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## A META-ANALYSIS OF PRESCRIPTION STIMULANT EFFICACY: ARE STIMULANTS NEUROCOGNITIVE ENHANCERS?

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A META-ANALYSIS OF PRESCRIPTION STIMULANT EFFICACY: ARE  
STIMULANTS NEUROCOGNITIVE ENHANCERS?

BY

MARISA E. MARRACCINI

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE  
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2015

DOCTOR OF PHILOSOPHY IN SCHOOL PSYCHOLOGY

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## ABSTRACT

Prescription stimulant use for neurocognitive enhancement is a significant problem among college students with and without ADHD. The primary reason students report misusing stimulant medication is to enhance academic functioning. Given that increasing numbers of students are misusing prescription stimulants, it is critical to explore whether empirical findings support neurocognitive benefits of prescription stimulants. Hence, the primary purpose of this meta-analytic study was to examine the potential effects of prescription stimulants on cognitive functioning of adults with and without ADHD. A systematic search and retrieval process resulted in the calculation of effect sizes from 91 studies. Fourteen meta-analyses were conducted across three levels of constructs, ranging in scope from broad to narrow. Findings indicated significant, but small effect sizes for cognition ( $g = 0.15$ ), as well as the broad cognitive constructs of abilities of focused behavior ( $g = 0.14$ ), learning and memory ( $g = 0.10$ ), and executive function ( $g = 0.13$ ). Small effect sizes were also revealed for the narrow cognitive constructs of inhibitory control, working memory, processing speed, declarative learning and memory, and self-regulation. Effects were the greatest for declarative long-term memory ( $g = 0.50$ ) that was assessed 1 to 7 days following drug administration and learning, suggesting that ADHD medication may proffer academic benefits for college students. Studies investigating the effects of ADHD medication on measures of non-declarative memory and planning and decision-making, however, resulted in effect sizes that approached zero. Furthermore, 23 variables (e.g., study design, participant characteristics, medication type) were assessed as potential moderators, but the majority of analyses did not reveal significant differences between outcomes. Of particular note, differences between the

neurocognitive effects of ADHD medication on adults with and without ADHD were not supported. These findings suggest that ADHD medication may indeed act as a neurocognitive enhancer, but only for specific domains of cognition. Considering that college students are already engaging in illegal use of prescription stimulants for academic enhancement, as well as the potential for stimulant misuse to have serious side effects and adverse outcomes, these results point to the glaring need for public policy concerning the misuse of prescription stimulant medications.

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## **DEDICATION**

For Violet

“Because you are alive, everything is possible.”

Thích Nhất Hạnh

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## **CHAPTER 1: BACKGROUND**

### **Statement of the Problem**

The efficacy of prescription stimulant and prostimulant medications for the reduction of Attention-Deficit/Hyperactivity Disorder (ADHD) symptomatology among adults and children has been well documented through clinical trials and meta-analyses (Faraone, 2012; Faraone & Biederman, 2002; Faraone & Buitelaar, 2010; Faraone and Glatt, 2010). Prescription stimulant use for cognitive enhancement, however, as opposed to ADHD symptom management, is a growing problem among college and non-college students with and without ADHD (Babcock & Byrne, 2000; Dupont, Coleman, Bucher, & Wilford, 2008; Dussault & Weyandt, 2013; Hall, Irwin, Bowman, Frankenberger, & Jewett, 2005; Janusis & Weyandt, 2010; Judson & Langdon, 2009; Low & Gendaszek, 2002; McCabe, Knight, Teter & Wechsler, 2005; Novak et al., 2007; Pilkinton & Cannatella, 2012; Rabiner et al., 2009; Verdi, Weyandt, & Zavras, 2014; Weyandt et al., 2009; Weyandt et al., 2013a). Given the consistent finding that college students report enhancing academics as their primary reason for misusing stimulant medication (Advokat, Guidry & Martino, 2008; Bossaer et al., 2013; DeSantis, Noar & Webb, 2008; Garnier-Dykstra et al., 2012; Habibzadeh et al., 2011; Rabiner et al., 2009; Teter et al., 2005; White et al., 2006; Weyandt et al., 2009), and adults with ADHD have indicated productivity as a motivation for stimulant misuse (Novak et al., 2007), it is important to examine the potential effects of prescription stimulant medications on cognitive enhancement. While two reviews have assessed the effect of prescription stimulants on cognition in adults with and without ADHD, and have concluded that the effects of stimulant medications on

cognitive enhancement vary according to population and task (Advokat, 2010; Smith & Farah, 2011), these reviews relied on studies that were underpowered and varied in design, potentially impeding comparisons across studies. Indeed, Smith and Farah (2011) stated that although larger clinical studies assessing the cognitive effects of stimulants are warranted, such studies are unlikely to be funded given “cognitive enhancement falls between the two stools of research funding” (i.e., disease-oriented and pharmaceutical funders) (p. 736). Additionally, in their meta-analysis examining prescription stimulant efficacy for ADHD symptoms, Faraone, Biederman, Spencer, and Aleari (2006) reported that comparing effect sizes and results across prescription stimulant studies without using statistical techniques to account for study differences (e.g., meta-analysis) would result in biased conclusions. Therefore, a meta-analysis examining the efficacy of prescription stimulant medications for cognitive enhancement in adults with and without ADHD, accounting for medication type, medication dose and study design, would greatly contribute to the literature.

To date, no systematic meta-analyses concerning ADHD medication for neurocognitive enhancement including adults with and without ADHD have been conducted. Furthermore, previous meta-analytic studies (Ilieva, Hook, & Farah, 2015) have only explored the effects of amphetamine (AMP) and methylphenidate (MPH) on working memory, episodic memory and inhibitory control, but no studies have conducted meta-analyses concerning the effects of ADHD medication on the cognitive behaviors related to vigilance, processing speed, non-declarative memory, planning and decision-making, or self-regulation. Findings from such a study will provide important implications for the use and misuse of prescription stimulants as a “smart

pill” (Smith & Farah, 2011, p. 717) for adults seeking to enhance their cognitive functioning and college students hoping to improve their academic outcomes. Therefore, this meta-analytic study will examine whether prescription stimulants play a role in multiple domains of cognitive functioning of adults with and without ADHD. The primary hypothesis is that prescription stimulant and prostimulant medications will demonstrate general positive effects on cognition among adults with and without ADHD. Secondary hypotheses are that the greatest benefits will be found for a) samples of adults receiving the highest stimulant and prostimulant doses, b) samples of adults within studies that time the administration of stimulant and pro-stimulant medication to peak during learning, c) samples of adults with lower cognitive baseline functioning, and d) samples that include adults with ADHD.

### **Attention-deficit/hyperactivity disorder (ADHD)**

Attention-deficit hyperactivity disorder (ADHD) is a childhood-onset neurodevelopmental disorder characterized by clinical levels of inattention, impulsivity, and/or hyperactivity (American Psychiatric Association, 2013) with genetic, environmental, and biological bases (Biederman, 2005; Weyandt, 2006). Although symptoms of ADHD were previously believed to attenuate by adulthood, studies examining adults with ADHD have demonstrated that clinical levels of inattention, impulsivity, and hyperactivity may persist into adulthood for a majority of individuals (Biederman, 2005; Faraone et al., 2000; Wilens, Faraone, & Biederman, 2004). In particular, symptoms of ADHD in adults may manifest as internal restlessness, difficulty with relaxation, excessive talking, excessive fidgeting, and difficulty with sitting for long periods (Kooij et al., 2010; Weyandt, et al., 2003;

Weyandt, Hays & Schepman, 2005). Prevalence rates of ADHD have been estimated to approximate 5% among children and adolescents and between 2.5 and 4% among adults (American Psychiatric Association, 2013; Kessler et al., 2006). Negative long-term consequences, such as school dropout, lower likelihood of college completion, and decreased levels of work productivity and performance, have been associated with ADHD (Adamou et al., 2013; Barkley et al., 2002). Furthermore, college students with ADHD have demonstrated impaired neuropsychological, social, emotional, academic and psychological functioning compared to college students without ADHD (Weyandt et al., 2013b).

### **Pharmacotherapy Treatment for ADHD**

Recommended treatment of ADHD in adults is similar to that of children, involving a multimodal approach including psycho-education, pharmacotherapy, coaching, cognitive behavior psychotherapy, and/or family therapy (Kooij et al., 2010). First-line psychopharmacotherapy treatments for adults with ADHD include approximately ten types of stimulant medications, such as long acting oros-methylphenidate, mixed amphetamine salts (MAS), and dexamethylphenidate (d-AMP), as well as lisdexamfetamine dimesylate (LDX), a prostimulant (Kooij et al., 2010). The most commonly prescribed stimulant medications among adults, however, include methylphenidate (MPH), with trade names of Ritalin or Concerta, and amphetamine (AMP), generally prescribed in the form of MAS composed of d-AMP, with the trade name of Adderall (Arnold, 2000; Heal, Cheetham & Smith, 2009; Smith & Farah, 2011). Specifically, MPH and MAS have been estimated to make up 34.5% and 43.4% respectively of ADHD medication prescriptions for adults (Castle et al.,

2007). Additional pharmacotherapies include non-stimulant medication, such as atomoxetine (ATX), which potentially has a lower abuse potential given its chemical structure. ATX is a selective inhibitor of norepinephrine (NE) (or noradrenaline) transporters and is believed to increase dopamine (DA) and NE concentrations in the prefrontal cortex (PFC) (Marquand et al., 2011; Swanson et al., 2006). Nonstimulant medication, as well as medications such as long-acting bupropion, modafinil, and guanfacine, may be effective for patients unresponsive to stimulants or who have conditions that contraindicate stimulant use (e.g., cardiac conditions, addiction) (Kooij et al., 2010).

All of the catecholaminergic stimulant medications approved by the FDA for use by adults with ADHD contain either MPH or AMP (Weisler & Childress, 2011). Although stimulants as a class are believed to enhance neurotransmission of both DA and NE throughout the central nervous system, the underlying mechanisms of action vary according to stimulant type and are not completely understood (Arnold, 2000; Faraone & Buitelaar, 2010; Heal et al., 2009; Weyandt, 2006). For instance, some studies suggest that MPH blocks DA transporters, with higher doses resulting in higher occupancy of DA transporters (Volkow et al., 1998) and does not involve other presynaptic activity (Arnold, 2000). AMP, however, is thought to increase the release of DA and NE, in addition to blocking DA reuptake (Arnold, 2000; Weisler & Childress, 2011). LDX also results in increased DA and NE neurotransmitters and blocking of DA reuptake because it is a long-acting prodrug that when absorbed into the bloodstream is hydrolyzed into d-AMP and L-lysine, a naturally occurring amino acid (Heal et al., 2009; Pennick, 2010; Rowley et al., 2014). Limited by their half-life,

short-acting agents last between two to five hours and long-acting agents may last between six and 12 hours; therefore, in adults, a combination of both immediate and extended release stimulants may best help control symptoms of ADHD throughout a 12-16 hour day (Weisler & Childress, 2011). Stimulant medications, e.g., MPH, are believed to improve ADHD symptoms because of their effects on the catecholaminergic neurotransmission in fronto-subcortical circuits that are associated with cognitive processes, such as goal-driven behaviors, attentional processes, and response inhibition (Britton, 2012; Weyandt, 2006).

### **Efficacy of Prescription Stimulant and Prostimulant Medication**

#### **ADHD Symptoms**

While the efficacy of pharmacotherapy for the reduction of ADHD symptoms has been clearly established among samples of children and adolescents with ADHD, fewer studies have examined effects among adults (Wilens et al., 2004). Still, a plethora of studies demonstrating the positive effects of both stimulant and prostimulant medications with adult populations exist (e.g., Adler et al., 2008; Adler et al., 2009; Bouffard, Hechtman, Minde, & Iboni-Kassab, 2003; Faraone, 2012; Jain et al., 2007; Kooij et al., 2004; Spencer et al., 2005; Spencer et al., 2007; Spencer, Adler, Weisler, & Youcha, 2008; Stein et al., 2011; Weisler et al., 2006). A recent meta-analysis conducted by Faraone and Glatt (2010) revealed that both short-acting and long-acting stimulants yielded greater effects for the improvement of symptoms related to ADHD compared to the effects of non-stimulants (e.g., ATX, Bupropion, and Modafinil).

## **Cognition**

High school students with ADHD have been found to be less likely to graduate, less likely to attend and graduate from college, and perform worse academically than students without ADHD (Adamou et al., 2013; Advokat, Lane, & Luo, 2011; Barkley et al., 2002; Barkley, Fischer, Edelbrock, & Smallish, 1990; Bussing et al., 2012; Faraone et al., 1993). Although deficits in academic performance are associated with behavioral tendencies such as disruptive behavior, inattention, and difficulty remaining seated (Barkley, 2006; Danforth, Connor, & Doerfler, 2014; Faraone et al., 1993), deficits in cognitive functioning are often assumed to be precursors to symptoms of ADHD (although some researchers are criticizing this assumption) (Coghill et al., 2013). In fact, improvements in cognition, defined as multiple processes of knowing that involve attention, memory and reasoning (Gerrig & Zimbardo, 2014), are generally a *perceived* benefit of stimulant medication by stimulant misusers (DeSantis et al., 2008; Rabiner et al., 2009).

**Children, Adolescents, and Adults.** Studies and reviews examining the cognitive effects of prescription stimulant medication on children and adolescents have suggested these medications may indeed act as neurocognitive enhancers in some domains of cognition, although with only modest effects. Coghill and colleague's (2013) recent review and meta-analysis examined the effects of MPH on cognitive functions in children and adolescents with ADHD and found that MPH showed small to moderate positive effects compared to placebo for memory, reaction time, reaction time variability, and response inhibition. Results were based on findings from 36 studies using psychometrically sound instruments to measure executive and

nonexecutive neurocognitive outcomes. Furthermore, Repantis and colleagues (2010) conducted a systematic meta-analysis examining the effects of MPH and Modafinil for neuroenhancement among healthy children, adolescents and adults and found a positive effect of MPH for memory, but not for attention, mood, or executive function (Repantis et al., 2010). Furthermore, one review (Weyandt et al., 2013a) found overall improvements related to attention, impulsivity, memory and response inhibition for children and adults with ADHD. Most recently, in their systematic review of the effects of prescription stimulants and stimulant misuse among adolescents and adults, Weyandt et al. (2014) found that prostimulants associated with improvements in executive function tasks and some domains of cognition for college students and adults, including performance productivity in adults between the ages of 18 to 45.

**Adults.** Regarding the potential for ADHD medication to be used as a cognitive neuroenhancer for adults specifically, two reviews have reported mixed findings related to the effects of prescription stimulant medication on cognition among adults with ADHD (Advokat, 2010) and without ADHD (Advokat, 2010; Smith & Farah, 2011). Additionally, one meta-analysis (Ilieva et al., 2015) suggests that MPH and AMP may have small effects on cognition in healthy adult populations.

In their review on the effects of stimulant medications on cognition, Smith and Farah (2011) concluded that stimulant medication may have positive effects on learning for healthy adults between the ages of 18 and 45. Cognitive effects were assessed via both declarative and non-declarative learning tasks, with effect sizes ranging from small to large. The findings related to other components of cognition from Smith and Farah's review, however, were mixed. Specifically, studies examining



effects on working memory demonstrated mixed results, with significant findings ranging from small to large effects. Studies examining cognitive control, i.e., cognitive processes involving the resisting of impulses, yielded more null findings than significant findings, yet the reported effect sizes were generally large, with greater enhancement for individuals performing worse prior to treatment.

Advokat (2010) reported similar results in a review of studies examining the effects of MPH and AMP on cognition in children and adults with and without ADHD. Specifically, Advokat reported that while studies exploring the effects of stimulants on cognition generally demonstrated improvements in focused attention among adults without ADHD, a *worsening* of selective attention and distractibility may occur as evidenced by increased errors on tests of cognitive flexibility and set-shifting (e.g., IDED, WCST) (Dyme et al., 1982; Rogers et al., 1999), as well as decreased response latencies (i.e. increased impulsivity) (Dyme et al., 1982; Elliott et al., 1997). Advokat concluded that although short-term acquisition does not improve and may actually be worsened by prescription stimulants, when prescription stimulants are acting during a period of memory consolidation they may improve long-term retention of information among adults without ADHD. These positive effects on memory acquisition, however, may differ according to baseline functioning (i.e., those with lower functioning may benefit more). Unfortunately, the effects of stimulants may also impede other types of performance requiring ‘cognitive flexibility,’ perhaps because of increased arousal leading to more impulsivity in individuals with higher baseline performance compared to individuals with lower baseline performance (Advokat, 2010, p. 1262). Among adult samples with ADHD, Advokat reported that

prescription stimulants have led to improvements in sustained attention (e.g., Barrilleaux and Advokat, 2009; Wilson, Cox, Merkel, Moore, & Coghill, 2006) and positive effects on verbal memory performance over 3-6 months (Kurscheidt et al., 2008). Advokat (2010) noted, however, that some studies have reported inconsistent and null effects from prescription stimulants on tests of distractibility, i.e., interference in reaction time, and planning.

A recent meta-analysis (Ilieva et al., 2015) investigating prescription stimulant effects on inhibitory control, working memory, and episodic memory supported many of the conclusions drawn by Advokat (2010) and Smith and Farah (2011). Specifically, Ilieva et al.'s findings revealed significant, but small effects of AMP and MPH on inhibitory control, working memory, and short-term episodic memory, as well as moderate effects on delayed episodic memory. The latter finding, however, was qualified with an indication for publication bias, leading the researchers to conclude these larger effects may not be an accurate representation for delayed episodic memory.

Although there is evidence that healthy individuals perceive cognitive enhancement and may receive small, but significant cognitive benefits from taking prescription stimulant medications, a number of alternative reasons may explain their self-perceived and small effects of enhanced cognition; i.e., placebo effects, altered perception of quality of work, or enhanced energy and motivation to improve productivity (Hildt, Lieb, & Franke, 2014; Ilieva et al., 2015; Smith & Farah, 2011). Furthermore, limitations related to study designs (e.g., insufficient power to detect statistical significance, poor psychometric properties of outcome measures, doses of

medication that are too low to proffer effects) likely contribute to the mixed findings of prescription stimulant effects on cognition. A systematic meta-analysis examining individual components of cognition in addition to memory and inhibitory control, taking into account variability across studies, will help to elucidate whether and how prescription stimulants play a role in cognitive functioning of adults.

### **Stimulant Misuse**

The research examining the efficacy of stimulant medication among populations with ADHD is relatively clear regarding reductions in ADHD symptoms, but less clarity exists regarding cognitive effects. Yet, non-medical stimulant use, which involves using prescription stimulant medication for reasons outside the scope of a prescription (Weyandt et al., 2013a), is a growing problem among college students who report misusing stimulants primarily to enhance academic functioning (e.g., Bossaer et al., 2013; Garnier-Dykstra et al., 2012; Verdi et al., 2014; Weyandt et al., 2013a). Weyandt and colleagues (2013a; 2014) conducted systematic reviews of stimulant misuse among college students and found the most common reasons students reported engaging in stimulant misuse related to increased concentration, studying, and performing well on tests. In fact, students engaging in stimulant misuse have reported perceiving enhanced cognition (DeSantis et al., 2008; Rabiner et al., 2009) and shown less concern towards the ethical and safety ramifications of stimulant misuse (Judson & Langdon, 2009).

Stimulant misuse is especially concerning given both AMP and MPH are classified as a schedule II drug by the FDA, indicating these drugs have a high potential for abuse that could lead to physiological and/or psychological dependence

(Kollins, 2007; Weyandt et al., 2014). Furthermore, numerous studies have reported on the extensive side effects and potential for adverse outcomes related to ADHD medication, including insomnia, appetite loss and anorexia, emotional lability, abdominal cramps, nausea and vomiting, dizziness, and nervousness, as well as changes in blood pressure and heart rate (Heal & Pierce, 2006; Weyandt et al., 2014). It is encouraging to note, however, that findings from a recent study hold promise for a brief expectancy challenge intervention to weaken positive cognitive enhancement expectancies (Looby, Young, & Earlywine, 2013).

Unfortunately, college students and adults are engaging in non-medical prescription stimulant use and misuse at alarmingly high rates, with lifetime prevalence rates ranging from between 5 and 55% among college students and 7 and 29% among adults outside of the college setting (Weyandt et al., 2013a; Weyandt et al., 2014). Therefore, researchers (e.g., Weyandt et al., 2013a) have called for more studies examining the cognitive effects of prescription stimulants among adults without ADHD. College students with ADHD, however, should not be overlooked because these students may be more susceptible to stimulant misuse and diversion than students without ADHD (Weyandt et al., 2014). Therefore, research examining the neurocognitive effects of prescription stimulants among students with ADHD is warranted.

## **CHAPTER 2: Cognitive Constructs and Measures**

Cognition refers to the functional behavior of information-handling (Lezak, Howieson, Bigler & Tranel, 2012); however, prescription stimulants for neuroenhancement of cognition may refer to a variety of underlying constructs of cognition. Major classes of cognitive function have been described by Lezak and colleagues (2012) to include receptive functions, learning and memory, thinking, and expressive functions, all of which may be separated according to verbal and nonverbal functions. There are numerous neurocognitive instruments designed to test these major areas of cognition. Tests of abilities of focused behavior, learning and memory, and executive function are among some of the most common assessments of cognition (Lezak et al., 2012) that have been used to measure ADHD medication for neurocognitive enhancement. The following section provides a description of these constructs, as well as common tests designed to assess them. It is important to note, however, that these constructs overlap, as do the instruments designed to measure them. Even within each instrument, specific measures may represent varying cognitive constructs. For example, a Continuous Performance Task (CPT) may provide a measure of both commission errors and omission errors – the former measure may primarily capture the construct of sustained attention, while the latter measure may primarily capture inhibitory control. Therefore, the following review, which includes the most commonly reported cognitive constructs, instruments, and measures in the literature concerning ADHD medication and cognition, should be interpreted as an overall guide for understanding measurement of cognition.

## **Abilities of Focused Behavior**

Abilities of focused behavior involve vigilance (sustained attention and inhibitory control), processing speed, and working memory, all of which rely on speed of processing within a time-limited capacity and regulate the activity of cognitive functions (Lezak et al., 2012). Although these behaviors work in concert, specific measures have been developed to target attention, processing speed, and working memory separately (Lezak et al., 2012).

### **Vigilance and Inhibitory Control**

Vigilance, which involves sustained or focused attention (Lezak et al., 2012), is an essential component for human performance (Finomore, Matthews, Shaw & Warm, 2009). Tests of vigilance often involve the detection of a predetermined target among the presentation of sequential stimuli occurring over a period of time and sometimes require participants to ignore competing stimuli (Lezak et al., 2012). This latter requirement has also been used as a measure of inhibitory control or impulsivity by requiring participants to inhibit a response often related to a distractor target.

Inhibitory control has been defined as the ability to “override dominant, or habitual, automatic responses for the sake of implementing more adaptive, goal-directed behaviors” (Ilieva et al., 2015, p. 3). A similar, but related construct is selective attention, which refers to the ability to attend to a prioritized stimulus while simultaneously ignoring competing input and information that is irrelevant (Buehner, Mangels, Krumm & Ziegler, 2005; Repantis et al., 2010). Three different components of inhibition have been proposed by Friedman and Miyake (2004) that include prepotent response inhibition, resistance to distraction, and resistance to proactive

interference. In a recent meta-analysis examining the performance within Go/No-go tasks, Wright and colleagues (2014) identified two commonly measured components of inhibitory control: cancellation, i.e., stopping a response that is already underway and withholding, i.e., stopping a prepared but uninitiated response. Withholding can be measured with go/no-go tasks, including continuous performance tasks using a go/no-go framework (Wright et al., 2014).

Instruments commonly used to assess vigilance and/or inhibitory control include anticacades tasks, Digit Vigilance, Flankers task, general Go/No-Go tasks, Rapid Visual Information Processing (RVIP), Stroop tasks, and the Stop-Signal Task (Ilieva et al., 2013; Lezak et al., 2012; Llorente et al., 2001; Silber, Croft, Papafotiou, & Stough, 2006; Turner, Blackwell, Dowson, McLean, & Sahakian, 2005; Wright et al., 2014). Outcome measures within these tasks may either capture vigilance or inhibitory control. For example, measures of error of omission may best capture sustained attention while measures of errors of commission may be best used to assess inhibitory control (Lezak et al., 2012).

**Antisaccades.** Antisaccade tasks, which are usually paired with prosaccade or predictive saccade tasks, require participants to fixate on a central target that moves in opposite directions of the fixation point. While predictive saccades require participants to follow the same direction of the target moving in a predictable manner, antisaccade tasks require participants to generate a saccade in the opposite direction of the pseudorandomised moving target, i.e., inhibiting their response to look at the target (Allman et al., 2010). Predictive saccade tasks are commonly used as estimates of motor planning and temporal processing and antisaccade tasks are used as measures of

response inhibition (Allman et al., 2012). Error rates for antisaccade tasks have been found to be elevated among some children with ADHD (Rommelse et al., 2008).

**Digit Vigilance.** A measure of sustained attention, Digit Vigilance is a subtest of the Cognitive Drug Research (CDR) battery, which is a computerized neuropsychological battery developed for the use with drug development research (Gualtieri, 2004; Silber et al., 2006). The task requires respondents to press a key each time they view a target digit. Outcome measures for Digit Vigilance include accuracy, reaction time, and commission errors (Silber et al., 2006).

**Flanker.** Flanker tasks present participants with images of congruent and incongruent target items, requiring participants to identify the direction of the target item as quickly as possible. The original standard Eriksen Flankers task required participants to respond to a central letter of a congruent or incongruent string of letters in which participants were instructed to make directional responses associated with specific letters (de Bruijn et al., 2004; 2005; Servan-Schreiber et al., 1998). More recent versions have used images of five horizontally aligned arrows in place of letters, requiring participants to identify the direction of the central arrow as quickly as possible (Ilieva et al., 2013). Congruent trials present arrows that are all pointing in the same direction and incongruent trials present arrows pointing in different directions, where the central arrow is pointed in the opposing direction to the peripheral arrows (Ilieva et al., 2013). Outcomes of Flanker tasks are usually measured with response error and Response Time (RT). Further, a specific measure of inhibition cost has been calculated by dividing the median RT of incongruent trials by the median RT of congruent trials (Ilieva et al., 2013).



**Go/No-Go.** Go/No-go tasks require participants to respond as quickly and accurately as possible to a series of signals that reinforces a response tendency to these signals (go-signals). Within a portion of subtest trials, participants must inhibit this response tendency in response to a different signal (no-go signal) (Wright et al., 2014). There are numerous versions of go/no-go tasks, varying according to type of stimuli (visual, auditory, etc.) (Wright et al., 2014). Three different versions of Go/No-go tasks are described below, including the Continuous Performance Test (CPT), the Sustained Attention to Response Test (SART), and Test of Variables of Attention (TOVA).

CPT instruments are designed to measure sustained attention or vigilance and behavioral inhibition or impulsivity and have been shown to be sensitive for the measurement of drug treatment effects (Connors, 2000; DuPaul et al., 2012; Spreen & Strauss, 1998). The CPT was initially developed by Rosvold, but the most common version currently used is Connor's CPT (Lezak et al., 2012; Spreen & Strauss, 1998). The computerized version of Connor's CPT requires the user to press a specified key every time they see a letter other than X appear on the screen (DuPaul et al., 2012; Lezak et al., 2012; Spreen & Strauss, 1998). Other versions of the CPT follow a similar format to Connor's CPT, varying by visual or auditory modality, all of which yield similar data for evaluation (omissions, commissions, interstimulus interval, measures of sensitivity –  $d'$ , and response criterion –  $\beta$ ) (Spreen & Strauss, 1998).

