response inhibition, working memory, interference control, and task switching.

As noted above, in individuals diagnosed with ADHD, deficits in the areas of working memory and response inhibition are some of the most well-documented impairments associated with the disorder (Castellanos et al., 2002). As previously described, working memory involves the ability an individual has to simultaneously store and process information. In individuals with ADHD, this ability is impaired, as the “processing” component of working memory is disrupted by what the individual perceives to be “more salient” information. From a new thought while performing a task, to a distracting image a driver sees as he or she is on his or her way home, individuals with ADHD have a hard time choosing one response over another when there is a high incoming information load. To measure this in the lab, researchers most often turn to tasks such as the previously described N-back, or even simpler ones, such as the digit and spatial span tasks. The N-back task requires participants to override the obvious response to a stimulus, and instead react to a stimulus that occurred one or more trials earlier. The digit span and spatial span tasks are much simpler, and merely require the participant to verbally or manually (by pointing) repeat a given series of numbers forward (basic attention span) and backward (working memory). Working memory tasks such as these have been shown to indicate an executive functioning deficit in adults with ADHD, although specific deficits vary as a function of the test used to measure them.
A recent meta-analysis of working memory tasks used in ADHD extrapolated several notable features of working memory deficit in ADHD. A difference was noted for memory tasks using visuospatial cues, versus those with verbal cues, wherein individuals with ADHD performed worse than controls on verbal tasks, but comparably with controls when they were able to use visuospatial cues. In order to compare performance in these two areas, one must examine “effect sizes.” Effect sizes refer to how far apart two sets of data are in standard deviation units. For example, verbal measures, such as the Auditory Consonant Trigrams task, showed an effect size around 0.83, a large effect, signifying that the average person in the ADHD group scored 0.83 standard deviations lower than the average person in the control group.

On the other hand, visual working memory measures such as the Simon task showed a medium effect size around 0.47 (Hervey, Epstein & Curry, 2004).

Deficits in inhibition control are also well-documented in individuals with ADHD. In a meta-analysis of studies examining a variety of tasks, including tasks of inhibition, effect sizes were consistently high, with increasing levels of difficulty, or load, showing a likewise increase in effect size. Tasks examined included the Stop Signal task, a well-known, reliable response inhibition task, with a high effect size around 0.83. Also included in the study’s meta-analysis was the Stroop task, which was used in the present study. The effect sizes for the Stroop Task were medium – around 0.47 (Hervey et al., 2004). This data indicates a persistent and significant effect of response inhibition tasks as they relate to ADHD, and how individuals with ADHD might struggle in these areas of cognition.
In addition to behavioral performance differences on working memory and inhibition tasks, differences in neurological activation have been seen in persons with ADHD while performing these tasks. For example, in a recent study using functional near infrared spectroscopy (fNIRS), significant decreases in blood flow in the prefrontal cortex were found when individuals with ADHD performed an inhibition task (the Stroop Task), as compared to healthy controls (Serap, Tapsin & Akin, 2009).

ADHD subtypes may affect these executive functioning deficits, although recent studies are casting doubt on the power they have to significantly affect performance. Two recent studies in particular have shown no differences in working memory or selective attention between the different subtypes of ADHD and their matched controls. Rather, the authors suggest that it is in the area of impulsivity that subtypes may significantly differ in performance (Nigg, Willcutt, Doyle & Sonuga-Barke, 2004; Solanto, Gilbert, Raj, Zhu & Pope-Boyd, 2007). As such, we might expect that individuals diagnosed with either “ADHD, hyperactive subtype,” or “ADHD, combined subtype,” would be more likely to perform poorly on tasks of inhibitory control than individuals diagnosed with “ADHD, inattentive subtype.” It is important to note, however, that both subtypes appear to show fundamental working memory problems, which is the primary focus of the present study.

In the present study, we focused on the concept of cognitive control through the examination of both working memory and response inhibition. Measuring aspects of working memory and inhibitory control, and how they relate to neurological
functioning, may lead to a delineation of the specific pathophysiology of ADHD, and enable us to create better diagnostic criteria and treatment options for those affected.

**Genetics**

While genetics are not a primary investigation of the present study, ADHD genetic findings support many of the executive functioning/frontal lobe theories and arguments (discussed below) surrounding ADHD. Several neuropsychological theories uniting specific genetic profiles of individuals with ADHD have been suggested. Among these, the most popular are those of “delay aversion” and the “dopamine hypothesis of ADHD.” Although structural abnormalities help us to identify regions of the brain worth focusing on, these two theories focus on the genetic abnormalities associated with ADHD, giving us a better depiction of the basis of the structural differences and the cognitive deficits.

The “dopamine hypothesis” of ADHD states that there is a lack of the neurotransmitter dopamine in the brains of individuals diagnosed with ADHD. In individuals with ADHD, a lack of dopamine has been traced back to many genes, two of which have been at the forefront of the research on the topic. The genes DAT-1 (dopamine transporter), and DRD-4 (dopamine receptor), are often expressed in dysfunctional ways in people with ADHD. For example, the overexpression of DAT-1 causes dopamine (DA) to be removed from the synapse too quickly, whereas the under-expression of DRD-4 leads to a decreased amount of receptors embedded into the post-synaptic neuronal membrane, decreasing the amount of places where present
DA can bind. Both result in dysfunctional signaling systems, which are unable to process and associate cues with reinforcement (Gizer, Ficks & Waldman, 2009). This inability may lead to many of the cognitive effects seen in individuals with ADHD, such as deficits in working memory. An examination of genetics is not included in the present study, but the theories that surround it do present a means by which many cognitive aspects of ADHD can have a united basis.

Dopaminergic pathways are primarily associated with reward – hence the “high” associated with drug use – and theories about dopamine’s role in ADHD have been informed by the existing substance abuse literature. Dopaminergic neurons are primarily found in the striatal pathway and the prefrontal cortex – two areas found to be abnormal in individuals with ADHD. Problems with DRD-4 or DAT-1, therefore, may have lasting effects that manifest as ADHD-like symptoms (Groman, James & Jentsch, 2008).

Dopamine is theorized to be involved in reward processing and learning. In other words, our ability to learn and process information relies on the ability of the dopamine system to reward us for cues (the transfer of signaling to those “objects” that precede reinforcement) (Tripp & Wickens, 2008). When we are rewarded, dopamine neurons in our brain fire and lead us to associate whatever we just did with the reward (the dopamine) received. This is conditioned learning.

Theoretically, in individuals with ADHD, this reward system has been affected by genetics in such a way that cues (those things that lead to reward) can’t be associated with the reward. This, in turn, results in many of the impulsive behaviors
associated with ADHD. If an individual with ADHD cannot associate cues with rewards, he or she cannot delay gratification. That is, he or she will not be able to make the “cognitive leap” that engaging in a cue and then waiting for the reward will result in the reward in the same manner that engaging in a cue and immediately receiving the reward would. This inability to form cues is known as the delay aversion hypothesis of ADHD. It is based in the idea that individuals with ADHD cannot delay gratification, but it also correlates (and is perhaps explained better by) the dopamine hypothesis of ADHD. Lower levels of dopamine might lead to this theorized inability to associate cues with reward. Thus dopaminergic findings both support and provide insight for the delay aversion hypothesis.

What happens when we can’t associate cues with reinforcement? This is one of the key insights to cognitive deficits associated with ADHD. Failure to form reward pathways results in impulsive behaviors (an inability to inhibit responses), and can just as easily result in inattentive symptoms. For example, a child with ADHD who is sitting in a classroom may be more immediately rewarded by watching a bird swoop by the window; he is unable to associate long-term reward – doing well in school – with his behavior in the moment (Kebir, Tabbane, Sengupta & Joober, 2009). With delay aversion and the dopamine hypothesis in mind, we must seek to qualify those cognitive deficits that occur in individuals with ADHD.

With regard to working memory, the delay aversion hypothesis holds some interesting implications. Delay aversion states that individuals diagnosed with ADHD find immediate rewards more reinforcing, because they are not able to establish the
cues that would allow them to delay gratification. As working memory necessitates constant action of two systems - the storage of information as well as the processing of it - according to the delay aversion hypothesis, an individual with ADHD may have noticeable deficits in this process. If a person with ADHD cannot create cues in order to delay gratification, he or she is unable to process the information he or she is receiving in an efficient manner. In working memory tasks, this inability to form cues may manifest as an inability to stay on task, as the cues associating reward with attention over time have not been established, and in fact, cannot be established. Many would argue that this leads to a decreased ability in the individual with ADHD to perform well on working memory tasks (Barkley, 1997).

