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Do the stimulant medications improve neuropsychological performance of college students with ADHD?

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DO THE STIMULANT MEDICATIONS IMPROVE NEUROPSYCHOLOGICAL PERFORMANCE OF COLLEGE STUDENTS WITH ADHD?

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ABSTRACT

Attention Deficit/Hyperactivity Disorder (ADHD) is a prevalent disorder estimated to affect 5% to 10% of school-aged children and approximately 4% of adults worldwide. The defining symptoms are hyperactivity, impulsivity and inattention, which are all acutely reduced by the stimulant medications, methylphenidate and amphetamine. Nevertheless, in spite of robust short-term efficacy, long-term follow-up studies fail to show drug effects on academic achievement of ADHD students. Because recent research indicates that the medications also do not normalize performance of ADHD patients on some neuropsychological tests, we thought this might shed some light on the causes of ADHD students' academic underachievement. There is a consistent body of evidence showing that adults with ADHD are impaired on neuropsychological tests of vigilance, verbal memory/fluency, response interference, and planning ability. In our study we used 4 neuropsychological tests: d2 Test, Control Oral Word Association Test, Stroop Tests, and Tower of London Test to test vigilance, verbal fluency, response interference, and planning ability respectively. We found that undergraduate students with ADHD did not show significant deficits except in Stroop interference, compared to normal controls. ADHD medications improved Stroop interference in ADHD students; however, medications did not help ADHD students perform better than normal students in domains of functions where no deficits were found.

INTRODUCTION

History of ADHD

The first published description of ADHD is attributed to Dr. George Still in 1902. He observed problems of overactivity, inattention, and poor "inhibitory volition", which are now the three core symptoms that define ADHD in the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV). He labeled the condition "morbid defect of moral control". The condition was termed "postencephalitic behavior disorder" in 1922 (Horst & Hendren, 2005; Solanto & Castellanos, 2001).

In 1937, Charles Bradley found that amphetamine (Benzedrine) had a calming effect, and improved classroom behaviors of hyperactive children. Since then, stimulants have become widely used with children diagnosed as hyperactive, hyperkinetic, learning disabled, or with minimal brain dysfunction. Methylphenidate (Ritalin) was introduced to treat children with hyperactivity in 1956 (Dodson, 2005).

In the 1950s, this condition was renamed the "hyperactive child syndrome", and the name was changed again, to the "hyperkinetic reaction of childhood" in the DSM-II in 1968. The DSM-III(1980) renamed the syndrome "Attention Deficit Disorder" (ADD) with or without hyperactivity, emphasizing inattention as a component of the disorder. In DSM-III-R (1987), the symptom of overactivity was restored and the condition was renamed "Attention Deficit/ Hyperactivity Disorder" (ADHD).

The current edition, DSM-IV(1994) recognizes 3 subtypes of ADHD: "Predominantly Inattentive" (IN), "Predominantly Hyperactive - Impulsive" (HI), and the "Combined" (CB) subtype, based on the three categories of ADHD symptoms: inattention, hyperactivity, and impulsivity (see Appendix I). Six of the nine inattention symptoms must be present for at least 6 months for a diagnosis of the IN type. Six of the nine hyperactivity-impulsivity symptoms must be present for at least 6 months for a diagnosis of the HI type. If both of the above criteria are met, it is called the CB type (Solanto & Castellanos, 2001).

Laboratory Evaluation of Symptoms

Studies indicate that overactivity in children with ADHD is a core symptom, not simply secondary to inattention (Solanto & Castellanos, 2001). In a study conducted by Porrino et al. (1983), activity counts of hyperactive and control participants were recorded continuously for 7 days using solid-state monitors worn around the waist. Activity counts for children with ADHD were significantly higher across a variety of situations, including sleep and during the weekend. Activity counts for the children with ADHD were also higher, but not significantly so, during lunch/ recess and physical education. Corkum, Tannock, and Moldofsky (1998) also found that children with ADHD displayed more movements during sleep than normal controls.

Impulsivity has been demonstrated mostly by results on Continuous Performance Test (CPT), and Stop Signal Task (SST). In the most common version of the CPT, participants are required to respond whenever any letter *except* the letter 'X' appears on the computer screen. When the letter X appears on the screen, the participant must withhold the response. In the Stop Signal Task participants are required to press a corresponding key as quickly as possible when the stimuli (such as the letter "X" or "Y") appear, and, conversely, not to respond when a nonrelevant signal appears. Both children and adults

with ADHD have been found to make significantly more commission errors (tend to overrespond when 'X' appears) in a CPT (Epstein, Conners, & Sitarenios, 1998; Epstein, et al., 2003; Epstein, Johnson, Varia, & Conners, 2001). The Stop Signal Task produced a pooled effect size of 0.85 between ADHD adults and normal controls (Hervey, Epstein, & Curry, 2004).

Deficits in attention are mainly measured by CPT. Children and adults with ADHD make more errors of omission (tend to underrespond to 'non-X' stimuli), and have longer and more variable reaction times than those without the diagnosis (Hervey, et al., 2004; Leth-Steensen, King Elbaz, & Douglas, 2000).

Clinical Assessment

There is currently no single clinically valid test for ADHD. A complete evaluation of a child suspected of having ADHD should include the following: clinical interviews with the patient and the parent, information about the patients' school or day care functioning, evaluation for comorbid psychiatric disorders, and review of the patients' medical, social, and family histories. The rating scales for children mainly include: ADHD Rating Scale-IV, Conners Rating Scales, and Vanderbilt ADHD Diagnostic Parent and Teacher Scales (Pliszka, Bernet, & Bukstein).

Diagnosing ADHD in adults is a more comprehensive process that involves the evaluation of symptom severity and frequency, childhood onset of symptoms, chronicity and pervasiveness of symptoms, and degree of impairment in major life activities. ADHD rating scales for adults mainly include: Conners' Adult ADHD Rating Scales (CAARS); Brown Attention-Deficit Disorder Rating Scale for Adults; Wender Utah Rating Scale; Current Symptom Scales; ADHD Rating Scale-IV, and the Adult ADHD Self-Report Scale (K. R. Murphy & Adler, 2004; Rösler, et al., 2006). The CAARS (Macey, 2003) include a set of self-report and observer-report scales; both types have a long, a short and a screening version. The CAARS allow not only the calculation of DSM-IV oriented inattention, impulsivity and hyperactivity scores, but also measures of emotional liability and problems with self-concept.

Brown Attention-Deficit Disorder Rating Scale for Adults was developed before DSM-IV was published. It is a self report scale based on a series of symptoms reported by high school and college students with non-hyperactive ADD. It assesses 5 dimensions of symptoms, which include organizing work, sustaining attention and concentration, sustaining alertness and effort, managing frustration and other emotions, and using working memory.

Wender Utah Rating Scale is a self-report, retrospective scale that evaluates the patient's childhood ADHD symptoms. It has 61 items which assess inattention, hyperactivity and impulsivity together with emotional dysregulation and conduct problems.

Current Symptoms Scales include self-report and observer-report versions. The scale includes 3 main sections. The first section assesses inattention, impulsivity, and hyperactivity symptoms. The second sections rates how often any ADHD symptoms have interfered in patients' ability to function normally across a variety of situations. The last section rates oppositional defiant disorder symptoms.

ADHD Rating Scale-IV is based on the 18 symptoms in the DSM-IV. It is a self report scale for adults, and parent/teacher report scale for children. The Adult ADHD Self –Report Scale is a World Health Organization instrument, composed of 18 questions based on the criteria for ADHD from the DSM-IV.

Epidemiology

Attention Deficit/ Hyperactivity disorder is a worldwide, highly prevalent disorder, estimated to affect 5%-10% of children (Faraone, Sergeant, Gillberg, & Biederman, 2003) and 4 % of adults (J Biederman, 2005). Although ADHD is perceived by many to be an American disorder, its prevalence is in the same range in many other countries. According to a recent review, the prevalence in children and adolescents is about 8.5% in Africa, 4% in Asia, 5% in Europe, 11% in South America, 6% in North America, and the pooled worldwide prevalence is 5.8% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007).

Male sex, low socioeconomic status, and young age are associated with an increased prevalence of ADHD. Girls more commonly have the IN type, and also less commonly have accompanying Oppositional Defiant Disorder (ODD)/Conduct Disorder (CD) and disruptive disorders, factors leading to lower rates of diagnosis. Low socioeconomic status is more likely to be correlated with prenatal stress, low birth weight, and severe early deprivation, all of which are factors that may cause ADHD. The lack of appropriate description of adult symptoms may reduce the prevalence of ADHD in adulthood, for the original descriptions were derived from a child focused perspective, and do not reflect what are thought to be more salient aspects of adult ADHD (Spencer, Biederman, & Mick, 2007).

Comorbidity

It is well established that ADHD frequently is comorbid with other psychiatric disorders. In children with ADHD approximately 60% have oppositional defiant disorder, 15% have conduct disorder, 25% have mood disorders, 28% anxiety disorders, and 26% have a learning disorder. About 30% of adults with ADHD have comorbid antisocial disorders, 32% have mood disorders, 50% have anxiety disorders, and 26% have alcohol/drug dependency (J Biederman, 2005).

Etiology

There is growing evidence that the principal cause of ADHD is genetic. Faraone et al. (2005) reviewed 21 independent twin studies from Australia, Sweden, the UK, and many sites in the U.S. that estimated heritability to be 0.76.

Recent studies suggest that the genetics of ADHD is complex; ADHD is the product of neither sex-linked nor Mendelian (single gene) genetic transmission. Seven candidate genes show statistically significant evidence of association with ADHD: the dopamine D4 receptor (DRD4), the dopamine D5 receptor (DRD5), the dopamine transporter gene (SLC6A3), the dopamine β-hydroxylase gene (DBH), the serotonin transporter gene (SLC6A4), the serotonin 1B receptor gene (HTR1B), and synaptosomal-associated protein-25 (SNAP-25). Non-genetic causes of ADHD are neurobiological in nature, consisting of such factors as prenatal stress, low birth weight, traumatic brain injury, maternal smoking during pregnancy, and severe early deprivation (J. Biederman & Faraone, 2005).