The SART is also a type of continuous performance task. It requires respondents to press keys when presented with frequent non-target digits and to withhold from pressing keys when presented with the less frequent target digits

(Robertson, Manly, Andrade, Baddeley, & Yiend, 1997; Sofuoglu, Waters, Mooney, & Kosten, 2008). Error scores on the SART may indicate impairments in sustained attention considering they are associated with a “drift” from controlled processing into automatic responding (Sofuoglu et al., 2008). Some of the primary outcome measures from the SART may include commission errors, omission errors, and reaction time (Sofuoglu et al., 2008).

Finally, the TOVA is a visual CPT that requires participants to discriminate between a predetermined target among nontargets (Agay, Yechiam, Carmel, & Levkovitz, 2014). The first half of the test is similar to other CPTs, requiring attention sustained over time and primarily measuring omission errors (i.e., inattention). The second half of the test, however, is similar to a fast paced Go/No-Go task and requires participants to respond quickly without making errors of commission (i.e., inhibiting responses) (Llorente et al., 2001).

**RVIP.** A subtest within the CANTAB (Cambridge Cognition, 2015), one of the most well known computerized neurocognitive batteries (Gualtieri, 2004), the RVIP task requires respondents to respond to infrequent three-digit sequences among serially presented digits (Turner et al., 2005). Between 2 to 9 digits are presented at a rate of 100 digits per minute for 10 minutes in a pseudo-random order (Cambridge Cognition, 2015; Whiting et al., 2008). Digits are shown in a white box in the center of a computer screen. Outcome measures may include target sensitivity (A') and response bias (B'), as well as mean latency (Turner et al., 2005).

**Stroop Tasks.** Cognitive research indicates that it takes more time for people to state the names of color blocks than it does to read color words, and it takes even

more time for people to state the names of color words embedded in opposing (incongruent) color blocks (Lezak et al., 2012). The latter finding has been attributed to problems with response conflict, inhibitory control and selective attention, making it an effective measure of focused attention and executive function (Lezak et al., 2012). Therefore, Stroop tasks require participants to read aloud from a list of words presented in three varying formats: a list of words (colors) presented in black ink, a list of colored bars or blocks, and a list of words (colors) presented in an incongruent color (Lezak et al., 2012; Taylor & Russo, 2000). The number of trials, items, and colors included in the task vary among research studies and outcome measures may include time, error, and/or the number of items read in a specified duration of time (Lezak et al., 2012).

**Stop-Signal.** The Stop-signal task typically provides a measure of inhibitory control related to cancellation, or the stopping of a response that is already underway (Wright et al., 2014). Participants are trained to respond to a Go-trial and to inhibit their responses in the No-Go trials (Nandam, Hester, & Bellgrove, 2014). Stop-signal tasks vary according to stimuli and tasks. For example, Nandam et al. (2014) used a Stroop Task to test inhibitory control with the stop-signal format and Aron, Dowson, Sahakian, & Robbins (2003) used pointing arrows similar to a Flankers task that the researchers termed a “tracking” stop-signal task. Outcome measures used to measure inhibitory control may include RT for no-signal trials, discrimination errors, the 50% inhibition threshold (calculated by subtracting the stop-signal delay from the Mean RT), and the intraindividual coefficient of variation (ICV), a measure of response

variability calculated by dividing the standard deviation of the Go RT by the Mean RT (Aron et al., 2003; Nandam et al., 2011).

### **Processing Speed**

Processing speed typically refers to the amount of time required to make an accurate judgment of a stimulus (Cella & Wykes, 2013; Owsley, 2013) and is usually measured by simple tests of response time (Lezak et al., 2012). More complex tasks of attention, such as symbol substitution tests, involve visual scanning, motor persistence, sustained attention, response speed, and visuomotor coordination (Lezak et al., 2012) and are also commonly conceptualized as tests of processing speed. Some of the tasks used for the assessment of visual processing speed may include the detecting of a target's presence, target discrimination, target recognition, and locating a target according to its spatial location (Owsley, 2013). Common measures of processing speed include the Digit Symbol Substitution Test (DSST), Simple Reaction Tests (SRT), Choice Reaction Tests (CRT), and the Trail-Making Test (trail A; TMT-A) (Litchenberger & Kaufman, 2009; Repantis et al., 2010; Sánchez-Cubillo et al., 2009).

**Simple Reaction Tests and Choice Reaction Tests.** SRTs require participants to respond to one sensory stimulus, while CRTs require participants to respond to multiple sensory stimuli (Repantis et al., 2010). The Stimulus Evaluation Response Selection (SERS) task, which involves a stimulus and response pattern, encompasses an SRT and CRT. For the SERS easy task, which is analogous to an SRT, the respondent must press the same key each time an X appears without any distractors on the screen. For the hard task, similar to a CRT, the respondent must select a key

related to the location of the X, which appears embedded in four stars (Halliday, Callaway, Naylor, Gratzinger, & Prael, 1986; Naylor, Halliday & Callaway, 1985).

**DSST.** Completed with paper and pencil, the DSST measures attention, motor performance, response speed and visuomotor coordination (Silber et al., 2006). The task provides a list of nine individually paired digits and symbols that participants use as a key to substitute numbers with symbols as efficiently as possible (Litchenberger & Kaufman, 2009). Silber et al., 2006). On the *Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV)*, the DSST score is combined with the Symbol Search task score to generate a standard score of processing speed that measures skills in speed of mental problem-solving, attention, and hand-eye coordination.

**TMT-A.** The Trail Making Test has been used to assess scanning and visuomotor tracking, divided attention and cognitive flexibility and is often used to measure executive function because of the importance of mental flexibility when alternating between numbers and letter sets (Lezak et al., 2012). It is considered to be one of the most widely used neuropsychological assessment instruments (Sánchez-Cubillo et al., 2009). It is completed with paper and pencil and includes two components, trail A (TMT-A) and trail B (TMT-B) (Silber et al., 2006), the latter of which will be described in more detail under the category of working memory. TMT-A, which is completed first, requires participants to draw a continuous line that connects 24-circled digits in ascending order (Silber et al., 2006). Performance is measured by task completion time (Silber et al., 2006). Although commonly associated with divided attention, recent findings indicate that *Test-A* is most closely related to processing speed (Sánchez-Cubillo et al., 2009).

## **Working Memory**

Although working memory may be considered a function of attention, memory and/or executive function, and there is considerable debate about how best to define it, working memory is generally considered to be responsible for brief or temporary storage of information that allows for active maintenance and manipulation for complex cognitive operations (Lezak et al., 2012; McCabe, Roediger, McDaniel, Balota, & Hambrick, 2010). Working memory is highly associated with the general factor of intelligence (*g*) possibly because of the importance for short-term storage within both constructs (Colom, Abad, Quiroga, Shih, & Flores-Mendoza, 2008); however, the two constructs are clearly distinct from one another as evidenced by a meta-analysis examining correlations of working memory and *g* (Ackerman, Beier, & Boyle, 2005). While there is an abundance of measures available to assess WM, some of the most readily used measures include Digit Span (DS), Spatial Working Memory (SWM), Spatial Span (SS), Sternberg Memory Task, and the *n*-back (Cambridge Cognition, 2015; Lezak et al., 2012; Litchenberger & Kaufman, 2009; Turner et al., 2005). The Trail-Making Test-B may also be considered a test of WM given recent findings indicate it is most closely related to WM (Sánchez-Cubillo et al., 2009).

**DS.** Wechler's DS includes the repetition of a sequence of numbers forwards and backwards in the same order they are presented (Litchenberger & Kaufman, 2009). While cognitive assessments combine the two scores for an overall measure of working memory, the two subtests are theoretically distinct (Lezak et al., 2012; Litchenberger & Kaufman, 2009). DS backwards is most closely aligned with working

memory, while DS forwards is an assessment of overall attentional capacity (Lezak et al., 2012).

**n-back.** Used frequently for research involving functional magnetic resonance imaging (fMRI), the *n*-back requires respondents to determine if a target is the same as one presented “*n*” steps prior to the target (Lezak et al., 2012). For example, using a 2-back condition, a correct response to the sequence of numbers 4-3-9-7-2-3-2 would be “yes” following the second 2.

**SS.** The SS is an assessment of working memory capacity described as a visuospatial analogue to Wechsler’s DS. The test involves a visual display of white squares that change in color and the respondent must remember the order of color changes with numbers of squares increasing from two to nine. Outcome measures include span length, errors, number of attempts and latency (Cambridge Cognition, 2015; Turner et al., 2005).

**Sternberg Memory Task.** For the Sternberg Memory Task, participants are required to remember a random sequence of digits that are presented sequentially and then presented with a target digit. Participants must determine if the target digit matches one of the digits presented previously in the sequence of numbers quickly as possible (Neubauer, Riemann, Mayer, & Angleitner, 1997).

**SWM.** A measure of working memory, as well as strategy, the SWM requires participants to search for tokens within boxes visually displayed on a computer screen (Cambridge Cognition, 2015). Levels of difficulty range from 6-box to 8-box tasks (Turner et al., 2005). The test yields data for within-search errors (selecting boxes that

were previously found to be empty) and between-search errors (selecting boxes where a token was already retrieved).

**TMT-B.** The second part of the TMT, TMT-B, is similar to the task of TMT-A, but requires participants to draw a continuous line connecting numbers and letters in ascending order while alternating between number and letter (e.g., 1-A-2-B-2-C, etc.) (Silber et al., 2006). A comprehensive review of the construct validity of the TMT suggests that TMT-B is primarily a measure of working memory, but also measures task-switching ability (Sánchez-Cubillo et al., 2009). Performance on the TMT is measured by task completion time.

### **Learning and Memory**

Memory, learning and “intentional access to memory stores,” are critical components within all cognitive functions. Even mild impairments of memory can have profound effects of human functioning (Lezak et al., 2012). Memory refers to the ability to retain and access information and it can be divided into three stages: 1) the selection and processing of information; 2) immediate storage of memory involving temporary holding of information and requiring rehearsal for longer-term retention; and 3) long-term storage of memory achieved through consolidation of information, i.e., learning. Learning generally refers to the organization and consolidation of information, in some cases requiring effort and attention, i.e., declarative memory, but in other cases occurring incidentally, i.e., non-declarative memory (Lezak et al., 2012).

### **Declarative Learning and Memory**

Declarative learning and memory refers to the abilities to explicitly learn and remember information, objects, and events (Kumari et al. 1997; Lezak et al., 2012).



Memory retrieval may involve recall, which refers to remembering of information, or recognition, which relies on a stimulus to trigger remembering of information (Lezak et al., 2012). Both episodic memory - memories that are “localizable in time and space” - and semantic memory - memories that do not rely on time or space (e.g., the alphabet) have been studied (Lezak et al., 2012, p. 31); however episodic memory is most commonly tested in research studies assessing stimulant effects on cognition (Ilieva et al., 2015). Episodic memory is largely contingent on working memory efficiency (McCabe et al., 2010).

Tests of episodic memory may be verbal (recall and recognition of stories, word lists, phrases, or passages) or visual (tests of drawing or design reproduction) (Lezak et al., 2012). Tests may require memorization of lists, spatial location, images, or paired associations. In addition to visual and verbal tests requiring recall or recognition, common standardized memory tests include the Auditory Verbal Learning Test (AVLT), California Verbal Learning Test (CVLT), Paired Associates Learning (PAL) Test, and Rey Verbal Auditory Learning Task (RVALT) (Cambridge Cognition, 2015; DuPaul et al., 2012; Klaassen, Riedel, Deutz, & Van Praag, 2002; Lezak et al., 2012; Linssen, Sambeth, Vuurman, & Riedel, 2014a; Makris, Rush, Frederich, Taylor, & Kelly, 2007; Spreen & Strauss, 1998).

**Tests of Recall or Recognition.** Research assessing learning or memory has used a variety of tests of recall or recognition that may be verbal or visual. Verbal recall and recognition tasks may require respondents to remember information from stories, word lists, phrases, or passages (Lezak et al., 2012). Visual recall and recognition tasks include memory of pictures or objects.

**AVLT.** The AVLT involves the learning of a 15-word list (Lezak et al., 2012). An adapted version of the AVLT, the Visual Verbal Learning Test (VLT) that includes 30 words has also been used in the literature (Klaassen et al., 2002; Linssen et al., 2014a). Outcome measures include immediate free recall of words, as well as delayed verbal free recall and recognition tests given 30 minutes and 24 hours after learning (Linssen et al., 2014a).

**CVLT.** The CVLT is an assessment of strategies and processes related to verbal learning and memory (DuPaul et al., 2012; Spreen & Strauss, 1998) that assesses a respondent's use of semantic associations for learning (Lezak et al., 2012). It measures immediate and delayed word list recall and recognition (DuPaul et al., 2012) and involves two word lists, the second of which is designed to be an interference with the learning of the first (Spreen & Strauss, 1998). Some of the data provided by the CVLT include: total recall and recognition, semantic and serial learning strategies, serial position effects, learning rate, perseverations and intrusions in recall, and false positives, i.e., commissions (Spreen & Strauss, 1998).

**PAL.** Assessing visual episodic memory and new learning, the PAL is a subtest of the Cambridge Neuropsychological Test Automated Battery (CANTAB) battery that yields outcome measures related to error, number of trials required to locate patterns, memory scores, and stages completed (Cambridge Cognition, 2015). The PAL tests visuospatial associations utilizing cues to learn associations (Turner et al., 2003). For example, Kinsbourne, De Quiros, & Tocci Rufo (2001) used a version of the PAL in which a computer randomly generated pairings of stimulus in response,

requiring the respondent to memorize a digit associated with a consonant. Outcome measures may include accuracy, error, and total number of trials.

**RVALT.** The RVALT assesses immediate memory, new learning, susceptibility to interference, and recognition memory. It includes 15 nouns that are read aloud followed by a free recall test. An interference of 15 words is presented and then delayed recall of the original lists is measured. Finally, recognition is measured through the presentation of a story including the original list of words (Spreen & Strauss, 1998).

### **Non-declarative Learning and Memory**

Non-declarative learning and memory involves an unconscious remembering of knowledge typically subdivided into procedural memory or learning and priming or perceptual learning (Kumari et al., 1997; Lezak et al., 2012). Procedural learning and memory refers to rule-based learning in which performance improves with practice (Kumari et al., 1997). Priming or perceptual learning and memory involve recall based on cues related to prior learning or associations (Lezak et al., 2012). Simple tasks of probabilistic learning, as well as the Repeated Acquisition of Response Sequences Task (RA), have been used in the literature to measure non-declarative memory (Makris et al., 2007).

**RA.** Although primarily used to test cognitive behavior with animal models (Cohn & Paule, 1993), the RA Task has been used in human studies as well. It requires participants to learn new response sequences within individual sessions in order to measure an overall rate of learning (Cohn & Paule, 1993; Makris et al., 2007). For example, in their investigation of the behavioral and subjective effects of d-AMP

and modafinil, Makris and colleagues used the RA Task involving the learning of a 10-response order on four keys.

**Probabilistic Learning.** Probabilistic and reversal learning involves associative learning based on punishing and rewarding feedback in which participants must modify learned associations throughout the task (Clarke, Dalley, Crofts, & Robbins, 2004; van der Schaaf, Fallon, Huurne, Buitelaar, & Cools, 2013).

### **Executive Function**

Executive function refers to capacities that allow for independent, purposive, self-directed, and self-serving behavior (Lezak et al., 2012; Weyandt & Willis, 1995) even “in the face of irrelevant competing inputs or more habitual but inappropriate response patterns” (Farah et al., 2004, p. 422). Among other functions, executive function may include control functions that inhibit prepotent responses, cognitive/mental shifting, cognitive flexibility, regulation and monitoring of performance, goal maintenance, planning, and working memory (McCabe et al., 2010). Lezak et al. (2012) conceptualized these functions to comprise the constructs of volition (i.e., capacity for intentional behavior), planning and decision-making, purposive action, self-regulation and effective performance. It is important to note that there is a substantial amount of overlap between executive function abilities and other cognitive constructs (Farah et al., 2004; Repantis et al., 2010) and there is an ongoing debate about how best to conceptualize executive function, i.e. as a unitary construct or as separate, but synergetic, constructs (McCabe et al., 2010; Weyandt, 2006). The following sections describe some of the most commonly explored executive function

constructs among studies related to prescription stimulants: planning and decision-making and self-regulation.

### **Planning and Decision-Making**

Among other capacities, planning and decision-making require looking ahead, objective assessments, perceiving alternatives, weighing choices, and utilizing conceptual frameworks (Lezak et al., 2012). Memory, impulse control, and sustained attention are all necessary components of planning and decision making behavior. Tests of planning and decision-making may include gambling tasks and tower tests (Lezak et al., 2012).

**Gambling Tasks.** Although a number of iterations of gambling tasks are available, the most common task is the Iowa Gambling Task (IGT). The IGT is played with cards on a computer in which the participant selects varying decks and cards with the purpose of minimizing losses and winning as much money as possible (Lezak et al., 2012).

**Tower Tests.** The Tower of London Spatial Planning Task (NTOL) is the most commonly used version of the tower tasks, which require participants to rearrange rings or balls of varying colors to arrive at the solution using the least number of moves and in the most direct way (Lezak et al., 2012).

### **Self-regulation**

Self-regulation assessments may either measure productivity *or* flexibility and the capacity to shift (Lezak et al., 2012); however, tasks of self-regulation have most commonly focused on flexibility and set-shifting, as opposed to productivity, among studies examining ADHD medication effects on self-regulation. Assessments of

flexibility have also been used to identify levels of creativity (Lezak et al., 2012) and some measures of verbal fluency assess the ability to think flexibly, switch response sets, self-regulate and self-monitor (Lezak et al., 2012). In particular, verbal fluency tests measure how well individuals organize information (Lezak et al., 2012).

Therefore, tasks of self-regulation may include tasks assessing productivity, flexibility, the capacity to shift, creativity, and verbal fluency (i.e. organization). One important distinction to note relates to the difference between tasks of flexibility and tasks of non-declarative learning and memory. Although some tasks of flexibility utilize associative learning similar to tasks measuring non-declarative memory, tasks measuring flexibility require respondents to shift their thinking by changing the rules during the task (i.e., reversal or probabilistic learning that is not constant).

In addition to general tasks designed to assess set-shifting or switch-costs, the Wisconsin Card Sorting Test (WCST) and the Intra-Extra Dimensional Set-shift Task (IDED) are common tests of cognitive flexibility (Lezak et al., 2012; Wild & Musser, 2014). Both probabilistic and reversal learning paradigms have also been used as measures of cognitive flexibility. Measures assessing creativity might include the Alternative Uses Task, the Group Embedded Figures Task, the Drawing Task from the Abbreviated Torrance Test for Adults, and the Remote Associations Task. Finally, common verbal fluency measures include the Controlled Oral Word Association Test (COWAT) and the Verbal Fluency Test (Elliott et al., 1997; Farah, Haimm, Sankoorikal, & Chatterjee, 2009; Lezak et al., 2012).

**Cognitive Flexibility Tasks.** The IDED has been described as an analog to the WCST on the computer (Wild & Musser, 2014). It assesses set formation and

maintenance, shifting, and attentional flexibility (Wild & Musser, 2014). Participants view two color-filled shapes and must learn through trial and error based on computer driven feedback which response is correct (Cambridge Cognition, 2015). The test becomes increasingly difficult as it progresses through nine stages, transitioning from intra-dimensional to extra-dimensional rules (Wild & Musser, 2014). The WCST is used to assess abstract concepts and set-shifting (Spreeen & Strauss, 1998) by requiring participants to deduce a pattern by matching cards of varying symbols and shapes based on the examiner's cues (Lezak et al., 2012).

As described previously, probabilistic and reversal learning are a kind of associative learning based on punishing and rewarding feedback that require modifications to learned associations throughout the task (Clarke et al., 2004; Schaaf, Fallon, ter Huurne, Buitelaar, & Cools, 2013). These tasks may provide a measure of cognitive flexibility when they require a shift in thinking in response to an unexpected outcome, e.g., shift analysis as examined by van der Schaaf et al. (2013).

**Creativity Tasks.** Used to measure divergent thinking, the *Alternative Uses Task* requires participants to listen to a list of objects and describe as many alternative uses for the objects within a specified period of time as possible (Farah et al., 2009). Stimuli is presented verbally and responses also given verbally (Farah et al., 2009).

The Drawing Task is a standardized subtest from the Abbreviated Torrance Test for Adults used to measure divergent thinking (Farah et al., 2009). Participants are presented with an incomplete figure and instructed to make a picture, as well as providing the picture with a title (Farah et al., 2009). Norm-referenced scoring is based on fluency, originality, elaboration, and flexibility and some of the criterion-

referenced creativity indicators are scored based on openness, unusual visualization, and movement (Farah et al., 2009).

Finally, two tasks used to measure convergent creative thinking have included the Group Embedded Figures Task and the Remote Associations Task. The former instrument is a nonverbal task that has been used to test convergent creative thinking (Farah et al. 2009). Participants must reorganize the elements of a geometric design in order to reveal embedded figures (Farah et al., 2009). The Remote Associations Task requires participants to supply one word associated with three words (Farah et al., 2009).

**Verbal Fluency Tasks.** Two instruments used to measure verbal fluency include the COWAT and the Verbal Fluency Test. The COWAT requires participants to list as many words as possible that begin with a certain letter (Lezak et al., 2012). In addition to verbal fluency, it has been suggested to measure task persistence and divided attention (Taylor & Russo, 2000). Benton's Verbal Fluency Test is another instrument used to measure verbal fluency. This test is similar to the COWAT and requires participants to generate as many words as possible that start with a specific letter falling under a semantic category such as "animals" (Elliott et al., 1997).



## CHAPTER 3: Research Justification and Predictions

### Prescription Stimulants for Neurocognitive Enhancement of Cognition in Adults

The positive effects of prescription stimulants on cognitive functioning among children and adolescents with ADHD have been explored (Coghill et al., 2013), but to date no systematic meta-analysis has been conducted concerning adults with and without ADHD. Although Ilieva et al. (2015) reported on the cognitive effects of MPH and AMP for inhibitory control, working memory, and episodic memory, questions remain about the cognitive effects of other ADHD medications (pro-stimulants and non-stimulants) and how prescription stimulant medication may influence other cognitive processes such as sustained attention, processing speed, planning and decision-making, and creativity. Indeed, Ilieva et al. suggested a number of areas for future researchers to address, including how ADHD medication may influence sustained attention and processing speed and whether particular groups of healthy adults, such as those with low cognitive performance prior to medication, may benefit more or less than other populations.

Given the rise of stimulant misuse across college populations with and without ADHD, it is important to understand if prescription stimulants proffer cognitive effects, i.e., neurocognitive enhancement, or if they *impair* other areas of cognitive functioning. Therefore, in an attempt to elucidate whether prescription stimulants affect cognition, the proposed study will explore the following questions: 1) Are prescription stimulant medications effective for enhancing cognition among adults with and without ADHD? 2) What types and doses of prescription stimulants and what timing of ingestion of medications yield the greatest and smallest effects on cognition?

3) Does baseline functioning of cognition impact the effect of prescription stimulants on cognition? 4) Do prescription stimulants enhance or impair different sub-components of cognition (e.g., vigilance tasks, memory tasks, and executive function tasks)? 5) Do the effects of prescription stimulants vary for adults with and without ADHD?

Based on a previous research (e.g., Advokat, 2010; Smith & Farah, 2011), the following hypotheses will be examined for adults with and without ADHD:

- 1) Medications for the treatment of ADHD (prescription stimulant, prostimulant and nonstimulant medications) will demonstrate general positive effects on tasks of focused behavior, learning and memory, and executive function among adults with and without ADHD.
- 2) The relationship between prescription stimulant, prostimulant, and nonstimulant ADHD medications and cognition will vary according to dose, with higher doses yielding greater effects than lower doses among adults with and without ADHD.
- 3) The relationship between prescription stimulant, prostimulant, and nonstimulant ADHD medication and cognition will vary according to timing of dose, with activation of stimulant during learning processes yielding greater effects than activation at other times among adults with and without ADHD.
- 4) The relationship between prescription stimulant, prostimulant, and nonstimulant ADHD medication and cognition will be consistent across medication activation types (short-acting, medium-acting, or long-acting medications) among adults with and without ADHD.

- 5) Prescription stimulant, prostimulant, and nonstimulant medication ADHD effects on cognition will negatively correlate with baseline cognitive functioning of adults with and without ADHD.
- 6) The relationship between prescription stimulant, prostimulant, and nonstimulant ADHD medications and cognition will vary according to ADHD status, with greater effects among adults with ADHD compared to adults without ADHD.

## CHAPTER 4: Methodology

### Literature Searches

A systematic search and retrieval process was conducted according to Lipsey and Wilson's (2001) guide for meta-analysis, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 27-item checklist (Liberati et al., 2009; Moher, Liberati, Tetzlaff, & Altman, 2009), and Okoli and Schabram's (2010) eight-step guide to systematic literature reviews. The study attempted to identify and retrieve all empirical studies and datasets that examined cognitive effects of prescription stimulants and prostimulants conducted at any time. The search and retrieval process was conducted between the months of June and October 2014 and included a comprehensive search of the following bibliographic databases: PsycINFO, MEDLINE, ScienceDirect, and Dissertations and Theses (PROQUEST). A combination of the following keyterms were used: *Prescription stimulant, dextroamphetamine, Adderall, methylphenidate, Ritalin, Concerta, lisdexamfetamine, Vyvanse, atomoxetine or Strattera, and cognitive, cognition, learning, memory, or executive function*. Note that for the searches conducted within Dissertations and Theses, terms were searched within the category of "anywhere except full text" (ALL) and for PsycINFO terms were searched without the selection of a field; however, for MEDLINE and ScienceDirect terms were searched within "keyterms." In addition to searches within bibliographic databases, studies were searched within the following review articles: Advokat, (2010), Linssen et al. (2014b), Smith & Farah, (2011), Repantis et al., (2010). Titles, abstracts, and full articles were examined to assess if studies met eligibility criteria, described in the following section.

The present study's search and retrieval process was similar to two recent systematic reviews that addressed the effects of ADHD medication on neurocognitive enhancement. However, the present study differed from previous publications in a number of meaningful ways. First, while the present study included adults with and without ADHD, Linssen et al. (2014b) and Ilieva et al. (2015) included studies using samples of healthy adults only. Furthermore, the present study included studies that administered stimulants, prostimulants and nonstimulants, as opposed to MPH only like Linssen et al. and AMP and MPH only like Ilieva et al. A final major difference between studies relates to the cognitive outcomes included for analysis. While Ilieva et al. selected studies based on specific tests of cognition, limiting key terms to predetermined tests, Linssen et al. selected studies based on a previous review (Nuechterlein et al., 2004) of the effects of MPH for cognitive enhancement that categorized neuropsychological tests into six domains (speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory and reasoning). The present study, however, attempted to include a variety of tests to measure multiple domains of cognition that were not predetermined, i.e., the present study did not specify particular domains of cognition prior to data collection. Instead, the present study attempted to retrieve as many studies as possible that explored the cognitive effects of ADHD medication and then coded results according to cognitive literature and theory described in Chapter 2. This method was chosen in order to include the maximum number of studies available, reduce self-selection bias, and capture the variability in study findings. The present study was the first meta-analysis to provide insight about ADHD medication's effects in populations that

include adults with and without ADHD and to explore particular areas of cognition (planning and decision-making, self-regulation, processing speed). This study also addressed issues concerning previous reviews that have relied on studies that were underpowered and varied in design, requiring statistical techniques to account for study design variability.

### **Selection of Studies**

Although meta-analysis is a powerful method that can help elucidate the true effect of a treatment or intervention (Kraemer, Gardner, Brooks, & Yesavage, 1998), results are limited by the quality of available published studies. Many criticisms of meta-analysis stem from the decision to either maintain open inclusion criteria (leading to a variety of studies that may not be comparable) or to adopt rigid inclusion criteria (resulting in less meaningful findings because of the exclusion of potentially meaningful studies) (Kraemer et al., 1998). Therefore, the present study attempted to include as many quality studies as possible without excluding potentially meaningful studies. Methods of analysis and eligibility criteria were documented in a protocol prior to data collection and analysis as recommended by PRISMA (Liberati et al., 2009; Moher et al., 2009). Studies were selected for review based on the following criteria:

- 1) The study was published in English.
- 2) The study used a placebo-controlled design.
- 3) The sample included human subjects only, at least 18 years of age; if the study included special groups, only data involving healthy controls or individuals with ADHD were included.