**Structural Neuroimaging**

As previously mentioned, frontal-striatal neurological pathways are implicated in ADHD as executive function-mediating centers, helping individuals plan and process the actions they take to meet the challenges of everyday life (Willis & Weiler, 2005). Neuroimaging studies assessing structural and functional abnormalities focus on these frontal-striatal neurological pathways. As mentioned earlier, one of the main cognitive deficits that focuses the search for structural abnormalities in ADHD is in the area of executive function. Skills such as working memory, response inhibition, and decision-making are considered neural correlates of ADHD, and problems in these areas are associated with the ventral and dorsolateral prefrontal areas of the brain and the fiber tracks that serve to connect them. In studies using diffusion tensor, magnetic
resonance imaging (DT-MRI), fiber pathways subserving attention and executive functions were significantly smaller in adults with previously diagnosed childhood ADHD (including all subtypes) compared to healthy controls (Makris et al., 2008).

Structural MRI studies have typically been conducted in children with ADHD, but with regard to literature that exists on adults with ADHD and structural imaging, several areas of difference have been noted. The beginnings of a structural basis of ADHD lie with the “prefrontal” theory of ADHD, which suggests some deficit in the prefrontal lobes of individuals with ADHD. This theory is born of the success of stimulant medication use in children with ADHD (a drug that effects fronto-striatal pathways), and also from mouse models implicating frontal dopamine circuits in hyperactivity. With this starting point, MRI seeks to delve into the structural differences between the brains of individuals with ADHD versus controls. After the prefrontal cortex, other areas of interest in ADHD include the dorsal anterior cingulate cortex, the corpus callosum, the basal ganglia (striatum), and cerebellum.

In studies with children, many different structural abnormalities have been found. Children with ADHD seem to exhibit a smaller overall cerebrum volume, although there is some debate over the specific areas of volume difference. Structural studies examining the PFC have noted that it has a smaller volume in individuals with ADHD versus controls (Valera, Faraone, Murray & Seidman, 2007). The dorsal anterior cingulate cortex has strong connections to the prefrontal cortex, and is implicated in complex cognitive processing (Cohen & Miller, 2001). The right posterior cingulate may have a reduction in volume in individuals with ADHD. The
The corpus callosum is essential for communication between the two hemispheres of the brain. Structural abnormalities in the posterior part of the corpus callosum are implicated in ADHD. The striatum is made up of the caudate, putamen, and globus pallidus. Striatal lesions in animals produce hyperactivity and deficits in working memory. The striatum is also rich in dopaminergic neurons, which, as previously mentioned, have been implicated in ADHD. Smaller striatal structures have been found in numerous studies of structural abnormalities individuals with ADHD. Lastly, smaller cerebellar volumes have been found to be associated with children diagnosed with ADHD (Valera et al., 2007).

In adults with ADHD, no overall cerebral volume differences were found between controls and individuals with ADHD. However, a significant volume decrease was found in the frontal cortex for individuals diagnosed with ADHD versus controls (Seidman, Valera & Makris, 2005). This supports the theory that a structural abnormality associated with ADHD in adults and in children involves the fronto-striatal circuits. Structural studies are excellent places to start when we want to pinpoint areas that might, in turn, show functional differences as well. Once a structural area of abnormality has been identified, we can conduct a functional neuroimaging study to examine what blood flow (oxygenation) levels can tell us about activation patterns during specific cognitive processes, such as working memory tasks.

**Functional Neuroimaging**
Research using functional imaging techniques has also found areas of differentiation on tasks examining aspects of executive function and cognitive control in individuals with ADHD. Functional imaging allows researchers to examine activation patterns in a desired population while participants are actively engaged in a task. This type of research is unique and very powerful in that it gives us a privileged glance into the activity of the brain as a person struggles to answer questions or complete a problem set. A functional imaging study gives us a real-time lens into the “mind.” With event-related scans, we are able to measure activation as it correlates to performance, and we can make conclusions about what certain areas of the brain might be used for, and how much they differ with regard to activation in individuals with disorders such as ADHD.

In a study using positron emission tomography scanning to examine decision-making patterns in ADHD (Ernst, Kimes & London, 2003), activation in the dorsolateral and prefrontal cortex areas, usually associated with executive functions such as decision-making, was noticeably less profuse in adults with ADHD compared to controls. As subtypes were not specified in the study, an examination of how ADHD subtypes may have affected performance and neurological outcomes was not possible. The study also noted that individuals with ADHD performed tasks testing decision-making skills using significantly fewer cognitive areas (such as the anterior cingulate and the hippocampus, involved in emotion and memory processes), possibly demonstrating why individuals diagnosed with ADHD experience deficits in motivated behavior formation (Ernst, et al., 2003).
Studies using functional imaging have also been done to examine neural activation during response inhibition, using tasks such as the previously described “go/no go” measure. In a recent study, Durston and colleagues (2003) examined children (aged 8-16), for differences in fronto-striatal regions during a go/no-go task. These regions were found to be hypoactive during the task, but with an interesting caveat to the previously mentioned adult study. Whereas in the adult study, participants were shown to have a less diffuse region of activation than controls, there was a more diffuse network of activation in children with ADHD performing go/no-go tasks. One possible reason for these differences is maturation – whereas adults were seen to have a less diffuse region of activation for decision-making tasks, children, whose systems are less developed, showed a greater diffusion of activation for go/no-go tasks. Even though the tasks were slightly different, we would expect similar regions to be activated for both tasks, regions involved in executive functioning and cognitive control. The study controlled for ADHD subtypes (including an equal number of each), removing doubts about the validity of the results as they apply across all subtypes of the disorder (Durston, Tottenham, Thomas, Davison & Eigsti, 2003).

In participants who have never taken medication for their disorder, similar results regarding response inhibition and fronto-striatal pathways have been found (Rubia, Smith, Brammer, Toone & Taylor, 2005). Recent research with medication-naïve individuals has shown significant decreases, using fMRI, both in the right inferior prefrontal cortex, and the precuneus and posterior cingulate gyrus during motor inhibition tasks, similar to the go-no-go task previously described. Under-
activation of the inferior prefrontal cortex was seen when individuals successfully inhibited a motor response, and underactivation in the precuneus and posterior cingulate gyrus (also structures involved in decision making, reward, and response inhibition) was seen when individuals failed to inhibit.

Ventral striatal regions have also been implicated in reward processing in individuals diagnosed with ADHD. In a recent study by Plichta and colleagues (Plichta, Vasic, Wolf, Lesch & Brummer, 2009) the ventral striatal reward system was found to be hypo-responsive during both the immediate and delayed trials of a reward processing task. The group of fourteen adults included in the study were all diagnosed with the combined subtype of ADHD, and were seen to have hypoactivation of their ventral striatal pathways regardless of whether their reward was delayed or not. However, in the same study, it was noted that on delayed trials (where the individual had to wait for the reward) individuals diagnosed with ADHD showed hyperactivation in their caudate nucleus and amygdala. The results from the delayed reward trials support the delay aversion hypothesis of ADHD, which states that the cognitive and behavioral deficits associated with ADHD arise from problems individuals with the disorder have in matching waiting for a reward and the satisfaction of receiving the actual reward. Examining these correlations provides insight to the neurological basis for the executive functioning deficits associated with ADHD.

With regard to working memory, several studies have examined activation patterns while subjects performed working memory tasks. A recent study using Blood Oxygenation Level Dependent fMRI was used to examine forty adults, twenty with
ADHD and twenty matched controls, on a 2-back working memory task (Valera et al., 2005). Subtypes were not included in the study and thus did not factor as determinants of observed psychological or neurological effects. While there were no significant differences in the performance of each group (ADHD versus control) on the working memory task, there were significant decreases in activation in the cerebellar and occipital regions for the ADHD group, as well as a trend for decreased activation in the right prefrontal cortex while performing the task.