Medication Treatment

The first line medications for ADHD treatment are amphetamine and methylphenidate. The second line agents include atomoxetine, modafil, pemoline, bupropion, tricyclic antidepressants (TCAs), Monoamine Oxidase Inhibitors (MAOIs), and alpha-2-adrenergic agonists.

First Line Medications

Amphetamine and methylphenidate are psychostimulants, which are believed to enhance neurotransmission of dopamine and norepinephrine. There are immediate release stimulants effective for 3 to 6 hours, and long acting stimulant formulations effective for 8 to 12 hours. Immediate-release methylphenidates approved by the US Food and Drug Administration (FDA) include Ritalin (methylphenidate hydrochloride; 5, 10 or 20mg tablets) and Focalin (dexmethylphenidate hydrochloride).

Long-acting methylphenidate formulations include: Concerta (methylphenidate hydrochloride; 18, 27, 36 or 54 mg controlled-release tablets), Ritalin LA (methylphenidate hydrochloride; 10, 20, 30, or 40 mg controlled-release capsules), Ritalin SR (methylphenidate hydrochloride; 20 mg controlled-release tablets), Metadata CD (methylphenidate hydrochloride; 10, 20, 30, 40 or 60 mg controlled-release capsules), Metadate ER (methylphenidate hydrochloride; 10 or 20 mg controlled-release tablets), Methylin ER (methylphenidate hydrochloride; 10 or 20 mg controlled-release tablets), Daytrana (10, 15, 20 or 30 mg controlled-release methylphenidate transdermal patch) and Focalin XR (5, 10, 15 or 20 mg controlled-release capsules).

Dexedrine (dextroamnphetamine sulfate; 5 mg tablets), DextroStat (dextroamphetamine sulfate; 5 or 10 mg tablets) and Adderall (mixed amphetamine salts; 5, 7.5, 10, 12.5, 15, 20 or 30mg tablets) are immediate release amphetamine formulations, whereas Adderal XR (mixed amphetamine salts, 5, 10, 15, 20, 25 or 30 mg controlled-release capsules) and Dexedrine Spansule (dextroamphetamine sulfate; 5, 10 or 15 mg controlled-release capsules) are long acting amphetamine (Dodson, 2005; Findling, 2008). The newest formulation lisdexamfetamine dimesylate (trade name Vyvanse), is a prodrug that is therapeutically inactive until it is converted to active form by natural metabolic processes (Faraone, 2008).

For methylphenidate, most patients respond to 0.3 to 1.0 mg/kg body weight per dose when taken 2 to 3 times daily. The starting dose of amphetamine, is generally between 2.5 and 5.0 mg taken twice daily; the dose can be increased to effect to a maximum of 40 mg daily. The most common side effects of stimulants include hypertension, insomnia, decreased appetite, stomachache, headache, and dizziness (Horst & Hendren, 2005)

Second Line Medications

Pemoline (Cylert) used to be a first line stimulant for ADHD treatment. It is no longer recommended routinely because of its association with hepatotoxicity. In animal models, pemoline appears to release presynaptic dopamine and block dopamine uptake (Patrick & Markowitz, 1997). Pemoline can be given once daily, and the typically initial dose is 37.5 mg (Horst & Hendren, 2005). Common adverse effects include hepatotoxicity, insomnia, decreased appetite, abdominal pain, irritability and headaches.

Atomoxetine (Strattera) is an effective non-stimulant agent for ADHD treatment. It blocks the reuptake of norepinephrine. Atomoxetine is started at 0.5 mg/kg daily. Therapeutic effects may take up to 4 to 6 weeks. Possible side effects include hepatotoxicity, depressed appetite, dizziness, increased blood pressure and pulse (Horst & Hendren, 2005).

Bupropion is a non-selective inhibitor of dopamine transporter (DAT) and norepinephrine transporter (NET) and is also an antagonist at neural nicotinic acetylcholine receptors (Dwoskin, Rauhut, King-Pospisil, & Bardo, 2006). Bupropion is effective in ADHD at doses of 100 to 300 mg daily, 2 to 3 times/day. Side effects include decreased seizure threshold, fatigue, headache, dry mouth, sweating, constipation, and nausea (Horst & Hendren, 2005).

Tricyclic antidepressants (TCAs) that show efficacy in the treatment of ADHD include amitrityline, desipramine, imipramine, and nortriptyline. It is assumed that their activities in ADHD are attributed to their actions on dopamine and norepinephrine reuptake (Banaschewski, Roessner, Dittmann, Janardhanan Santosh, & Rothenberger, 2004). The use of TCAs is limited by reports of sudden death of unexplained origin in children associated with desipramine treatment. Common adverse effects of TCAs include sedation, weight gain, dry mouth, constipation, postural hypotension, and sexual dysfunction. Dose is lower and onset is faster (2 to 3 days) than for depression, usually 10 to 25 mg daily (Horst & Hendren, 2005).

Monoamine Oxidase Inhibitors (MAOIs) include phenelzine and selegiline. The mechanism of MAOIs in reducing ADHD symptoms is probably related to their ability to block the metabolism of norepinephrine and dopamine (Banaschewski, et al., 2004). There is scientific evidence in support of the use of MAOIs in ADHD, but their use is limited by the dietary restrictions required to avoid a hypertensive crisis which is associated with tyramine-containing foods (such as most cheeses) and drug interactions(such as cold medicines, amphetamines) (Horst & Hendren, 2005).

Alpha-2-adrenergic agonists include clonidine and guanfacine. It is likely that guanfacine and clonidine have therapeutic effects in ADHD patients by strengthening Pre-Frontal Cortex (PFC) regulation of attention and behavior through direct stimulation of postsynaptic, alpha-2-adrenoceptors in the PFC (Arnsten, Scahill, & Findling, 2007). Potential cardiovascular risks such as hypotension associated with alpha-2 agonists limit their usefulness. Clonidine therapy is initiated at a once daily dose of 0.05 mg. Guanfacine therapy is initiated at 0.5 mg daily (Horst & Hendren, 2005).

Modafinil (Provigil), which has been used to promote wakefulness for narcolepsy, has also shown some efficacy against ADHD. Modafinil is a psychostimulant that differs from amphetamine in structure, neurochemical profile, and behavioral effects. The primary effect of modafinil is that it potentiates both DA and NE neurotransmission by directly binding the dopamine transporter (DAT) and norepinephrine transporter (NET) (Minzenberg & Carter, 2008). Common side effects are insomnia, abdominal pain, anorexia, cough, fever, and rhinitis. Children may require higher doses (300 mg daily) than adults (200 mg daily) due to differences in metabolism (Horst & Hendren, 2005).

REVIEW OF RELATED LITERATURE

Stimulant Medications and Academic Achievement

Stimulant drugs have been used successfully for decades to improve the behavioral impairments of hyperactivity, impulsivity, and inattention, in children diagnosed with ADHD. A voluminous literature supports the benefits of stimulants for improving classroom manageability and increasing attention and academic productivity in children. Medications may improve the quality of note-taking, scores on quizzes and worksheets, writing output and homework completion. Nevertheless, they do not normalize the ability to learn and apply knowledge. It has been recognized for over 30 years, that there is little evidence that these drugs improve the academic achievement of ADHD diagnosed children.

As described by Loe and Feldman (2007) in their recent review, there is now substantial longitudinal data to conclude that "academic underachievement and poor educational outcomes associated with ADHD are persistent." Children with ADHD have a consistently lower full-scale IQ than normal controls. They score significantly lower on reading and arithmetic achievement tests, use more remedial academic services, are more likely to be placed in special education classes, more likely to be expelled, suspended or repeat a grade, compared with controls. By the time they reach adolescence, individuals with ADHD fail more grades, have lower report card scores, lower class rankings, and worse scores on standardized achievement tests than "matched normal controls." They take more years to complete high school, and have lower rates of college attendance and graduation.

The first review of this topic was that of Barkley and Cunningham (1978) who summarized 17 short-term research studies ranging from 2 weeks to 6 months, and found stimulant drugs produced little improvement in the academic performance of hyperkinetic children. Measures of math, reading, spelling and word analyses (most commonly taken from the Wide Range Achievement Test – WRAT) were not consistently improved with stimulants. In 6 out of 9 long term studies, lasting at least one year (and as long as 5 to 10 years), drugs had little impact on long term academic outcome as well. It was noted that a substantial proportion of ADHD-diagnosed children were in special schools or classes, had failed one or more grades, had reading or arithmetic difficulty and were having problems sitting still and studying.

The authors acknowledged that many long-term studies didn't include control groups, and many medicated children didn't stay on the drugs during the entire follow-up period. Nevertheless, it was concluded that, in spite of various procedural differences, the outcomes were the same – stimulant drugs had little impact on the "…long-term academic outcome or adjustment of hyperkinetic children. If the drugs contribute positively, they appear to reduce disruptive behavior rather than improve academic performance."

In considering possible reasons for this negative result, Barkley and Cunningham offered some suggestions. One concerned the age of the child at the start of treatment. If treatment was begun when the child was older, he or she may have already failed to learn the necessary skills to acquire more complex academic concepts. A second possibility was that stimulant medication might make hyperactive children less aware of their environment, perhaps more intellectually constricted and rigid and less inquisitive or interested in learning. *Third, it was admitted that the stimulant drugs might not affect the underlying cause of the academic dysfunction.*

A subsequent review by Gadow (1983) also showed that the effect of stimulant drugs on standardized achievement test scores was not particularly robust. He discussed a meta-analysis by Kavale (1982) which showed an overall mean effect size of .39 for all measures of academic achievement across studies. This was calculated to be equivalent to a 15% increase for medicated subjects compared with comparison groups – which may not represent a clinically meaningful improvement. He suggested a number of methodological issues that might obscure drug effects on academic achievement. First, he raised the possibility that different drugs might affect various tasks differently. Second, he noted that the dosage associated with improved cognitive performance was often less than one-half the best dose for suppressing conduct problems, and, that doses were often chosen to control classroom behavior rather than cognitive performance. In fact, he noted that the doses required to manage disruptive behavior might actually *worsen* cognitive effects. Third, he suggested that short-acting agents might not provide sufficient coverage throughout the school day, such that information presented in the morning would be experienced while the child was under the influence of medication, while material presented in the afternoon might not be. This argument is related to the issue of State Dependent Learning (SDL) (Swanson & Kinsbourne, 1976). SDL refers to the partial loss of information during recall when learning has occurred in one state (e.g., drug) and retrieval in another (e.g., placebo). At present, the relationship between SDL and short- or long-term drug-induced achievement gains is not clear (Becker-Mattes, Mattes, Abikoff, & Brandt, 1985; Gan & Cantwell, 1982; Shea, 1982; Stephens, Pelham, & Skinner, 1984; Swanson & Kinsbourne, 1976; Weingartner, Langer, Grice, & Rapoport, 1982).