- 4) The sample size was greater than one; single case studies were excluded.
- 5) The study investigated the effects of d-AMP, MPH, LDX, or ATX; if the study investigated additional drugs, only data involving the stimulants listed previously and placebo were included.
- 6) The study addressed variables related to effects of prescription stimulants on cognition most closely aligned with neurocognitive enhancement. Specific dependent variables included behavioral measures of focused behavior, memory, learning and executive function. Dependent measures were not limited beyond these broad constructs; however, assessments of cognitive function that were not behavioral (i.e., self report) and those that simulated behavior (e.g., simulated driving) were excluded.

An amendment to the protocol was made after the search and retrieval process had begun. Protocol modifications are not uncommon nor inappropriate for systematic reviews; however, researchers are encouraged to describe and justify any protocol modifications, taking into account the potential for increased selective reporting bias (Liberati et al., 2009). The protocol was modified during data collection to specify additional criteria for inclusion as outlined below:

- 7) The procedure did not limit sleep for participants; studies investigating sleep deprivation or studies that deprived participants of sleep were excluded. There is a large body of literature (e.g., Baranski & Pigeau, 1997; Kilgore et al., 2008; Kilgore, Grugle, & Balkin, 2012) investigating the effects of prescription stimulant medication on sleep deprivation. Because the present study was focused on cognition within healthy adults samples and adults with ADHD and

sleep did not relate to the present study's hypotheses, studies investigating sleep deprivation were excluded to reduce any additional confounds across findings. Based on this framework for decision-making, it is unlikely this protocol amendment resulted in an increase in bias.

- 8) Studies that used drug discrimination learning procedures, i.e., teaching participants to discriminate between drugs or doses of drugs, were not included in the present study in order to minimize confounds associated with these learning tasks.
- 9) Studies that used a single-blind design, where participants were unaware of the type of drug administered but researchers were aware, were included.
- 10) Studies that included participants who reported regular drug use (e.g., MDMA as reported in Kuypers & Ramaekers, 2005) or were conducted among prison populations (Ginsberg, Hirvikoski, Grann, & Lindefors, 2012) were excluded. Although the eligibility criteria determined prior to data collection specified that only populations reported as healthy and/or with ADHD diagnoses would be included, examination of the literature search revealed the need to specify these requirements further. An increase in bias was not suspected as a result of this amendment considering the focus of the study was on the effects of ADHD medication within the context of neuroenhancement, which would exclude other types of drug users and prison populations.
- 11) Studies that focused on latent inhibition, which refers to the slowing of learning about consequences of a stimulus resulting from the stimulus having been inconsequential in the past (Kumari, 1997), were excluded. This process



is distinctly separate from the focus of neuroenhancement and its exclusion reflects the overall study's focus.

### **Data Extraction and Coding**

Once all studies were identified and retrieved, data were extracted and coded according to a standardized coding manual (see Appendix A). A comprehensive coding sheet included the following variables: study descriptors (name of study, country of researcher, year of publication), descriptive statistics (sample size, reported ES statistics, effect direction and raw data to recalculate ES), sample descriptors (participant demographics of mean age, special groups, ethnicity and sex), participant descriptors (cognitive abilities prior to medication), participant diagnostic characteristics (ADHD status), variables related to methods and procedures (form of data analysis, type of outcome score used [change score or post treatment score], study design [parallel or crossover study], and use of counterbalancing, minimum days of washout between treatments), stimulant medication descriptors (stimulant medication type, stimulant dose, stimulant dose type [fixed dose or titration to best dose], and time of dose relative to assessment and/or learning), and dependent constructs and measures related to cognition.

Dependent constructs and measures were further coded based on methods used by previous research and on the theoretical constructs of cognition described in the preceding chapter. Therefore, the exact dependent constructs used in this study were identified after all other data were extracted and coded. Accordingly, studies addressed at least one of 10 narrow constructs of cognition, grouped according to three broad categories of cognition: (1) Abilities of Focused Behavior, including the narrow

constructs of (a) Vigilance, (b) Inhibitory Control, (c) Processing Speed, and (d) Working Memory; (2) Learning and Memory, including (a) Declarative Memory – Immediate (measured within 20 minutes of learning), (b) Declarative Memory – Delayed (measured after 20 minutes, but within the same day as learning), (c) Declarative Memory – Long-term (measured after more than a day from learning), and (d) Non-declarative Learning; or (3) Executive Function, including (a) Planning and Decision Making and (b) Self-regulation.

In order to estimate a single ES that most accurately captured each cognitive construct, specific measures considered to be representative of the construct were selected from each instrument. Table 1 displays a list of the selected measures organized by construct and instrument. Although these measures varied according to individual constructs, in general, measures of error and accuracy were selected first, and measures of Reaction Time (RT) were excluded unless they were the only extractable data for a given study. Exceptions to this convention were for the constructs of processing speed and planning and decision-making, in which RT was considered an important component for measurement of these constructs and was therefore included as a primary measure.

Selected measures of vigilance included accuracy, errors of omission, and attentiveness ( $d'$ ). An attempt was made to include accuracy and attentiveness in addition to errors of omission, considering some studies have reported a ceiling effect for omission errors (e.g., Boonstra et al., 2005). One study (Agay et al., 2014) calculated a measure of sustained attention with a weighted averaging of response

time,  $d'$  (accuracy over time, mostly impacted by errors of commission), and response time variability, and was also coded as an assessment of vigilance.

Based on previous meta-analyses concerning inhibitory control (Ilieva et al., 2015; Smith, Mattick, Jamadar, & Iredale, 2014), errors of commission on tests of attention were selected as measures of inhibitory control. (Note that measures of attention related to omission errors were used to measure vigilance; therefore, in some cases individual measures within the same instrument were considered to be representative of differing constructs). In general, commission errors, i.e., false alarms, reflect difficulties with restraint and inhibition (Lezak et al., 2012). For instruments designed to measure inhibitory control specifically, conventions were based on measures selected by previous researchers (Ilieva et al., 2015; Smith et al., 2014; Westerhausen, Kompus, & Hugdahl, 2011). For Stop-Signal tasks the probability of inhibiting a response and the Stop-Signal Reaction Time, calculated by subtracting the mean Stop delay from the mean Go RT, were favored (Ilieva et al., 2015; Smith et al., 2014). Similarly, effect sizes from measures of the Stroop task included Interference, defined as the performance (errors or RT) in a neutral condition subtracted from the performance in the incongruent condition, which has been considered an inverse gauge of inhibition (MacLeod, 1991; Westerhausen et al., 2011). When Stroop task results were reported for individual measures of error or RT only, incongruent errors/RT were selected to measure susceptibility to interference (Ideström & Schalling, 1970). Measures from the Flanker included the difference or ratio between congruent and incongruent accuracy (Ilieva et al., 2015) and when error was reported for incongruent individually, measures of incongruence were selected. Measures

selected from the Go/No Go task included accuracy and errors of commissions (Ilieva et al., 2015; Smith et al., 2014). Finally, for the antisaccade task, error saccades to the target were selected (Ilieva et al., 2015).

Most studies ( $k = 5$ ) that reported measures of processing speed from the provided a standard or accuracy score; one study (Wardle et al., 2013) provided the area under the curve (AUC). Therefore, both standard scores and AUC were selected as measures of processing speed from the DSST. Measures of simple and choice reaction tests included response time, accuracy rate, and errors. Primary measures of working memory included accuracy, sensitivity, and error measures; RT was selected in the cases where none of these measures were provided (see Table 1).

In order to measure declarative learning and memory, error and accuracy scores were selected from studies. Outcomes may have included recall (free and cued), recognition, sensitivity, and confabulations, among others. Specific measures of non-declarative memory, however, included accuracy/error measures, as well as learning rate measures indicative of the amount of time required to learn an association.

For planning and decision-making, measures of accuracy or error, number of steps or attempts required to reach accuracy, time required for making a decision, and estimates of probability related to quality of choices were selected. To measure self-regulation, standard scores reported for measures of creativity and verbal fluency were selected. For cognitive flexibility, preferred measures from the WCST included categories achieved (number of correct sorts indicating an understanding of the idea), perseverative errors (where higher errors reflect difficulty in understanding the concept and may indicate difficulties with conceptual flexibility), trials to complete

first category (indicating conceptualization readiness to shift), as well as overall accuracy and error measures (Lezak et al., 2012; Spreen & Strauss, 1998). Measures from IDEED and other instruments measuring cognitive flexibility were similar, including discrimination, reversal and shift errors/accuracy. One study included a switch-cost paradigm. For this study, the switch-cost measure, calculated by subtracting the average response time on repetition trials from switch trials, was used (Samanez-Larkin et al., 2013).

Table 1  
*Measures by Construct and Task*

Instrument	Accuracy	Error	RT	Other
<b>Vigilance</b>				
<i>Continuous Performance Task (CPT)</i>	Accuracy Detectability/ attentiveness	Omission		
<i>Digit Vigilance Test</i>	Accuracy			
Oddball Task		Omission		
<i>Rapid Visual Information Processing (RVIP)</i>	Detectability/target sensitivity	Omission		
<i>Sustained Attention to Response Test (SART)</i>		Omission		
<i>Test of Variables of Attention (TOVA)</i>	Accuracy over time	Omission		
Mackworth Clock Test				
Miscellaneous Tasks of Attention	Sensitivity	Errors Bias <sup>a</sup>		
<b>Inhibitory Control</b>				
Antisaccades		Antisaccade error		
Change Task (extension of Stop-			MRT (Stop-	

Instrument	Accuracy	Error	RT	Other
Signal Task)			Signal, Change Response)	
<i>Continuous Performance Task (CPT)</i>		Commission		
<i>Digit Vigilance Test</i>		Commission		
<i>Flanker</i>	Difference/ratio between congruent and incongruent accuracy	Difference/ratio between congruent and incongruent error Incongruent error <sup>a</sup>		
Go/No-Go	No-Go accuracy	No-Go error Commission		
Oddball Task		Commission		
<i>Rapid Visual Information Processing (RVIP)</i>		Commission		
<i>Sustained Attention to Response Test (SART)</i>		Commission		
Stop-Signal Task	Probability of inhibiting response		Stop Signal RT (mean go RT minus mean stop delay) <sup>a</sup>	
<i>Stroop Task</i>		Error interference	RT interference <sup>a</sup>	

Instrument	Accuracy	Error	RT	Other
		Incongruent errors <sup>a</sup>		
<i>Test of Variables of Attention (TOVA)</i>		Commission		
<b>Working Memory</b>				
<i>Digit Span (DS) - Wechsler, Guild</i>	Standard score Longest span*			
<i>Dot-Letter Task</i>	Accuracy		RT <sup>a</sup>	
<i>n-back</i>	Accuracy	Omission Commission	RT <sup>a</sup>	
Number Recognition Object-relocation	Standard score		Latency <sup>a</sup>	
<i>Spatial Delay Response</i>	Accuracy			
Spatial Location	Accuracy		RT <sup>a</sup>	
<i>Spatial Working Memory (SWM)</i>	Accuracy Strategy score Positive fit	Between Within Total Absolute		
<i>Spatial Span (SS)</i>	Span length	Errors		



Instrument	Accuracy	Error	RT	Other
<i>Sternberg's Memory Test</i>	Recall of Consonants	Error Rate		
<i>Trail Making Test-B (TMT-B)</i>			RT	
Visual Working Memory Task	Accuracy			
Processing Speed				
DSST	Standard score			
Simple/Choice Reaction Time Tests:				
-Contingent Negative Variation (CNV) Stop Light Task				
-CNV Lines Task		Errors	RT	
-Stimulus Evaluation Response Selection (SERS)		Omission	Distraction time	
-Simple Motor Response		Commission		
-Motor Reaction Task				
-Simple Reaction Time Test				
-Visual Search Task				
Spatial Orienting Task		Errors	RT	
<i>Trail Making Test-A (TMT-A)</i>			RT	
Declarative Learning & Memory (Immediate, Delayed, & Long-term)				
<i>California Verbal Learning Test (CVLT)</i>	Level of Recall			

Instrument	Accuracy	Error	RT	Other
<i>Guild Memory Test</i>	Recall Paired Associates score Designs			
<i>Paired Associates Learning Test (PAL)</i>	Accuracy	Errors		Total trials <sup>a</sup>
<i>Pattern Recognition Memory Task</i>	Accuracy			
Recall of Words, Pictures, Stories, Objects Recognition of Words, Pictures, Stories, Objects	Recall Recognition Sensitivity (d')	Commission Intrusions Confabulations Response bias (C)		
<i>Key Verbal Auditory Learning Task (RVALT)</i>	Accuracy Trials 1-5 Score Trial 1 Score <sup>a</sup> Sensitivity	Errors		Number of Trials <sup>a</sup>
Non-Declarative Learning & Memory				
Probabilistic Learning	Accuracy	Mean errors to criterion Perseverative errors		Feedback sensitivity
<i>Repeated Acquisition of Response Sequences Task (RA)</i>	Correct response rate	Incorrect response rate		
Learning Tasks	Learning rate			

Instrument	Accuracy	Error	RT	Other
Reversal Learning Tasks	Reward accuracy Punishment accuracy	Errors		
<b>Planning &amp; Decision Making</b>				
<i>Iowa Gambling Task (IGT)</i>	Probability of accuracy Advantageous choices	Disadvantageous choices	Deliberation time <sup>a</sup> Latency of RT <sup>a</sup>	Mean attempt of moves
<i>Tower of London Spatial Planning Task (NTOL)</i>	Accuracy		Latency* RT <sup>a</sup>	Mean attempt of moves
<b>Self Regulation</b>				
<i>Controlled Oral Word Association Test (COWAT)</i>	Accuracy Standard score			
<i>Drawing Task from the Abbreviated Torrance Test for Adults</i>	Standard score			
<i>Group Embedded Figures Task</i>	Accuracy			
<i>Intra-Extra Dimensional Set-shift Task (IDED)</i>	Accuracy	Total ED Perseverative Discrimination Reversal		
Probabilistic Learning	Accuracy	Mean errors to criterion		

Instrument	Accuracy	Error	RT	Other
		Perseverative errors		
<i>Remote Association Task</i>	Accuracy			
Switch Cost and Switch Setting Tasks			Switch cost	
<i>Verbal Fluency Test</i>	Fluency			
<i>Wisconsin Card Sorting Test (WCST)</i>	Accuracy Trials to Complete First Category	Perseverative Errors Failures/errors		Conceptual Level Number of Categories

*Notes.* \* indicates a measure that was selected secondary to other measures; ED = Extra Dimensional; RT = Response Time.

To test the study hypotheses, specific moderating variables were coded based on the following rationale:

- 1) Medication Dose (low or high): Because the study included a variety of medications (AMP, MPH, ATX, and LDX), dose level was coded separately as high or low for each drug. Specifically, a doses coded as “high” included the following:  $\geq 20$ -mg (AMP),  $\geq 40$ -mg (MPH),  $\geq 50$ -mg (LDX), and  $\geq 70$ -mg (ATX). “Low” doses were those that fell below this convention. When studies reported dose in units of mg/kg, doses were multiplied by the global average adult weight of 62-kg (Walpole et al., 2012) and then coded accordingly.
- 2) Timing of Dose Activation (during, prior, or after learning): Timing of dose activation was coded as occurring during learning processes, prior to learning process, or after learning processes according to the medication type used in each study. Studies utilizing pharmacokinetic data have indicated that plasma levels peak after oral ingestion of AMP between 2-3 hours (Angrist et al., 1987; Wachtel, ElSohly, Ross, Ambre & de Wit, 2002), MPH between 1-2 hours (Kimko, Cross, & Abernethy, 1999; Volkow et al. 1998), LDX between 2-4 hours (Wigal et al., 2010) and ATX between 1-2 hours (Sauer, Ring, & Witcher, 2005). Therefore, doses administered within these time windows for each medication were coded as occurring “during learning,” doses administered prior were coded as occurring “prior to learning,” and doses administered following were coded as occurring “after learning.”

- 3) Medication Activation Types (short-acting or medium/long-acting treatment): Medications were coded as either short-acting treatments or medium or long-acting according to the following criteria: Short-acting stimulants included amphetamine/dextroamphetamine (Adderall), dextroamphetamine sulfate (Dexedrine, Dextrostat), dexamethylphenidate (Focalin), or MPH (Methylin, Ritalin); medium or long-acting stimulants, prostimulants, and non-stimulants included methylphenidate sustained release (Metadate CD, Metadate ER, Methylin ER, Ritalin LA, or Ritalin SR), amphetamine/dextroamphetamine (Adderall XR), methylphenidate (Concerta), methylphenidate (Daytrana), d-amphetamine sulfate (Dexedrine Spansules), dexamethylphenidate (Focalin XR), atomoxetine (Strattera), and lisdexamfetamine dimesylate (Vyvanse) (Cascade, Kalali, & Weisler, 2008). When studies reported medications as MPH or AMP, without specifying anything further, medications were coded as short-acting.
- 4) Baseline Cognitive Functioning: When available, effect size data were recorded separately for participants with low cognitive baseline scores and those with high cognitive baseline scores prior to medication administration. Additionally, when studies reported assessments of overall cognitive functioning prior to medication administration the particular assessment and scores were recorded. Specific measures included the Wechsler Adult Intelligence Scale (WAIS), the National Adult Reading Test (NART), the Wide Range Achievement Test, the Wechsler Abbreviated Scale of Intelligence (WASI) and the Peabody Picture Vocabulary Test. Because the

majority of studies that included cognitive assessments prior to drug administration reported verbal abilities, if multiple measures were available, measures of verbal abilities were selected first. Scores were transformed to a percentile equivalent based on standard scores.

- 5) ADHD Status (yes or no): Studies were also coded based on recruited sample populations; samples including participants with ADHD were coded as “yes” and samples including participants without ADHD were coded as “no.” Only participants with ADHD were included in the present study in studies that reported findings across samples with and without ADHD.

Additional coded variables that were included to assess the influence of study design variability on stimulant effects were:

- 6) Study design (crossover or parallel): Studies were coded as using either a crossover or within-subjects design or a parallel or between-subjects design.
- 7) Participant Group Assignment (yes or no): For parallel studies, randomization into treatment vs. placebo was coded; for crossover studies, randomization into varying orders of sessions was coded (e.g., placebo then treatment vs. treatment then placebo).
- 8) Measurement Order (yes or no): Counterbalancing of treatment was coded.
- 9) Randomization (yes or no): Studies were coded according to randomization of participants into treatment and placebo groups.
- 10) General Sample Characteristics (adults, university students, or elderly adults): Samples were coded to include adults, university students, and/or elderly populations.

- 11) Sample Recruitment Characteristics (community, clinic, university): Studies were coded as recruiting participants via local communities, clinics (hospitals or inpatient/outpatient settings), and/or university campuses.
- 12) Age of Sample: Mean age, standard deviation of age, and age range were coded.
- 13) Gender Distribution: Percent female was coded as an estimate of gender distribution.
- 14) Years of Education: Studies' participants' mean years of education was recorded.
- 15) Number of Sessions: Studies were coded according to number of sessions included in study design.
- 16) Minimum Wash-out Days: For crossover studies only, the minimum number of wash-out days between drug treatment(s) and placebo were recorded.
- 17) Number of Doses: The number of relevant doses reported was coded for each study.
- 18) Medication Dose Type (fixed or titrated): Studies were coded as either administering medication with a fixed dose or a titrated dose; studies administering titrated doses of medications were also coded according to average number of days participants maintained final medication doses.
- 19) Learning/Practice Effects (yes or no): For all cognitive outcome variables with the exception of non-declarative memory, studies that provided a learning or practice session prior to drug or placebo treatment were coded.



20) Inclusion of Other Drugs (yes or no): Some studies investigated the effects of drugs not relevant to the present study and were coded accordingly.

21) Inclusion of Non-behavioral Measures (yes or no): Studies that conducted cognitive assessments in conjunction with neurological (e.g., fMRI, Event Related Potentials [ERP]) or physiological (e.g., electroencephalogram [EEG], electrocardiogram [EKG]) assessments were coded in order to account for any influence of non-behavioral measures. Studies that utilized biological assessments (e.g., blood samples, saliva samples, blood pressure) were not coded in this category.

22) Medication Types (stimulant, prostimulant, or nonstimulant medications): Medications were coded as either stimulant (AMP and MPH), prostimulant (LDX), or nonstimulant (ATX) medications. The following criteria was used when studies investigated the effects of a combination of these medications: Effect sizes were combined for studies investigating the effects of both AMP and MPH; for studies investigating ATX, as well as MPH or AMP, only data related to MPH or AMP were selected given the importance of assessing prescription stimulant effects that have been reported to be more commonly misused for academic enhancement (e.g., Bossaer et al., 2013; Garnier-Dykstra et al., 2012; Verdi et al., 2014; Weyandt et al., 2013a); additionally, only data related to LDX were selected when studies reported results for both LDX and another stimulant or nonstimulant ADHD medication because of the fewer number of studies that investigated LDX effects.

23) Significant and Non-significant Findings (yes or no): Studies that reported both significant and non-significant results for all measures were coded and studies that reported only significant (or only non-significant) findings were coded.

### **Statistical and Other Software**

Microsoft Word, Microsoft Excel, Google Sheets, Biostat's Comprehensive Meta-Analysis, and SPSS 17.0 were employed to conduct all data analyses. A comprehensive coding manual was created in Microsoft Word. Microsoft Excel was used for literature search tracking and Google Sheets was used for data extraction, storage, and computation of study ES. Google Sheets allows for more than one researcher to enter and access data at a time. Finally, statistical analysis for the meta-analysis was run using SPSS and Biostat's Comprehensive Meta-Analysis (Borenstein, Hedges, Higgins, & Rothstein, 2015).

### **Statistical Analyses**

Meta-analyses, which pool weighted estimates of effects into a common metric across studies, taking into account study variability and yielding more power than individual studies (Aloe, 2014; Lipsey & Wilson, 2001), were conducted on the retrieved studies. In total, 14 individual meta-analyses were conducted across three levels ranging in scope from broad to narrow. Analyses were conducted across three levels to capture results from as many studies as possible without sacrificing individual differences. Findings from the analyses conducted on the broadest level of concepts may help account for the high degree of overlap inherent to individual cognitive constructs and cognitive instruments. For example, tests of learning and memory also require working memory and processing speed skills and tests of

cognitive flexibility require skills related to vigilance. Findings from the analyses conducted on the narrowest level of concepts, however, may help elucidate any important differences that may otherwise have been lost when averaged within broad constructs.

At the broadest level, all cognitive constructs were averaged to comprise cognition in general; this level involved only one meta-analysis that included all of the identified studies. The second set of analyses included the relatively broad constructs of abilities of focused behavior, learning and memory, and executive function. Mean effect sizes were calculated by averaging across multiple tests that were categorized according to one of the three broad constructs, resulting in 3 meta-analyses at this level. A final set of analyses, involving the narrowest level of constructs, included 10 individual meta-analyses, one for each dependent variable of cognition: constructs related to abilities of focused behavior included sustained attention, inhibitory control, processing speed, and working memory; constructs considered under the category of learning and memory were declarative memory - immediate, declarative memory - delayed, declarative memory – long-term, and non-declarative learning; and constructs associated with executive function were planning and decision-making and self-regulation. Tasks were coded according to these constructs based on previous research and cognitive theory presented in Chapter 2 (see Table 1 for measure selection).

Primary analyses included effect size calculation for maximum change in cognition of treatment compared to control. Additional analyses included visual inspection of outliers, homogeneity tests of ES distribution, analyses of publication bias, and exploration of potential moderating variables.

## Assessment of Effect Size

Effect size was calculated from a variety of statistics. Whenever possible, effect size was calculated using descriptive data, i.e., means and standard deviations. When descriptive statistics were not reported, statistics of  $F$  (in cases of  $df = 1$ ) and  $t$ , reported from inferential statistics were used. If both sample size and exact  $p$  values were reported, but  $F$  or  $t$  statistics were not, estimates of  $F$  and  $t$  statistics were computed interpolating from the  $t$ -distribution table of inverse distribution functions provided by Lipsey and Wilson (see Appendix B, Table 13, in Lipsey & Wilson, 2001). The order of degrees of approximation was based on recommendations by Lipsey and Wilson (2001), as well as the finding that compared to effect sizes based on inferential statistics, descriptive statistics lead to reduced bias in repeated measures designs (Ilieva et al., 2015; Dunlap, Cortina, Vaslow, & Burke, 1996). For missing raw data necessary for effect size computation, a request for more information was made to researchers; otherwise, studies with missing data for effect size computation were excluded.

Hedge's  $g$  was selected as the measure of effect size for the present study. Hedge's  $g$  was chosen because (a) the majority of studies reporting an effect size examining the effects of prescription stimulants on cognition reported standardized mean differences, (b) Hedge's  $g$  can be calculated when studies report insufficient descriptive statistics, and (c) when calculated among samples of at least 20, the magnitude of positive bias from Hedge's  $g$  as an estimator of the population parameter is small (Kline, 2004). Hedge's  $g$  (for standardized mean difference) and Proportion Difference were calculated and converted to standardized mean difference (Hedge's  $g$ )

for comparing across studies. Hedge's  $g$  is typically calculated by taking  $d$ , which is the difference of group means divided by the pooled within group standard deviation (Borenstein et al., 2009; Hedges, 1981; Lipsey & Wilson, 2001), then multiplying by the coefficient  $J$ , a correction factor to account for small sample bias defined as:

$$J = 1 - \frac{3}{4df-1} \quad (1)$$

(Borenstein et al., 2009). The formulas for calculating Hedge's  $g$  vary according to study design and available data. In general, however, the formula for Hedge's  $g$  is:

$$g = J \times d \quad (2)$$

(Borenstein et al., 2009; Lipsey & Wilson, 2001).

For studies using a between-subjects or parallel design, which compares a treatment and a control group, Hedge's  $g$ , pooled within group standard deviation ( $S_p$ ) and standard error of  $g$  ( $SE_g$ ) were calculated with the formulas below:

$$g_{BS} = J \times \frac{M_{DRUG} - M_{PBO}}{S_p} \quad (3)$$

$$S_{p_{BS}} = \sqrt{\frac{(n_{DRUG}-1)S_{DRUG}^2 + (n_{PBO}-1)S_{PBO}^2}{n_{DRUG} + n_{PBO} - 2}} \quad (4)$$

$$SE_{g_{BS}} = J^2 \times \sqrt{\frac{n_{DRUG} + n_{PBO}}{n_{DRUG}n_{PBO}} + \frac{d^2}{2(n_{DRUG} + n_{PBO})}} \quad (5)$$

(Borenstein et al., 2009; Lipsey & Wilson, 2001). When descriptive statistics were not available, but  $t$  statistics,  $F$  statistics and/or  $p$  values were reported, Hedge's  $g$  was calculated for a between-subjects or parallel design by using the following formulas:

$$g_{BS} = J \times t \sqrt{\frac{n_{DRUG} + n_{PBO}}{n_{DRUG}n_{PBO}}} \quad (6)$$

$$g_{BS} = J \times \sqrt{\frac{F(n_{DRUG} + n_{PBO})}{n_{DRUG}n_{PBO}}} \quad (7)$$

(Lipsey & Wilson, 2001). Note that if only  $p$  values were reported, the  $t$  statistic was interpolated from the  $t$ -distribution table of inverse distribution functions provided by Lipsey and Wilson (see Appendix B, Table 13, in Lipsey & Wilson, 2001).