The ventral lateral prefrontal cortex is also implicated in functional imaging studies of working memory. In a recent study, a group of twenty females, aged 11-17, ten with ADHD and ten matched controls, were measured for blood-oxygenated level dependent (BOLD) signals while performing a working memory task. The study showed that in the “high load” section of the delayed matching, working memory task, individuals with ADHD activated the inferior frontal gyrus and the extra-striate cortex significantly less than controls (Sheridan, Hinshaw & D’Esposito, 2007). No behavioral differences were noted between the groups, and the researchers interpreted the decreased activation seen in the frontal gyrus and the striatum as a reflective of inefficiency. They suggested that individuals with ADHD have some inherent structural deficit that doesn’t allow them to organize their task performance and brain activity as efficiently as individuals without ADHD can. This inefficiency can describe many of the symptoms of ADHD, and why individuals with ADHD struggle with complicated, organized behavior.
Another recent study by Ehlis and colleagues, conducted with 13 adults with ADHD and 13 age- and gender-matched controls, showed that adults with ADHD had decreased activation in the ventro-lateral prefrontal cortex using NIRS technology during an N-back working memory task. No subtypes were described in the paper, so an examination of their possible effects was not included. When individuals were under the highest working memory load (2-back), not only did they make the highest percentage of omission errors of all the trials, they also showed reduced amounts of oxygenated hemoglobin (activity is indicated by how much oxygen, and this blood flow, is reaching an area) in the ventro-lateral prefrontal cortex, indicating reduced activation (Ehlis, Bahne, Jacob, Herrmann & Fallgatter, 2007).

In the above mentioned studies, there are significant differences in the activation profiles (hypo versus hyper-activation) associated with tasks and regions of the brain, although the findings are inconsistent. Although there has been a multitude of conflicting research on whether we can expect decreased or increased activation on working memory tasks, the issue may be one of research design. There are three significant factors in research design that may lead to these inconsistencies. The first is the issue of the type of task being examined. We can reasonably expect that a task examining working memory will necessarily involve some different brain areas, and show different brain activation patterns, than a task examining response inhibition. The second, which is rarely considered in existing research, is the difficulty level of the task itself. A working memory task in which an individual is asked to listen to and repeat a series of numbers is perhaps less challenging than a task in which a
participant has to keep in mind specific rules and visual cues for a card sorting task, and thus is likely to involve less cortical activation. The third factor is the actual behavioral performance of the individuals with ADHD as compared to controls. Some of the most interesting comparisons are made when the behavioral performance between the individuals with ADHD and controls are not significantly different – yet their patterns of brain activation while completing the tasks are.

In literature on working memory and aging, this factor has taken center stage, as the importance of matching older adults on task performance with younger individuals, is explored. Matching working memory ability, for example, between older adults and younger, and subsequently comparing functional activation patterns, has revealed different findings than studies that do not match the two age groups on cognitive ability. In addition, the difficulty level of the cognitive task itself is an important factor. If individuals are matched on performance (low vs. high), both older and younger individuals exhibit an inverted U-curve of performance, with their levels of neural activation increasing until the difficulty of the task causes them to perform poorly, and likewise show a drop in neural activation (Nagel et al., 2009).

This is a possibility with any research conducted using functional imaging, especially with individuals who have been diagnosed with ADHD, as they often show symptoms of inattention. As an individual with ADHD performs any task while hooked up to a functional imaging machine, he or she will show an activation increase as long as he or she is engaged in the task and the task is challenging. This is the upward slope of the inverted U. However, if the task becomes too hard, the individual
may disengage, becoming frustrated and unwilling to finish the rest of the task. This is
the downward slope of the inverted U. It is also true that if an individual goes into
performing a task, such as the Stroop Task, with substantial previous experience with
the task, he or she will not find the task difficult, and therefore we will not see the
upward slope of the inverted U, as the individual does not have to increase activation
in order to perform well on the task – the task is already automatic. Controlling for
previous ability in any research design, as well as matching on task performance helps
to control for this inverted U curve. Without matching on general ability and on task
performance, the results of the tasks mentioned above might have been lost in other
considerations, without the proper context to examine the results of the study.

With consideration of these methodological issues, Table 1 illustrates how
prior neuroimaging studies on working memory compare on each of these factors and
what conclusions can be drawn from their data as a result. Many of the studies
included in the table were drawn from a meta-analysis of child ADHD literature
(Durston et al., 2008). However, more recent literature supports the conclusions that
were formed in the meta-analysis concerning functional imaging of working memory
in individuals with ADHD, as well as supporting the applicability research findings in
children being equally applicable to adults (Cubillo, et al., 2010; Passarotti, Sweeny &
Pavuluri, 2010; Suskauer, et al., 2008). Perhaps the most fascinating results focus on
the role of the frontal lobes in working memory, and how deficits in these areas are
seen repeatedly in the examination of adults with ADHD. The table demonstrates the
existence of several scenarios worth mentioning. The first is that the majority of
studies reported no behavioral differences on the working memory tasks between their controls and their individuals with ADHD; however, they all showed significantly different activation in prefrontal areas while performing the working memory tasks. It is notable, however, that no studies specifically matched their control and ADHD samples on general working memory ability (i.e., on tasks independent of those used during the imaging protocol).

The second key feature of the studies examined is task difficulty, and changes in brain activation that correspond to this difficulty. For example, most studies that examined a more challenging task, such as the N-back, noted significant underactivation of areas such as the frontal, cerebellar, and ventrolateral prefrontal cortex (VLPFC). Tasks that are “easier” such as digit span showed a more varied series of activation patterns, with some areas being under-activated and some being over-activated. However, the majority of studies found underactivation in frontal areas in individuals with ADHD, regardless of task difficulty. Thus, in the present study, we hypothesized that young adults with ADHD would show lower DLPFC activation during cognitive tasks, relative to controls.

With similar focus on the methodological issues mentioned above, Table 2 outlines how prior neuroimaging studies on response inhibition compare on factors such as behavioral versus neurological response. Similarly to the data presented in Table 1, many studies found no behavioral differences when comparing the mean task scores (usually reaction times and accuracy), but did find significant differences in brain activation. It is also important to note, however, that several studies mentioned
in Table 1, using the same tasks the present study employed, found both behavioral differences and differences in brain activation. In particular, one study in the table examined the same response inhibition task as the present study (the Stroop Word Color task). The study examined a group of 23 young adults (mean age = 19.00 years) using fMRI while they performed a Stroop word/color task. Significant differences ($F(2,88) = 7.87, p < 0.001$) were seen on mean reaction times between controls and individuals diagnosed with ADHD, but no significant differences ($p > 0.05$) were found between controls and individuals with ADHD on accuracy. Individuals with ADHD showed less activation than controls in the left posterior dorsolateral prefrontal cortex and in the left middle dorsolateral prefrontal cortex. However, individuals with ADHD showed greater activation than controls in the right insula, left and right superior temporal gyri, and posterior cingulate cortex. The article suggests that individuals with ADHD show less activation of brain regions that support “top-down attentional control,” and are less able to disengage in regions that process less relevant material, as well as less able to disengage from the default attention network (which is theorized to be controlled, in part, by the cingulate cortex) (Banich, 2009).

While done using the same task, these results provide an important point of caution to the present study. Finding behavioral differences (as the previous study did when examining reaction times) makes interpreting differences in brain activation difficult. Differences in behavioral performance could be significantly influencing the neurological data. As previously discussed, behavioral performance is something that is often not controlled for, but that can be fundamentally important to the
interpretation of differences in brain activation seen during a task. Differences in behavioral performance can indicate the underlying effort, for example, that an individual is putting forth on a task. If the individual performing the task is less engaged, frustrated, or has an inability to cognitively engage past a certain level of task difficulty, he or she will not only perform worse, but will also have (theoretically) decreased activation as they devote less effort to the task. This “breaking point” above which he or she can’t activate any more, or this point of “disengagement,” are not reflected in many of the interpretations of behavioral and neurological data in the literature. When examining the results of the present study, taking behavioral performance into account will be a very important step in determining whether there was significantly different brain activation between my two groups or not.

In all neuroimaging studies to date that used a Stroop or Stroop-like task, both behavioral differences and neuroimaging differences were identified. Thus, it is unknown how much of a contributor actual cognitive engagement/effort might have been to the neuroimaging findings obtained, and brain activation differences seen simultaneously with behavioral differences should therefore be cautiously interpreted.

**Present Study**

To examine particular aspects of ADHD, the present study used a multi-dimensional, endophenotypic approach. Using a heterogeneous model allowed us to focus on specific neuropsychological deficits using neuroimaging, without focusing solely on ADHD symptoms. This unique outlook enabled us to examine a novel
question in ADHD literature – do specific neuropsychological abilities interact with a diagnosis of ADHD to change brain activation patterns during task completion?