Fourth, the duration of treatment might not have been long enough to provide benefit for performance on achievement tests, because such tests assess concepts taught over several grade levels. Fifth, the argument was made that previous studies did not take into account the contribution of co-morbid diagnoses, especially learning disabilities, or the inclusion of different subtypes of ADHD in the experimental populations. Sixth, prior research had not considered the relationship between drug effects and task variables. For example, if stimulant drugs produced cognitive perseveration (akin to amphetamine-induced stereotypies) then learning based on the ability to be cognitively 'flexible' might be impaired.

Gadow concluded that, if a positive effect of stimulants on academic achievement exists, "…it is not very robust especially with regard to adolescent and adult outcome."

Almost 8 years later, Swanson et al. (1991) acknowledged that "Even though it has been established that stimulants do improve *productivity,* it is still unclear whether stimulants alone improve long-term academic *achievement*, and, that…"whether this widespread clinical practice has a long term beneficial effect on learning or academic achievement is still an open question." He suggested that "there are at least 2 reasons why beneficial effects may be obscured in research studies." The first is that higher-than-optimal doses may be prescribed which might impair rather than improve learning. They used the term 'cognitive toxicity,' to describe a situation in which the optimal dose for improving learning might be lower than the optimal dose for improving behavior. Although this point had previously been raised by Gadow, little research had since been conducted to evaluate this possibility.

The second point was that "…treatment may be overinclusive if diagnostic groups are targeted in which a significant proportion of cases do not have favorable cognitive response to medication." In other words, outcomes might be poor because of the inclusion of non-responders. However, it has since been

shown that most patients do respond to stimulant medications if efforts are made to determine which drug would be most effective. A meta-analysis of the five studies in children that compared MPH to AMPH in blind crossover conditions found that about 37% of patients had a clearly better outcome on an amphetamine preparation, and 26% had a clearly better response to methylphenidate. The other 37% of stimulant responders could use either molecule with equal benefit (Greenhill, et al., 1996). Therefore, over-inclusiveness (i.e. of non-responders) should not be an issue.

Based on their literature review, Carlson and Bunner (1993) concurred that stimulants have strong positive effects on direct measures of academic performance of children with ADHD. However, long term effects, which were measured by the Wide Range Achievement Test (WRAT), the Peabody Individual Achievement Test (PIAT), the Stanford Achievement Test (SAT), and failed grades, were not seen. In general, they summarized the same studies discussed in the earlier reviews of Gadow and Swanson et al and proposed the same interpretation, namely, the issue of low versus high doses, the possibly insufficient duration of treatment, and the different types of outcome measures used. *Interestingly, the one explanation for the lack of long-term improvement in academic achievement that was not repeated was the possibility, raised by Barkley and Cunningham in 1978, that stimulant medications are simply unable to influence those etiologic variables which create, or contribute to the ADHD students' academic difficulties.*

Neuropsychological Assessments of Adult ADHD

Intuitively, it would seem logical that drugs which improve attention and concentration would improve learning and academic achievement. Yet, for over 30 years the data show that this is not the case. *Therefore, the long term goal of our investigations is to try to find out why the stimulant medications don't improve academic achievement.*

Adults with ADHD exhibit a range of neuropsychological impairments in attention, behavioral inhibition, working memory, and motor speed. Although such deficits have been studied extensively in children, it is only recently that reviews of this topic have been published in regard to adults, most notably (Frazier, Demaree, & Youngstrom, 2004; Hervey, et al., 2004; Schoechlin & Engel, 2005; Woods, Lovejoy, & Ball, 2002).

Each of these reviews took a particular approach to the issue. Woods et al. (2002), which was the first review of adult neuropsychological performance, included a broad range of articles, Hervey et al. (2004) included 33 published studies of adults only, Frazier et al. (2004) listed 123 studies, (which included all ages), and Schoechlin and Engels (2005) included 24 studies of adults only.

In each case, comparisons were made between individuals with ADHD and 'healthy' or 'normal' control participants, i.e. psychiatric and other comorbid conditions were excluded, there was no analysis according to subtype of ADHD, and participants with ADHD were tested while unmedicated.

Although there was a great deal of overlap in these reviews with respect to the various *specific* neuropsychological tests that were chosen for the assessments, there were major differences among the authors in the way the tests were categorized, that is, in regard to the particular 'functional domain' that they were presumed to represent:

1. Woods et al. (2002) organized the specific tests into 6 categories: Attention/Executive Function, Learning/Memory Functioning, Intellectual Functioning, Language Skills, Motor Skills and Self-Report Measures.

2. Hervey et al. (2004) used the following 7 domains: Attention, Response Inhibition, Other tests of Executive Function, Memory and Learning, Processing Speed, Intelligence and Other.

3. Frazier et al. (2004) chose 4 categories: Intellectual Composites, Achievement Measures, Nonexecutive Functioning and Executive Functioning, and

4. Schoechlin and Engel used 10 'functional neuropsychological domains": Verbal Intelligence, Verbal Memory, Executive Functioning, Abstract Problem-Solving/Working Memory, Figural Memory, Visual-figural Problem Solving, Fluency, Simple Attention, Sustained Attention and Focused Attention.

Although the number of domains differed among these reviews, there was much overlap in the specific tests that were discussed. *In other words, the same neuropsychological tests were put into different 'domain' categories by the respective authors.* In particular, while each review included an 'Executive Function' domain, the specific tests or the number of tests that were put into this category was not the same. For example, Frazier et al. included 8 individual tests (plus 2 different versions of one test, the Trail Making Test) in their Executive Function category. Woods et al., in the combined category of Attention/Executive Function also have 8 different tests (including the same two Trail Mating versions). In contrast, Schoechlin and Engel distributed their group of tests across more domains (10 instead of 4) and only 2 tests were included in their Executive Function category - the Wisconsin Cart Sort and the Tower of Hanoi.

Nevertheless, in spite of this inconsistency in the categorization of neuropsychological tests into functional domains, there are some common generalizations that can be taken from these reviews.

1. Regardless of how the measure is categorized, whether as 'sustained attention,' 'focused attention' or 'divided attention,' tests that assess attention consistently show a significant difference between ADHD and control participants, in that ADHD – diagnosed individuals are impaired. This would be expected in a population that is designated as having attention deficits. Although there are a variety of tests used to evaluate **attention,** the most commonly used tasks are the Continuous Performance Test (CPT), the Go/No-Go task, the Rapid Visual Information Processing (RVIP) task and the Stop Signal Test. These tests have characteristics that require sustained alertness or 'vigilance' to stimuli presented relatively rapidly on a computer screen, such that the participants are ready to react when a rare stimulus appears during relatively long periods of time.

2. The Stroop Color-Word Interference Test is another commonly used assessment. This task is presumed to measure the influence of 'response interference,' which provides an index of 'distractibility.' In this test, the subject first names colors and color words as quickly as possible. After this phase, "incongruent" color words are given and the subject must inhibit the response to say the color of the *written word*, and, instead give the correct color that the word is *written in*. Measures include the reading time for the congruent and incongruent words, and the number of errors. All reviews conclude that ADHD adults are reliably found to be impaired relative to control groups on this test.

As one recent example, King et al. (2007) confirmed that the ADHD group (n =22) were slower and made more errors than the matched control group (n=22) on the Stroop Test.

3. It is consistently reported that verbal memory/fluency (such as auditory verbal list learning) is worse in ADHD adults relative to controls, although that is not always the case with visual stimuli. In other words, ADHD adults perform more poorly than normal individuals on tests with verbal stimulus presentations than with visual presentations. One common test involves asking the participant to name, within 60 seconds, as many items as possible that begin with a particular letter of the alphabet. This deficit is made worse if distracting stimuli are also presented.

4. Perhaps most surprising, each of these reviews concluded that there was no reliable difference between adults with ADHD and normal control participants in Executive Function. This not only differs from the literature in children, it is …"inconsistent with the current view that ADHD is the result of a deficit in behavioral inhibition that secondarily leads to deficits in executive function…" (Schoechlin & Engel, 2005).

A couple of explanations for this lack of a differential impairment in Executive Function have been proposed. One possibility is that the deficit seen in children with ADHD is due to an abnormality, or a delay, in frontal-lobe maturation, which recovers in adulthood (Rubia, et al., 2000). Another reason may be that the Wisconsin Cart Sort Test, which is commonly used as a measure of Executive Function in adults, has no time limit. Without the additional time constraint, individuals with ADHD may be able to match normal controls even when the demands are more complex (Hervey, et al., 2004).

In addition to the 4 review papers, information about deficits in adults with ADHD was obtained by McLean et al. (2004), who conducted a study in which they tested two groups of adults (27 to 30 years old), one diagnosed with ADHD (n=19) and the other of normal control participants (n=19), on a variety of neuropsychological tests. The tests were part of a standard battery called the CANTAB (Cambridge Neuropsychological Test Automated Battery) and included several tasks involving spatial memory, as well as the Go/No-Go, and the Tower of London task.

The Tower of London (TOL; sometimes referred to as the Tower of Hanoi) is a test of 'planning' ability. There are several versions, but the general situation is that participants are presented with two arrays of colored balls or disks (which can now be shown on a computer monitor, as shown in the picture below). Subjects are required to determine the minimum number of moves needed to arrange the items in one array, to match the arrangement shown in the other, or 'goal,' array. Once decided, the subjects must indicate the correct solution, by actually moving the items on the touch-sensitive screen, or by indicating the appropriate number of moves necessary to match the two arrays, depending on the specific version used. The problem can be increased in difficulty, requiring 3, 4, 5 etc. moves. Dependent measures include the 'planning time,' or latency to first response, time to solve the problems, and accuracy, or number of moves above the minimum.