Within-subjects or crossover designs require a different set of formulas for calculating Hedge's  $g$  than between-subjects or parallel designs. While between-subjects studies' natural unit of deviation is the standard deviation within groups, the standard deviation of the difference score ( $SD_{DIFF}$ ) is the statistic of interest for estimating the natural unit of deviation for within-subjects studies (Borenstein et al., 2009). In particular,  $SD_{DIFF}$  uncovers the relationship between variables as opposed to the variables themselves (Elliott et al., 1997). Because most studies did not report the standard deviation of the difference score, an estimate was calculated by using the following formula, where  $r$  refers to the population correlation of scores in treatment level drug with those in treatment level placebo, i.e., correlation of repeated measures:

$$SD_{DIFF} = \sqrt{SD_{DRUG}^2 + SD_{PBO}^2 - 2rSD_{DRUG}SD_{PBO}} \quad (8)$$

(Maxwell & Delaney, 2004). Because none of the studies included in the present analysis provided a measure of  $r$ , statistics of available test-retest reliability were used as an estimate of the correlation of repeated measures. In the cases where test-retest reliability was not available for a given test, reliability estimates reported for similar measures were used. Exact test-retest reliability coefficients used as an estimate of the correlation between repeated measures are displayed according to construct and measure in Appendix B.

Depending on the descriptive statistics provided by the studies, a number of formulas were available to calculate Hedge's  $g$  for within-subjects or crossover

studies. Formulas used to calculate Hedge's  $g$  and standard error of  $g$  for within-subjects or crossover designs using descriptive statistics are below:

$$g_{WS} = J \times \left( \frac{(M_{DRUG} - M_{PBO}) \times \sqrt{2(1-r)}}{SD_{DIFF}} \right) \quad (9)$$

$$SE_{g_{WS}} = J^2 \times \sqrt{\left( \frac{1}{n} + \frac{d^2}{2n} \right) 2(1-r)} \quad (10)$$

(Borenstein et al., 2009). Formulas used to calculate Hedge's  $g$  for within-subjects studies that only provided inferential statistics, i.e.,  $t$  statistics,  $F$  statistics (where  $df = 1$ ), and/or  $p$  values were:

$$g_{WS} = J \times t \sqrt{\frac{1}{n} [2(1-r)]} \quad (11)$$

$$g_{WS} = J \times \sqrt{\frac{F}{n} [2(1-r)]} \quad (12)$$

(Dunlap, Cortina, Vaslow, & Burke, 1996), where equation 12 was calculated based on the equation  $F = t^2$ .

One study reported results as a dichotomized variable (percent of improvement); therefore the following formula was used to convert proportion of differences to Hedge's  $g$ :

$$g = J \times (2 \times \arcsine[\sqrt{p_{drug}}] - 2 \times \arcsine(\sqrt{P_{PBO}})) \quad (13)$$

(Lipsey & Wilson, 2001).

Finally, many studies reported the standard error of the mean (SE), which was converted to standard deviation based on the formula:

$$S = SE\sqrt{n} \quad (14)$$

(Lipsey & Wilson, 2001; Meyers, Well, & Lorch, 2010).

## Weighting of Studies

After all effect sizes were extracted and converted to Hedge's  $g$ , they were weighted by their inverse variance weight ( $w$ ) in order to weight studies according to sample size. Inverse variance weight was calculated by taking the reciprocal of the standard error squared, reported in equations 5 and 10 for between and within-subjects designs respectively:

$$w = \frac{1}{SE_g^2} \quad (15)$$

## Confidence Intervals

A 95% Confidence Interval (CI) was computed for each effect size in order to provide a range of effect size estimates that the effect size is likely to fall 95% of the time. For Hedge's  $g$ , a 95% CI was estimated by first calculating  $g$  and the standard error, shown in the previous equations and then using the following formulas for a lower limit (LL) and an upper limit (UL) of the CI:

$$LL_g = g - 1.96 \times SE_g \quad (16)$$

$$UL_g = g + 1.96 \times SE_g \quad (17)$$

(Borenstein et al., 2009). CI estimates are reported numerically and graphed using a forest plot for each effect size.

## Interpretation of Effect Sizes

Cohen (1992) proposed estimates to assess the magnitude of the mean effect (Cohen's  $d$ ). Within Cohen's proposed conventions, magnitudes of effects may be considered small (0.20), medium (0.50) or large (0.80). The present study used these conventions as a general guide for interpreting effect size; however, estimates were also considered in the context of studies investigating ADHD medication efficacy,



which have reported significant standardized mean differences ranging between  $d = 0.4$  and  $d = 1.5$  for prescription stimulant and prostimulant medication (Faraone et al., 2006; Faraone & Glatt, 2010; Weyandt et al., 2014). These effects have varied by medication type, with one meta-analysis reporting a standardized mean difference of long-acting stimulants and prostimulants as  $d = 0.73$ , short-acting stimulants as  $d = 0.96$ , and nonstimulants as  $d = 0.39$  (Faraone & Glatt, 2010). While these effect sizes relate to the reduction of ADHD symptomology, magnitudes of effects related to enhanced cognition could be expected to follow a similar, but likely smaller, convention.

### **Homogeneity of Variance**

Homogeneity of variance is important to consider prior to combining effect sizes across studies as it represents an estimate of excess or true variance.

Homogeneity of the effect size distribution was tested visually, with forest plots, and statistically, with the use of the  $Q$  statistic and  $I^2$  (95% CI) index. The  $Q$  statistic is a standardized measure that approximates to a chi-square distribution with  $k - 1$  degrees of freedom, where  $k$  is the number of studies (Hedges & Olkin, 1984; Huedo-Medina, Sánchez-Meca, Marín-Martínez, & Botella, 2006) and a statistically significant  $Q$  is indicative of a heterogeneous distribution, signaling the potential to test for moderators (Lipsey & Wilson, 2001), where:

$$Q = \sum_{i=1}^k w_i (g_i - M)^2 \quad (18)$$

(Borenstein et al., 2009; Lipsey & Wilson, 2001); for this formula,  $w_i$  is equal to the study weight ( $\frac{1}{SE^2}$ ),  $g_i$  refers to the study ES,  $M$  is the summary effect, and  $k$  represents the number of studies (ES) (Borenstein et al., 2009; Lipsey & Wilson, 2001).

## **Model of Analysis**

A random effects model, which assumes that measured effect sizes are subject to sampling error and random effects variance (Lipsey & Wilson, 2001), was chosen *a priori* given the heterogeneity of the design of studies and cognitive measures as recommended by Field and Gillett (2010) and Hunter and Schmidt (2000) (however results from both a random and fixed effects model are reported). Biostat's Comprehensive Meta-analysis was used to provide a random effects mean effect size, computed by weighting each effect size by the inverse of its variance ( $w_i$ ), and confidence intervals, computed by multiplying the standard error by a critical  $z$ -value (Hedges & Olkin, 1984). Therefore, each study was weighted by the inverse of its variance calculated for a random effects model, which not only includes the within-study variance, but also an estimate of between-study variance (Borenstein et al., 2009).

## **Statistical Tests of Moderators**

An important consideration regarding meta-analysis is its susceptibility to overlook important influences, such as the social context of the study, the quality of the study, and theoretical influences/implications (Lipsey & Wilson, 2001). For example, in their meta-analysis assessing stimulant effects on ADHD symptomatology, Faraone & Glatt (2010) suggested systematic variability across methodology between classes of drugs may have produced misleading results. Therefore, the present study sought not only to measure the enhancing neurocognitive effects of prescription stimulant medications, but also to investigate variables that may moderate these effects by comparing the variance between two groups. Statistical tests

of moderators were conducted for variables identified *a priori* as described previously (dose, timing of dose, type of drug, baseline functioning, ADHD status), as well as any of the additional variables yielding a significant  $Q$  statistic. Because the moderating variables of interest were both categorical (type of drug, ADHD status) and continuous (dose, timing of dose, baseline functioning), analog to analysis of variance (ANOVA) and weighted regression analysis (meta-regression) were run for tests of moderators.

A mixed effects model, which uses a random effects model for the combination of studies within subgroups and a fixed effects model across each subgroup (Borenstein et al., 2009), was used to test categorical moderators (i.e., subgroup analysis). Subgroup analyses were conducted with the analog to ANOVA, which is similar to a standard ANOVA given both the pooled group variance ( $Q_W$ ) and the between group variance ( $Q_B$ ) were used with the formulas:

$$Q_W = \sum_{i=1}^k w_i (g_i - M_j)^2 \quad (19)$$

and

$$Q_B = \sum_{i=1}^k w_j M_j^2 - \frac{(\sum w_j M_j)^2}{\sum w_j} \quad (20)$$

where  $w_j$  is equal to the sum of weights for each subgroup,  $M_j$  refers to the weighted mean effect size for each subgroup,  $w_i$  is equal to the study weight ( $\frac{1}{SE^2}$ ),  $g_i$  refers to the study effect size,  $M$  is the summary effect,  $k$  represents the number of studies (effect size) and  $j$  refers to the number of groups (Borenstein et al., 2009; Lipsey & Wilson, 2001).

To test for the continuous moderators, a mixed effects model (method of moments) for weighted regression analysis or meta-regression was used. Similar to

regression or multiple regression, meta-regression assesses level of study as a covariate and uses effect sizes as dependent variables, as opposed to level of subject and individual scores in regressions (Borenstein et al., 2009). A  $Q$  test, similar to that of the  $Q$  test for the analog to ANOVA, was run to assess multiple predictor variables simultaneously. The  $Q$  statistic was separated into the variability accounted for by the regression ( $Q_R$ ) and the error or residual variance ( $Q_V$ ), the comparable statistics to  $Q_W$  and  $Q_B$  in the analog to ANOVA, respectively (Borenstein et al., 2009; Lipsey & Wilson, 2001).

To assess an analog to proportion of variance, *true* variance explained was calculated by:

$$R^2 = 1 - \left( \frac{T_{unexplained}^2}{T_{total}^2} \right) \quad (21)$$

where  $R^2$  represents the variance of true effect sizes across studies (Borenstein et al., 2009).

### **Assumption of Independence**

Meta-analysis relies on the assumption that each measure of effect is representative of independent studies. Yet, most studies investigating prescription stimulant effects reported findings from multiple outcomes, yielding a potential for multiple effect size estimates. Therefore, a protocol to handle studies with more than one effect size was used, including the following guidelines:

- (1) When more than one cognitive construct was reported within a single study, data were calculated to estimate effect sizes for each construct separately and used in separate meta-analyses of each narrow construct (e.g., sustained attention, inhibitory control, working memory, etc.). Mean effect sizes from

these narrow constructs were then averaged together to calculate a mean effect size for each of the three broader constructs. Specifically, for abilities of focused behaviors, a mean effect size was calculated by averaging sustained attention, inhibitory control, working memory, and processing speed; the mean effect size for learning and memory was calculated by averaging declarative memory (immediate, delayed, and long-term) and non-declarative memory; and planning and decision-making and self-regulation were averaged together to calculate the mean effect size for executive function. Similarly, mean effect sizes from these three broader constructs were then averaged together to calculate a mean effect size for cognition in general.

- (2) When data were available to calculate an effect size generated from multiple measures per construct in a single study, only the most relevant measures were averaged to calculate a single effect size. Relevant measures were determined separately for each construct and were reported previously (see Table 1).
- (3) When data were available to calculate more than one effect size because a single study investigated the cognitive effects of multiple drug doses, effect sizes across doses were averaged and estimates of doses were averaged (e.g., a study investigating the cognitive effects of 10mg and 20 mg of MPH was averaged to 15mg of MPH).
- (4) When data were available to calculate more than one effect size because a single study investigated more than one type of stimulant medication (e.g., d-AMP and MPH), effect sizes were averaged for both drug types. If data were available to calculate more than one effect size due to the inclusion of a

stimulant and non-stimulant medication, however, only data related to the stimulant medication were selected.

- (5) When data were available to calculate more than one effect size within a single study exploring stimulant effects on both adults with and without ADHD, only effect sizes from adults with ADHD were included given fewer studies investigated populations of adults with ADHD.
- (6) Effect sizes from studies that investigated effects across varying time intervals of drug administration were averaged (e.g., a study measuring WM at 60 and 120 minutes post drug administration was averaged to 90 minutes). Exceptions to this convention were studies that included data across multiple time-points for declarative learning and memory, where outcome variables were calculated separately for immediate (less than 20 minutes after learning), delayed (a minimum of 20 minutes, but occurring the same day as learning), and long-term (a minimum of 1 day). For the broader construct of learning and memory, however, these effect sizes, as well as any calculated from non-declarative learning and memory, were averaged together to calculate a mean effect size.
- (7) Effect sizes from studies that investigated effects across multiple sessions were averaged.

## **Outliers**

In order to verify accurate data entry and to account for potential effects of context within studies, a careful examination of any study level effect size outliers was conducted. In the case where outliers were identified because of large sample sizes, parallel analyses that included and excluded these outliers were conducted. To

maintain as much data as possible, only extreme outliers (falling more than 3 standard deviations away from the mean) that were identified as irrelevant or out of context were removed from the final analysis.

### **Missing Data**

Missing data can refer to missing studies, where studies cannot be identified (further discussed in the section on publication bias), missing effect sizes, where data are unavailable to calculate an effect sizes within a study, and missing moderators. While efforts were made to request descriptive and/or inferential data for every eligible study that was missing the necessary data to calculate measures of effects, studies where data were not available for effect size calculations were excluded from the final analysis.

Most studies reported descriptive data across variables that resulted in both positive and negative effect sizes. Therefore, when data were missing and was reported simply as significant or “non-significant,” without a  $t$  or  $F$  statistic or descriptive data, no effect size was recorded. For studies that reported enough data to calculate the effect size for significant outcomes only, but did not report the minimal data to compute an effect size for other outcomes of the same construct (reported as “non-significant”), a dummy variable with the effect size set to zero was used to account for positive bias. For example, Finke et al. (2010) provided the means and standard deviations, as well as the  $t$  statistic, for significant differences between MPH and PBO found within adults with low baseline scores, but did not reported any descriptive statistic data for the “non-significant” differences between drug groups within the high performing group. To estimate an effect size for comparing across

studies (that did not separate findings by baseline functioning), the effect size was calculated by averaging the significant findings with an effect size of zero. On the other hand, Fillmore, Kelly, and Martin (2004) reported both significant and “non-significant” *p*-values from simple effects tests for a measure of processing speed, but did not report enough statistics to calculate any effect size for drug effects on inhibitory control. In this case, an effect size including all outcome measures was calculated for processing speed, but no effect size was calculated for inhibitory control.

Regarding missing moderator data, case analysis for studies that did report moderator data were employed. A decision to omit data, as opposed to imputing data, was made given the variability across studies. For ANOVA analog, results were calculated with the inclusion of missing categories, as well as with the exclusion of these categories.

### **Publication Bias**

Publication bias, which generally refers to the increased likelihood of studies with significant findings being published compared to studies without significant findings, may stem from missing data within included studies (e.g., when data were extracted from studies that only report significant findings as described previously) or from missing data that cannot be extracted from studies because they were never published due to non-significant findings. The latter phenomenon is referred to as the “file drawer” problem, which can significantly distort and misrepresent the size of effects found through meta-analysis (Bradley & Gupta, 1997). The present study utilized a variety of methods aimed at reducing the level of publication bias during the



literature search and retrieval process and during the stage of analysis. First, focused efforts were made during the search and retrieval process to access unpublished data (i.e., dissertations), as well as missing articles through interlibrary loan and by way of contacting researchers directly. In a similar vein, researchers were contacted with requests for missing data in the cases where retrieved articles did not provide sufficient data to calculate an estimate of effect size. During the analysis stage, six different methods were utilized to assess level and presence of publication bias: Egger's regression index, the funnel plot, Duval and Tweedie's trim and fill, Rosenthal's *fail-safe* N, Orwin's adapted version of Rosenthal's *fail-safe* N, and an assessment of publication bias as a moderating variable.

In order to assess the presence of sampling bias on the mean effects, both visual inspection of a funnel plot and a statistical evaluation of Egger's test of funnel plot asymmetry with regression intercept (Egger, Smith, Schneider, & Minder, 1997; Lipsey & Wilson, 2001). Funnel plots are a visual display of effect sizes by their standard errors where studies with smaller error variances are clustered near the top of the plot and studies with larger error variances are dispersed near the bottom of the plot, falling to the right and left of the mean. Visual inspection reveals the presence of bias when higher numbers of studies are shown to the bottom and right of the mean, which indicates studies relying on small sample sizes and generating large effect sizes.

It is important to note, however, that this method of visual inspection can be difficult to interpret and may not always proffer an accurate representation of bias - for example, the heterogeneity of the studies may also influence the dispersion of studies (Egger et al., 1997). Therefore, Egger's test of funnel plot asymmetry with regression

intercept, which provides a quantitative estimate of the bias represented in the funnel plot (Borenstein et al., 2009), was also used to assess the presence publication bias. For this test, the standardized effect (i.e., the effect size divided by standard error) is regressed on the inverse of the standard error, an estimate of precision. Studies with higher estimates of standard error yield a precision estimate that is closer to zero and thus tend to represent studies relying on small sample sizes. Conversely, studies with lower estimates of standard error yield a precision estimate moving away from zero, indicating studies with more robust sample sizes. The absence of bias is represented by a regression line that approaches the intercept of the origin and the presence of bias is depicted by a regression line that deviates from this pattern.

Duval and Tweedie's trim and fill analysis was utilized to identify how eliminating the bias would impact the measure of effect (Borenstein, 2009). Specifically, this analysis identifies specific studies to be trimmed, leading to a symmetrical funnel plot. Following the general guidelines of four or more studies indicating a high risk of publication bias (Borenstein et al., 2009; Sutton, 2009), imputations were conducted only for analyses that revealed four or more. Once identified, studies were removed from contributing to the overall mean effect. In order to calculate variance, however, the identified studies were then returned to the analysis by imputing mirror images on the opposite side of the funnel plot.

In order to assess the magnitude of the effects of publication bias, Rosenthal's *fail-safe* N and Orwin's adapted version of Rosenthal's *fail-safe* N were used. Rosenthal's method, intended to account for the *file-drawer* effect, computes the number of missing studies with nil effects that would need to be added to the analyses

in order to yield a non-significant effect (i.e.,  $p > .05$ ) (Borenstein, 2009) and can be calculated by:

$$N_R = \frac{[\sum Z(p_i)]^2}{Z_\alpha^2} - n \quad (22)$$

(Rosenberg, 2005). For this equation,  $n$  signifies the number of studies,  $Z(p_i)$  represents the Z-scores for significance values, and  $Z_\alpha$  is the one-tailed Z-score connected to the predetermined alpha-level. This method has been criticized for a number of reasons, namely that it relies on statistical significance as opposed to clinical significance and that it assumes the missing studies' mean effect size to be non-significant (Borenstein, 2009). Therefore, Orwin's method was also employed, which determines the number of studies with predetermined effect sizes needed to reduce the mean effect size to a predetermined level, in this case .10, which would represent very small effects (Lipsey & Wilson, 2001). Orwin's N was calculated using the following equation:

$$N_O = \frac{n(\bar{E}_O - \bar{E}_m)}{\bar{E}_m - \bar{E}_n}, \quad (23)$$

where  $n$  represented the number of studies,  $\bar{E}_O$  represented the mean of the studies computed in the meta-analysis,  $\bar{E}_n$  reflected the mean of the added  $N_O$  studies, and  $\bar{E}_m$  was the predetermined effect size (Rosenberg, 2005). Finally, the present study also included an assessment of publication bias within published studies by including a variable of publication bias as a potential moderating variable as described previously (i.e., studies reporting only significant findings were identified and coded).

## CHAPTER 5: RESULTS

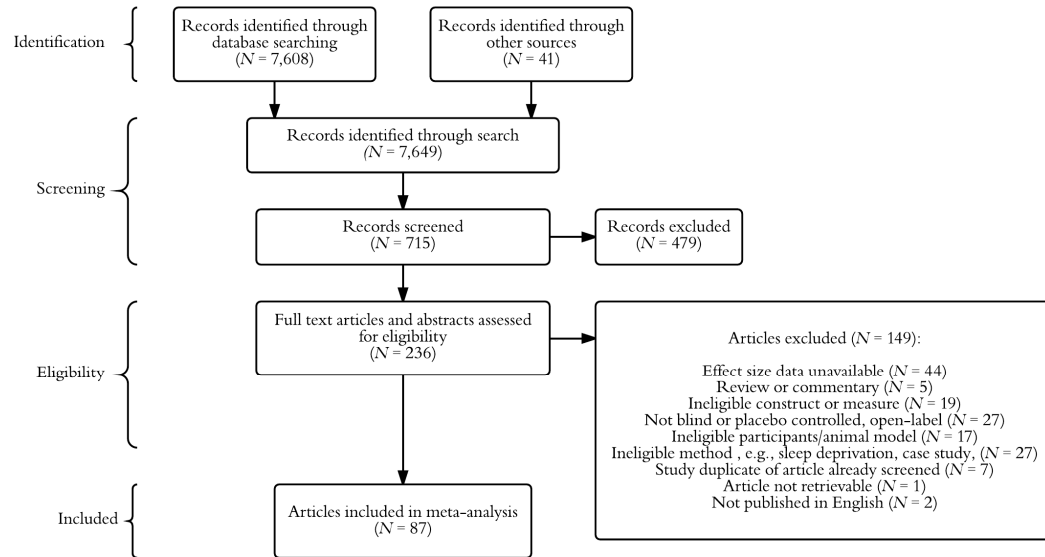
### Search Results

The search process is summarized in Figure 1. A total of 7,608 titles were initially identified via the bibliographic databases PsycINFO (2,445), MEDLINE (3,683), ScienceDirect (670), and Dissertations and Theses (809) based on the keyterms listed previously. Forty-one studies were identified from review articles examining the effects of ADHD medication on cognition. Based on a manual review of titles, 715 abstracts were selected for review for eligibility based on inclusion criteria. Of the reviewed abstracts, a total of 236 titles were identified as potentially meeting criteria and these publications were retrieved or requested. After manual review of full text, another 105 titles were eliminated based on eligibility criteria. A total of 131 titles were maintained, meeting all inclusion criteria. After a thorough examination of available effect size statistics, 52 manuscript titles and 3 dissertation titles were identified as eligible for inclusion, but missing data. Of these titles, researchers of 39 publications were contacted with requests for missing data; contact information was unavailable for the remaining 13 researchers. Researchers of 11 studies supplied the required effect size statistics and were maintained in the study. The remaining 44 titles (including 50 studies) that met inclusion criteria, but did not have sufficient data to calculate effect sizes, are described in Appendix C.

A final 87 titles, including 91 studies (four titles reported for two separate studies) reporting data to calculate at least one effect size were included in this study. Included studies resulted in a total of 2,778 participants for this study. Data were extracted from original manuscripts and raw data sent from researchers. Final studies

included in the study were published between 1958 and 2014. Characteristics of the final 91 studies included in analyses can be seen in Tables 2 and 3.

*Figure 1*  
Search and Retrieval Process Results



**Table 2**  
*Characteristics of Studies Included for ADHD Medication Effects on Neurocognitive Enhancement of Cognition*

Study	Instrument(s) (Construct)	ADHD Status	N	Recruitment	Ethnicity (Percent)	Mean Age (Range)	Percent Female	Design (days between treatment)	Adminis- tration Type	Medi- cation (Type)	Average Dose (Level)	Dose Time (Acti- vation)
Agay, Yechiam, Carmel, & Levkovitz (2010)	DS (WM) TOVA (V, IC) IGT (PD) RPM (CF)	Yes	26	Clinic; Community	NR	32.25	57.69	Parallel	Fixed	MPH (SA)	15-mg (Low)	40 (Prior)
Agay, Yechiam, Carmel, & Levkovitz (2014)	DS (WM) WM Task (WM) TOVA (V) IGT (PD)	Yes	20	Community	NR	20.9 (20- 40)	NR	Crossover (NR)	Fixed	MPH (SA)	0.28- mg/kg (Low)	60 (During)
Allman et al. (2010)	Antisaccade (IC)	No	24	NR	NR	NR (18-34)	29.17	Crossover (2)	Fixed	AMP (SA)	0.3-mg/kg (Low)	180 (During)
Allman, Ettinger, Joobar, & O'Driscoll (2012)	Antisaccade (IC)	No	29	NR	Caucasian (100%)	26.2	0	Crossover (6)	Fixed	MPH (SA)	20-mg (Low)	90 (During)
Aron, Dowson, Sahakian, & Robbins (2003)	Stop-Signal Task (IC)	Yes	13	Clinic	NR	26.2 (18- 41)	23.08	Crossover (3)	Fixed	MPH (SA)	30-mg (Low)	75 (During)
Ballard, Gallo, & de Wit (2013)	Recall of Pictures (DM-L)	No	25	University; Community	NR	NR (18-35)	48.00	Crossover (NR)	Fixed	AMP (SA)	15-mg (Low)	2880 (After)
Ballard, Gallo, & de Wit (2014)	Recall of Pictures (DM-L) Recognition of Words (DM-L)	No	31	Community	NR	22.6 (18- 35)	51.61	Crossover (NR)	Fixed	AMP (SA)	15-mg (Low)	86.25 (Prior)
Barch & Carter (2005)	Stroop (IC) DLT(WM)	No	22	Community	NR	36.6	45.45	Crossover (2)	Fixed	AMP (SA)	0.25- mg/kg (Low)	150 (During)
Barkley, Murphy, O'Connell, & Connor (2005)	CPT (V, IC)	Yes	56	Clinic	White (83%); African American (3.7%); Hispanic (5.6%); Native American (5.6%); Other (1.9%)	31.3 (18- 65)	25.93	Crossover (7)	Fixed	MPH (SA)	15-mg (Low)	75 (During)

Study	Instrument(s) (Construct)	ADHD Status	<i>N</i>	Recruitment	Ethnicity (Percent)	Mean Age (Range)	Percent Female	Design (days between treatment)	Adminis- tration Type	Medi- cation (Type)	Average Dose (Level)	Dose Time (Acti- vation)
Ben-Itzhak, Giladi, Gruendlinger, Hausdorff (2008)	Go/No-Go (IC) Recognition of Object Orientation (DM-I)	No	26	Community	NR	73.18 (65- 90)	65.38	Crossover (7)	Fixed	MPH	20-mg (Low)	120 (during)
Boonstra, Kooij, Oosterlaan, Sergeant, & Buitelaar (2005)	CPT (V, IC) Stop Signal (IC)	Yes	43	Clinic	NR	38.4	51.16	Crossover (7)	Titrated	MPH (SA)	.75-mg/kg (High)	75 (During)
Breitenstein et al. (2004)	AWL (NDL)	No	40	University	NR	25.12 (20- 33)	0	Parallel	Fixed	AMP (SA)	0.25- mg/kg (Low)	120 (During)
Brignell, Rosenthal, & Curran (2007)	Recognition of Story (DM-I) Recall of Object (DM-I) Recall of Story (DM-D)	No	48	NR	NR	22.8 (18- 35)	52.08	Parallel	Fixed	MPH (SA)	40-mg (High)	120 (During)
Bron et al. (2014)	CPT (V, IC) TOVA (V, IC)	Yes	22	Clinic	NR	30.5 (18- 55)	22.73	Crossover (7)	Titrated	MPH (LA)	54-mg (High)	NR
Brumaghim, Klorman, Strauss, Lewine, & Goldstein (1987)a	SMT (WM)	No	19	University	NR	19.37	0	Crossover (NR)	Fixed	MPH (SA)	21.84-mg (Low)	70 (During)
Brumaghim, Klorman, Brumaghim, Klorman, Strauss, Lewine, & Goldstein (1987)b	SMT (WM)	No	14	University	NR	20	57.14	Crossover (NR)	Fixed	MPH (SA)	21.84-mg (Low)	70 (During)
Burns, House, Fensch, & Miller (1967)	Learning Task (NDL)	No	30	NR	NR	NR	NR	Parallel	Fixed	AMP (SA)	15-mg (Low)	150 (During)
Campbell- Meiklejohn et al. (2012)	<i>n</i> -back (WM)	No	38	Community	NR	23	100	Parallel	Fixed	MPH (SA)	20-mg (Low)	62 (During)
Chamberlain et al. (2007)	Stop Signal (IC) SWM (WM) RVIP (V, IC) IDED (SR)	Yes	20	Clinic	NR	NR	0.30	Crossover (5)	Fixed	ATX (LA)	60-mg (Low)	120 (During)
Chamberlain et al. (2009)	Stop Signal (IC)	No	19	Community	NR	28.95 (19- 46)	0	Crossover (5)	Fixed	ATX (LA)	40-mg (Low)	90 (During)