In the present study, we examined young adults with ADHD on both working memory and inhibition tasks, while also assessing changes in oxygenated hemoglobin concentrations using Near Infrared Spectroscopy (NIRS). NIRS is an imaging technology that allows us to measure prefrontal changes in oxygenated and deoxygenated hemoglobin concentrations, as well a tissue oxygenation index and cerebral blood volume (Weber, Lutschg & Fahnenstitch, 2005). Originally developed as a method to ensure a patient in an operating situation was still receiving sufficient blood flow to his or her brain, it can be used to study two areas of activity – the dorsolateral prefrontal cortex, and the base of the skull. Being able to view fluctuations in these values gives us an idea of the activity of the prefrontal areas in individuals diagnosed with ADHD (Negoro, et al., 2009).

In the present study, participants were divided into high and low working memory ability. Many studies have examined activation in the manner outlined above; however, very few studies have specifically examined whether neuropsychological ability/behavioral performance related to findings; rather, most prior studies just relied on there being no overall group differences in performance. Examining whether actual neuropsychological ability, regardless of diagnosis, relates to neuroimaging findings may be a pivotal step in establishing neurological differences between individuals with ADHD and controls, because it provides greater control over the behavioral variable. Without controls and individuals with ADHD performing equally well (or poorly) in
the domain of interest (in this case, working memory), it is difficult to establish whether differences in activation are due to true inequalities, or if they are due to confounding factors, such as the participant disengaging from the task because they are tired of answering or trying to remember.

As was previously mentioned, several studies have found hypoactivation of the dorsolateral prefrontal cortex, using both NIRS and BOLD neuroimaging techniques (Ehlis, et al., 2007; Valera, et al., 2005). In the present study, therefore, we hypothesized that adults previously diagnosed with ADHD would show decreased activation in the prefrontal lobes, as measured by a decrease in oxygenated hemoglobin while completing working memory and inhibition tasks, relative to healthy controls matched on behavioral performance.

Method

Participants

Participants were 60 undergraduate students from a Midwestern university. Individuals with self-reported neurological conditions (e.g. brain tumor, stroke, dementia) were excluded from participation, as such extremes in brain structure and function may confound the results.

ADHD group: 28 participants were recruited from the Psychology online electronic screen. Participants who indicated that they had been previously diagnosed and/or treated for ADHD were invited to participate in the present study. Diagnosis of ADHD was based on self-report as well as completion of the Conner’s Adult ADHD
Rating Scale (CAARS). Participants were 18-22 years old (mean = 19.6, SD = 1.3). There were 15 males and 13 females. On average, participants tested as “clinically significant” on the CAARS in the DSM-IV Inattentive symptoms category (average T-score = 67.9, SD = 11.5), and nearing clinical significance in the DSM-IV Hyperactive/Impulsive category (average T-score = 60.4, SD = 11.0). Fifty percent (14/28) of the individuals with ADHD had been diagnosed before the age of ten, and only 21.4% (6/28) were taking medication for their ADHD at the time of the study.

**Control group:** Control group participants (n = 32) were taken from a previous study with a similar design. Participants were 18-25 years old (mean age = 19.4, SD = 1.5). There were 11 males and 21 females.

Participants from both groups were also placed into one of two working memory groups based on their scores on the Digit Span backwards subtest of the Wechsler Adult Intelligence Scale – fourth edition (WAIS-IV). The mean for the entire sample (including both ADHD and control groups) was found to be a score of 9. Participants who scored a 9 or higher on the Digit Span backwards test were assigned to the “good working memory” group, whereas participants who scored below a 9 were placed into the “poor working memory” group. This created four cells of interest to the present study, outlined in Table 3. To examine whether the working memory groups were sorted well (using the mean to define “good” versus “bad” working memory ability), we performed a 2x2 ANOVA (diagnosis group x WM group). There was a small main effect for ADHD group, $F(1,56) = 4.43, p = 0.04$, suggesting that our attempt to make groups equal in working memory was not entirely successful.
However, there was a much larger main effect for working memory group, $F(1,56) = 69.26$, $p = 0.001$, which indicates that our groups were sorted well. There was no interaction between the two factors (ADHD group and working memory group), $F(1,56) = 1.77, p = 0.19$.

**Measures**

**Self-report ADHD Scale**

To measure present symptoms and their severity in individuals who indicated a previous history of treatment or diagnosis of ADHD, the present study administered the Conner’s Adult ADHD Rating Scale (CAARS). The CAARS was only administered to those individuals who indicated a previous history of treatment or diagnosis of ADHD in order to confirm presence of continued symptoms consistent with the disorder.

*Conners Adult ADHD Rating Scale (CAARS):* The CAARS is a measure used to assess adult symptoms of ADHD, based on four target areas of performance. Dimensions of Inattention/Cognitive Problems, Hyperactivity/Restlessness, Impulsivity/Emotional Liability, and Problems with Self-Concept are used to assess cognitive, behavioral, and affective qualities of individuals previously diagnosed with ADHD (Erhardt, Epstein, Conners, Parker & Sitarenios, 1999).

The ADHD index of the CAARS has good sensitivity (finding the individuals within a population who have ADHD who are correctly identified as having it), and adequate specificity (finding individuals who do not deserve a diagnosis of ADHD and correctly saying they don’t), with percentages of 71% and 75% respectively. The
CAARS has an overall accurate classification rate of 73%. It has good internal reliability coefficients: between 0.64-0.89 for young adults (between the ages of 18-29). Test-retest reliability correlations, approximately one month apart, were high, with 0.88 for the Inattention subscale, 0.90 for the Hyperactivity subscale, and 0.80 for the Impulsivity subscale (Erhardt, et al., 1999). The ADHD participants in the present study were asked to complete the questionnaire as though they were on medication for their ADHD, and individuals who endorsed high symptoms (T=60 or greater) consistent with ADHD on the CAARS DSM subscales were included in data analyses.

Executive Functioning Measures

Participants were matched for working memory ability by their scores on the digit span task. To test study hypotheses, participant’s activation patterns were compared during the first minute of the Stroop and N-back tasks.

*Digit Span subtest of the Wechsler Adult Intelligence Scale – Fourth Edition* (*WAIS-IV*; Wechsler, 2008) (Digit Span): The previously mentioned digit span task is used to measure attention and memory. In the present study, two of the three digit span tasks are used: digit span forward, and digit span backward. In the digit span forward task, individuals are asked to verbally repeat a set of numbers either forward (as they were said). This examines both normal short term memory and attention. In the digit span backward task, individuals are read a set of numbers, and are asked to verbally repeat the numbers in the reverse order. This examines working memory, as the
participant has to hold the numbers given in mind while simultaneously manipulating them to say them backward.

Digit Span has a very high internal consistency reliability coefficient (average across ages is \( r = 0.93 \)). Overall, Digit Span exhibits good test-retest reliability (\( r = 0.82 \)) with an inter-test period of 8-82 days (mean of 22 days) (Wechsler, 2008). Digit Span shows good validity as a measure of attention and working memory skills. Digit Span scores are correlated to scores on the working memory index of the Wechsler Memory Scale-III (WMS-III) (\( r = 0.57 \)). Digit Span is also highly correlated with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) attention index (\( r = 0.65 \)) and somewhat correlated with the immediate memory index (\( r = 0.33 \)) (Wechsler, 2008). Research has shown that on working memory measures of the WAIS-IV, which includes the digit span and letter number sequencing tasks, individuals with ADHD tend to score lower (Barkley et al., 2001; Mayes and Calhoun, 2007).

**N-Back Task:** The N-back task, also discussed previously, measures working memory. Participants are told to view a computer screen, on which a blue box lights up every time a voice says a letter. During the 1-back section of the task, the participant is told to press a key on the keyboard if the letter spoken matches the letter that came immediately before it. This task examines short-term memory and attentional span, as it only requires a brief gap between one word and the next. In the 2-back section of the task, the participant is told to press the key only if the letter they are hearing matches the letter that was two back in the sequence. The 2-back task
involves working memory, because it requires that the participant keep the letter given two back in order to decide whether to press the key or not. Errors are measured as omissions (failing to press the key) or commissions (pressing the key unnecessarily). The N-back task has been found to be strongly correlated with other working memory span tasks, and therefore has been shown to be a valid task measuring working memory control (Kane & Engle, 2002; Oberauer, Sub, Schulze, Wilhelm & Wittmann, 2000; Oberauer, Sub, Wilhelm & Wittmann, 2003).