Although the ADHD group was often slower than the controls (a longer reaction time on most tasks is a consistent finding in the literature) McLean et al. (2004) found no difference between the two groups on other measures of most tests, with the exception of the Tower of London. In that task the ADHD group performed significantly worse than the control group on the more difficult problems, in the 'percentage of correct first choices,' that is, on choosing the correct number of moves to solve the problem.

Young et al. (2007) recently conducted a more detailed examination of this task in 26 ADHD - diagnosed adults and 26 control subjects. In brief, this study determined the planning latencies and accuracy on the TOL, with problems increasing in difficulty, using a computerized program. The task could be solved in 3, 4 or 5 moves, with one attempt allowed for each problem. The ADHD group was faster and equal in accuracy to controls until the most difficult task. At that point, they didn't inhibit their responses, and were therefore less accurate than control subjects. In other words, the planning time of the ADHD group did NOT increase with task difficulty, unlike that of the control group, and eventually, as the task became more difficult, their accuracy suffered.

In summary, in spite of differences across individual studies in regard to the way in which various functional deficits are categorized, there is a consistent body of evidence showing that adults with ADHD are impaired, relative to normal adults, on tests of 'vigilance,' 'response interference (Stroop),' 'verbal memory/fluency,' and 'planning ability (Tower of London).'

Effect of Medication on Neuropsychological Performance in Adult ADHD

There is increasing evidence that medications do not necessary normalize neuropsychological outcomes in children with ADHD (Bedard, Ickowicz, & Tannock, 2002; Gualtieri & Johnson, 2008), and this also seems to be the case for adults. For example, in one early study Riordan et al. (1999) showed the usual impairment of unmedicated adult ADHD patients on a battery of neuropsychological tests, including verbal memory, motor and processing speed and distractibility. Although these measures generally improved overall after methylphenidate, no significant task-specific effects were described.

One function which is reliably improved by stimulant medication is **sustained attention,** or **vigilance**, assessed with the CPT (Barrilleaux & Advokat, 2009), Go/No Go (Tucha, et al., 2006; Wilson, Cox, Merkel, Moore, & Coghill, 2006), or the similar RVIP test in the CANTAB (Turner, Blackwell, Dowson, McLean, & Sahakian, 2005). One exception to this generalization is Aron et al. (2003), who found no significant improvement in the percent of errors on the Stop Signal Test in adults with ADHD relative to controls (0.4%), regardless of whether they were medicated (1.6%) or unmedicated (2.5%) – even though methylphenidate did improve their ability to inhibit their latency of incorrect responding.

Schweitzer et al. (2004) also report improvement with methylphenidate on an auditory arithmetic task, the Paced Auditory Serial Addition Task. This test involves computer-generated random numbers, which are presented to both ears through earphones, 1 every 200 ms. Participants were instructed to add each number to the preceding number and vocalize their answers. (A control condition was included, which required participants to generate and vocalize random numbers). On this test, nonmedicated ADHD-diagnosed adults (82% correct answers) performed significantly worse than control participants (93% correct). After methylphenidate the ADHD score increased to 89%, which was no longer different from the control value.

Kurscheidt et al. (2008) reported a retrospective analysis of neuropsychological test results of 34 patients on chronic methylphenidate treatment. Compared to their baseline performance before treatment, the drug significantly improved measures of attention (such as the Go/No-Go; the Frankfurt Attention Inventory Test) and 'verbal memory performance' (not described), and this was maintained for at least 3 to 6 months of treatment – but other tasks were not affected. Turner et al. (2005) did not find

improvement in 18 adult ADHD patients on a variety of spatial tests with methylphenidate. Muller et al. (2007) reported that medicated adult patients with ADHD (n=30) were still impaired, relative to control adults (n=27) on the number of errors made on the Stroop test, on the latencies for first movement, problem solving and total time on the Tower of London test, and on the number of words elicited on a verbal fluency test.

The most comprehensive test battery results were recently published by Biederman et al. (2008), in a naturalistic study of young adults (15 to 25 years old, mean of 19 years) from data collected between July 1998 and April 2003. Like others, these authors showed that stimulants had the largest beneficial effects on measures of sustained attention (vigilance measures) and verbal learning. Also like other studies, stimulant medication did not significantly improve measures of 'interference,' and 'processing speed,' taken from the Stroop test.

One disadvantage of the studies which have assessed the effect of stimulants on neuropsychological performance is the fact that they could not compare the effect of the medications in ADHD patients with drug effects in normal persons. However, there are two studies that describe such results. Elliott et al. (1997) examined the effect of methylphenidate (20 and 40 mg) and placebo pills in 28 healthy male volunteers. Half of the group received the drug on the first session and placebo on the second, and the other half were given the reverse treatment. Tests included some CANTAB tasks of spatial memory, as well as a verbal fluency task, and 2 versions of the Tower of London test.

Results were somewhat complicated by practice effects between the two sessions. For example, on the verbal fluency test, both groups produced more words on the second session, regardless of drug condition. With regard to the Tower of London test, the outcome was dependant on the particular version of the task that was used as well as the session order (whether placebo or drug treatment came first). Comparisons of drug versus placebo on session one showed that subjects on methylphenidate solved more of the 'four move' problems correctly than those on placebo (92.9% compared to 73.2%). Between sessions data showed that, on the 'new' version of the Tower of London test, similar to the one used by Young et al. (2007), accuracy (percentage correct) was good in subjects who had the drug first but then decreased during their second, placebo test. This suggested a drug-induced facilitation. Subjects who took placebo first did slightly better on the second session, when they were given the drug. The results were interpreted to mean that methylphenidate had two potentially conflicting effects on performance – it facilitated cognitive performance in novel situations but decreased the response latency, so that subjects responded impulsively.

The second study (Turner, et al., 2003) assessed the effect of methylphenidate in 60 healthy 'elderly' male volunteers, average age of 61 years, at the same doses and on many of the same tests, using the CANTAB battery. In contrast to the results in younger adults (Elliott, et al., 1997), there were no effects on sustained attention tests, such as the Stop Signal Reaction Time, or on the Tower of London tasks. *One important difference between these two studies is that the Turner et al experiment used a between subjects design, with subjects randomized to receive either a placebo or one of the two drug doses.*

Lastly, there are two reports which have studied the effects of the non-stimulant medication, modafinil, on the CANTAB test battery, both by Turner's group. One was conducted in healthy controls (2003) and one in adults diagnosed with ADHD (2004). Modafinil, like stimulants, improved performance of

normal adults on the Stop Signal Task, by reducing the latency to inhibit responses and by reducing errors. However, while the inhibitory latency was also reduced in ADHD subjects, their error rate was not improved and was actually much worse under the drug. Both groups showed no effects on other attention tests, and both groups showed a statistical improvement on the Tower of London task, although the absolute changes were very modest. Although preliminary, the evidence suggests that modafinil does not have the same effect on neuropsychological tests as the stimulant medications.

In summary, the results obtained with stimulant medications (which have so far been primarily methylphenidate formulations) show improvement on tests requiring sustained attention, and *perhaps* on verbal fluency, although the outcomes on that measure are mixed. The Stroop test of 'interference' does *not* appear to be improved by stimulants. Performance on the Tower of London 'planning' task also does not seem to be reliably improved by stimulants, although this conclusion may depend on the specific requirements of the particular version that is used, and the time constraints imposed.

On the basis of the information available in the literature, it seems reasonable that a systematic investigation of the neurocognitive effects of stimulant medications in adults with ADHD should include an assessment of the Stroop Test, a test of verbal fluency, and the Tower of London test. In addition, to avoid confounds introduced by practice with the tests, it would be desirable to use a between group design, in which normal control participants are compared to a group of ADHD-diagnosed participants who are tested while off their medication and a different group of ADHD-diagnosed participants who are tested while on their medication.

CURRENT STUDY

Participants

99 participants were recruited from the psychology extra-credit system in spring 2009, and 5 from Dr. Advokat's classes in the fall 2009. All participants who completed the experiment received a $5 payment and extra credit for a psychology class. There were 36 participants for on medication ADHD group (ONMED), 33 participants for off medication ADHD group (OFFMED), and 35 participants for non-ADHD control group (CONTROL).

Neuropsychological Assessments

D2 Test of Attention

The d2 Test is a timed test of selective attention (Brickenkamp & Zillmer, 1998). The test consists 14 test lines with 47 characters in each line. Each character consists of a letter,'d' or 'p' marked with one, two, three or four small dashes. The participant is required to scan the lines and cross out all occurrences of the letter'd' with two dashes while ignoring all other characters. Here are some selective instructions we used from the d2 test manual.

"Please pay attention. After the word "examples" on your recording blank you see three small letters marked with dashes. These are the letter'd' as in 'dog', and each is marked with two dashes. The first'd' has two dashes on the bottom, the second has two on the bottom, and the third 'd' has one dash on the top and one on the bottom, still making two dashes all together. I would like you to cross out every letter'd' that has two dashes by making a single line through the letter. Try doing this first with the three examples, and then try the practice line. You are not supposed to cross out the other letters. Thus, a 'd' which has more than two or fewer than two dashes should not be crossed out, and the letter 'p' as in 'pig' should never be crossed out, no matter how many dashes it has. Do you have any questions right now?"

"Please do not turn your recording blank over yet. Put your pencil down for a moment and listen carefully now. On the other side of your recording blank you will see 14 lines with the same letters you have worked on in the practice line. For each one of the 14 lines you should start on the left side, work to the right and cross out each'd' with two dashes. This is exactly the same task you did in the practice line. Start with the first line. After 20 seconds I'll say: 'Stop, next line' and you will stop working on that line and immediately start working on the next line. After another 20 seconds I'll say 'Stop, next line' and you will immediately start working on the next line. Work as quickly as you can without making mistakes.'"

Controlled Oral Word Association Test

The Controlled Oral Word Association Test (COWAT) is a widely used procedure for assessing verbal fluency. The test consists of three, 1-min trials in which the participants is asked to produce as many words beginning with a certain letter of the alphabet as they are able, without giving proper nouns or similar root words with slightly different endings (Ruff, Light, Parker, & Levin, 1996). The experimenter's instructions for the COWAT are as follows: "I am going to say a letter of the alphabet, and I want you to say as quickly as you can all the words you can think of which begin with that letter.