Study	Instrument(s) (Construct)	ADHD Status	<i>N</i>	Recruitment	Ethnicity (Percent)	Mean Age (Range)	Percent Female	Design (days between treatment)	Adminis- tration Type	Medi- cation (Type)	Average Dose (Level)	Dose Time (Acti- vation)
Chevassus et al. (2013)	Stroop (IC) Recall of Pictures (DM-1) DS (WM) DSST (PS) SRT (PS) CRT (PS)	No	12	NR	NR	26 (21-35)	0	Crossover (17)	Fixed	MPH (SA)	20-mg (Low)	150 (After)
Clark, Geffen, Geffen (1986a)	Task of Attention (IC)	No	12	NR	NR	NR (18-30)	0	Crossover (NR)	Fixed	MPH	0.65- mg/kg (High)	60 (during)
Clatworthy et al. (2009)	SWM (WM) Reversal Learning (SR)	No	10	Community	NR	NR (22-32)	0	Crossover (3)	Fixed	MPH (SA)	60-mg (High)	60 (During)
Coons et al. (1981)a	CPT (V, IC)	No	13	Clinical	NR	23.84	0	Crossover (6.9 (mean))	Fixed	MPH	20-mg (Low)	105 (During)
Coons et al. (1981)b	CPT (V, IC)	No	23	University	NR	19.68	0	Crossover (7.61 (mean))	Fixed	MPH	20-mg (Low)	87.5 (During)
Costa et al. (2013)	Go/No-Go (V, IC) Stop-Signal (IC)	No	50	6	NR	23.65 (18- 30)	0	Crossover (7)	Fixed	MPH	40-mg (High)	60 (during)
de Bruijn, Hulstijn, Verkes, Ruijt, & Sabbe (2004)	Flanker (IC)	No	12	NR	NR	22.58 (19- 39)	41.67	Crossover (NR)	Fixed	AMP (SA)	15-mg	210 (After)
de Wit, Enggasser, & Richards (2002)	DS (WM)	No	26	6	63.89% Caucasian; 2.78% African- American; 16.67% Asian; 16.67% Hispanic	24 (18-44)	0.5	Crossover (3)	Fixed	AMP	15-mg (Low)	NR
Duke & Keeler (1968)	TMT-A (PS) TMT-B (WM)	No	8	University	NR	NR	0	Crossover (NR)	Fixed	AMP (SA)	30-mg (High)	NR



Study	Instrument(s) (Construct)	ADHD Status	<i>N</i>	Recruitment	Ethnicity (Percent)	Mean Age (Range)	Percent Female	Design (days between treatment)	Adminis- tration Type	Medi- cation (Type)	Average Dose (Level)	Dose Time (Acti- vation)
DuPaul et al. (2012)	CVLT (DM-I, DM-D) CPT (V, IC)	Yes	24	University	African American (4.17%); White (91.67%); Asian/Pacif ic Islander (4.17%)	20.17 (18- 23)	37.5	Crossover (0)	Fixed	LDX (LA)	50-mg (High)	180 (During)
Elliott et al. (1997)	SWM (WM) RVIP (V) NTOL (PD) IDED (SR) VF (SR) RAT (SR) GEF (SR)	No	28	Community	NR	21.25	0	Crossover (7)	Fixed	MPH (SA)	30-mg (Low)	90 (During)
Farah, Haimm, Sankoorikal, Smith, & Chatterjee (2009)	AUT (SR) Drawing of TTA (SR)	No	16	NR	NR	21.25 (21- 30)	75.00	Crossover (7)	Fixed	AMP (SA)	10-mg (Low)	30 (Prior)
Faraone et al. (2005)	Stroop (IC)	Yes	536	Clinic	NR	NR	NR	Parallel	Titrated	ATX (LA)	90-mg (High)	NR
Fillmore, Kelly, & Martin (2005)	RIP (WM)	No	22	NR	NR	21.5 (18- 30)	54.54	Crossover (2)	Fixed	AMP (SA)	11.25- mg/70-kg (Low)	90 (Prior)
Finke et al., 2010	Whole-report task (PS, DM-I) RVALT (DM-I) PAL Task (DM-I)	No	18	Community	NR	NR (20-35)	50	Crossover (7)	Fixed	MPH	40-mg (High)	180 (after)
Fleming, Bigelow, Weinberger, & Goldberg (1995)	SDR (WM) CPT (V, IC) COWAT (SR) WCST (SR)	No	17	Community; Institution websites	NR	27.5	47.06	Crossover (7)	Fixed	AMP (SA)	0.25- mg/kg (Low)	60 (Prior)
Gilbert, Donnelly, Zimmer, & Kubis (1973)	DS (WM) GMT (DM-I)	No	78	Community	NR	NR (60-NR)	NR	Parallel	Titrated	MPH (SA)	20-mg (Low)	NR
Graf et al. (2011)	Go/No-Go (IC)	No	12	NR	NR	27.1	0	Crossover (6)	Fixed	ATX (LA)	80-mg (High)	120 (During)
Halliday, Callaway, Naylor, Gratzinger, & Prael (1986)a	SERS (PS)	No	16	Community	NR	NR (30-60s)	100	Crossover (7)	Fixed	MPH (SA)	10-mg (Low)	45 (Prior)

Study	Instrument(s) (Construct)	ADHD Status	<i>N</i>	Recruitment	Ethnicity (Percent)	Mean Age (Range)	Percent Female	Design (days between treatment)	Adminis- tration Type	Medi- cation (Type)	Average Dose (Level)	Dose Time (Acti- vation)
Halliday, Callaway, Naylor, Gratzinger, & Prael (1986)b	SERS (PS)	No	24	Community	NR	26 (21-69)	0	Crossover (7)	Fixed	MPH; AMP (SA)	10-mg (Low)	45 (Prior)
Hester et al. (2012) Nandam, Hester, & Bellgrove (2014)	Go/No-Go (IC)	No	27	University	NR	22 (18-35)	0	Crossover (7)	Fixed	MPH (SA)	30-mg (Low)	120 (During)
Hink, Fenton, Pfefferbaum, Tinklenberg, & Kopell (1978)	AAT (V, IC)	No	16	NR	NR	NR (20-28)	0	Crossover (2)	Fixed	MPH	10-mg (Low)	60 (during)
Ideström & Schalling (1970)	Stroop (IC) DSST (PS) RTT (PS) Go/No-Go (IC) Flanker (IC) Recognition of Faces (DM-D)	No	22	Military	NR	NR (19-22)	0	Crossover (NR)	Fixed	AMP (SA)	10-mg/70- kg (Low)	60 (Prior)
Ilieva , Boland , & Farah (2013)	Recognition of Words (DM-D) DS (WM) <i>n</i> -back (WM) RAT (SR) GEF (SR)	No	46	University; Community	Caucasian (100%)	24 (21-30)	66.67	Crossover (7)	Fixed	AMP (SA)	20-mg (High)	75 (Prior)
Izquierdo et al. (2008)	Retention of facts (DM-L)	No	20	NR	NR	NR (35-74)	45.00	Parallel	Fixed	MPH (SA)	10-mg (Low)	5760 (After)
Kinsbourne, De Quiros, & Tocci Rufo (2001)	PAL (DM-I)	Yes	17	Clinic	NR	34	58.82	Crossover (NR)	Fixed	MPH (SA)	11.67-mg (Low)	120 (During)
Kollins et al. (2015)	<i>n</i> -back (WM) CPT (V, IC) SMR (PS)	No	16	NR	NR	24.6 (18- 45)	37.50	Crossover (2)	Fixed	MPH (SA)	25-mg (Low)	150 (After)
Kornetsky (1958)	CVA (PS) SLT (NDL)	No	8	NR	NR	NR (18-22)	37.50	Crossover (NR)	Fixed	AMP (SA)	8.5-mg (Low)	150 (During)
Kratz et al. (2009)	Go/No-Go (V, IC)	No	14	NR	NR	NR (20-40)	42.86	Crossover (7)	Fixed	MPH	20-mg (low)	95 (during)
Levin, Conners, Silva, Canu, & March (2001)	CPT (V, IC)	Yes	20	NR	NR	37.75 (19- 56)	35.00	Parallel	Fixed	MPH (MA)	20-mg (Low)	NR
Linssen et al. (2011)	SRT (PS)	No	19	2	NR	23.4 (19- 37)	0	Crossover (2)	Fixed	MPH	20-mg (Low)	155 (after)

Study	Instrument(s) (Construct)	ADHD Status	<i>N</i>	Recruitment	Ethnicity (Percent)	Mean Age (Range)	Percent Female	Design (days between treatment)	Adminis- tration Type	Medi- cation (Type)	Average Dose (Level)	Dose Time (Acti- vation)
Linssen, Vuurman, Sambeth, & Riedel (2012)	Stop-Signal (IC) SWM (WM) NTOL (PD) IDED (SR) RVALT (DM-I, DM-D, DM-L)	No	19	Community	NR	23.4 (19- 37)	0	Crossover (2)	Fixed	MPH (SA)	23.33-mg (Low)	90 (During)
Linssen, Sambeth, Vuurman, & Riedel (2014)	PAL (DM-I) SWM (WM) SMT (WM)	No	30	Community	NR	20.7 (18- 28)	33.33	Crossover (2)	Fixed	MPH (SA)	40-mg (High)	120 (During)
Makris, Rush, Frederich, Taylor, & Kelly (2007)	SNRT (WM) DSST (PS) RA (NDL)	No	11	University; Community	African American (8.33%); Caucasian (36.36%); Hispanic (25%); Pacific Islander (8.33%); Asian/Nativ e American (8.33%); Asian/Cauc asian (8.33%)	26.3 (21- 35)	54.54	Crossover (2)	Fixed	AMP (SA)	0.08- mg/kg (Low)	155 (During)
Marquand et al. (2011)	Spatial Location (WM)	No	15	University; Community	NR	NR (20-39)	0	Crossover (NR)	Fixed	MPH (SA)	30-mg (Low)	135 (After)
Mattay et al. (1996)	WCST (SR)	No	8	NR	NR	25 (22-32)	50	Crossover (7)	Fixed	AMP (SA)	0.25- mg/kg (Low)	120 (During)
Mattay et al. (2000)	<i>n</i> -back (WM)	No	10	NR	NR	30	20	Crossover (7)	Fixed	AMP (SA)	0.25- mg/kg (Low)	120 (During)
Mehta et al. (2000)	SWM (WM)	No	10	NR	NR	34.8	0	Crossover (14)	Fixed	MPH (SA)	40-mg (High)	90 (During)

Study	Instrument(s) (Construct)	ADHD Status	<i>N</i>	Recruitment	Ethnicity (Percent)	Mean Age (Range)	Percent Female	Design (days between treatment)	Adminis- tration Type	Medi- cation (Type)	Average Dose (Level)	Dose Time (Acti- vation)
Moeller et al. (2014)	Stroop (IC)	No	15	Community	African American (66.67%); Caucasian (20.00%); Other (13.33%)	38.9	6.67	Crossover (7)	Fixed	MPH (SA)	20-mg (Low)	90 (During)
Muller et al. (2005)	Motor Reaction Task (PS)	No	12	Community	NR	69.8 (61- 80)	66.67	Crossover (7)	Fixed	MPH (SA)	20-mg (Low)	90 (During)
Nandam et al. (2011)	Stop-Signal (IC)	No	24	University	NR	NR (18-35)	0	Crossover (7)	Fixed	MPH (SA)	30-mg (Low)	165 (After)
Naylor, Halliday, & Callaway (1985)	SERS (PS)	No	8	University	NR	NR (30-39)	100	Crossover (7)	Fixed	MPH	11.67-mg (Low)	45 (Before)
Oken, Kishiyama, & Salinsky (1995)	DS (WM) SOT (PS) VST (PS)	No	23	NR	NR	25 (21-39)	52.17	Crossover (NR)	Fixed	MPH (SA)	0.20mg- /kg (Low)	60 (During)
Pauls et al. (2012)	Stop-Signal (IC)	No	16	2	NR	23.6 (19- 30)	0	Crossover (5)	Fixed	MPH	40-mg (High)	90 (during)
Ramasubbu, Singh, Zhu, & Dunn (2012)	<i>n</i> -back (WM)	No	13	University	NR	28	61.54	Crossover (1)	Fixed	MPH (SA)	20-mg (Low)	60 (During)
Rapoport, Buchsbaum, & Weingartner (1980)	CPT (V)	No	31	University	NR	22.35 (18- 30)	0	Crossover (2)	Fixed	AMP (SA)	0.38- mg/kg (High)	47.5 (Prior)
Rogers et al. (1999)	IDED (SR)	No	32	NR	NR	20.5	0	Parallel	Fixed	MPH (SA)	40-mg (High)	NR
Samanez-Larkin et al. (2013)	DSST (PS) SCT (SR)	No	40	NR	NR	22.4 (18- 31)	47.5	Crossover (1)	Fixed	AMP (SA)	0.43- mg/kg (High)	90 (Prior)
Schlösser et al. (2009)	Probabilistic Learning (NDL)	No	12	NR	NR	26.8	0	Crossover (0)	Fixed	MPH	40-mg (High)	90 (during)
Servan-Schreiber, Carter, Bruno, & Cohen (1998)	Flanker (IC)	No	10	2	NR	NR (24-39)	50	Crossover (3)	Fixed	AMP	0.25- mg/kg (Low)	120 (during)
Silber, Croft, Papafotiou, & Stough (2006)	DS (WM) TMT-B (WM) DSST (PS) TMT-A (PS) DVT (V, IC)	No	20	Community	NR	25.4 (21- 32)	50.00	Crossover (7)	Fixed	AMP (SA)	0.42- mg/kg (High)	180 (During)
Sofuoglu, Waters, Mooney, & Kosten (2008)	SART (V, IC)	No	12	Community	NR	27.7	41.67	Crossover (3)	Fixed	AMP (SA)	20-mg (High)	120 (During)

Study	Instrument(s) (Construct)	ADHD Status	<i>N</i>	Recruitment	Ethnicity (Percent)	Mean Age (Range)	Percent Female	Design (days between treatment)	Adminis- tration Type	Medi- cation (Type)	Average Dose (Level)	Dose Time (Acti- vation)
Spencer et al., 1998	Stroop (IC)	Yes	21	Clinic	NR	34 (20-59)	52.38	Crossover (7)	Titrated	ATX (LA)	76-mg (Low)	NR
Strauss et al. (1984)	CPT (V)	No	22	University	NR	19.23	0	Crossover (7)	Fixed	MPH (SA)	20-mg (Low)	75 (During)
Studer, Wangler, Diruf, Kratz, Moll, & Heinrich (2010)	Visual WM Task (WM)	No	11	NR	NR	29.7	54.54	Crossover (7)	Fixed	MPH (SA)	40-mg (High)	120 (During)
Taylor & Russo (2000)	Stroop (IC) DS (WM) VF (SR)	Yes	22	Community	NR	40.8 (18- 59)	40.91	Crossover (4)	Titrated	AMP (SA)	25-mg (Low)	180 (After)
Taylor & Russo (2001)	Stroop (IC) VF (SR)	Yes	17	Clinic	NR	41.2 (21- 57)	58.82	Crossover (4)	Titrated	AMP (SA)	2.50-20- mg (Low)	240 (During)
Theunissen, Elvira, van de Bergh, & Ramaekers (2009)	MCT (V, IC) Stop-Signal (IC)	No	16	Community	NR	21.8 (19- 29)	31.25	Crossover (NR)	Fixed	MPH	20-mg (Low)	120 (During)
Turner, Robbins, Clark, Aron, Dowson, & Sahakian (2003)	PAL (DM-I) DS (WM) SWM (WM) SSP (WM) RVIP (V, IC) NTOL (PD) IGT (PD) IDED (SR) Pattern Recognition Memory Task	No	60	Community	NR	61.55	0	Parallel	Fixed	MPH (SA)	30-mg (Low)	90 (During)
Turner, Blackwell, Dowson, McLean, & Sahakian (2005).	(DM-I, DM-D) <i>n</i> -back (WM) SWM (WM) RVIP (V, IC)	Yes	18	Clinic	NR	28.44 (35- 74)	NR	Crossover (7)	Fixed	MPH (SA)	30-mg (Low)	75 (During)
Unrug, Coenen, & van Luijelaar (1997)	Recall of Vocabulary (DM-I, DM-D) DS (WM)	No	12	University	NR	24 (19-27)	50.00	Crossover (10)	Fixed	MPH (SA)	20-mg (Low)	60 (During)
van der Schaaf, Fallon, Ter Huurne, Buitelaar, & Cools (2013)	Reversal Learning (NDL) Reversal Learning - shift (SR)	No	19	University	NR	20.9 (19- 24.4)	52.63	Crossover (7)	Fixed	MPH (SA)	20-mg (Low)	165 (After)
Verster et al. (2010)	Recall of Words (DM-I, D)	Yes	18	NR	NR	38.3	38.89	Crossover (6)	Titrated	MPH (SA)	14.7-mg (Low)	180 (After)

Study	Instrument(s) (Construct)	ADHD Status	<i>N</i>	Recruitment	Ethnicity (Percent)	Mean Age (Range)	Percent Female	Design (days between treatment)	Adminis- tration Type	Medi- cation (Type)	Average Dose (Level)	Dose Time (Acti- vation)
Ward, Kelly, Foltin, & Fischman (1997)	Number Recognition (PS) DSST (PS)	No	6	NR	Caucasian (66.66%)	29.7 (27- 35)	0	Parallel	Fixed	AMP (SA)	7.5- mg/70kg (Low)	205 (During)
Wardle, Hart, Palmer, & de Wit (2013)	<i>n</i> -back (WM) DSST (PS) WCST (SR)	No	192	Community	Caucasian (96%); Hispanic (4%)	23.3 (18- 35)	49.50	Crossover (2)	Fixed	AMP (SA)	11.66-mg (Low)	102 (Prior)
Weitzner (1965)	PAL (DM-I) Digit-Letter Coding Tests (PS) Recall of Names (DM-L)	No	96	University	NR	NR	NR	Parallel	Fixed	AMP	14- mg/70kg (Low)	120 (During)
Whiting, Chenery, Chalk, Darnell, & Copland (2008)	Recognition of Names (DM-L) RVIP (V, IC)	No	37	NR	NR	23.21 (18- 34)	70.27	Parallel	Fixed	AMP (SA)	10-mg (Low)	125 (During)
Zeeuws & Soetens (2007)	Recall of Words (DM-I, DM-D, DM-L)	No	36	University	NR	NR (18-25)	0	Crossover (7)	Fixed	AMP (SA)	10-mg (Low)	60 (Prior)
Zeeuws, Deroost, & Soetens (2010a)	Recall of Words (DM-I, DM-D; DM-L)	No	17	University	NR	21.56 (18- 30)	0	Crossover (7)	Fixed	AMP (SA)	10-mg (Low)	75 (Prior)
Zeeuws, Deroost, & Soetens (2010b)a	Recall of Words (DM-I, DM-D, DM-L)	No	24	University	NR	21.1 (18- 25)	0	Crossover (7)	Fixed	AMP (SA)	10-mg (Low)	60 (Prior)
Zeeuws, Deroost, & Soetens (2010b)b	Recall of Words (DM-I, DM-D, DM-L)	No	16	University	NR	21.4 (18- 25)	0	Crossover (7)	Fixed	AMP (SA)	10-mg (Low)	60 (Prior)

*Notes.* AAT = Auditory Attention Task; AMP = Amphetamine; ATX = Atomoxetine; AUT = Alternative Uses Test; AWL = Associative Word Learning; COWAT = Controlled Oral Word Association Test; CPT = Continuous Performance Task; CRT = Choice Reaction Time; CVA = Choice Visual Attention; CVLT = California Verbal Learning Test; DLT = Dot-Letter Task; DM-I = Declarative Memory – Immediate; DM-D = Declarative Memory – Delayed; DM – L = Declarative Memory – Long-term; DS = Digit Span; DSST = Digit Symbol Substitution Task; DVT = Digit Vigilance Task; GEF = Group Embedded Figures; GMT = Guild Memory Test; IC = Inhibitory Control; IDED = Intra-Extra Dimensional Set-Shift Task; IGT = Iowa Gambling Task; LA = Long-Acting; LDX = Lisdexamfetamine Dimesylate; MPH = Methylphenidate; NDL = Non-Declarative Learning; NR = Not Reported; PAL = Paired Associates Task; PD = Planning and Decision-Making; PS = Processing Speed; RA = Repeated Acquisition of Response Sequences Task; RAT = Remote Associations Task; RIP = Rapid Information Processing Task; RTT = Reaction Time Test; RVALT = Rey Verbal Auditory Learning Task; RVIP = Rapid Visual Information Processing; SA = Short-Acting; SART = Sustained Attention to Response Test; SDR = Spatial Delay Response; SCT = Switch Cost Task; SERS = Stimulus Evaluation Response Selection; SLT = Simple Learning Task; SMR = Simple Motor Response; SMT = Sternberg Memory Task; SNRT = Sternberg Number Recognition Task; SOT = Spatial Orientation Task; SRT = Simple Reaction Test; SSP = Spatial Span Task; SWM = Spatial Working Memory; SR = Self-Regulation; TOVA = Test of Visual Attention; TMT = Trail-Making Task; NTOL = Tower of London Spatial Planning Task; TTA = Torrance Test for Adults; V = Vigilance; VF = Verbal Fluency; VST = Visual Search Task; WCST = Wisconsin Card Sorting Test; WM = Working Memory.

Table 3  
*General Characteristics of the Studies*

	<i>k</i> (91)	Percent	Mean	<i>SD</i>
ADHD Status				
Yes	16	17.58		
No	75	82.24		
Sample Characteristics				
Adults (Miscellaneous)	75	82.42		
College/University Students	12	13.19		
Elderly Adults	4	4.40		
Recruitment Characteristics				
University	31	34.06		
Community	28	30.77		
Clinic	13	14.28		
Military	1	1.10		
Not Reported	26	28.57		
Mean Age	71	78.02	28.09	10.32
% Female	87	95.60	30.26	28.16
Years of Education	12	13.19	14.47	1.11
Baseline Cognitive Functioning	15	16.48	79.80	10.89
Country of Researcher				
Australia	4	4.40		
Europe	39	42.86		
Israel	4	4.40		
North America	44	48.35		
South America	1	1.10		
Sample Size ( <i>n</i> )	30.53	58.28		
Study Design				
Parallel (Between-Subjects)	14	15.38		
Crossover (Within-Subjects)	77	84.62		
Average number of days between sessions	63	69.23	5.48	
Learning or Practice Session				
Yes	31	34.06		
No Report	49	53.85		
NA <sup>a</sup> (Studies only testing learning and memory)	11	12.09		
Medication Type				
Stimulant	85	93.41		
AMP	34	37.36		
MPH	52	57.14		
Prostimulant LDX	1	1.10		
Nonstimulant ATX	5	5.49		
Medication Dose Level <sup>b</sup>				
Low	69	75.82		
High	22	24.18		

Table 3  
*General Characteristics of the Studies*

	<i>k</i> (91)	Percent	Mean	<i>SD</i>
Medication Dose Type				
Fixed	83	91.21		
Titrated	8	8.79		
Medication Type				
Short-Acting	83	91.21		
Medium or Long-Acting	8	8.79		
Timing of Dose Activation				
Prior to Learning	17	18.68		
During Learning	54	59.34		
After Learning	11	12.09		
NR	9	9.89		
Inclusion of Other Drugs				
Yes	25	27.47		
No	66	72.53		
Cognitive Construct				
Abilities of Focused Behavior	74	81.32		
Vigilance	24	26.37		
Inhibitory Control	43	47.25		
Working Memory	32	35.16		
Processing Speed	18	19.78		
Learning & Memory	29	31.87		
Declarative - Immediate	18	19.78		
Declarative - Delayed	11	12.09		
Declarative- Long-term	9	9.89		
Non-declarative	6	6.59		
Executive Function	17	18.68		
Planning and Decision Making	5	5.50		
Self Regulation	15	16.48		
Inclusion of Non-behavioral Measures (e.g., fMRI, PET)				
Yes	28	30.77		
No	63	69.23		
Reported Significant and Non-significant Findings				
Yes	85	93.41		
No	6	6.589		

*Notes:* <sup>a</sup>studies examining learning and memory and no other constructs were not included in these results. <sup>b</sup>for studies reporting dose in mg/kg average dose was estimated by multiplying by average adult weight worldwide of 62kg (Walpole et al., 2012) and for studies reporting multiple doses or ranges of doses, the average was used. High doses were considered to be  $\geq 20$ mg (AMP),  $\geq 40$ mg (MPH),  $\geq 50$ mg (LDX), and  $\geq 70$ mg (ATX).



The remainder of the results is organized based on three levels of analyses, ranging in scope from broad to narrow. First, at the broadest level, findings from the analysis including all cognitive constructs are presented. Second, findings from the analyses including the relatively broad constructs of abilities of focused behavior, learning and memory, and inhibitory control are presented. Finally, findings from analyses conducted across the narrowest level of cognitive constructs are presented last.

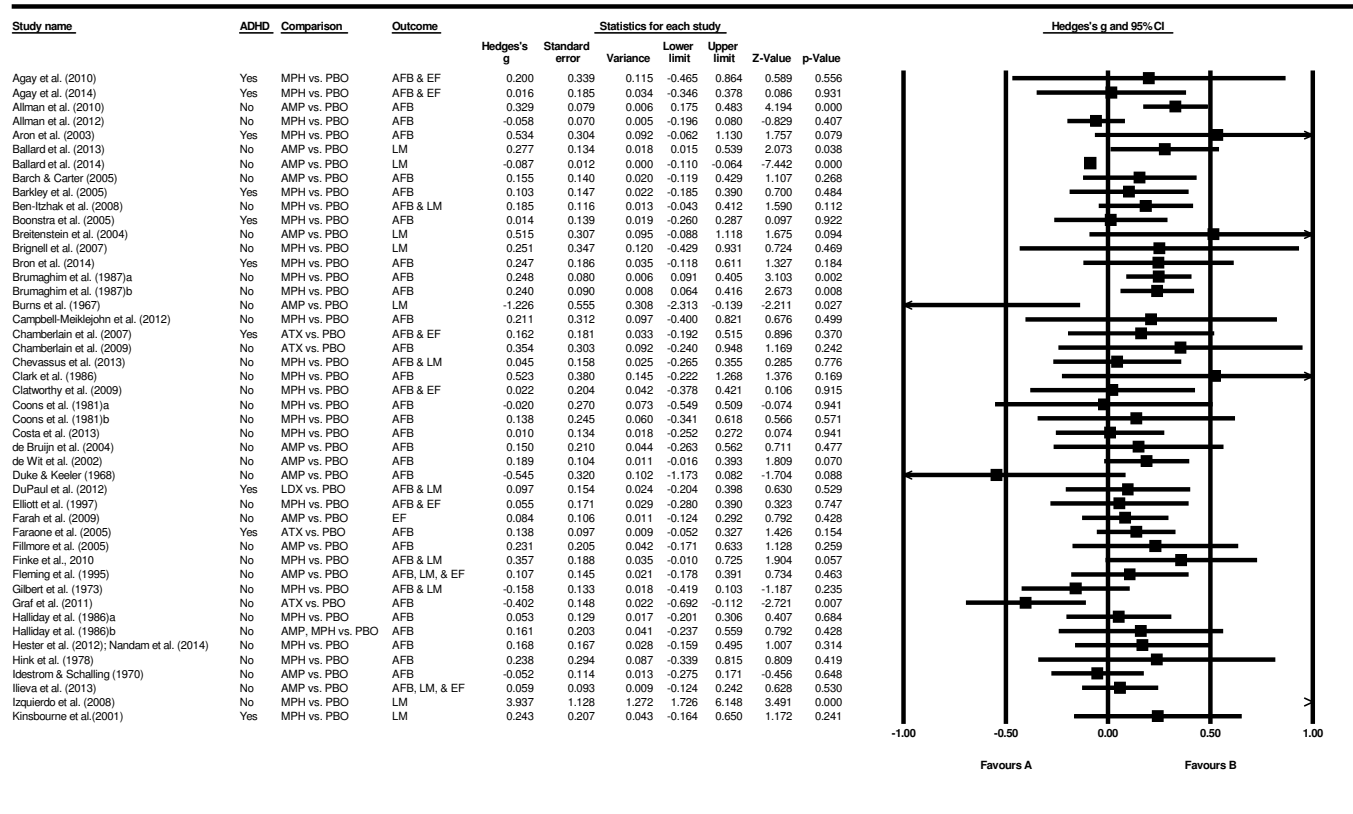
## **Neurocognitive Enhancement**

### **Neurocognitive Enhancement of Cognition**

Because cognitive constructs overlap considerably, the first analysis involved averaging the effect sizes from each of the three cognitive areas (abilities of focused behavior, learning and memory, and executive function). This analysis included data extracted from all 91 studies that investigated the neurocognitive effects of ADHD medication on cognition, including abilities of focused behavior ( $k = 74$ ), learning and memory ( $k = 29$ ), and executive function ( $k = 17$ ). Effect sizes resulted from a total of 2,778 participants (see Appendix D for the individual measures). Table 4 displays the descriptive data and effect size estimates (Hedge's  $g$ ) from each of the 91 studies. Effect sizes ranged from  $g = -1.226$  to  $g = 3.937$ . Under the random effects model the mean effect size was  $g = 0.147$  and significantly different than zero ( $SE = 0.027$ , 95% CI [0.095, 0.199],  $p < .001$ ). The fixed effects model resulted in a large reduction of the mean effect size ( $g = -0.005$ ,  $SE = 0.009$ , 95% CI [-0.023, 0.014],  $p = .621$ ). The homogeneity of variance analysis yielded a  $Q$  statistic that was significant ( $Q [90] = 300.435$ ,  $p < .001$ ).