A meta-analysis of 24 studies found that, in addition to several other brain regions, the dorsolateral and mid-ventrolateral prefrontal cortex is reliably activated bilaterally during various forms of the N-back test (Owen, McMillan, Laird & Bullmore, 2005). These findings are relevant for the study of ADHD, given the evidence reviewed above, there are clear functional, structural, and cognitive impairments seen in the disorder, and using tasks that examine certain deficits allows us to examine specific features of ADHD itself.

*Stroop Color and Word Test* (Stroop task), The classic Stroop task (Golden, 1978) examines inhibition. In the task, two measures of baseline are obtained initially. First, the participant is asked to read black-ink words on a page as fast as he or she can. The number the participant is able to read in forty-five seconds is recorded. He or she is then asked to name the colors of x’s on a page as fast as he or she can. Again, the number he or she gets in forty-five seconds is recorded. These are used for baseline, and are compared to the third part of the task, which involves the participant
being asked to name the colors of words printed on a page, ignoring the word itself (for example, the word “green” printed in blue ink).

This task examines inhibition, as it asks the participant to override his or her programmed, powerful response tendency, which is to simply read the word printed, and to instead follow the task guidelines and say the color of ink. Test-retest reliability for the Golden Stroop Test is high for young adults ($r = 0.83$ for Word, $r = 0.74$ for Color, and $r = 0.67$ for Color-Word with an inter-test interval of one or two weeks (Franzen, Tishelman, Sharp & Friedman, 1987). The Stroop task appears to be correlated with other commonly used tasks of impulsivity and inattention in ADHD, such as the stop-signal task (May and Hasher, 1998). The task also appears to tap an inability to manage interference in individuals with ADHD (Homack and Riccio, 2004), as well as being tied to the frontal lobes, which has been extensively implicated in ADHD (Mead et al., 2002).

Equipment

Near Infrared Spectroscopy (NIRS): NIRS is used to measure cerebral oxygenation. The particular device used in the present study was a 2-channel NIRS machine, the INVOS 5100 Cerebral Oximeter (Somanetics Corporation, Troy, MI, USA). The INVOS measures regional cerebral oxygen saturation ($r$SO$_2$), using the fact that oxygenated and deoxygenated hemoglobin absorb near-infrared light differently, and thus, a version of the Beer-Lambert Law can be used to measure changes in $r$SO$_2$ based on light absorption measurements. Two disposable sensors are used, each of
which contains a light emitting diode (LED), which alternates between emitting light of wavelengths 730 and 810 nm, and two optodes that receive the reflected light, located 3 and 4 cm away from the LED. The system measures the light absorption 15 times per second, and when 50 samples are gathered (every 3.3 seconds), the number is averaged and sent to the display (Thavasothy, Broadhead, Elwell, Peters & Smith, 2002). The device measures oxygenation from the brain tissue a few centimeters underneath the sensors (Somanetics Corporation), hence, given that the sensors are placed on the forehead, they measure activity in the dorsolateral prefrontal cortex.

The INVOS calculates rSO$_2$ by assuming an arterial to venous blood ratio of 25% : 75%. Research on the INVOS has shown that, rather than using the INVOS to obtain absolute measurements of cerebral oxygenation, more accurate data can be obtained by looking at trends (i.e. measuring how cerebral oxygenation has changed over a certain period of time) (Thavasothy et al., 2002). Studies comparing NIRS recordings to fMRI data have found the two methods to yield similar results, supporting the validity of NIRS as a measure of cerebral oxygenation and functional neuroimaging (Mehagnoul-Schipper et al., 2002; Toronov et al., 2001).

Procedure

Each participant has completed the testing protocol on an individual basis in a two-hour session. After arriving in the clinic, participants signed informed consent (See Figure 3). Participants were then connected to the NIRS with two electrodes placed on the forehead (See Figure 2). These electrodes constantly measured blood flow in the prefrontal regions, and event marks were used for the beginning and end of
every task. The prefrontal regions, as previously mentioned, have been repeatedly implicated in executive functioning, including the executive function of working memory. Activation is assumedly represented by blood flow, that is, when an area of the brain is being used more frequently, blood flow to that area will increase.

After having the electrodes placed on their foreheads, participants were then administered the neuropsychological battery described above. As individuals performed the working memory battery, the changes in their blood flow were observed, as measured by the NIRS. A numerical value was assigned to blood flow via a right and a left electrode. As blood flow increases, so did the numerical value. The values were plotted over time, and a line graph depicting the changes in blood flow over time was generated (See Figure 3). The values from the first one minute of data at baseline were averaged as a representation of baseline activation. This was compared with the average activation across the first minute or two of the challenging (test) sections of each task.

At the end of experiment, participants who had been previously diagnosed with ADHD were compensated with $10 and two extra credit points, while participants who did not indicate that they had been previously diagnosed with ADHD (control participants) were compensated with two extra credit points for an undergraduate psychology class (note these participants were taken from a different study, explaining the difference in compensation).

Results
The ADHD and Control groups were not significantly different in age, $t < 1; p = 0.57$, or gender distribution, $\chi^2 (1) = 2.24; p = 0.13$.

**Behavioral Task Performance**

2 (Diagnosis group) x 2 (WM group) ANOVAs were used to compare performance on the Stroop interference subtest and the 2-back test. See Table 4. Of note, one participant was omitted from the analysis of behavioral performance on the Stroop task due to the fact that he was red-green color blind. On the Stroop task, there was no main effect of ADHD group, $F(1,55) < 1, p = 0.66$. Likewise, there was no main effect for working memory group, $F(1,55) = 2.28, p = 0.14$, nor was there a significant interaction between the two, $F(1,55) < 1, p = 0.55$. On the N-back task, there was also no main effect for ADHD group on behavioral performance, $F(1, 56) < 1, p = 0.64$. There was, however, a main effect for working memory group, $F(1, 56) = 7.37, p = 0.009$, with the poor working memory participants, collapsed across diagnosis, performing worse on N-back compared to good working memory participants. There was no significant interaction between working memory and ADHD status, $F(1,56) < 1, p = 0.86$.

**Imaging**

2 (Diagnosis Group) x 2 (WM group) ANOVAs were used to compare brain activation during the Stroop and N-back tasks. To examine brain activation across the difficulty levels of the tasks, change scores were calculated. See Table 5.

For the Stroop task, the change score was calculated by subtracting the average of the first minute of the Word-Color section of the task from the average of the first
minute of the Interference part of the task. This change score reflects how much the individual’s brain activation changed from the less challenging part of the task to the more demanding part of the task. On the Stroop task, there was no significant main effect for WM group, $F(1,52) = 1.05, p = 0.31$, or diagnosis group, $F(1,52) < 1, p = 0.72$. There was also no significant interaction between the groups, $F(1,52) = 1.37, p = 0.25$.

For the N-back task, the change score was calculated by subtracting the average of the first minute of the 1-back section of the task from the average of the first minute of the 2-back section of the task. On the N-back, there was no significant main effect for WM group $F(1,52) = 1.85, p = 0.18$, but there was a significant main effect seen for diagnosis group, $F(1,52) = 3.95, p = 0.05$, with the ADHD participants showing less change than the controls (See Figure 4). There was no significant interaction seen between the groups, $F(1,52) = 1.76, p = 0.19$. To examine the direction of the trend towards an interaction between diagnosis group and working memory group, we performed t-tests to compare brain activation within the good and bad working memory groups. The brain activation in the “good,” ADHD working memory group was not significantly different, $t_{(29)} < 1, p = 0.60$, from the brain activation of the “good” control group. However, the brain activation in the “bad” working memory ADHD group was significantly less, $t_{(24)} = 2.07, p = 0.05$, than that of the “bad” working memory control group (See Figures 5 and 6).

Discussion
To examine the heterogeneous disorder of ADHD, the present study focused on two specific cognitive functions, known as working memory and response inhibition, respectively. By narrowing our frame of reference to lie within these two specific areas of cognitive functioning, we were able to examine both behavioral performance and brain activation across our tasks.