You may say any word at all except proper names, such as names of people or places. So you would not say "Rochester" or "Robert." Also, do not use the same words again with a different ending, such as "eat" and "eating."

"For example, if I say "S," you could say, "sun," "sit," "shoe," or "slow." Can you think of other words beginning with the letter "S" Wait for the subject to give a word, indicate if the word is correct, and ask the participants to give another word beginning with letter "S." Once two appropriate words beginning with the demonstration letter are given, say, "That is fine. Now I am going to give you another letter, and again say all the words beginning with that letter that you can think of. Remember, no names of people or places, just ordinary words. Also, if you should draw a blank, I want you to keep on trying until the time limit is up. You will have a minute for each one." The first letter is C, and 1 minute is allowed, and the same applies for the letters F and L.

The score is expressed as the total number of correct words across all three trials.

Computerized Stroop Color and Word Test

The Computerized Stroop Color and Word Test (Bedard, et al., 2002) proposed for this study consists of three blocks presented in a fixed order: word reading, color naming, and incongruent color naming of color words. For each block, there are 60 word or color stimuli appearing one by one on the center of the computer screen. For each block, the participant is instructed to read the words (block 1) or name the colors (block 2 and 3) aloud as quickly and as accurately as possible. In the word reading block, stimuli are three color words (blue, red, and green) in black ink. In the color naming subtest, stimuli are a series of five Xs (i.e., XXXXX) in all blue, all red, or all green ink. Finally, in the incongruent color naming block (interference condition), stimuli are the color words blue, red, and green printed in an incongruent color. The participant has to name the color of the *ink* in which the word is printed. We use a voice response box to record the reaction time for each trial. The voice response box works by recording the latency between the appearance of a stimulus and the reactive voice produced by the participant. The experimenter records accuracy by pressing related keys on the computer key board: # 1 for red, # 2 for green and # 3 for blue.

The experimenter's instructions for Stroop Test are as follows: "This is an implementation of the Stroop task. There will be 3 blocks of trials under different conditions. The colors you will see are RED, BLUE, GREEN. Press any key to begin."

The instruction for block 1 (word reading) is: "You will see several words. Read the word aloud. Please be as quick as you can but don't sacrifice speed for accuracy. We will start with a few practice trials." Then the experimenter displays 5 practice trials for block #1. After that, the computer screen displays: "You will see several words. Read the word aloud. Please be as quick as you can but don't sacrifice speed for accuracy. Ask the experimenter if you have questions. Press any key to begin. "

The instruction for block 2 (color naming) is "You will see several items. Name the color of the item displayed aloud. Please be as quick as you can but don't sacrifice speed for accuracy. We will start with a few practice trials." Then the experimenter displays 5 practice trials for block 2. After that, the computer screen displays: "You will see several items. Name the color of the item displayed. Please be

as quick as you can but don't sacrifice speed for accuracy. Ask the experimenter if you have questions. Press any key to begin. "

The instruction for block 3 (incongruent colored-word naming) is "You will see several items. Name the color of the item displayed aloud and ignore other information. Please be as quick as you can but don't sacrifice speed for accuracy. We will start with a few practice trials." Then the experimenter displays 5 practice trials for block 3. After that, the computer screen displays: "You will see several items. Name the color of the item displayed. Please be as quick as you can but don't sacrifice speed for accuracy. Ask the experimenter if you have questions. Press any key to begin. "

Performance for each condition is scored as the mean reaction time for all the correct trials and correct reaction rate. So there are six outcome variables in Computerized Stroop Test: word reading reaction time, word reading correct reaction rate, color naming reaction time, color naming correct reaction rate, incongruent color naming of color words reaction time, and incongruent color naming of color words correct reaction rate.

Computerized Tower of London Test

The Computerized Tower of London Test (also known as the Tower of Hanoi) is an adaptation of the neuropsychological test devised by (Shallice, 1982). Two arrangements are presented on the computer screen, a right one that represents the goal arrangement and a left one that has to be rearranged. The test consists of 27 problems presented in random order, 9 problems for each difficulty level: 3 move problems, 4 move problems, and 5 move problems.

The participants are instructed to inspect the right array, to start only when confident of executing the entire sequence of moves needed, and to complete the problems in the minimum number of moves.

Instructions for Tower of London Test are as follows: "The object of this puzzle is to move the beads on the left so that they are in the goal arrangement. That is, the beads should end up like the arrangement shown on your right. You can only move one bead at a time. Both the location and color arrangement shown on the right are the goal you are to achieve. Try to achieve this goal in as few moves as possible. Click the mouse button when the bar is positioned below the bead you want to move, position the bar under the peg on which you wish to place the bead and click the mouse button a second time. The bead will drop onto the peg. Now we are going to have a few practice trials." Then participants have a few practice trials with feedback information. Practice trials end after they solve 3 problems in minimum moves. "There will be 30 trials. Start only when you are confident of executing the entire sequence of moves needed, and try your best to complete each trial in as few moves as possible. "
There is no time limit for completing any task. The computer records the latencies for each problem, including planning time and subsequent execution time. It also records the number of moves above the minimum required to solve a particular problem and the number of problems solved in the minimum number of moves. *Planning time* is the latency between presenting the problem and the first disk touched. *Subsequent execution time* is the time between the selection of the first disk and the completion of the problem. *Moves above the minimum* is the number of additional moves taken to solve a problem over and above the minimum number needed to solve it.

There are twelve outcome variables in the Tower of London Test: planning time, subsequent execution time, moves above the minimum, and number of problems solved in the minimum number of moves for 3-move, 4-move, and 5-move problems (Young, Morris, Toone, & Tyson, 2007).

Procedure

We made an appointment with participants to come to a computer laboratory in the psychology department of Louisiana State University. For the ONMED group, participants were required to take their medicine 1 hour before they started the experiment. For the OFFMED group, participants were required to refrain from medication for at least 24 hours before they came to start the experiment. The informed consent was obtained before the 4 neuropsychological tests. To reduce the order effect, a counterbalanced design was used to administer the 4 tests for each of the 3 groups. Taped instructions were played to the participants. The d2 test takes about 8 minutes; the Controlled Oral Word Association Test takes about 8 minutes; the Stroop Color and Word Test takes about 15 minutes; the Tower of London Test takes about 15 minutes, depending on different participants. It takes about 1 hour for each participant to complete the experiment.

Data analysis

The data were analyzed using the Statistical Package for Social Scientists 15.0 (SPSS 15.0).

Hypothesis I: Based on evidence from previous research (Barrilleaux & Advokat, 2009; Frazier, et al., 2004; Hervey, et al., 2004; Schoechlin & Engel, 2005; Woods, et al., 2002), we predicted that the OFFMED group would perform worse than the CONTROL group in d2 test; we also predicted that the ONMED group would perform as well as the CONTROL group, and better than the OFFMED group.

A one-way ANOVA was to be used to examine if scores on the COWAT differed among the groups. If groups were significantly different, LSD post hoc pairwise comparisons would be conducted to determine which groups differed from one another.

Hypothesis II: Based on evidence from previous research (J Biederman, et al., 2008; Müller, et al., 2007), we predicted that the OFFMED group would perform more poorly than the CONTROL group in the Controlled Oral Word Association Test; we also predicted that the ONMED group would perform as well as the CONTROL group, and better than the OFFMED group.

A one-way ANOVA was to be used to examine if the scores on the COWAT differed among the groups. If groups were significantly different, LSD post hoc pairwise comparisons would be conducted to determine which groups differ from one another.

Hypothesis III: Based on evidence from previous research (Bedard, et al., 2002; J Biederman, et al., 2008), we predict that the OFFMED group will perform more poorly than the CONTROL group in Stroop Test; the ONMED group will perform better than the OFFMED group in color naming and word reading, but not incongruent color naming of color words; the ONMED group will perform as well as the CONTROL group in color naming and word reading, but worse in incongruent color naming of color words.

One-way ANOVAs were used to examine group differences in reaction time and correct reaction rate for word reading, color naming, and incongruent color naming of color words. If the groups were significantly different in the six outcome variables of the Stroop Test, then LSD post hoc pairwise comparisons would be conducted to examine which groups differed from one another in reaction time and correct reaction rate.

Hypothesis IV: Based on evidence from previous research (McLean, et al., 2004; Müller, et al., 2007; Young, et al., 2007), both the OFFMED group the ONMED group will perform worse than the CONTROL group; the ONMED group will perform as poorly as the OFFMED group. All participants will perform more poorly as the difficulty levels of the problems increase in Tower of London test.

A 3(CONTROL vs. OFFMED vs. ONMED) ×3 (3-move vs. 4-move vs. 5-move problems) mixed design ANOVA was to be used to examine the effects of groups and the difficulty levels of the problems, and the interaction between groups and difficulty levels on planning time. LSD post hoc pairwise comparisons would be conducted to determine which groups differ from one another. The same analysis procedure applied to subsequent execution time, number of moves above the minimum, and percent of problems solved in the minimum number of moves. One way ANOVAs were also conducted to see group effects for the outcome variables of each difficulty level separately.

Results

A total of 104 undergraduate students completed the 4 neuropsychological tests and a survey. There were 3 groups: the Control group (n = 35) of without ADHD; ADHD Off Med group (n = 33) which consisted of students diagnosed with ADHD but not taking ADHD medications while doing the experiment, and the ADHD On Med group (n = 35), consisting of students diagnosed with ADHD, who were on medication while doing the experiment. All participants who completed the experiment received a $5 payment and extra credit for a psychology class.

Table 1 shows the demographic characteristics of the participants. There was no significant difference among the 3 groups in age (the mean was between 20 and 21 years), gender and race (more than 80% were Caucasians). Most participants were juniors (the mean number of semesters in college was between 5 and 6). The 3 groups were not significantly different in their GPAs (mean scores were 2.94 to 3.05) or ACT scores (the mean was approximately 24). The ADHD Off Med group received their diagnosis at an earlier age (the mean age was 13.29) than the ADHD On Med group (the mean age was 17.14), $t(66) = -3.837$, $p<0.001$. The ADHD groups were not significantly different in the 3 subtypes of ADHD; 54% were diagnosed with the inattentive subtype, 27% the combined subtype, 6% the hyperactive subtype, and 13% said they did not know which subtype they had.