Table 4  
ADHD Medication Neurocognitive Effects on Cognition

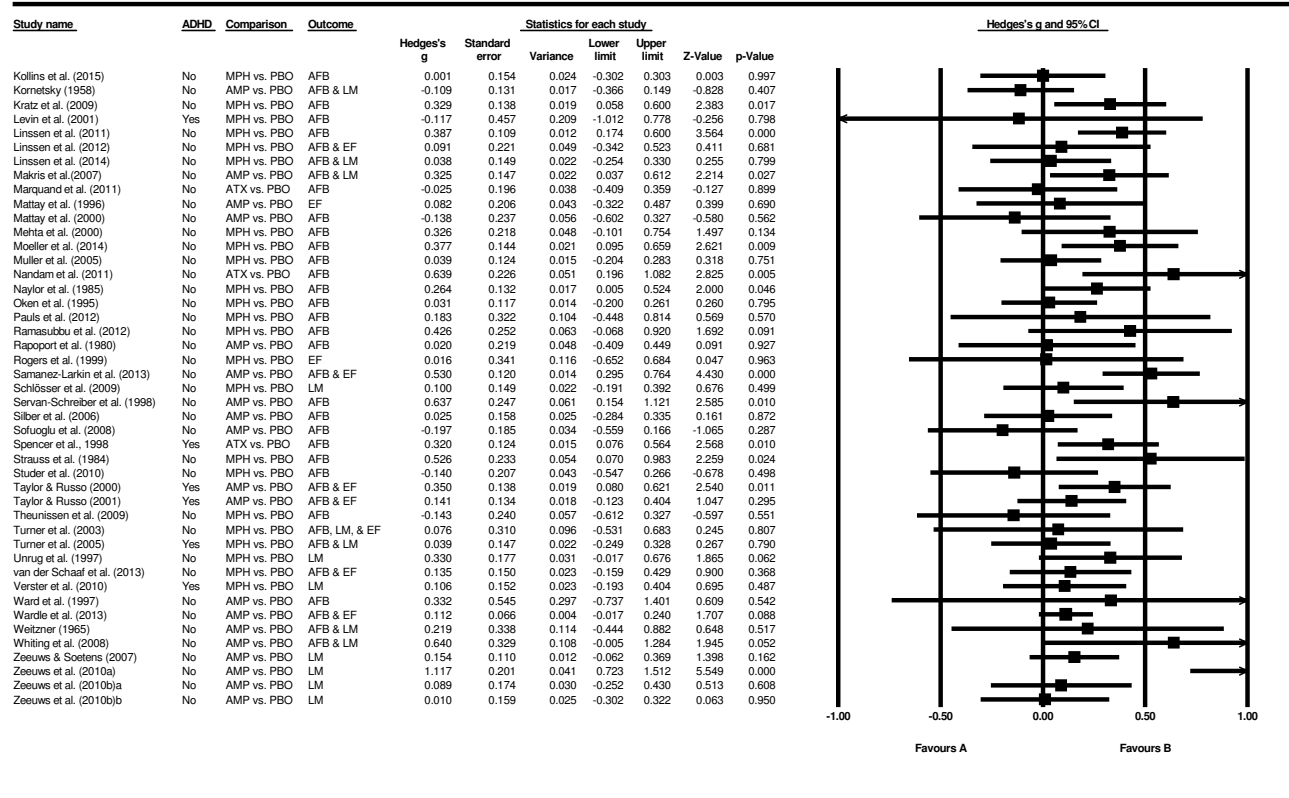
## Meta Analysis



## Meta Analysis

Table 4 continued

## Meta Analysis



## Meta Analysis

Notes. AFB = Abilities of Focused Behavior; AMP = Amphetamine; ATX = Atomoxetine; EF = Executive Function; LDX = Lisdexamfetamine Dymesylate; LM = Learning and Memory; MPH = Methylphenidate; PBO = Placebo.

## Outlier Examination

Studies with effect sizes falling outside 3 standard deviations ( $SD = 0.257$ ) of the mean ( $g < -0.626$  or  $g > 0.920$ ) were examined as potential outliers. Three studies were identified under this criterion: Burns et al. (1967),  $g = -1.226$ , 95% CI[-2.313, -0.139], Izquierdo et al. (2008),  $g = 3.397$ , 95% CI[1.272, 1.726], and Zeeuws et al. (2010a),  $g = 1.117$ , 95% CI[0.723, 1.512]. Table 5 displays the mean effect sizes with inclusion of all studies, with the removal of each study individually, with the removal the two studies potentially skewing the mean effect size in a positive direction, and with the removal of all studies.

*Table 5*  
Outlier Summary of ADHD Medication and Cognition

Analysis	$k$	Model	$g$	95% CI		$p$	$Q$ ( $df$ )
				LCL	UCL		
All studies	91	Fixed	-0.005	-0.023	0.014	.621	300.435** (90)
		Random	0.147	0.095	0.199	<.001	
Burns et al. (1967) removed	90	Fixed	-0.004	-0.023	0.014	.647	295.582** (89)
		Random	0.150	0.098	0.202	<.001	
Izquierdo et al. (2008) removed	90	Fixed	-0.005	-0.023	0.014	.600	288.221** (89)
		Random	0.145	0.094	0.196	<.001	
Zeeuws et al. (2010a) removed	90	Fixed	-0.007	-0.026	0.011	.450	269.313** (89)
		Random	0.137	0.087	0.187	<.001	
All studies with extreme positive effects removed	89	Fixed	-0.007	-0.026	0.011	.433	257.084** (88)
		Random	0.135	0.086	0.184	<.001	
All studies removed	89	Fixed	-0.007	-0.026	0.011	.455	252.254** (87)
		Random	0.138	0.089	0.187	<.001	

Notes. \*  $p < .01$ ; \*\*  $p < .001$ .

The first study that was examined as a potential outlier was conducted by Burns and colleagues in 1967. The researchers examined the effects of AMP and magnesium pemoline on learning rate in male college students. In order to stabilize variance, an arcsine transformation was performed on outcome data. Results from this study indicated that college students administered AMP demonstrated a significantly slower rate of learning compared to those administered placebo. When this study was removed from the analysis, the mean effect was  $g = 0.150$ , resulting in only a slight increase from the original mean effect size of  $g = 0.147$ .

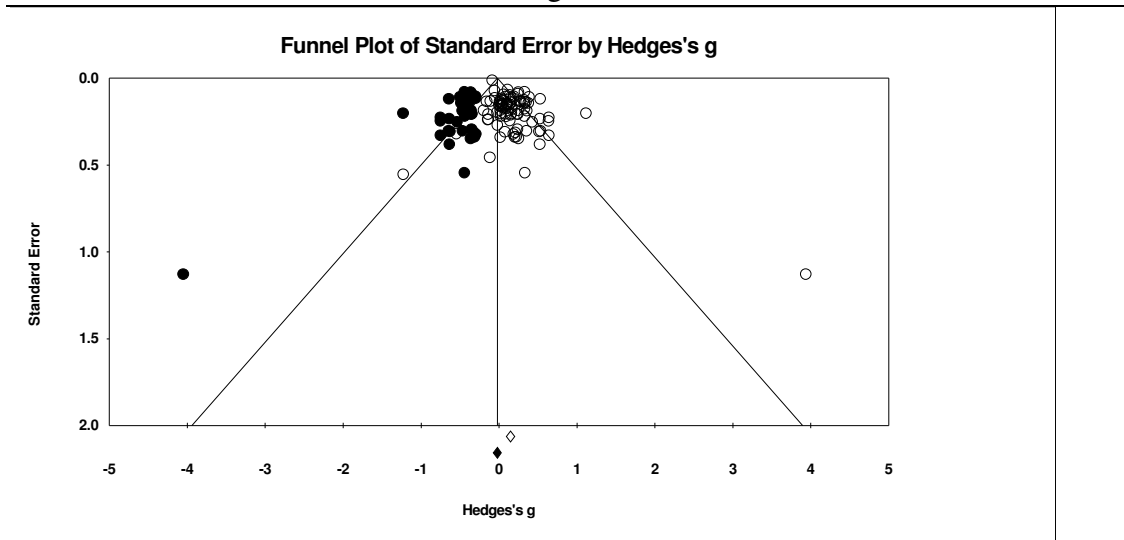
Izquierdo and colleagues (2008) examined the effects of MPH on a learning task involving the memorization of explicit factual information about the 1954 World Soccer Cup. Assessment occurred 2 and 7 days after drug administration and learning. Examination of the individual effect sizes revealed that the 7-day delay resulted in an extremely large effect size ( $g = 1.843$ ) and the 2-day delay was much smaller ( $g = 0.412$ ), tempering the study's mean effect size. Similar discrepancies were found in Zeeuw et al.'s (2010a) study that examined the effects of *d*-AMP on memory, where the mean effect size for long-term delayed word recall was very large ( $g = 1.707$ ), but the mean effect sizes for immediate ( $g = 0.935$ ) and delayed ( $g = 0.710$ ) delayed memory were smaller. Removing Izquierdo et al.'s (2008) study from the main analysis resulted in only a slight reduction in the mean effect size to  $g = 0.145$ . The removal of Zeeuw et al.'s (2010a) study also resulted in a reduced mean effect size ( $g = 0.137$ ). When both studies were removed there was a reduction in the mean effect size to  $g = 0.135$  from  $g = 0.147$ .

A decision to maintain these studies was made given their minimal effects on the mean effect size and relevance to the present study's investigation. Furthermore, previous research has indicated that prescription stimulant medication may result in the greatest benefits for recall and recognition of information assessed days after drug administration and learning (Advokat et al., 2010; Ilieva et al., 2015; Smith & Farah, 2011). Therefore, the large effect sizes from the studies with extreme positive values may be meaningful to the present study's investigation.

### **Publication Bias Analysis**

Analysis of publication bias indicated minimal risk with a Rosenthal's  $N$  of 1,480 to lead to a  $p$ -value at or above an alpha of .05 and Orwin's  $N$  of 42 to reduce the measure of effect to  $g = 0.10$ . Trim and fill analysis suggested the imputation of 38 studies resulting in a reduction in the mean effect size to  $g = -0.023$ , 95% CI [-0.075, 0.030] (see Figure 2 where the filled circles represent imputed values) and Egger's regression was significant ( $B = 1.451$ ,  $SE = 0.193$ ,  $t(89) = 7.534$ , 95% CI [1.069, 1.834],  $p < .001$ ). Findings suggest that this analysis was subject to a high degree of publication bias.

Figure 2  
Funnel Plot with Observed Studies for Cognition



Because the trim and fill procedure relies on model assumptions as explanations for missing studies and because it is easily influenced by a small number of deviant studies (Borenstein et al., 2009), a post-hoc analysis was conducted to better understand the influence of study precision on the skewed findings. Specifically, a cumulative meta-analysis in which studies were added in order of largest to smallest sample sizes, used as an estimate of precision, was conducted. For this analysis, if the point estimates (standardized mean differences) remain stable for the larger studies, but shift for the smaller studies, a deeper understanding of the variability of effect sizes is gleaned (Borenstein et al., 2009).

Results from the cumulative meta-analysis are displayed in Table 6 and suggest that the effect sizes remained relatively stable for larger studies and smaller studies. The removal of studies with standard errors greater than  $SE = 0.300$  resulted in a slight reduction to  $g = 0.142$  in the overall mean effect size. When studies with standard errors greater than  $SE = 0.200$  were removed, the effects were also minimal, resulting in a reduction in the mean effect size to  $g = 0.121$ . Even at this conservative

level, Trim and fill analysis suggested the imputation of 25 studies resulting in a reduction in the mean effect size to  $g = -0.046$ , 95% CI [-0.100, 0.009] and Egger's regression remained significant ( $B = 1.733$ ,  $SE = 0.258$ ,  $t(52) = 6.725$ , 95% CI [1.216, 2.250],  $p < .001$ ). These findings confirm the previous finding that suggested a high degree of bias.

*Table 6*  
Cumulative Meta-Analysis of ADHD Medication and Cognition

Analysis	$k$	Model	$g$	95% CI		$p$	$Q (df)$
				LCL	UCL		
All studies	91	Fixed	-0.005	-0.023	0.014	.621	300.435 <sup>**</sup>
		Random	0.147	0.095	0.199	<.001	(90)
Studies with $SE \geq 0.300$ removed	74	Fixed	-0.007	-0.026	0.011	.437	264.596 <sup>**</sup>
		Random	0.142	0.089	0.195	<.001	(72)
Studies with $SE \geq 0.200$ removed	54	Fixed	-0.016	-0.035	0.003	.090	200.410 <sup>**</sup>
		Random	0.121	0.066	0.177	<.001	(89)

Notes. \*  $p < .01$ ; \*\*  $p < .001$ .

### Moderator Analysis

The potential for the presence of moderating effects was indicated by the significant  $Q$  statistic (indicating between study variance). Effect sizes and moderator analyses identified *a priori* are displayed in Table 7. Meta-regression and analog to ANOVA did not reveal any significant continuous variables (age, gender distribution, years of education, baseline cognitive functioning, number of sessions, number of days on medication) or categorical variables (ADHD status, sample characteristics, study design, randomization, counterbalancing, training/practice effects, medication administration, medication dose, medication, medication activation type, timing of



dose activation, number of doses, inclusion of other drugs, inclusion of non-behavioral measures) as moderators.

Although not statistically significant, ANOVA analog revealed trend level ( $p < .10$ ) differences between the different recruitment types of studies  $Q(6) = 11.945$ ,  $p = .063$ . Follow-up two-group ANOVA analog analyses revealed significantly larger effect sizes among studies that conducted recruitment within communities ( $g = 0.268$ ) compared to studies recruiting participants within university settings ( $g = 0.082$ ),  $Q(1) = 7.908$ ,  $p = .005$ . as well as trend level differences compared to studies that did not report recruitment settings ( $g = 0.118$ ),  $Q(1) = 3.736$ ,  $p = .053$ . Larger effect sizes from studies that conducted recruitment within communities compared to studies recruiting participants within clinical settings ( $g = 0.154$ ) approached significance,  $Q(1) = 2.739$ ,  $p = .098$ . Comparisons including military recruitment settings, and recruitment settings that combined university and community or clinic and community were not conducted given the small number of studies for each category. Homogeneity analysis within recruitment type revealed significant results for recruitment conducted within university settings,  $Q(22) = 51.862$ ,  $p < .001$ , and within community settings,  $Q(21) = 41.646$ ,  $p = 0.005$ ; these analyses were not significant for the remainder of recruitment settings (clinic, military, university and community, clinic and community), but a significant  $Q$  statistic was found for studies that did not report recruitment settings,  $Q(25) = 69.121$ ,  $p < .001$ .

Table 7  
*Effect Sizes and Moderator Analyses for Cognition*

Variable	<i>k</i>	<i>g</i>	<i>SE</i>	95% CI		<i>p</i>
				LCL	UCL	
Mean Effect Size						
Fixed	91	-0.005	0.009	-0.023	0.014	.621
Random	91	0.147	0.027	0.095	0.199	<.001 <sup>a</sup>
Homogeneity	$Q [90] = 300.435, p < .001^a$					
ADHD Status						
Yes	16	0.159	0.039	0.082	0.236	.776
No	75	0.145	0.030	0.086	0.204	
Sample Characteristics						
Misc. Adults	75	0.151	0.029	0.094	0.209	.337
University Students	12	0.181	0.065	0.054	0.309	
Elderly Adults	4	0.036	0.081	-0.122	0.194	
Recruitment Characteristics						
University	23	0.082	0.042	-0.000	0.163	.063
Community	22	0.268	0.051	0.167	0.369	
Clinic	11	0.154	0.046	0.064	0.244	
Military	1	-0.052	0.114	-0.275	0.171	
Clinic & Community	2	-0.027	0.194	-0.408	0.354	
University & Community	6	0.140	0.052	0.038	0.243	

Table 7  
*Effect Sizes and Moderator Analyses for Cognition*

Variable	<i>k</i>	<i>g</i>	<i>SE</i>	95% CI		<i>p</i>
				LCL	UCL	
NR	26	0.118	0.058	0.005	0.232	
Study Design						
Crossover	77	0.148	0.027	0.094	0.202	.948
Parallel	14	0.156	0.114	-0.067	0.378	
Learning/Practice Practice or Training Effects						
Yes	31	0.142	0.041	0.061	0.222	.112
No	49	0.114	0.032	0.052	0.176	
NA (Studies only testing learning and memory)	11	0.318	0.092	0.137	0.499	
Randomized						
Yes	60	0.172	0.020	0.133	0.211	.168
No Report	31	0.097	0.050	-0.002	0.196	
Counterbalanced						
Yes	39	0.139	0.038	0.064	0.215	.781
No Report	52	0.153	0.032	0.091	0.216	
Medication Administration						
Fixed	83	0.148	0.028	0.092	0.204	.922

Table 7  
*Effect Sizes and Moderator Analyses for Cognition*

Variable	<i>k</i>	<i>g</i>	<i>SE</i>	95% CI		<i>p</i>
				LCL	UCL	
Titrated	8	0.142	0.058	0.027	0.256	
Medication Dose						
Low	69	0.170	0.031	0.109	0.231	.112
High	22	0.076	0.051	-0.024	0.175	
Medication						
AMP	33	0.155	0.048	0.062	0.248	.990
MPH	51	0.143	0.027	0.090	0.197	
LDX	1	0.097	0.154	-0.204	0.398	
ATX	5	0.094	0.134	-0.168	0.357	
AMP & MPH	1	0.161	0.203	-0.237	0.559	
Medication Activation Type						
Short-acting	83	0.152	0.028	0.097	0.206	.619
Medium or Long-acting	8	0.104	0.092	-0.076	0.284	
Timing of Dose Activation						
Prior	17	0.157	0.060	0.039	0.274	.751
During	54	0.131	0.029	0.075	0.186	
After	11	0.220	0.080	0.064	0.377	
NR	9	0.131	0.073	-0.012	0.275	

Table 7  
*Effect Sizes and Moderator Analyses for Cognition*

Variable	<i>k</i>	<i>g</i>	<i>SE</i>	95% CI		<i>p</i>	
				LCL	UCL		
Inclusion of Other Drugs							
Yes	25	0.084	0.050	-0.015	0.183	.156	
No	66	0.168	0.031	0.107	0.229		
Inclusion of Non-behavioral Measures							
Yes	28	0.148	0.040	0.069	0.227	.994	
No	63	0.149	0.032	0.086	0.211		
Significant and Non-significant Findings							
Yes	85	0.144	0.028	0.090	0.198	.577	
No	6	0.184	0.067	0.052	0.317		
Variable	<i>k</i>	<i>Q<sub>R</sub></i>	<i>B</i>	<i>SE</i>	<i>B</i> 95% CI		<i>p</i>
					LCL	UCL	
Study Year	91	2.06	0.003	0.002	-0.001	0.007	.151
Demographics							
Mean Age	69	0.02	-0.000	0.003	-0.006	0.005	.890
% Female	85	0.08	0.000	0.001	-0.002	0.002	.772
Years of Education	12	0.37	-0.030	0.049	-0.126	0.066	.542
Baseline Cognitive Functioning	15	0.10	0.001	0.004	-0.007	0.010	.758
Number of Sessions	91	0.02	-0.002	0.015	-0.031	0.026	.876

Variable	<i>k</i>	<i>Q<sub>R</sub></i>	<i>B</i>	<i>SE</i>	<i>B</i> 95% CI		<i>p</i>
					LCL	UCL	
Number of Doses	91	0.01	-0.005	0.040	-0.081	0.072	.905
Days on Medication	91	0.08	-0.001	0.003	-0.006	0.005	.780
Days Between Sessions	91	0.02	-0.002	0.015	-0.031	0.026	.876

Note. <sup>a</sup> indicates significance of mean effect size.

### Missing Data

A total of 50 studies were excluded from the analysis involving the effects of ADHD medication on neurocognitive enhancement of cognition (see Appendix C). Studies were excluded because of missing data critical for calculating effect sizes, such as univariate statistics, means, standard deviations, and/or the standard deviation of the difference scores. Fourteen of the studies (28.00%) reported mixed results that included both positive, negative and non-significant findings, 1 (2.00%) study reported significant impairments, 14 studies (28.00%) reported non-significant findings, and 18 (36.00%) studies reported significant positive effects related to ADHD medication and cognition. A final 3 studies (6.00%) did not report findings related to cognitive effects (because the focus was on non-behavioral assessments) or were unavailable to review. The variability of significant, non-significant, and mixed findings across missing studies supports the findings from the present analysis

### Neurocognitive Enhancement by Broad Constructs

#### Neurocognitive Enhancement of Abilities of Focused Behavior

Abilities of focused behavior included vigilance (*k* = 24), inhibitory control (*k* = 43), working memory (*k* = 32), and processing speed (*k* = 18). Seventy-four studies included abilities of focused behavior as a cognitive outcome variable, including a

total of 2,376 participants. Fourteen of these studies investigated medication effects on abilities of focused behavior among adults with ADHD and 60 investigated effects among adults without ADHD. Furthermore, these studies examined the effects of AMP ( $k = 23$ ), MPH ( $k = 44$ ), LDX ( $k = 1$ ), ATX ( $k = 5$ ), or AMP and MPH ( $k = 1$ ). Table 8 displays the descriptive statistics, as well as the mean effect sizes, from each of the 74 studies addressing abilities of focused behavior. A random effects model analysis resulted in a statistically significant mean effect size of  $g = 0.140$  ( $SE = 0.024$ , 95% CI [0.094, 0.186],  $p < .001$ ), with effect sizes ranging between  $g = -0.664$  to  $g = 0.639$ . The fixed effects model yielded similar results ( $g = 0.148$ ,  $SE = 0.017$ , 95% CI [0.115, 0.181],  $p < .001$ ) and the heterogeneity of variance indicated significant between study variance,  $Q(73) = 120.770$ ,  $p < .001$ .

Table 8  
*ADHD Medication Neurocognitive Effects on Abilities of Focused Behavior Study and Mean Results*

## Meta Analysis

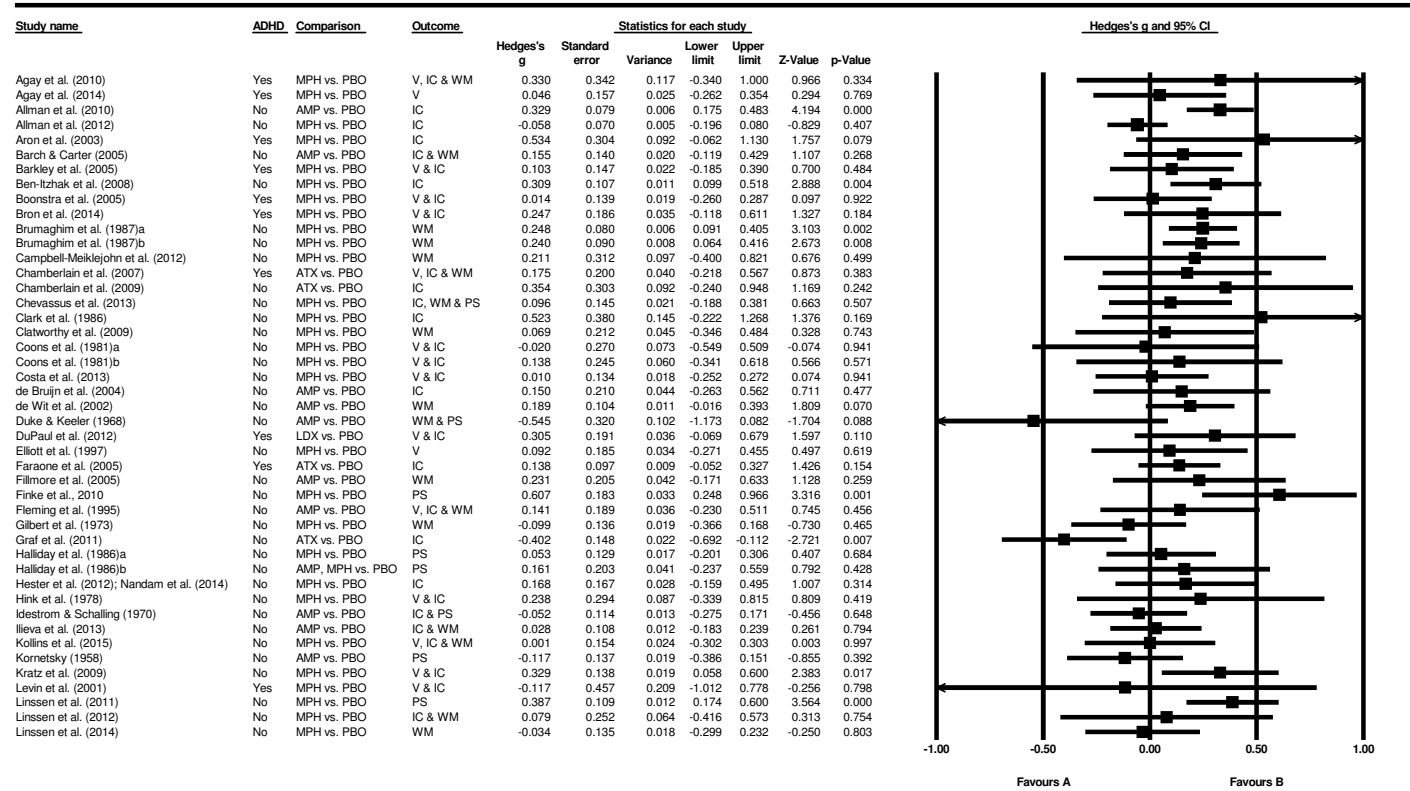
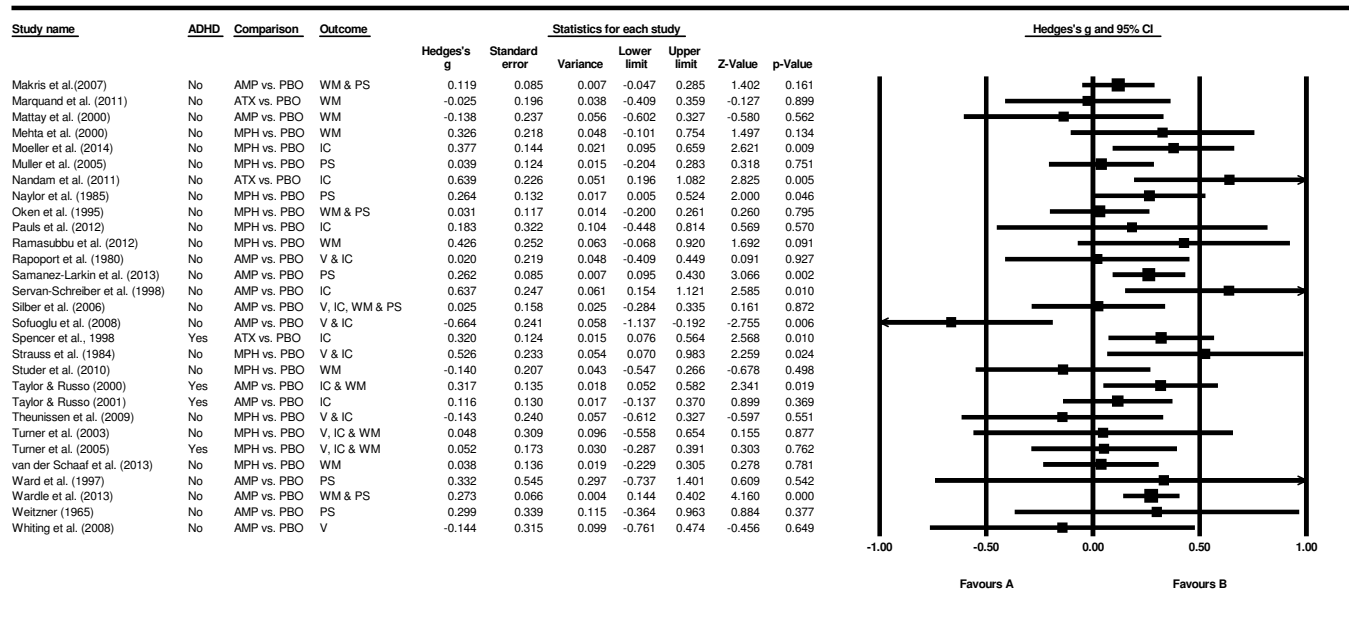




Table 8 (continued)

## Meta Analysis



### Meta Analysis

Notes. AMP = Amphetamine; ATX = Atomoxetine; IC = Inhibitory Control; LDX = Lisdexamfetamine Dymesylate; MPH = Methylphenidate; PBO = Placebo; PS = Processing Speed; V = Vigilance; WM = Working Memory.