An interesting split occurred between the two neuropsychological tasks with regard to behavioral performance. While there was no significant main effect for working memory group, diagnosis group, or an interaction between the two on the Stroop task, there was a significant main effect of working memory group on the N-back task. While individuals with ADHD and controls performed similarly on the Stroop task, individuals with poor working memory, regardless of diagnosis, performed worse on the N-back task. This result is consistent with the type of task the N-back is. While the N-back is a working memory task, the Stroop is a response inhibition task. Individuals who were previously matched on a different working memory task, the Digit Span back task, as was true in the present study, would be expected to perform with similar aptitude (either poorly or well) on the N-back task, which tests the same cognitive ability. Individuals in either diagnosis group (diagnosed with ADHD or not) who were placed into the “good” working memory group, based on their performance on the Digit Span task, performed well on the N-back task, and vice versa.

The Stroop task, which examines response inhibition, has been used before in ADHD research, although behavioral performance results have been mixed. While
Some neuropsychological studies have shown that individuals with ADHD perform worse on the task than controls, many have also seen equal performance on other inhibition tasks (Hervey et al., 2004). In addition, because the present study’s participants tended to report clinically significant inattentive symptoms, but were less likely to report clinically significant hyperactive/impulsive symptoms, they were more likely to have the inattentive subtype of ADHD (Nigg, Willcutt, Doyle & Sonuga-Barke, 2004). Participants who are more inattentive than hyperactive/impulsive may be less likely to have behavioral impairments in tasks measuring the domain of inhibition, such as the Stroop.

With regard to the imaging findings, no significant main effects of diagnosis group or working memory group were found for brain activation during the Stroop task. There are a couple of reasons we may not have seen differences in brain activation based on diagnosis. One is related to the important methodological issue of behavioral performance. As previously mentioned, no previous neuroimaging studies using a Stroop or Stroop-like task could be found that did not also show behavioral differences. Behavioral differences might belie an underlying inability of individuals with ADHD to activate above a certain level, or to engage beyond a certain point in the task; thus, prior studies may have found activation differences because of lack of cognitive effort or engagement, rather than because of a difference related to diagnosis. However, the present study did not find any behavioral differences in the Stroop task, and also did not find any activation differences when completing the task. Another potential reason for differences in our findings relative to prior research is
that we could only focus on one brain region when using the NIRS. The three prior neuroimaging studies that examined inhibition tasks in adults with ADHD found that adults with ADHD showed a hypoactive profile in the prefrontal areas of the brain, but an overactive profile in more posterior areas of the brain, such as the striatum, cerebellum, and posterior cingulate cortex. With the limitations of the NIRS, we could not examine the possibility of other areas of activation.

Because the present study was not able to examine areas beyond the dorsolateral prefrontal cortex, non-frontal differences in activation may have been present, but unseen. Future studies should include neuroimaging assessment of multiple areas of interest and control for behavioral performance differences, in order to better ascertain the distinct profile and pattern of activation seen in individuals with ADHD as they perform tasks of inhibition.

With regard to the domain of working memory, in contrast to behavioral performance findings, the present study found brain activation on the N-back task to be mainly dependent on diagnosis group, not working memory group. There was a significant main effect of diagnosis group found on the N-back task for changes in brain activity from the less demanding section of the task (1-back) to the more demanding section of the task (2-back). Regardless of whether they had good or bad working memory, individuals with ADHD activated less on the more demanding part of the task than controls. However, there was a trend towards a significant main effect of working memory ability, as well as a trend towards a significant interaction between working memory ability and diagnosis. The trend towards an interaction
indicated that individuals with ADHD and poor working memory ability activated less than controls with poor working memory as the N-back task got harder. However, individuals with ADHD and good working memory activated similarly to controls with good working memory during the task. While the present study did not find this interaction to be significant, a larger sample size might reveal a significant interaction.

What would an interaction between working memory ability and diagnosis group mean? The most salient answer to this question lies in emphasizing working memory ability. Many studies have not acknowledged the possibility that pre-existing ability can influence the patterns of activation seen during a working memory task.

Take the following example to illustrate the importance of this concept. Imagine that Study #1 has individuals with ADHD who have good working memory, but are not evaluated as such. When they compare the individuals with ADHD to controls at the end of the study, they may conclude that individuals with ADHD do not have significantly different brain activation from controls. However, in Study #2, the participants with ADHD have poor working memory. When the researchers compare their two groups, they may conclude that individuals with ADHD have less activation than controls. Both studies are mistaken in their conclusions, however, because they did not account for a significant variable – pre-existent working memory ability.

Emphasizing pre-existent working memory ability is very important. However, even with these groups defined, differences in activation were still seen in the present study; not all of the difference inactivation could be explained merely by working memory ability either. Why do individuals with ADHD and poor working memory
activate less during the N-back task than controls with good or bad working memory or than individuals with ADHD with good working memory? To examine the nature of this potential interaction in more detail, the use of more levels of the N-back could be employed in future studies. Whereas the present study only examined behavioral and neurological information on the 1-back and 2-back sections of the N-back task, a 3-back level could also be implemented. Increasing the level of difficulty yet again might reveal the “cutoff” point, above which individuals with ADHD cannot activate any more, but also more clearly delineate the role of working memory ability in explaining this “cutoff” point, even in those without ADHD.

The idea of a “plateau” of activation has been discussed before in the aging literature. Individuals show increased brain activation as the task difficulty goes up, as long as they are still engaged in the task. When a task becomes too difficult, individuals tend to disengage, and stop putting a lot of effort into finishing the task. The brain activation at this point starts to decrease. The pattern of this “increase until max ability is reached,” and then “decrease after max ability is reached,” is referred to as the “Inverted U-Curve” (Mattay et al., 2006).

In the aging literature, an interesting interaction has been seen between working memory ability and age. In a recent study, thirty younger (20-30 years old), and thirty older (60-70 years old) individuals were tested with a spatial working memory task with three load levels. Older adults activated less than younger adults as the task difficulty increased, but similarly to our study, an examination of old high performers versus old, low performers revealed a significant split between the two
groups. Older adults with good working memory ability showed an activation profile across the difficulty levels of the task that resembled the young group’s. As the task became more difficult, older adults with good working memory continued to activate, similarly to young adults with either good or bad working memory. In contrast, older individuals with bad working memory had significantly decreased activation as the task load became harder, deactivating before any of the other groups. The study even notes, “The [decrease in activation] seen at high load in the older sample was primarily driven by old low performers” (Nagel et al., 2009, 22554). The results of this study can be explained using an inverted U-curve (See Figure 7). Older individuals with bad working memory reach their point of maximum ability (point C) much sooner than older individuals with good working memory or young individuals. After the older individuals with bad working memory reach point C, they begin to deactivate. This results in the “hypo-active” profile of older adults, similarly to the hypo-active profile seen in the present study with individuals with ADHD on a working memory task. This study is an example of how working memory ability can interact with another significant variable (in their case, age), to influence the pattern of brain activation seen.

With more levels of the N-back, future studies could look for the possibility of an inverted U-curve in individuals with ADHD. If individuals with ADHD with poor working memory disengage from the task sooner, we would expect to see an inverted U-curve that has a peak at lower levels of task difficulty. This would lend credence to the idea that individuals with ADHD with poor working memory ability have some
structural or neurochemical abnormality that disallows activation above a certain
difficulty level. The idea of a structural or neuro-chemical abnormality in the frontal
lobes of individuals with ADHD is just one of many explanations for differences in
performance and activation seen during tasks of working memory. In the present
study, we were not able to examine structural or neurochemical or genetic bases for
our findings. Future studies may attempt to make headway on some of these questions
in ways that we could not. In any future study, however, the research presented here
emphasizes a need for assessment of pre-existing working memory ability.