The results of the 4 neuropsychological tests, d2 test, the Control Oral Word Association test (COWAT), Stroop Test, Tower of London test, are summarized in Table 2.

In the COWAT, the total number of words beginning with “C”, “F”, and “L”, spoken within a 1-minute time limit, was counted for each participant. A one way ANOVA showed no significant differences among the 3 groups. The average number of words was 41.97 for the Control group, 40.67 for the ADHD Off Med group and 40.40 for the ADHD On Med group.

Table 1. Participant Characteristics

	Control N=35	ADHD off med N=33	ADHD on med N=36	P value
Age in years (± SD)	20.43±2.39(35)	20.67±2.13(33)	21±1.87(36)	0.496
Gender % (N)				0.173
Male	31.4(11)	51.5(17)	33.3(12)	
Female	68.6(24)	48.5(16)	66.7(24)	
Race % (N)				0.183
Caucasian	80.0(28)	87.9(29)	94.4(34)	
Other	20.0(7)	12.1(4)	5.6(2)	
Total semesters (± SD) (N)	5.11±3.45(35)	5.85±3.29(33)	6.19±3.09(36)	0.375
LSU GPA (± SD)	3.05±0.59(34)	2.94±0.47(32)	3.02±0.45(36)	0.656
ACT Score (± SD)	24.67±3.52(30)	24.18±2.49(30)	24.13±3.65(34)	0.775
Age received diagnosis		13.29±4.10(32)	17.14±4.07(35)	0.001
Subtypes % (N)				0.769
Combined		33.3(11)	22.2(8)	
Hyperactive		6.1(2)	5.6(2)	
Inattentive		48.5(16)	58.3(21)	
Don’t know		12.1(4)	13.9(5)	

Table 2. Neuropsychological Test Results (± SD)

	Control N=35	ADHD off med N=33	ADHD on med N=36	P value
D2 test**				
TN	573.97±46.06	557.48±59.42	569.42±60.66	0.458
E1	16.03±10.94	17.54±16.28	14.56±12.18	0.646
E2	1.86±6.34	1.61±3.35	1.17±1.46	0.666
CP	234.25±31.85	224.88±35.56	235.69±33.79	0.362
Controlled oral word association test(N)	41.97±10.45(34*)	40.67±7.86(32*)	40.40±9.17(35*)	0.757
Stroop test				
Word reading RT (ms)	457.63±41.48	479.88±72.23	441.36±41.11	0.013
Color naming RT (ms)	515.83±53.57	536.18±78.60	504.47±59.10	0.124
Interference RT (ms)	683.43±95.07	741.06±160.18	667.19±86.38	0.028
Word reading accuracy (%)	99.17±1.53	99.46±1.11	99.01±1.45	0.400
Color naming accuracy (%)	99.81±0.83	98.99±1.58	99.44±1.34	0.035
Interference accuracy (%)	99.05±1.45	97.51±3.76	97.90±2.37	0.050
Tower of London Test				
Moves above minimum				
Moves above 3	0.16±0.22	0.18±0.24	0.10±0.22	0.246
Moves above 4	0.35±0.57	0.29±0.37	0.22±0.36	0.473
Moves above 5	1.27±1.04	1.54±1.04	1.02±0.90	0.093
Planning time (s)				
Planning time 3	4.62±1.16	5.35±2.25	5.04±1.76	0.234
Planning time 4	4.11±1.75	4.62±2.15	4.52±2.04	0.526
Planning time 5	5.34±5.04	6.23±5.53	5.83±4.47	0.764
Total time (s)				
Total time 3	10.18±1.85	11.22±2.90	10.72±2.05	0.177
Total time 4	12.53±4.23	12.91±3.91	12.54±2.76	0.892
Total time 5	18.54±6.20	22.00±9.07	19.97±5.99	0.142

* Missing data due to technical problems

**TN= total number of letters processed; E1=number of mistakes due to omitting “d2’s; E2=number of mistakes due to crossing out irrelevant letters; CP=number of correctly crossed out letters

There were 4 outcome variables in the d2 test: TN (total number of letters processed), E1 (number of mistakes due to omitting "d2's"), E2 (number of mistakes due to crossing out irrelevant letters), and CP (number of correctly crossed out letters). One way ANOVAs were conducted for each of the 4 outcome variables. There were no differences among the groups in any of the 4 outcome variables. The average TN was 573.97 for the control group, 557.48 for the ADHD off med group and 569.42 for the ADHD on med group. The average E1 was 16.03 for the control group, 17.54 for ADHD off med group, and 14.56 for ADHD on med group. There were very few E2 mistakes, just between 1 and 2 among the 3 groups. The average CP was 234.25 for the control group, 224.88 for the ADHD off med group and 235.69 for the ADHD on med group.

There were 2 outcome variables, reaction time (RT, milliseconds), and reaction accuracy (percent) for each of the 3 conditions in the Stroop test: word reading, color naming and interference (incongruent color naming) tasks. One way ANOVAs were conducted to compare differences among groups. LSD post-hoc tests were used if a main effect was found. No significant group effect was found for the color naming RT. However, there was a significant effect among the groups in word reading RT, $F(2, 101) = 4.551$, $p < 0.05$, and interference RT, $F(2, 101) = 3.722$, $p<0.05$. With regard to the word reading RT, LSD post-hoc tests showed the ADHD On Med group (441.36 ms) reacted significantly faster than the ADHD Off Med group (479.88 ms) $p<0.05$ (see Figure 1a.). The Controls were not different from either of the ADHD groups.

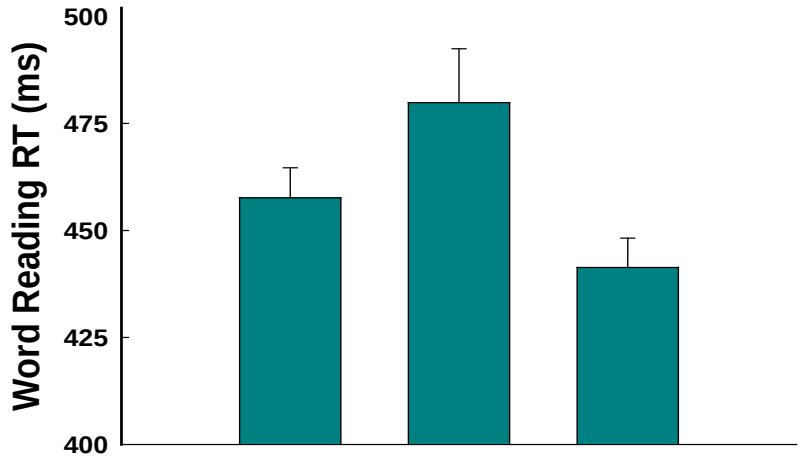
With regard to the interference score, both the Control group (683.43 ms) and the ADHD On Med group (667.19ms) reacted faster than the ADHD Off Med group (741.06 ms), $p<0.05$(see Figure 1b.), and did not differ from each other.

No significant group effect was found for word reading accuracy. However, there was a significant effect among the groups in color naming accuracy, $F(2, 101) = 3.473$, $p<0.05$, and interference accuracy, $F(2, 101) = 3.082$, $p=0.05$. LSD post hoc tests showed that the Control group made fewer mistakes (was more accurate) than the ADHD Off Med group in color naming (99.81% vs. 98.99%) (see Figure2a.), $p<0.05$, and interference (99.05% vs. 97.51%), $p<0.05$(see Figure 2b.). The ADHD On Med group did not differ from the other 2 groups on these measures.

Test of homogeneity of variance showed that the 3 groups did not have homogeneous variance in word reading RT, $p<0.05$, color naming RT, $p<0.05$, and interference RT, $p<0.05$. The ADHD Off Med group had larger variance than the other 2 groups in Stroop test RTs.

There were 3 outcome variables for each of the 3 problem levels on the Tower of London test; moves above minimum, planning time and total time for each of 3 conditions. A 3(CONTROL vs. OFFMED vs. ONMED) ×3 (3-move vs. 4-move vs. 5-move problems) mixed design ANOVA was used to examine the effects of groups and the difficulty levels of the problems, and the interaction between groups and difficulty level. There were no significant effects among groups or interaction between groups and difficulty levels in moves above minimum, planning time and total time. There was a main effect of difficulty levels in moves above minimum $F(2, 192) = 113.347$, $p<0.001$, planning time $F(2,192) = 8.981$, $p<0.001$, total time $F(2,192) = 182.334$, $p<0.001$. In addition, one way ANOVAs showed no group differences in any of the outcome variables in each difficulty levels separately.

A



B

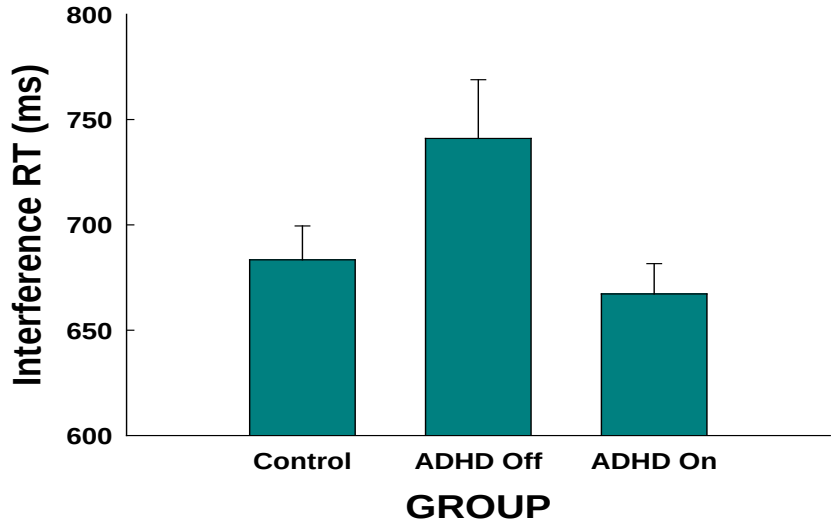
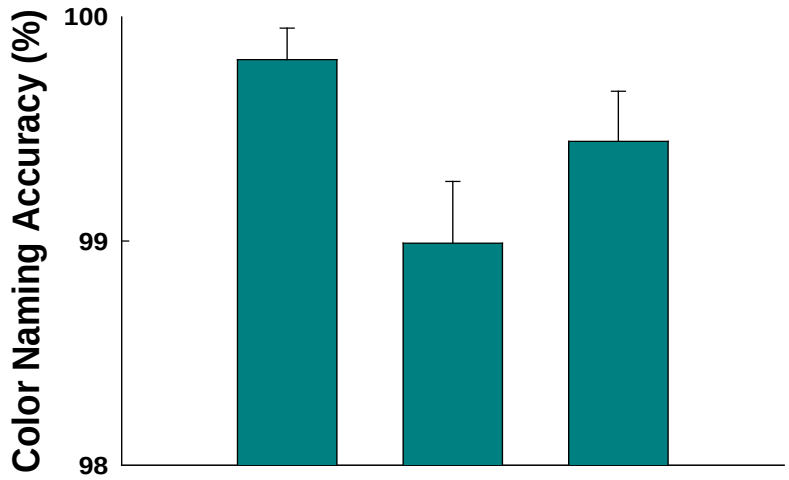


Figure 1

A. Stroop Word Reading RT
ADHD On (Med) group (441.36 ms) reacted significantly faster than ADHD Off (Med) group (479.88 ms), $p<0.05$. The Controls were not different from either of the ADHD groups. Bars represent standard errors of mean.