## Outlier Evaluation

Studies with effect sizes falling outside 3 standard deviations ( $SD = 0.206$ ) of the mean ( $g < -0.479$  or  $g > 0.759$ ) were examined as potential outliers. Two studies were identified under this criterion: Sofuoglu et al. (2008),  $g = -0.664$ , 95% CI[-1.137, -0.192], and Duke & Keeler (1968),  $g = -0.545$ , 95% CI[-1.173, 0.082]. Table 9 displays the mean effect sizes with inclusion of all studies, as well as with the removal of each individual study and the removal of both studies potentially skewing the mean effect size in a negative direction.

Table 9  
*Outlier Summary of ADHD Medication and Abilities of Focused Behavior*

Analysis	$k$	Model	$g$	95% CI		$p$	$Q$ ( $df$ )
				LCL	UCL		
All studies	74	Fixed	0.148	0.115	0.181	<.001	120.770 <sup>**</sup> (73)
		Random	0.140	0.094	0.186	<.001	
Sofuoglu et al. (2008) removed	73	Fixed	0.152	0.119	0.185	<.001	109.366 <sup>*</sup> (72)
		Random	0.146	0.102	0.190	<.001	
Duke and Keeler (1968) removed	73	Fixed	0.150	0.117	0.183	<.001	116.063 <sup>*</sup> (72)
		Random	0.143	0.098	0.189	<.001	
Both studies removed	71	Fixed	0.154	0.121	0.187	<.001	104.606 <sup>*</sup> (72)
		Random	0.149	0.106	0.193	<.001	

Notes. <sup>\*</sup>  $p < .01$ ; <sup>\*\*</sup>  $p < .001$ .

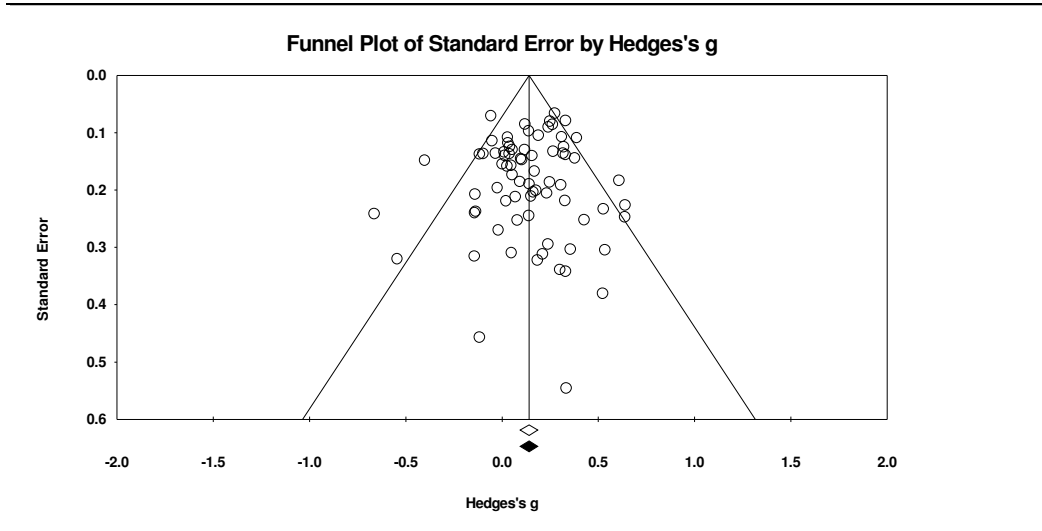
Duke and Keeler (1968) used AMP, as well as placebo, as a control for investigating the cognitive effects of psilocybin, a drug that has similar effects to Lysergic Acid Diethylamide (LSD). The researchers concluded that both psilocybin and AMP resulted in impairments in performance on the TMT. The removal of this study resulted in only a slight increase in the mean effect size ( $g = 0.143$ ) compared to

the original mean effect size of  $g = 0.140$ . Descriptive information concerning the second study potentially skewing the results in a negative direction (Sofuoglu et al., 2008) was described in the previous meta-analysis that included all cognitive variables. The removal of this study from the analysis also resulted in only a minimal increase in the mean effect size to  $g = 0.146$ . When both studies with extreme negative effect sizes were removed, the increase in the mean effect size to  $g = 0.149$  was also minimal. Therefore, both of these studies were maintained.

### **Publication Bias**

Analysis of publication bias indicated minimal risk with a Rosenthal's  $N$  of 669 to lead to a  $p$ -value at or above an alpha of .05 and some risk with an Orwin's  $N$  of 5 to reduce the measure of effect to 0.10. Under the fixed effects model, trim and fill analysis did not suggest the imputation of any studies to reduce positive bias; however, one study was identified for imputation due to negative bias resulting in a slight increase in the mean effect to  $g = 0.146$ , 95% CI [0.098, 0.194] (see Figure 3). Egger's regression was not significant [ $B = -0.240$ ,  $SE = 0.362$ ,  $t(72) = 0.665$ , 95% CI [-0.961, 0.480],  $p = .254$ ] represented by the symmetry shown in the funnel plot, which also indicates minimal bias.

Figure 3  
*Funnel Plot with Observed Studies for Abilities of Focused Behavior*



### Moderator Analysis

The significant  $Q$  statistic indicated heterogeneity among studies, suggesting the potential for moderator variables. Effect sizes and moderator analyses identified *a priori* were compared across studies for ADHD medication and Abilities of Focused Behavior (see Table 10). ANOVA analog revealed significant influence of randomization of groups,  $Q(1) = 6.693, p = .010$ , where significantly larger mean effect sizes were found for studies reporting randomization of groups ( $g = 0.182$ ) than studies that did not report randomization ( $g = 0.042$ ). Homogeneity tests revealed significant results for studies that did not report randomization,  $Q(22) = 42.600, p = .005$ , but not for studies that included groups that were randomized,  $Q(50) = 62.736, p = .107$ .

Significant differences were also revealed for inclusion of other drugs,  $Q(1) = 4.144, p = .042$ ; studies that investigated additional drugs resulted in smaller effect sizes ( $g = 0.052$ ) compared to studies that investigated only one drug ( $g = 0.172$ ).

Homogeneity tests were significant for both types of studies (included other drugs:  $Q(20) = 41.184, p = 0.004$ ; did not include other drugs:  $Q(52) = 70.841, p = .042$ ).

Although not significant, trend level differences were revealed between doses, where low doses resulted in larger effect sizes ( $g = 0.165$ ) than high doses ( $g = 0.057$ ) of medication. Meta-regression and analog to ANOVA did not reveal any other significant moderator variables.

Table 10  
*Effect Sizes and Moderator Analyses for Abilities of Focused Behavior*

Variable	$k$	$g$	$SE$	95% CI		$p$
				LCL	UCL	
Mean Effect Size						
Fixed	74	0.148	0.017	0.115	0.181	<.001 <sup>a</sup>
Random	74	0.140	0.024	0.094	0.186	<.001 <sup>a</sup>
Homogeneity	$Q(73) = 120.770, p < .001^a$					
ADHD Status						
Yes	14	0.172	0.042	0.089	0.254	.418
No	60	0.131	0.028	0.076	0.185	
Sample Characteristics						
Misc. Adults	60	0.134	0.027	0.082	0.186	.497
University Students	10	0.203	0.058	0.088	0.317	
Elderly Adults	4	0.092	0.105	0.097	0.189	
Recruitment Characteristics						
University	22	0.130	0.002	0.041	0.220	.083

Table 10  
*Effect Sizes and Moderator Analyses for Abilities of Focused Behavior*

Variable	<i>k</i>	<i>g</i>	<i>SE</i>	95% CI		<i>p</i>
				LCL	UCL	
Community	16	0.258	0.047	0.166	0.351	
Clinic	10	0.151	0.048	0.058	0.244	
Military	1	-0.052	0.114	-0.275	0.171	
Clinic & Community	2	0.031	0.225	-0.409	0.472	
University & Community	5	0.091	0.050	-0.007	0.189	
NR	18	0.089	0.058	-0.024	0.202	
Study Design						
Crossover	65	0.144	0.025	0.094	0.193	.350
Parallel	9	0.076	0.068	-0.057	0.209	
Learning/Practice Practice or Training Effects						
Yes	26	0.145	0.035	0.077	0.213	.804
No	48	0.134	0.032	0.072	0.195	
Randomized						
Yes	51	0.182	0.024	0.136	0.228	.010 <sup>a</sup>
No Report	23	0.042	0.049	-0.054	0.138	
Counterbalanced						
Yes	27	0.151	0.038	0.077	0.226	.698
No Report	47	0.132	0.030	0.072	0.192	

Table 10  
*Effect Sizes and Moderator Analyses for Abilities of Focused Behavior*

Variable	<i>k</i>	<i>g</i>	<i>SE</i>	95% CI		<i>p</i>
				LCL	UCL	
Medication Administration						
Fixed	67	0.138	0.026	0.088	0.189	.879
Titrated	7	0.148	0.057	0.035	0.260	
Medication Dose						
Low	55	0.165	0.023	0.119	0.211	.096
High	19	0.057	0.061	-0.062	0.176	
Medication						
AMP	23	0.121	0.043	0.037	0.206	.887
MPH	44	0.149	0.029	0.093	0.206	
LDX	1	0.305	0.191	-0.069	0.679	
ATX	5	0.096	0.137	-0.172	0.364	
AMP & MPH	1	0.161	0.203	-0.237	0.559	
Medication Activation Type						
Short-acting	66	0.141	0.024	0.094	0.189	.918
Medium or Long-acting	8	0.131	0.099	-0.062	0.324	
Timing of Dose Activation						
Prior	11	0.167	0.040	0.088	0.246	.622
During	47	0.119	0.001	0.058	0.181	

Table 10  
*Effect Sizes and Moderator Analyses for Abilities of Focused Behavior*

Variable	<i>k</i>	<i>g</i>	<i>SE</i>	95% CI		<i>p</i>
				LCL	UCL	
After	8	0.224	0.088	0.051	0.397	
NR	8	0.145	0.005	0.008	0.282	
Inclusion of Other Drugs						
Yes	21	0.052	0.053	-0.052	0.157	.042 <sup>a</sup>
No	53	0.172	0.024	0.124	0.219	
Inclusion of Non-behavioral Measures						
Yes	26	0.139	0.039	0.063	0.215	.984
No	48	0.140	0.030	0.082	0.199	
Significant and Non-significant Findings						
Yes	69	0.132	0.024	0.084	0.179	.194
No	5	0.271	0.105	0.066	0.476	

Variable	<i>k</i>	<i>Q<sub>R</sub></i>	<i>B</i>	<i>SE</i>	<i>B</i> 95% CI		<i>p</i>
					LCL	UCL	
Study Year	74	1.43	0.002	0.002	-0.001	0.006	.232
Demographics							
Mean Age	56	0.29	0.001	0.002	-0.003	0.005	.588
% Female	69	0.44	0.001	0.001	-0.001	0.002	.509
Years of Education	11	2.63	-0.084	0.052	-0.186	0.018	.105



Variable	<i>k</i>	<i>Q<sub>R</sub></i>	<i>B</i>	<i>SE</i>	<i>B</i> 95% CI		<i>p</i>
					LCL	UCL	
Baseline				0.004			
Cognitive Functioning	13	0.27	0.002		-0.006	0.011	.602
Number of Sessions	74	1.67	-0.015	0.011	-0.037	0.008	.196
Number of Doses	74	0.43	0.022	0.033	-0.043	0.087	.510
Days on Medication	74	0.02	-0.000	0.002	-0.004	0.004	.902
Minimum Washout Days Between Sessions	54	0.62	-0.007	0.009	-0.025	0.011	.431

Note. <sup>a</sup> indicates significance of mean effect size.

### Missing Data

Thirty-four studies were excluded from the analysis involving the effects of ADHD medication on neurocognitive enhancement of abilities of focused behavior (see Appendix C). Findings from these studies included results that were mixed, i.e., including positive significant differences and non-significant findings ( $k = 7$ ; 20.59%), results that revealed significant positive benefits ( $k = 12$ ; 34.29%), results that indicated significant negative effects ( $k = 1$ ; 2.94%), and results that were reported to be non-significant ( $k = 12$ ; 35.29%). Two studies did not provide enough information to report findings.

### Neurocognitive Enhancement of Learning & Memory

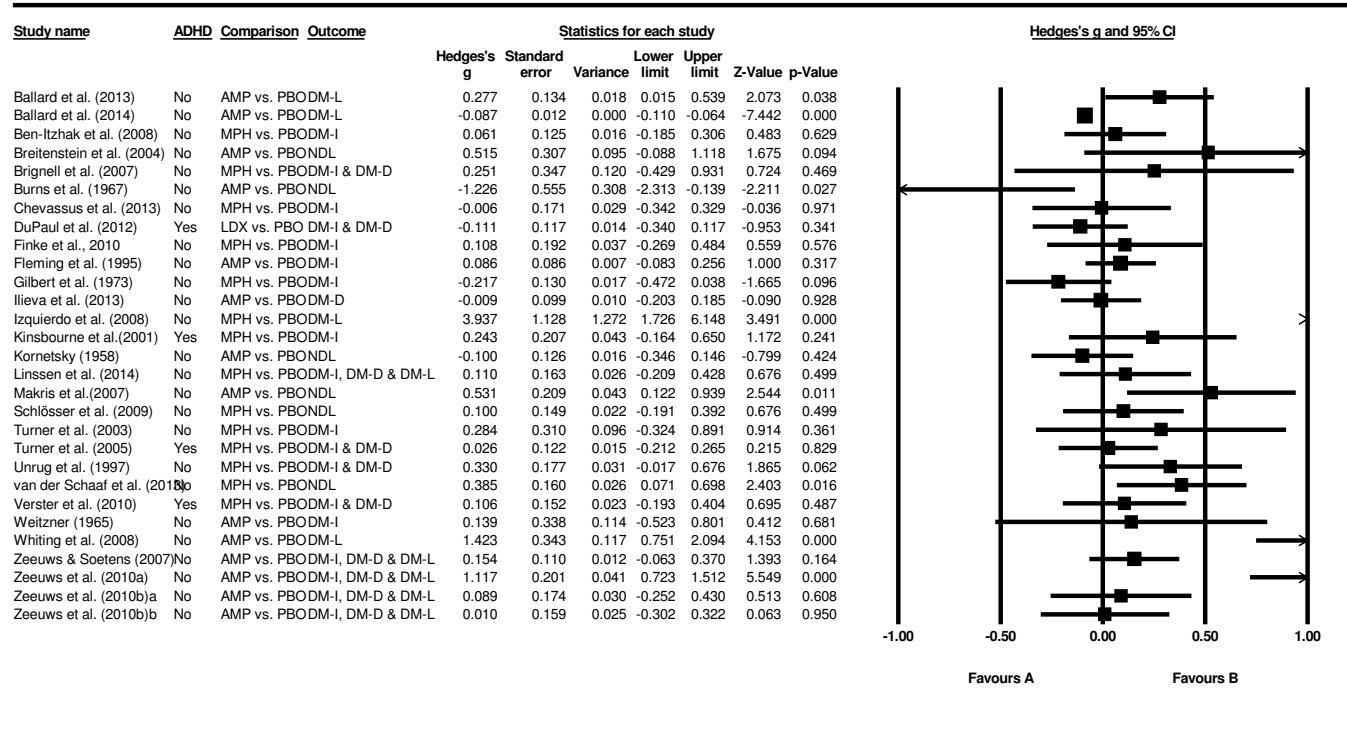
Twenty-nine studies that investigated the neurocognitive enhancement of prescription stimulant medication included learning and memory as an outcome variable. These measurements included both declarative memory – tested immediately after learning ( $k = 18$ ), tested with a short delay after learning ( $k = 11$ ), or tested with a long delay after learning ( $k = 9$ ) – and non-declarative memory ( $k = 6$ ). Effect sizes

were calculated based on findings from a total of 846 participants. Studies investigated the effects of AMP ( $k = 14$ ), MPH ( $k = 14$ ), and LDX ( $k = 1$ ) on enhancement of learning and memory among adults with ADHD ( $k = 4$ ) and adults without ADHD ( $k = 25$ ). Table 11 displays the descriptive data and ES estimates (Hedge's  $g$ ) from each of the 29 studies. The studies generated a statistically significant mean effect size of  $g = 0.152$  ( $SE = 0.052$ , 95% CI [0.050, 0.254],  $p = .004$ ) under a random effects model analysis, with effect sizes ranging from  $g = -1.226$  to  $g = 3.937$ . A fixed effects model yielded mean effect sizes in the reverse direction compared to those found with the random effects model ( $g = -0.060$ ,  $SE = 0.011$ , 95% CI [-0.081, -0.038],  $p < .001$ ). The heterogeneity of variance analysis was significant,  $Q(28) = 125.533$ ,  $p < .001$ .

Table 11

*ADHD Medication Neurocognitive Effects on Learning and Memory and Mean Results*

**Meta Analysis**



**Meta Analysis**

Notes. AMP = Amphetamine; DM-I = Declarative Memory – Immediate; DM-D = Declarative Memory Delayed; DM-L = Declarative Memory Long-Term; LDX = Lisdexamfetamine Dymesylate; MPH = Methylphenidate; ND L = Non-Declarative Learning; PBO = Placebo.

## Outlier Evaluation

Studies with effect sizes falling outside 3 standard deviations ( $SD = 0.280$ ) of the mean ( $g < -0.688$  or  $g > 0.992$ ) were examined as potential outliers. Four studies were identified under this criterion: Burns et al. (1967),  $g = -1.226$ , 95% CI [-2.313, -0.139], Zeeuws et al. (2010a),  $g = 1.117$ , 95% CI [0.723, 1.512], Whiting et al. (2008),  $g = 1.423$ , 95% CI [0.751, 2.094], and Izquierdo et al. (2008),  $g = 1.128$ , 95% CI [1.726, 6.148]. Table 12 displays the mean effect sizes with inclusion of all studies, as well as with the removal of each individual study, the removal of the three studies (Zeeuws et al., 2010a; Whiting et al., 2008; Izquierdo et al., 2008) potentially skewing the mean effect size in a positive direction, and the removal of all studies.

The first study that was examined as a potential outlier was conducted by Burns and colleagues in 1967 and was described previously. When this study was removed from the analysis, the mean effect was  $g = 0.161$ , resulting in only a slight increase from the original mean effect size of  $g = 0.152$ . Therefore, a decision was made to maintain the effect size from Burn et al. (1967).

The remaining potential outlier studies resulted in mean effect sizes substantially larger than the present study's mean effect size. As described previously, Izquierdo et al. (2008) and Zeeuws et al. (2010a) conducted studies resulting in large effect sizes for long-term memory. A third study (Whiting et al., 2008) examined the long-term effects of *d*-AMP on word memory. The removal of these studies individually resulted in the reduction of the mean effect size to  $g = 0.141$  (Izquierdo et al., 2008),  $g = 0.111$  (Zeeuws et al., 2010a), and  $g = 0.126$  (Whiting et al., 2008).

When all three effect sizes were removed there was a large reduction in the mean effect size to  $g = 0.076$  from  $g = 0.152$ .

Table 12  
*Outlier Summary of ADHD Medication and Learning and Memory*

Analysis	$k$	Model	$g$	95% CI		$p$	$Q$ ( $df$ )
				LCL	UCL		
All studies	29	Fixed	-0.060	-0.081	-0.038	<.001	125.533** (28)
		Random	0.152	0.050	0.254	.004	
Burns et al. (1967) removed	28	Fixed	-0.059	-0.081	-0.038	<.001	121.109** (27)
		Random	0.161	0.060	0.263	.002	
Zeeuws et al., (2010a) removed	28	Fixed	-0.063	-0.085	-0.042	<.001	91.252** (27)
		Random	0.111	0.019	0.202	.018	
Whiting et al., 2008 removed	28	Fixed	-0.061	-0.083	-0.040	<.001	106.787** (27)
		Random	0.126	0.030	0.223	.010	
Izquierdo et al. 2008 removed	28	Fixed	-0.060	-0.082	-0.039	<.001	112.976** (27)
		Random	0.141	0.043	0.239	.005	
All studies with extreme positive effects removed	26	Fixed	-0.065	-0.087	-0.044	<.001	59.830* (25)
		Random	0.076	-0.002	0.154	.057	
All studies removed	25	Fixed	-0.065	-0.086	-0.043	<.001	55.445* (24)
		Random	0.080	0.004	0.157	.039	

Notes. \*  $p < .01$ ; \*\*  $p < .001$ .

Outlier evaluation suggested that the effects from learning and memory measured with longer delays, i.e., long-term memory, resulted in effect sizes that were much larger than those from learning and memory measured with immediacy or short delays. Therefore, a decision was made to analyze long-term memory separately from immediate and delayed memory. Analyses were rerun to include only effect sizes from declarative and non-declarative learning and memory that was measured the same day

as learning. Effect sizes from measurements of long-term memory were analyzed as a narrow construct only and were not combined in the broad category of learning and memory.

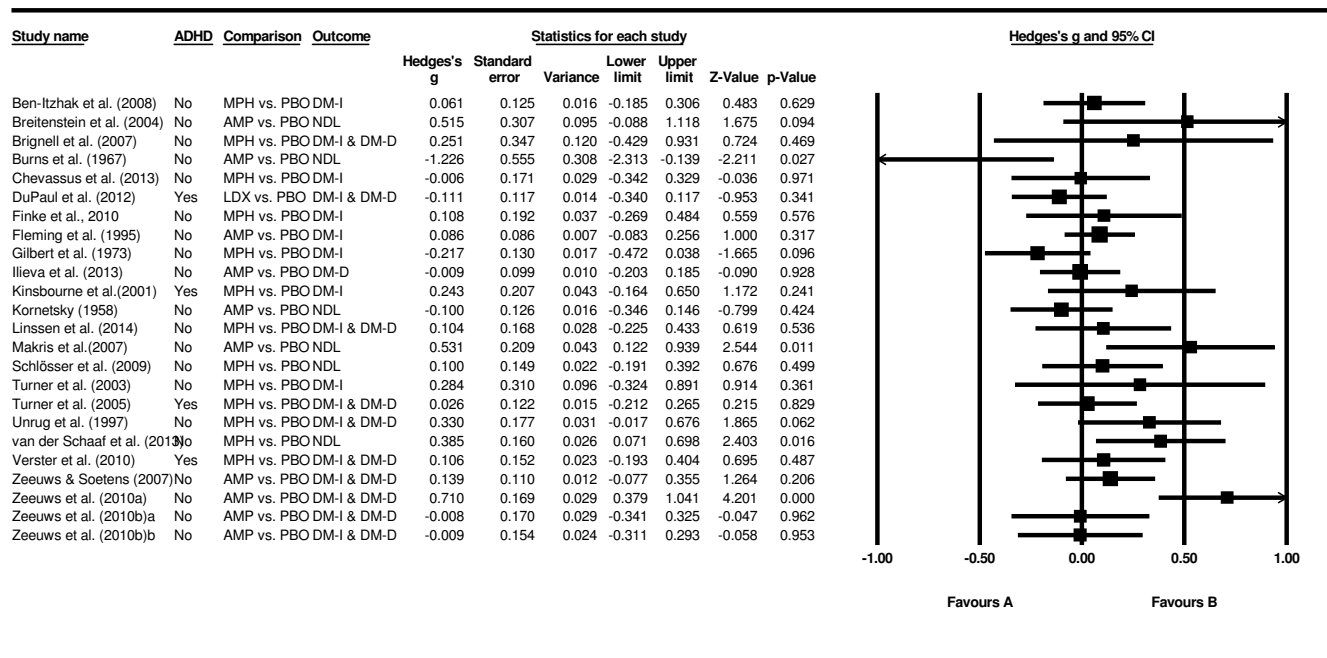
With long-term learning and memory removed, data were extracted from 24 studies ( $k = 24$ ) that investigated the neurocognitive effects of ADHD medication on declarative and non-declarative immediate and delayed learning and memory. Table 13 displays the descriptive data and effect sizes (Hedge's  $g$ ) from each of the 24 studies. The studies generated a statistically significant mean effect size of  $g = 0.104$  ( $SE = 0.045$ , 95% CI [0.015, 0.192],  $p = .021$ ) under a random effects model analysis, with effect sizes ranging -1.226 to 0.710. A fixed effects model resulted in a similar mean effect size to the random effects model ( $g = 0.082$ ,  $SE = 0.030$ , 95% CI [0.023, 0.192],  $p = .006$ ). The heterogeneity of variance analysis yielded a significant  $Q$  statistic,  $Q(23) = 49.139$ ,  $p = .004$ , indicating significant variability between studies.

A second outlier evaluation was conducted and studies with effect sizes falling outside 3 standard deviations ( $SD = 0.220$ ) of the mean ( $g < -0.557$  or  $g > 0.765$ ) were examined as potential outliers. The only study that met this criteria (Burns et al., 1967) was reviewed previously and maintained in the analysis.