The present study was limited by several factors, mostly due to the small
population of individuals with ADHD on campus. In order to obtain a larger sample
size, we were unable to control for (and remove) individuals exhibiting certain
behaviors or comorbid disorders. We were not able to gather a large body of
information on the diagnoses of our participants, other than self-report, nor were we
able to control for medication use before the study (both prescription and non-
prescription use of drugs, alcohol, or tobacco). Although previous studies have shown
similar patterns of hypoactivation across individuals with ADHD who were
medication-naïve and currently on medication (Rubia et al., 2005), other substances,
such as alcohol and tobacco, can influence prefrontal blood flow, and were not
controlled for. We would also recommend, as stated earlier, that future studies
examine subtypes as a significant influencing factor in the analysis of behavioral
performance and patterns of brain activation.
The present study demonstrated the need for an examination of pre-existent ability in any study examining brain activation in individuals with ADHD. Although we were unable to show a significant interaction between working memory and diagnosis group, future studies with larger sample sizes may be able to reveal a significant interaction. The present study has added to a body of evidence that suggests that individuals with ADHD have some inherent abnormality that inhibits them from activating above a certain level for tasks that require extended focus and attention. In future studies, the issues presented here can be explored in depth, with a focus on assessing pre-existent abilities, seeking to find a better etiology and method of diagnosis for ADHD.
References


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10.1177/108705479900300304


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doi:10.1016/j.neuroimage.2007.09.044


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.* doi: 10.1002/hbm.20665


doi:10.1016/j.braindev.2004.11.009
### Table 1

**Comparing Working Memory Performance and Brain Activation Across A Compilation of Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Task</th>
<th>Behavioral Performance</th>
<th>Neural Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheridan et al. (2007)</td>
<td>DMS</td>
<td>No significant differences in accuracy or RT’s between groups</td>
<td>VLPFC, inferior parietal lobule: activation less than controls</td>
</tr>
<tr>
<td>Valera et al. (2005)</td>
<td>N-back</td>
<td>No differences in performance</td>
<td>CB, inferior occipital gyrus: activation less than controls</td>
</tr>
<tr>
<td>Kobel et al. (2008)</td>
<td>N-back</td>
<td>ADHD significantly worse accuracy and RT’s with task difficulty</td>
<td>Decreases in left frontal, parietal, and the CB regions.</td>
</tr>
<tr>
<td>Hale et al. (2007)*</td>
<td>Digit Span: Forward vs. Baseline</td>
<td>No differences in accuracy</td>
<td>Temporal/occipital border, Precuneus/cuneus, Mid/posterior cingulate, DLPFC, VLPFC: activation greater than controls</td>
</tr>
<tr>
<td></td>
<td>Digit Span: Backward vs. Baseline</td>
<td>No differences in accuracy</td>
<td>Superior parietal lobule, Intraparietal sulcus, Supramarginal gyrus, Temporal/occipital border, activation less than controls; Angular gyrus, Superior temporal gyrus, Med cingulate gyrus: activation is greater than controls</td>
</tr>
<tr>
<td>Schweitzer et al. (2000)*</td>
<td>Auditory Addition</td>
<td>No differences in task performance.</td>
<td>PET scan: Significant increases in the anterior cingulate and medial frontal regions, decreases (underactivation compared to controls) in the left middle frontal regions</td>
</tr>
<tr>
<td>Authors</td>
<td>Task Type</td>
<td>Findings</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------</td>
<td>-------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Silk et al. (2005)</td>
<td>Mental Rotation</td>
<td>ADHD sig. less accurate than controls, but no sig. differences in RT’s. Caudate, Anterior PFC, DLPFC, VLPFC, parieto/occipital/ temporal association cortex activation <strong>less</strong> than controls; Mid/sup temporal gyrus, posterior cingulate, activation <strong>greater</strong> than controls.</td>
<td></td>
</tr>
<tr>
<td>Vance et al. (2007)</td>
<td>Mental Rotation</td>
<td>No differences in accuracy or RT. Caudate, precuneus/cuneus, and inferior parietal, activation <strong>less</strong> than controls.</td>
<td></td>
</tr>
<tr>
<td>Scheckelmann (2009)</td>
<td>Object WM vs Spatial WM</td>
<td>Significantly worse accuracy, but no differences in RT’s. fNIRS: significantly <strong>less</strong> activation in the VLPFC and DLPFC.</td>
<td></td>
</tr>
<tr>
<td>Wolf et al. (2009)</td>
<td>Object WM vs. Spatial WM, Modified activation task, similar to N-back</td>
<td>No significant differences in task performance or RT’s. Significantly <strong>lower</strong> activation in the VLPFC, the ACC, the superior parietal lobule, and the CB.</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* fMRI (functional magnetic resonance imaging) used unless otherwise noted., * = adult study, ACC = anterior cingulate cortex CB = cerebellum, DLPFC = dorso-lateral prefrontal cortex, DMS = Delayed Matching to Sample task, fNIRS: functional near-infrared spectroscopy, PET = positron emission tomography, PFC = prefrontal cortex, RT = reaction time, VLPFC = ventro-lateral prefrontal cortex, WM = working memory.
### Table 2.

Comparing Behavioral Performance and Brain Activation Across a Compilation of Inhibition Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Task</th>
<th>Behavioral Performance</th>
<th>Neural Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bush et al. (1999)*</td>
<td>Counting Stroop</td>
<td>No significant differences were seen in accuracy, ADHD significantly slower RT’s on interference trials</td>
<td><strong>Hypo-activation (lower)</strong> of the ACC</td>
</tr>
<tr>
<td>Zang et al. (2005)</td>
<td>Stroop-like task</td>
<td>Mean RT’s were not significantly different, ADHD (children) made significantly more errors</td>
<td>Activation of PFC, was <strong>lower</strong> across both conditions, control and interference task. In interference: ACC, basal ganglia, insula, and CB were <strong>lower</strong> than controls.</td>
</tr>
<tr>
<td>Banich et al. (2009)*</td>
<td>Word/Color Stroop</td>
<td>ADHD significantly slower RT’s, no significant differences in accuracy</td>
<td><strong>Hypo-activation</strong> of the DLPFC, <strong>greater</strong> activation in the right insula, superior temporal gyri, and posterior cingulate cortex</td>
</tr>
<tr>
<td>Baeyens et al. (2008)</td>
<td>Go/No-go</td>
<td>ADHD less accurate on unexpected events than controls.</td>
<td><strong>Lower</strong> during no-go trials (manipulation of stimulus type) in ACC, VLPFC. ADHD <strong>lower</strong> during manipulations of timing in CB.</td>
</tr>
<tr>
<td>Booth et al. (2005)</td>
<td>Go/No-go</td>
<td>ADHD: more errors, slower RT’s</td>
<td><strong>Lower</strong> activation in fronto-striatal regions (inferior, middle, superior, and medial frontal gyri, caudate nucleus, and globus pallidus)</td>
</tr>
<tr>
<td>Epstein et al. (2007)*</td>
<td>Go/No-go</td>
<td>ADHD had slower and more variable RT’s</td>
<td><strong>Greater</strong> activation of fronto-striatal regions than controls, DLPFC and VLPFC <strong>lower</strong> than controls</td>
</tr>
<tr>
<td>Study</td>
<td>Signal Type</td>
<td>Findings</td>
<td>Brain Region</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Pliszka et al. (2006)</td>
<td>Stop Signal</td>
<td>No significant differences between groups on RT’s</td>
<td>DLPFC was activated <strong>greater</strong> in ADHD subjects on successful “stop” trials, <strong>lower</strong> on unsuccessful inhibition in the ACC and the left VLPFC.</td>
</tr>
<tr>
<td>Rubia et al. (2008)</td>
<td>Stop Signal</td>
<td>ADHD showed greater variability in their RT’s to the “go” signals</td>
<td>During successful inhibition, ADHD showed <strong>lower</strong> activation in the DLPFC. During unsuccessful inhibition, ADHD showed <strong>lower</strong> activation in the posterior cingulate gyrus.</td>
</tr>
</tbody>
</table>

*Note. All studies used fMRI (functional magnetic resonance imaging) unless otherwise noted. * = Adult study, ACC = anterior cingulate cortex, CB = cerebellum, DLPFC = dorsolateral prefrontal cortex, PFC = prefrontal cortex, VLPFC = ventro-lateral prefrontal cortex.*
Table 3

Determining Validity of Working Memory Group Definitions Using Performance on Digit Span Back Task

<table>
<thead>
<tr>
<th></th>
<th>ADHD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good WM Mean (SD)</td>
<td>Bad WM Mean (SD)</td>
</tr>
<tr>
<td>Performance</td>
<td>9.7 (1.0)</td>
<td>7.1 (1.1)</td>
</tr>
</tbody>
</table>

*Note.* The Digit Span Backwards Task is a subtest on the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV), previously described above (Wechsler, 2008).
Table 4

*Behavioral Data from the Stroop and N-back Tasks*

<table>
<thead>
<tr>
<th></th>
<th>ADHD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good WM (n = 13)</td>
<td>Good WM (n = 20)</td>
</tr>
<tr>
<td></td>
<td>Bad WM (n = 14)</td>
<td>Bad WM (n = 12)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td><strong>Stroop Task</strong></td>
<td>52.0 (11.7)</td>
<td>55.5 (15.1)</td>
</tr>
<tr>
<td></td>
<td>48.9 (8.5)</td>
<td>48.4 (12.9)</td>
</tr>
<tr>
<td><strong>N-back Task</strong></td>
<td>86.8 (12.4)</td>
<td>87.9 (11.5)</td>
</tr>
<tr>
<td></td>
<td>77.0 (15.6)</td>
<td>79.2 (12.1)</td>
</tr>
</tbody>
</table>