B. Stroop Interference RT
The Control group (683.43 ms) and ADHD On (Med) group (667.19ms) reacted faster than the ADHD Off (Med) group (741.06 ms), $p<0.05$. Bars represent standard errors of mean.

A



B

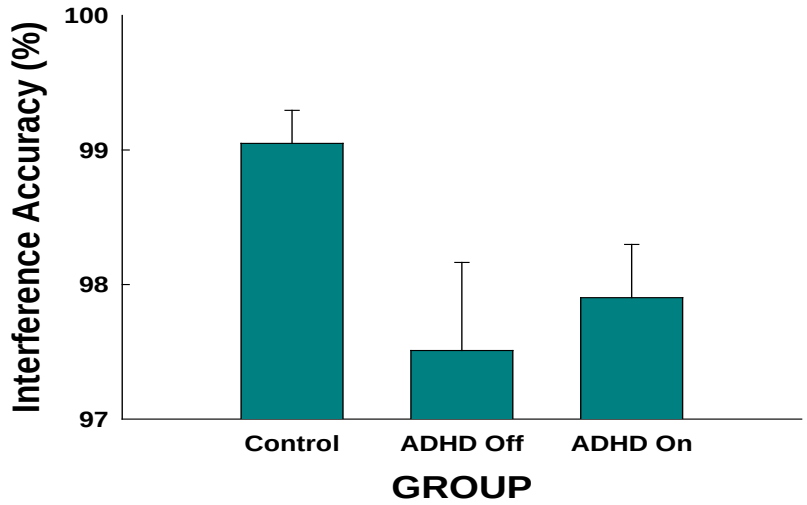


Figure 2

A. Stroop Color Naming Accuracy
Control group (99.81%) made fewer mistakes than the ADHD Off (Med) group (98.99%) in color naming, $p<0.05$. The ADHD On (Med) group did not differ from the other 2 groups. Bars represent standard errors of mean.

B. Stroop Interference Accuracy
The Control group (99.05%) made fewer mistakes than ADHD Off (Med) (97.51%) group in interference, $p<0.05$, and ADHD On (Med) group did not differ from the other 2 groups. Bars represent standard errors of mean.

Discussion

While Attention Deficit Hyperactivity Disorder (ADHD) remains one of the most common neurobiological disorders of childhood, it has been recognized that about 4.5% of adults also meet the criteria for this diagnosis, and, that it persists into adulthood in about two-thirds of children with the condition. Psychosocial difficulties of adults with ADHD have been well-documented, including marital and relationship problems, poor job performance, employment histories, and lower socioeconomic status. Adults with ADHD are less likely to attain the same educational (and occupational) level as those without the diagnosis relative to what would be predicted based on their IQ, and this outcome does not appear to be improved by pharmacotherapy. In one recent study, for example, although 84% of ADHD-diagnosed adults were statistically expected to be college graduates, only 50% reached this level of education (J Biederman, Petty, et al., 2008).

Nevertheless, in recent years there has been a substantial increase in the number of students with ADHD who are attending college. Over 30 years ago, the passage of special education and disability laws enabled a variety of qualified students with disabilities to graduate from college preparatory programs in high schools and enter colleges and universities. Specifically, the Americans with Disabilities Act (1990), the Individuals with Disabilities Education Act (1975) and Section 504 of the Rehabilitation Act (1973), mandated educational accommodation for students with disabilities, and more students with disabilities are now successfully completing high school and attending college. Students with "hidden disabilities," which includes ADHD, have represented the greatest increase. It is difficult to determine the prevalence of ADHD, but the best estimate is that 25% of students getting disability do so because of ADHD, and, that 2 to 8% of the undergraduate population "self-report" ADHD symptoms (Wolf, 2001).

These developments have substantially increased the pharmacological treatment of adults with ADHD, particularly in undergraduate populations (Wilens, et al., 2008). In adults, as with youth, first-line treatment options include the stimulant drugs, usually one of the many formulations of either methylphenidate or amphetamine (Connor & Steingard, 2004; Dodson, 2005; Faraone, Spencer, Aleardi, Pagano, & Biederman, 2004; Koesters, Becker, Kilian, Fegert, & Weinmann, 2008; Wilens, 2003). Predictably, the increase in stimulant prescriptions has resulted in a corresponding escalation of illicit use in college students, confirmed by numerous survey results (Advokat, Martino, & Guidry, 2008; Hall, Irwin, Bowman, Frankenberger, & Jewett, 2005; McCabe, Knight, Teter, & Wechsler, 2005; Teter, McCabe, Boyd, & Guthrie, 2003; Teter, McCabe, Cranford, Boyd, & Guthrie, 2005; White, Becker-Blease, & Grace-Bishop, 2006). Studies consistently show that most students report using stimulant medications, legally or illicitly, to improve academic performance, specifically to increase concentration, organization, and the ability to stay up longer and study (Advokat, et al., 2008; Aldhous, 2006; Blase, et al., 2009; Rabiner, Anastopoulos, et al., 2009a, 2009b; Rabiner, Anastopoulos, Costello, Hoyle, & Swartzwelder, 2009; Rabiner, Anastopoulos, Costello, Hoyle, & Swartzwelder, 2008; Teter, et al., 2005; White, et al., 2006; Wilens, et al., 2008).

Because stimulant medications are known to improve attention, it is understandable that students believe the drugs enhance their ability to study, and that students with self-reported attention difficulties are more likely to become illicit users than others (Rabiner, Anastopoulos, et al., 2009a, 2009b). Nevertheless, only recently has the effectiveness of ADHD medication treatment in students' adjustment to college life been explicitly examined (Rabiner, et al., 2008). Rabiner and colleagues found no difference between the ADHD-diagnosed undergraduates who used stimulant medications and those

who didn't, in regard to self-reported concerns with their academic performance, problems of inattentiveness, hyperactivity, depression or their social life. In other words medication treatment had no discernible effect in the transition to college of students with ADHD. This result was essentially replicated in a follow-up study by this group (Blase, et al., 2009). Students reporting a current ADHD diagnosis had lower GPAs, were more concerned about their academic performance, rated themselves as having higher levels of emotional stress and social concerns and as being less emotionally stable, than students without the diagnosis. Again, there was little evidence that medication improved the quality of life in any of these domains. We have recently confirmed that stimulant medication does not normalize academic achievement of college students with ADHD, and, that the GPA of ADHD-diagnosed college students is significantly reduced if these students have poor study habits, compared to their non-ADHD cohort with the same poor study habits (Advokat, Lane, Luo, 2009, submitted).

It is clear then, that stimulant medications alone do not normalize academic achievement of ADHD students. Although the drugs improve the ability of individuals (even without ADHD) to focus and 'pay attention,' they do not ameliorate the functional impairments responsible for the academic deficit. Even though the core deficit in ADHD involves attention problems, the disorder affects other neuropsychological processes that mediate adaptive cognitive functions. Numerous studies have administered neuropsychological assessments in adults with and without the disorder to try to characterize the cognitive impairments in ADHD. There is much inconsistency in the results of these studies but, on the basis of several reviews of this literature (Frazier, et al., 2004; Hervey, et al., 2004; Schoechlin & Engel, 2005; Woods, et al., 2002), 4 types of functional behaviors appeared to be most commonly used to compare the neuropsychological performance of adults with and without ADHD: 1. tests that specifically assess attention (vigilance); 2. tests of verbal memory/fluency; 3. tests that measure the influence of 'response interference,' (such as the Stroop test, which is believed to provide an index of 'distractibility,'); and 4. tests of 'planning ability,' such as the Tower of London. Although there are many differences across individual studies in o the way various functional deficits are categorized, there is a consistent body of evidence showing that adults with ADHD are impaired, relative to normal adults, on tests of 'vigilance,' 'response interference (Stroop),' in some types of 'verbal memory/fluency' assessments and in some aspects of 'planning ability (Tower of London),' depending on the measures used to analyze the results.

It is interesting that the ADHD Off Med group in our study was diagnosed at a significantly earlier age than the ADHD On Med group. Most of the participants from the Off Med group used to be treated with stimulant medications, and some were still taking medications regularly while others had stopped taking them. One possible reason they gave up medications is that they may have realized the medications might not be helping them much. In fact, in this case, the ADHD On Med group did not have higher college GPAs than the ADHD Off Med group, and all 3 groups in this study had comparable GPAs, about 3.0.

There is not much literature on the effect of stimulant medications on these neurocognitive functions. In brief, results obtained with stimulant medications (which have so far been primarily methylphenidate formulations) show improvement on tests requiring sustained attention, and *perhaps* on verbal fluency, although the outcomes on that measure are mixed. The Stroop test of 'interference' does *not* appear to be improved by stimulants. Performance on the Tower of London 'planning' task also does not seem to be reliably improved by stimulants, although this conclusion may depend on the specific requirements of the particular version that is used, and the time constraints imposed.