*Note.* The “Stroop Task” refers to the Stroop Word Color Task, Golden Version, previously described above (Golden, 1978). The “N-back task” refers to the N-back task, previously described above (Kane et al., 2002). WM = working memory, SD = standard deviation, ADHD = Attention Deficit Hyperactivity Disorder.
Table 5

*Brain Activation During the Stroop and N-back Tasks*

<table>
<thead>
<tr>
<th></th>
<th>ADHD</th>
<th></th>
<th>Controls</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good WM</td>
<td>Bad WM</td>
<td>Good WM</td>
<td>Bad WM</td>
</tr>
<tr>
<td></td>
<td>(n = 13)</td>
<td>(n = 14)</td>
<td>(n = 20)</td>
<td>(n = 12)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td><strong>Stroop Task</strong></td>
<td>0.37 (1.8)</td>
<td>-0.41 (0.8)</td>
<td>0.08 (1.1)</td>
<td>0.13 (1.5)</td>
</tr>
<tr>
<td><strong>N-back Task</strong></td>
<td>0.85 (0.86)</td>
<td>0.08 (1.4)</td>
<td>1.0 (1.0)</td>
<td>1.2 (0.7)</td>
</tr>
</tbody>
</table>

*Note.* Activations for the Stroop task were calculated as [(Average of first minute, Interference) – (Average of first minute, word-color)]. Activations for the N-back task were calculated as [(Average of first minute, 2-back) – (Average of first minute, 1-back)]. The “Stroop Task” refers to the Stroop Word Color Task, Golden Version, previously described above (Golden, 1978). The “N-back task” refers to the N-back task, previously described above (Kane et al., 2002). WM = working memory, SD = standard deviation, ADHD = Attention Deficit Hyperactivity Disorder.
Figure 1. The area in blue indicates the dorsolateral prefrontal cortex, the region of the brain the present study examined using NIRS.

Figure 2. Participant connected to a functional NIRS device (for the purposes of this study, we will be using the similar, simpler NIRS).
Ohio University Consent Form

Title of Research: Measuring Brain Activation in ADHD
Researchers: Kellina Lupas, Julie A. Suhr, Ph.D.

You are being asked to participate in research. For you to be able to decide whether you want to participate in this project, you should understand what the project is about, as well as the possible risks and benefits in order to make an informed decision. This process is known as informed consent. This form describes the purpose, procedures, possible benefits, and risks. It also explains how your personal information will be used and protected. Once you have read this form and your questions about the study are answered, you will be asked to sign it. This will allow your participation in this study. You should receive a copy of this document to take with you.

**Explanation of Study**

The purpose of this study is to compare brain oxygenation patterns of individuals who have a history of treatment for or diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) to those who have no history of ADHD, while they engage in thinking and memory tasks. Brain oxygenation can be used as a good measure of how active a certain area of the brain is, and can be evaluated by measuring blood flow. To measure blood flow in this experiment, we will be using a technique called Near-Infrared Spectroscopy (NIRS) to measure blood flow in the frontal part of the brain.

If you agree to participate in this study, you will complete several tasks of thinking and memory that will be administered to you on a one-on-one basis by a trained examiner or on a computer. While you are taking the tests, you will be attached to the NIRS device by electrodes that are placed on your forehead using an adhesive. Your total participation time should be less than 2 hours.

**Risks and Discomforts**

The risks involved in this study are minimal, although tests of memory and thinking can be anxiety-provoking for some people. No one performs perfectly on the cognitive tests we administer. Your examiner can answer any questions you might have about the tests you are completing if you have any concerns. The NIRS technique is harmless and non-invasive, and has been used for over a decade in hospital settings to monitor brain oxygenation during surgeries. It has been used previously in several studies conducted within the Ohio University Department of Psychology. Attaching the NIRS electrodes to your forehead will involve first swabbing your forehead with alcohol, and then using an adhesive strip on the electrodes to hold the electrodes on the forehead. An elastic headband will also be placed over the electrodes to minimize any gradual pulling.
**Benefits**

Participating in this experiment will give you first-hand experience with a neuroimaging technique. Furthermore, this research will help us to better understand how the brain changes in a disorder such as ADHD.

**Confidentiality and Records**

Records of your participation will be maintained in the locked confidential research files of the Study Director’s laboratory at Ohio University. Your data will be identified by a random code that cannot be linked to you. Once the data has been de-identified using this code, it will never be associated with your personal information. Your name will only be linked to the experiment in order to give you credit. Your name and address will be asked for so that OU Finance may have a record of who received monetary compensation, but they will not know in which study you participated.

The consent form, which will have your name on it, will be stored separately from the rest of the data. Results of the research may be used for the purposes of teaching, publication in professional journals, or presentation at professional meetings, but your personal identity will never be revealed as part of any of these activities.

Additionally, while every effort will be made to keep your study-related information confidential, there may be circumstances where this information must be shared with:

* Federal agencies, for example the Office of Human Research Protections, whose responsibility is to protect human subjects in research;
* Representatives of Ohio University (OU), including the Institutional Review Board, a committee that oversees the research at OU;

**Compensation**

You will receive a monetary sum and course credit for participating in the study. If you withdraw from participation during the first hour, you will receive 1 credit. If you withdraw from the study during the second hour prior to completing the study, you will receive 2 credits and $5.00. If you complete the study, you will receive $10.00 and two course credits.

**Contact Information**

If you have any questions regarding this study, please contact Kellina Lupas at KL111106@ohio.edu, (440)251-6826, or Dr. Julie Suhr, Ph.D., at suhr@ohio.edu, (740)593-1091.

If you have any questions regarding your rights as a research participant, please contact Jo Ellen Sherow, Director of Research Compliance, Ohio University, (740)593-0664.
By signing below, you are agreeing that:

- you have read this consent form (or it has been read to you) and have been given the opportunity to ask questions and have them answered
- you have been informed of potential risks and they have been explained to your satisfaction.
- you understand Ohio University has no funds set aside for any injuries you might receive as a result of participating in this study
- you are 18 years of age or older
- your participation in this research is completely voluntary
- you may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you and you will not lose any benefits to which you are otherwise entitled.

Signature_________________________________________ Date__________

Printed Name________________________________________

Version Date: [11/19/10]

Figure 3. A copy of the consent form given to participants with ADHD upon their arrival.
Figure 4. Comparison of brain activation in both diagnosis groups across the two levels of difficulty of the N-back task, with 1-back being the less difficult section of the task, and 2-back being the more difficult. “Mean Change in Brain Activation” refers to the average amount of deoxygenated hemoglobin that was recorded across the first minute of each section of the N-back task. Individuals with ADHD activated significantly less as a diagnosis group than controls.
Figure 5. Brain activation across both levels of N-back task difficulty, considering both diagnosis group and WM group. “C” = control, “A” = ADHD, “G” = good WM, and “B” = bad WM. This graph demonstrates that one of the driving factors for the “less activation” seen in individuals with ADHD is because the individuals with ADHD with poor working memory were not activating across the levels of task difficult like the controls and the individuals with ADHD with good WM were. This difference is seen in the slopes of the lines relative to one another – individuals with ADHD with bad WM have a much flatter line in comparison to controls and individuals with ADHD with good WM.
Examining the Trend Towards an Interaction Between WM Group and Diagnosis Group

![Graph showing change in brain activation during the N-back task.]

Figure 6. Change in brain activation during the N-back task with regard to WM group and Diagnosis Group. Individuals with ADHD with bad WM activated significantly less than controls with good or bad WM, or individuals with ADHD with good WM. “Mean Change in Brain Activation” refers to the amount of change in deoxygenated hemoglobin in the blood measured by the NIRS across the two task difficulty levels of the N-back task.
Figure 7. An inverted U-curve of activation. As task difficulty increases, individuals continue to activate, as long as they are engaged in the task (B). At some point (C), the task becomes too difficult for the individual, or the individual chooses to disengage, and deactivation begins (D). If an individual (such as an individual with ADHD with bad working memory) reaches point C while others are still on point B, he or she may appear to be hypoactive compared to others, because he or she cannot activate above a certain point, when the others still can.