On the basis of the literature survey, 4 specific hypotheses were made for the results of this study.

Hypothesis I: Based on evidence from previous research (Barrilleaux & Advokat, 2009; Frazier, et al., 2004; Hervey, et al., 2004; Schoechlin & Engel, 2005; Woods, et al., 2002), we predicted that the OFFMED group would perform worse than the CONTROL group in d2 test; we also predicted that the ONMED group would perform as well as the CONTROL group, and better than the OFFMED group.

In contrast to most of the literature, showing that adults with ADHD are impaired in vigilance tasks, such as the Continuous Performance Test (CPT), we did not find any deficit on the d2 cancellation test. This test was originally developed in Germany 1962, and the first published U.S. version was available in 1998. There are few articles reporting the results of the d2 test in U.S. ADHD populations. Barkley (1997) conducted a preliminary study testing 56 U.S. normal children and 40 U.S. ADHD children aged from 7 to 12, but whether ADHD children were impaired compared to normal children was not clear (Brickenkamp & Zillmer, 1998). A more recent study found that Chinese children diagnosed with ADHD by DSM-IV performed worse than the normal controls on the d2 test (Zhu et al. 2009). An early study showed that ADHD adults were not impaired in a letter cancellation test, a similar version of d2 test (Seidman, Biederman, Weber, Hatch, & Faraone, 1998). Our study is the first to report the results of college students with ADHD on the d2 test. According to the norms for the U.S. college population, the average scores for the d2 test are: TN=527, E1=17, E2=4, CP=201 (Brickenkamp & Zillmer, 1998). All of the 3 groups in our study were in the average range, ranking at about 70%.

Hypothesis II: Based on evidence from previous research (J Biederman, et al., 2008; Müller, et al., 2007), we predicted that the OFFMED group would perform more poorly than the CONTROL group in the Controlled Oral Word Association Test; we also predicted that the ONMED group would perform as well as the CONTROL group, and better than the OFFMED group.

It is often reported that adults with ADHD perform worse than normal adults in verbal fluency, which is usually measured by the Controlled Oral Word Association Test (Frazier, et al., 2004; Hervey, et al., 2004; Schoechlin & Engel, 2005; Woods, et al., 2002). However, our study did not show a deficit in this domain of function in college students with ADHD. According to Ruff et al. (1996), the total number of words beginning with “C” “F” “L” or “P” “R” “W” generated by normal participants (in 60 seconds for each letter) with 13 to 15 years of education is 40.5 ± 9.4 for males, and 39.4 ± 10.1 for females. Our study used the version of “CFL”, and the results of the 3 groups in our study were in the average range (34-45 words).

Nevertheless, our study is not the first to show this lack of verbal fluency deficit in ADHD adults (Barkley, Murphy, & Kwasnik, 1996; Johnson, et al., 2001; K. Murphy, Barkley, & Bush, 2001; Rapport, Van Voorhis, Tzelepis, & Friedman, 2001). The most recent study (Schecklmann, et al., 2008) showed that adults with ADHD not only had normal phonological verbal fluency performance (naming words with a certain category) but were above average in semantic verbal fluency performance (naming words with a certain initial letter). They proposed that ADHD patients might benefit from the symptom of ‘hyperfocusing,’ which was described as intense concentration on interesting and non-routine activities accompanied by temporarily diminished perception of the environment. In addition to hyperfocusing, a second reasonable interpretation is that there might not be an ADHD-related deficit in

verbal fluency after matching for age, gender, education, intelligence and other demographic characteristics.

Hypothesis III: Based on evidence from previous research (Bedard, et al., 2002; J Biederman, et al., 2008), we predict that the OFFMED group will perform more poorly than the CONTROL group in Stroop Test; the ONMED group will perform better than the OFFMED group in color naming and word reading, but not incongruent color naming of color words; the ONMED group will perform as well as the CONTROL group in color naming and word reading, but worse in incongruent color naming of color words.

It is well known that ADHD patients, both children and adults, are impaired on the Stroop interference measure, compared to control populations, with a medium effect size difference (Johnson, et al., 2001; K. Murphy, et al., 2001; Rapport, et al., 2001). Specifically, King et al (2007) showed that unmedicated ADHD adults reacted more slowly and made more mistakes than the control adults on the Stroop interference task. The results of our study are quite consistent with previous studies: the ADHD Off Med group performed more slowly and made more mistakes than the Control group in the measure of Stroop interference.

Biederman et al. (2008) showed, further, that medication did not normalize Stroop interference control in young adults with ADHD. In our study, the Interference RT of the On Med group *was* normalized. Yet, the Interference accuracy of the On Med group, although improved, was still not significantly different from either of the other two groups. Considering the small absolute difference in magnitude, it is surprising that the drugs did not fully eliminate the accuracy deficit along with the RT deficit. It may be speculated that a reduction in RT might be offset by an increase in impulsivity, although this suggestion requires empirical validation.

These inconsistent results about the effect of stimulant medications on interference control between our study and Biederman et al.'s study might also be due to different versions of Stroop tests being used (computerized vs. card Stroop test). Biederman used Golden's Stroop test, in which "participants are required to name as many words as they can in 45s in each card. The outcome variables are the number of items completed for the word card, the color card, and the color-word card, respectively" (Lansbergen, Kenemans, & van Engeland, 2007). In our computerized Stroop test, reaction time and accuracy were recorded trial by trial automatically by computer. In a meta-analysis of Stroop Interference and ADHD, Lansbergen et al. (2007) suggested that computerized versions of Stroop test work more accurately than card versions of Stroop test.

In addition to interference control, there are 2 other measures in Stroop test: word reading and color naming, which are less mentally demanding. Biederman et al. (2008) found that ADHD adults were slower in processing speed as measured by Stroop word and color naming and some other tests. We found that ADHD students were not slower in word reading and color naming compared to the controls; however, stimulant medications improved both, their processing speed and accuracy (of color words).

Hypothesis IV: Based on evidence from previous research (McLean, et al., 2004; Müller, et al., 2007; Young, et al., 2007), both the OFFMED group the ONMED group will perform worse than the CONTROL group; the ONMED group will perform as poorly as the OFFMED group. All participants will perform more poorly as the difficulty levels of the problems increase in Tower of London test.

In our study, there were no differences among the 3 groups in any of the outcome variables of the Tower of London test. Although our result differed from the studies mentioned above, Riccio et al. (2004) and Gropper and Tannock (2009) also did not find a deficit on this test in adults with ADHD. One possible reason for the inconsistencies is that different studies used different versions and different outcome variables of the TOL. For example, the main outcome variables in Young's study were planning time, subsequent execution time, and moves above the minimum for 3-move, 4-move, and 5-move problems separately; McLean used corrected first choice for easy and difficult levels separately; Muller used only 3 outcome variables: time to first movement, time for problem solving, and total time; Riccio used 7 outcome variables, but like Muller, he did not separate difficulty levels. It seems that in Young's study, the ADHD patients did as well as the controls in the 3-move problems, but as difficulty levels increased, ADHD patients tended to demonstrate worse planning than the controls. In our study, the participants completed 9 trials of 3-move problems, then 9 trials of 4-move problems, and finally 9 trials of 5-move problems. It's possible that ADHD participants benefited a lot from the "practice effect" of the 3-move problems. The 4-move and 5-move problems became less challenging, and thus they could do as well as the controls.

A second possible reason leading to mixed results is that different studies might include different percentages of male and female participants, and ADHD subtypes. For example, the majority of ADHD participants were males in Young's (77%) and McLean's (79%) studies, while only 42% were males in our study. Males were more likely to be diagnosed with the hyperactive/impulsive and the combined subtypes, while females were more likely to be diagnosed with the inattentive subtype. Young suggested lack of planning in ADHD adults was associated with impulsivity in her study. Since the majority of ADHD participants in our study were the inattentive type, they might suffer less impulsivity symptoms, and thus performed better in Tower of London test.

Conclusion

In brief, our results showed that undergraduate students with ADHD did not show significant deficits in most of the outcomes of the 4 neuropsychological tests in our study, compared to normal students. Undergraduate students with ADHD were not impaired in simple attention, verbal fluency, and planning ability relative to the control cohorts. The only statistical differences among the 3 groups occurred in the Stroop Test: ADHD students without medication performed worse than normal students in interference control. Medications improved interference control in ADHD students; however, medications did not help ADHD students perform better than normal students in domains of functions where no deficits were found.

It is possible that the ADHD group would have shown more impairment if the neuropsychological tasks were made more difficult. As noted by Frazier, Youngstrom, Glutting and Watkins, (2007), "…there is reason to believe that outcomes obtained with children and adolescents with ADHD may not hold for college students. College students with ADHD are likely to have (a) higher ability levels, (b) greater academic success during primary and secondary school, and (c) better compensatory skills than individuals with ADHD from the general population. College students with ADHD also experience a different set of stressors than young adults with the condition who do not seek postsecondary training…college students with ADHD may constitute a distinct subset of individuals with the disorder" (p. 54).

Nevertheless, even when research shows that ADHD-diagnosed college students do have significantly lower GPAs than normal control students, this difference is not eliminated by stimulant medications. The question remains, why? The most consistent neuropsychological deficit reported in the adult ADHD literature is on the Stroop test, particularly in the interference score. This is usually interpreted to mean that the impaired group is more 'distractible,' which would be consistent with a condition defined by an attention deficit. Yet, the absolute difference between the ADHD and normal subjects on this task is relatively modest, and, it is difficult to attribute the consistent deficit in academic achievement of ADHD-diagnosed college students simply to greater 'distractibility.'

At the same time, however, the 'interference' impairment is not eliminated by stimulant medications. This raises the question of whether or not the stimulant medications might themselves produce some functional impairment that limits the benefit they might offer for cognitive enhancement. There was no evidence in the present study that stimulants worsened any of the outcome measures. But, it has been suggested that stimulants might produce a 'cognitive toxicity,' that constricts flexibility of thinking, and that this might be a factor in the poor academic outcomes of children with ADHD (Gadow, 1983). Recently, Farah.et al. (2009) has shown that amphetamine does not reduce 'creativity' at least as assessed by neuropsychological tests in adults. But, the issue of possible stimulant-induced cognitive impairrment has not been systematically studied, and might be worth exploring in the future.

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