Table 13

*ADHD Medication Neurocognitive Effects on Learning and Memory – Immediate and Delayed and Mean Results*

**Meta Analysis**



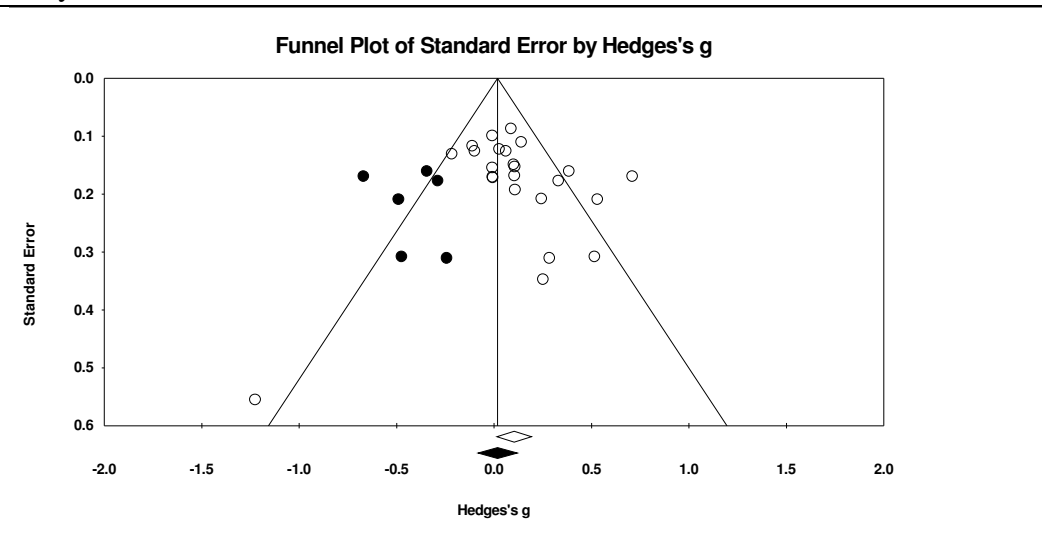
**Meta Analysis**

Notes. AMP = Amphetamine; DM-I = Declarative Memory – Immediate; DM-D = Declarative Memory Delayed; LDX = Lisdexamfetamine Dymesitylate; MPH = Methylphenidate; NDL = Non-Declarative Learning; PBO = Placebo.

## Publication Bias

Analysis of publication bias indicated minimal risk with a Rosenthal's  $N$  of 36 to lead to a  $p$ -value at or above an alpha of .05 and Orwin's  $N$  of 25 to result in a mean effect size of  $g = 0.05$  (this effect size was chosen considering the effect size was approaching the predetermined convention of  $g = 0.10$ ). Trim and fill analysis indicated the potential for bias (see Figure 8), suggesting imputation of 6 studies that resulted in an mean effect size that approached zero ( $g = 0.019$ , 95% CI [-0.082, 0.120]). Egger's regression, however, was not significant ( $B = 0.947$ ,  $SE = 0.844$ ,  $t(22) = 1.122$ , 95% CI [-0.804, 2.698],  $p = .137$ ).

*Figure 4*  
Funnel Plot with Observed Studies for Learning and Memory – Immediate and Delayed



## Moderator Analyses

The potential for the presence of moderating effects was indicated by the significant  $Q$  statistics across learning and memory constructs (indicating between study variance). Effect sizes and moderator analyses identified *a priori* were compared across studies for enhancement of learning and memory by ADHD medication are



displayed in Table 14. Although trend level ( $p < .10$ ) differences between short-acting and long-acting agents were found for stimulant activation type,  $Q(1) = 3.296, p = .069$ , only 1 study examined long-acting agents, precluding conclusions between the two medication types. Similar results were revealed for medication activation timing,  $Q(3) = 6.428, p = .093$ ; however when the 1 study that did not report medication administration timing was removed, results were not significantly different according to activation timing,  $Q(2) = 0.241, p = .886$ .

A significant trend of decreasing effect sizes related to increased number of days on medication ( $B = -0.019, p = .036, R^2 \text{ analog} = 0.27$ ) was revealed; however, this finding was limited by low variability, with only 4 of the 22 studies reporting more than 1 day (see Figure 5). Meta-regression also revealed a significant trend of increasing effect sizes ( $B = 0.006, p = .043, R^2 \text{ analog} = 0.17$ ) for more recent publications (see Figure 6). Significant differences were not found for any of other the potential moderating categorical or continuous variables; however, note that there were not enough studies ( $k = 3$ ) reporting number of years of education to run meta-regression for this variable.

Table 14  
*Effect Sizes and Moderator Analyses for Learning and Memory – Immediate and Delayed*

Variable	$k$	$g$	$SE$	95% CI		$p$
				LCL	UCL	
Mean Effect Size						
Fixed	24	0.082	0.030	0.023	0.142	.006 <sup>a</sup>
Random	24	0.104	0.045	0.015	0.192	.021 <sup>a</sup>

Table 14  
*Effect Sizes and Moderator Analyses for Learning and Memory –  
 Immediate and Delayed*

Variable	<i>k</i>	<i>g</i>	<i>SE</i>	95% CI		<i>p</i>
				LCL	UCL	
Homogeneity	$Q(23) = 49.139, p = .004^a$					
ADHD Status						
Yes	4	0.018	0.069	-0.118	0.154	.240
No	20	0.121	0.053	0.017	0.226	
Sample Characteristics						
Misc. Adults	17	0.119	0.047	0.027	0.210	.543
University Students	4	0.051	0.204	-0.349	0.450	
Elderly Adults	3	-0.027	0.127	-0.275	0.221	
Recruitment Characteristics						
University	6	0.037	0.056	-0.073	0.146	.497
Community	8	0.214	0.100	0.018	0.410	
Clinic	2	0.082	0.105	-0.124	0.287	
Military	0					
Clinic & Community	0					
University & Community	2	0.230	0.268	-0.296	0.755	
NR	6	0.002	0.090	-0.174	0.177	
Study Design						

Table 14  
*Effect Sizes and Moderator Analyses for Learning and Memory –  
 Immediate and Delayed*

Variable	<i>k</i>	<i>g</i>	<i>SE</i>	95% CI		<i>p</i>
				LCL	UCL	
Crossover	19	0.114	0.043	0.029	0.198	.649
Parallel	5	0.011	0.222	-0.425	0.446	
Randomized						
Yes	15	0.091	0.038	0.017	0.165	.992
No Report	9	0.090	0.109	-0.123	0.303	
Counterbalanced						
Yes	12	0.093	0.076	-0.056	0.242	.877
No Report	12	0.107	0.054	0.001	0.213	
Medication Administration						
Fixed	22	0.121	0.047	0.030	0.213	.265
Titrated	2	-0.065	0.161	-0.381	0.250	
Medication Dose						
Low	18	0.131	0.058	0.017	0.246	.157
High	6	0.014	0.059	-0.100	0.129	
Medication						
AMP	10	0.133	0.087	-0.037	0.304	.208
MPH	13	0.093	0.047	0.002	0.185	

Table 14  
*Effect Sizes and Moderator Analyses for Learning and Memory –  
 Immediate and Delayed*

Variable	<i>k</i>	<i>g</i>	<i>SE</i>	95% CI		<i>p</i>
				LCL	UCL	
LDX	1	-0.111	0.117	-0.340	0.117	
ATX	0					
AMP & MPH	0					
Medication						
Activation Type						
Short-acting	23	0.117	0.046	0.026	0.207	.069
Medium or Long-acting	1	-0.111	0.117	-0.340	0.117	
Timing of Dose Activation						
Prior	6	0.134	0.089	-0.039	0.308	.093
During	13	0.104	0.065	-0.025	0.232	
After	4	0.155	0.085	-0.012	0.322	
NR	1	-0.217	0.130	-0.472	0.038	
Inclusion of Other Drugs						
Yes	9	0.056	0.098	-0.137	0.249	.546
No	15	0.122	0.049	0.025	0.219	
Inclusion of Non-behavioral Measures						
Yes	2	0.102	0.111	-0.116	0.320	.975
No	22	0.106	0.049	0.009	0.202	

Table 14  
*Effect Sizes and Moderator Analyses for Learning and Memory – Immediate and Delayed*

Variable	<i>k</i>	<i>g</i>	<i>SE</i>	95% CI		<i>p</i>	
				LCL	UCL		
Significant and Non-significant Findings							
Yes	22	0.105	0.049	0.009	0.201	.993	
No	2	0.106	0.119	-0.127	0.340		
Variable	<i>k</i>	<i>Q<sub>R</sub></i>	<i>B</i>	<i>SE</i>	<i>B</i> 95% CI		<i>p</i>
					LCL	UCL	
Study Year	23	4.09	0.006	0.003	-0.000	0.012	.043 <sup>a</sup>
Demographics							
Mean Age	19	0.08	-0.001	0.004	-0.008	0.006	.776
% Female	21	0.14	-0.001	0.002	-0.004	0.003	.710
Years of Education <sup>b</sup>	3						
Baseline Cognitive Functioning	4	1.85	0.029	0.022	-0.013	0.072	.174
Number of Sessions	24	0.16	0.008	0.019	-0.030	0.045	.688
Number of Doses	24	0.01	0.007	0.068	-0.127	0.141	.916
Days on Medication	23	4.37	-0.019	0.089	-0.036	-	.036 <sup>a</sup>
Minimum Washout Days Between Sessions	17	0.03	0.002	0.013	-0.023	0.027	.872

Notes. <sup>a</sup> indicates significance of mean effect size; <sup>b</sup> indicates limited power precluding meta-regression analysis.

Figure 5  
*Scatter Plot of Number of Days on Medication and Mean Effect Sizes for Learning and Memory – Immediate and Delayed*

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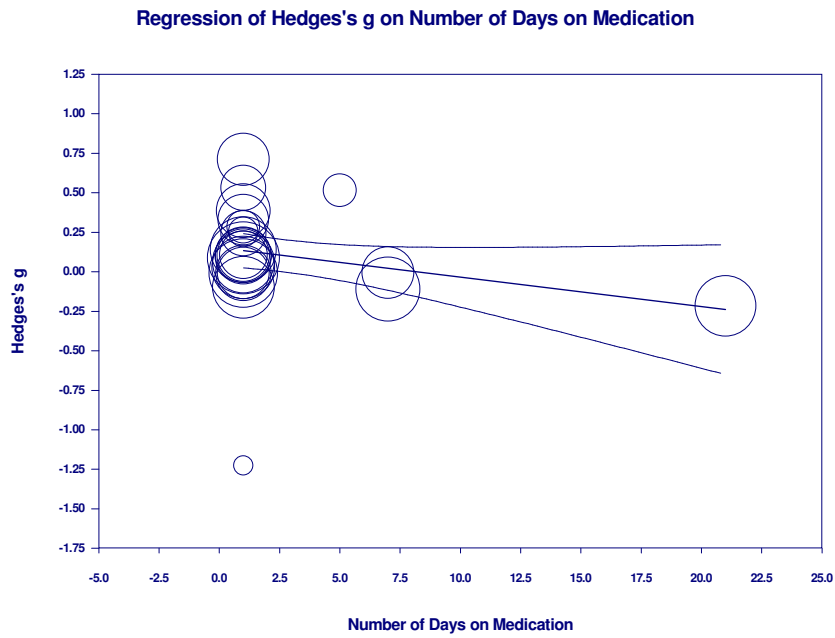
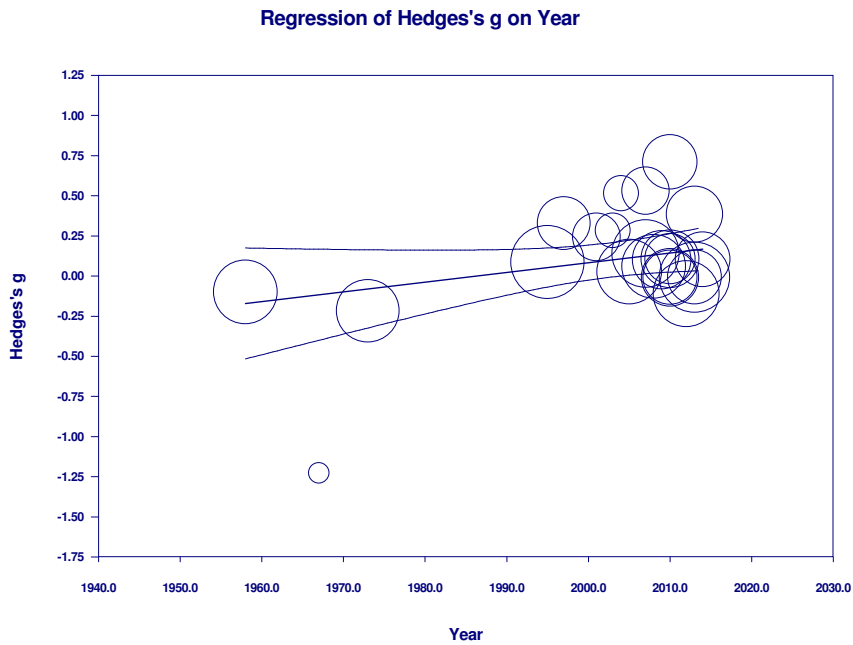


Figure 6  
*Scatter Plot of Year of Publication on Medication and Mean Effect Sizes for Learning and Memory – Immediate and Delayed*

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### **Missing Data**

Twenty-one studies were excluded from the analysis involving the effects of ADHD medication on neurocognitive enhancement of learning and memory (see Appendix C). Studies were excluded because of missing data critical for calculating effect sizes. Five studies (23.81%) reported findings that were mixed, including positive, negative, and/or non-significant findings. Six studies (28.57%) reported non-significant findings and 7 studies (33.33%) reported findings that indicated a significant improvement from ADHD medication. The remaining 3 studies (14.29%) did not report enough information to interpret the direction of effects or significance of analyses.

### **Neurocognitive Enhancement of Executive Function**

Executive function, including planning and decision-making ( $k = 5$ ), as well as self-regulation ( $k = 15$ ), was included as a cognitive outcome variable by 17 of the studies investigating the neurocognitive enhancement effects of ADHD medication. These studies examined the effects of AMP ( $k = 8$ ), MPH ( $k = 8$ ), and ATX ( $k = 1$ ) on executive function among adults with ( $k = 5$ ) and without ( $k = 12$ ) ADHD, including a total of 592 participants. Findings were analyzed for executive function as one construct and also analyzed separately for planning and decision-making, self-regulation, and inhibitory control. Table 15 displays the descriptive data and ES estimates (Hedge's  $g$ ) from each of the 17 studies. The studies resulted in a statistically significant mean effect size of  $g = 0.127$  ( $SE = 0.053$ , 95% CI [0.024, 0.230],  $p = .016$ ) under the random effects model, with effect sizes ranging from  $g = -0.104$  to  $g = 0.798$ . Under the fixed effects model, the mean effect size was slightly

reduced ( $g = 0.106$ ,  $SE = 0.033$ , 95% CI [0.042, 0.170],  $p < .001$ ). The heterogeneity of variance analysis was significant,  $Q (16) = 32.844$ ,  $p = .008$ .



Table 15  
*ADHD Medication Neurocognitive Effects on Executive Function and Mean Results*

## Meta Analysis

Study name	ADHD	Comparison	Outcome	Statistics for each study						Hedges's g and 95% CI	
				Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value		p-Value
Agay et al. (2010)	Yes	MPH vs. PBO PD		0.069	0.336	0.113	-0.590	0.728	0.205	0.838	
Agay et al. (2014)	Yes	MPH vs. PBO PD		-0.014	0.212	0.045	-0.430	0.402	-0.068	0.946	
Chamberlain et al. (2007)	Yes	ATX vs. PBO SR		0.149	0.161	0.026	-0.167	0.464	0.924	0.355	
Clatworthy et al. (2009)	No	MPH vs. PBO SR		-0.026	0.196	0.038	-0.410	0.358	-0.133	0.894	
Elliott et al. (1997)	No	MPH vs. PBO PD & SR		0.018	0.157	0.025	-0.289	0.325	0.117	0.907	
Farah et al. (2009)	No	AMP vs. PBO SR		0.084	0.106	0.011	-0.124	0.292	0.792	0.428	
Fleming et al. (1995)	No	AMP vs. PBO SR		0.092	0.160	0.026	-0.221	0.406	0.578	0.564	
Ilieva et al. (2013)	No	AMP vs. PBO SR		0.157	0.074	0.005	0.013	0.301	2.131	0.033	
Linssen et al. (2012)	No	MPH vs. PBO PD & SR		0.102	0.189	0.036	-0.268	0.473	0.541	0.588	
Mattay et al. (1996)	No	AMP vs. PBO SR		0.082	0.206	0.043	-0.322	0.487	0.399	0.690	
Rogers et al. (1999)	No	MPH vs. PBO SR		0.016	0.341	0.116	-0.652	0.684	0.047	0.963	
Samanez-Larkin et al. (2013)	No	AMP vs. PBO SR		0.798	0.154	0.024	0.496	1.099	5.189	0.000	
Taylor & Russo (2000)	Yes	AMP vs. PBO SR		0.384	0.140	0.020	0.108	0.659	2.732	0.006	
Taylor & Russo (2001)	Yes	AMP vs. PBO SR		0.165	0.139	0.019	-0.108	0.437	1.185	0.236	
Turner et al. (2003)	No	MPH vs. PBO PD & SR		-0.104	0.310	0.096	-0.711	0.503	-0.336	0.737	
van der Schaaf et al. (2013)	No	MPH vs. PBO SR		-0.017	0.152	0.023	-0.315	0.281	-0.110	0.913	
Wardle et al. (2013)	No	AMP vs. PBO SR		-0.049	0.065	0.004	-0.178	0.079	-0.751	0.452	

## Meta Analysis

*Notes.* AMP = Amphetamine; ATX = Atomoxetine; MPH = Methylphenidate; PBO = Placebo; PD = Planning and Decision-Making; SR = Self-Regulation.

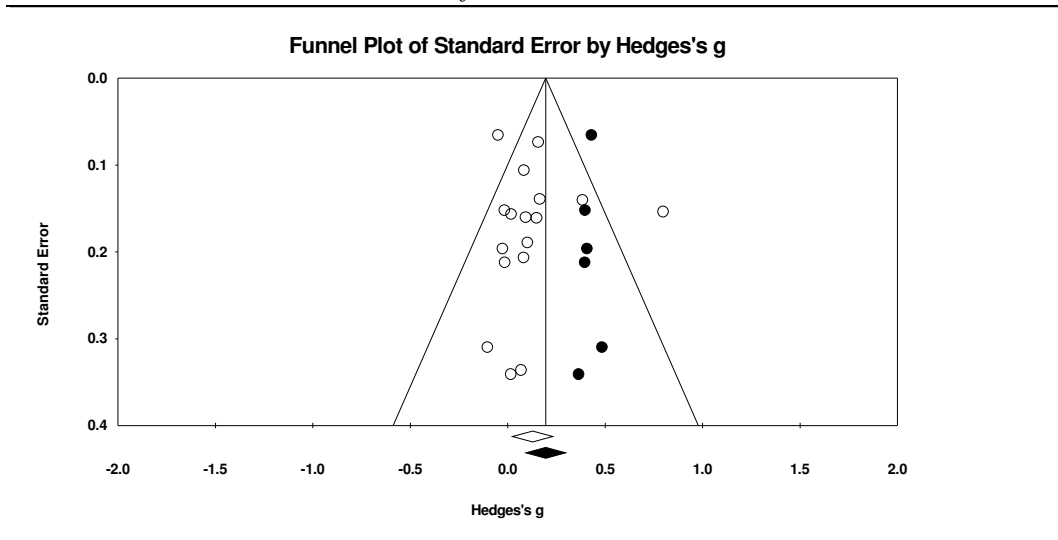
### **Outlier Evaluation**

Studies with effect sizes falling outside of 3 standard deviations ( $SD = 0.222$ ) of the mean ( $g < -0.528$  or  $g > 0.782$ ) were examined as potential outliers. Only one study, conducted by Samanez-Larkin et al. (2013), met these criteria with a mean effect size of  $g = 0.798$ . Findings from this study indicated amphetamine-induced benefits for cognitive flexibility that varied in size according to the status of dopamine within a thalamocortico-striatal network. Under both a random and fixed effects model, the removal of this study resulted in a reduction in the mean effect size to  $g = 0.073$  ( $SE = 0.033$ , 95% CI [0.008, 0.139],  $p = .028$ ) that remained significantly different from zero. Considering this study explicitly examined the effects of AMP on cognitive flexibility, the effect size resulting from this study fell only slightly outside of the criteria, and results from the meta-analysis remained significant with its removal, a decision to maintain the effect size from Samanez-Larkin et al. was made.

### **Publication Bias**

Rosenthal's  $N$  to lead to a  $p$ -value at or above an alpha of .05 was 31 and Orwin's  $N$  to reduce the measure of effect to  $g = 0.10$  was 4. Although Trim and fill analysis did not suggest imputation for any studies to account for positive bias, the imputation of 6 studies that may have contributed to negative bias was suggested. The imputation of these studies (shown in Figure 7) resulted in an increased effect size of  $g = 0.190$ , 95% CI [0.094, 0.296]. Egger's regression was not significant ( $B = 0.434$ ,  $SE = 0.810$ ,  $t(15) = 0.536$ , 95% CI [-1.291, 2.160],  $p = .300$ ) indicating minimal publication bias.

Figure 7  
*Funnel Plot with Observed Studies for Executive Function*



### Missing Data

Three studies that met the study criteria, but were missing data critical for calculating effect sizes, were excluded from the analysis involving the effects of ADHD medication on neurocognitive enhancement of executive function (see Appendix C). Two studies reported findings that were non-significant and one study did not provide information on the task of executive function. All of the studies examined measures of self-regulation.

### Moderator Analyses

The potential for the presence of moderating effects was indicated by the significant  $Q$  statistics (indicating between study variance). Effect sizes and moderator analyses identified *a priori* were compared across studies for EF enhancement of ADHD medication are displayed in Table 16. Significant results were not revealed by ANOVA analog or meta-regression.

Table 16  
*Effect Sizes and Moderator Analyses for Executive Function*

Variable	<i>k</i>	<i>g</i>	<i>SE</i>	95% CI		<i>p</i>
				LCL	UCL	
Mean Effect Size						
Fixed	17	0.106	0.033	0.042	0.170	<.001 <sup>a</sup>
Random	17	0.127	0.053	0.024	0.230	.016 <sup>a</sup>
Homogeneity	$Q(16) = 32.844, p = .008$					
ADHD Status						
Yes	5	0.198	0.076	0.048	0.347	.377
No	12	0.108	0.066	-0.021	0.238	
Sample Characteristics						
Misc. Adults	15	0.144	0.057	0.032	0.255	.472
University Students	1	-0.017	0.152	-0.315	0.281	
Elderly Adults	1	-0.104	0.310	-0.711	0.503	
Recruitment Characteristics						
University	8	0.048	0.058	-0.065	0.162	.706
Community	1	-0.017	0.152	-0.315	0.281	
Clinic	2	0.158	0.105	-0.048	0.364	
Military	0					
Clinic & Community	1	0.069	0.336	-0.590	0.728	
University & Community	1	0.157	0.074	0.013	0.301	

Table 16  
*Effect Sizes and Moderator Analyses for Executive Function*

Variable	<i>k</i>	<i>g</i>	<i>SE</i>	95% CI		<i>p</i>
				LCL	UCL	
NR	4	0.270	0.208	-0.138	0.677	
Study Design						
Crossover	14	0.138	0.057	0.026	0.250	.450
Parallel	3	-0.012	0.189	-0.383	0.359	
Randomized						
Yes	9	0.070	0.056	-0.039	0.180	.378
No Report	8	0.160	0.047	0.006	0.189	
Counterbalanced						
Yes	6	0.046	0.041	-0.034	0.126	.144
No Report	11	0.183	0.084	0.018	0.348	
Medication Administration						
Fixed	15	0.104	0.057	-0.007	0.215	.168
Titrated	2	0.273	0.109	0.059	0.488	
Medication Dose						
Low	13	0.055	0.038	-0.020	0.130	.288
High	4	0.264	0.193	-0.115	0.643	
Medication						
AMP	8	0.200	0.085	0.034	0.366	.217

Table 16  
*Effect Sizes and Moderator Analyses for Executive Function*

Variable	<i>k</i>	<i>g</i>	<i>SE</i>	95% CI		<i>p</i>
				LCL	UCL	
MPH	8	0.008	0.073	-0.167	0.464	
LDX	0					
ATX	1	0.149	0.161	-0.167	0.464	
AMP & MPH	0					
Medication Activation Type						
Short-acting	16	0.126	0.056	0.016	0.235	.895
Medium or Long-acting	1	0.149	0.161	-0.167	0.464	
Timing of Dose Activation						
Prior	6	0.184	0.108	-0.027	0.395	.230
During	8	0.074	0.064	-0.053	0.200	
After	1	-0.017	0.152	-0.135	0.281	
NR	2	0.330	0.130	0.076	0.585	
Inclusion of Other Drugs						
Yes	3	0.253	0.095	0.067	0.439	.186
No	14	0.106	0.058	-0.009	0.221	
Inclusion of Non-behavioral Measures						
Yes	3	0.297	0.279	-0.250	0.844	.432

Table 16  
*Effect Sizes and Moderator Analyses for Executive Function*

Variable	<i>k</i>	<i>g</i>	<i>SE</i>	95% CI		<i>p</i>	
				LCL	UCL		
No	14	0.076	0.034	0.009	0.143		
Significant and Non-significant Findings							
Yes	17	0.127	0.053	0.024	0.230	1	
No	0						
Variable	<i>k</i>	<i>Q<sub>R</sub></i>	<i>B</i>	<i>SE</i>	<i>B</i> 95% CI		<i>p</i>
					LCL	UCL	
Study Year	17	0.02	0.001	0.008	-0.015	0.017	.898
Demographics							
Mean Age	15	0.01	0.002	0.007	-0.011	0.014	.820
% Female	16	0.47	0.002	0.002	-0.003	0.006	.493
Years of Education <sup>b</sup>	3						
Baseline							
Cognitive Functioning	5	0.45	-0.008	0.012	-0.030	0.015	.501
Number of Sessions	17	0.00	-0.001	0.035	-0.070	0.068	.973
Number of Doses	17	2.36	-0.098	0.064	-0.222	0.027	.124
Days on Medication	17	1.43	0.025	0.021	-0.016	0.067	.231
Minimum Washout Days Between Sessions	13	1.64	-0.037	0.029	-0.094	0.020	.201

Notes. <sup>a</sup> indicates significance of mean effect size; <sup>b</sup> indicates limited power precluding meta-regression analysis.

### Summary of Neurocognitive Enhancement of Broad Constructs

Table 17 displays the mean effect sizes for ADHD medication on cognition overall, as well as on abilities of focused behavior, learning and memory, and executive function described in the previous sections. Mean effect sizes were small for each construct.

Table 17  
*Summary of ADHD Medication and Cognition*

Outcome	<i>k</i>	Model	<i>g</i>	95% CI		<i>p</i>	<i>Q (df)</i>
				LCL	UCL		
Cognition Overall	91	Fixed	-0.005	-0.023	0.014	.621	300.435** (90)
		Random	0.147	0.095	0.199	<.001	
Abilities of Focused Behavior	74	Fixed	0.148	0.115	0.181	<.001	120.770** (73)
		Random	0.140	0.094	0.186	<.001	
Learning and Memory – Immediate and Delayed	24	Fixed	0.082	0.023	0.192	.006	49.139* (23)
		Random	0.104	0.015	0.192	.021	
Executive Function	17	Fixed	0.106	0.042	0.170	<.001	32.844* (16)
		Random	0.127	0.024	0.230	.005	

Notes. \* indicates  $p < .01$ ; \*\* indicates  $p < .001$ .

### Neurocognitive Enhancement by Narrow Constructs

The remainder of the results is presented according to the ten narrow constructs encompassing abilities of focused behavior, learning and memory, and executive function.



## **Neurocognitive Enhancement of Narrow Constructs of Abilities of Focused Behavior**

### **Neurocognitive Enhancement of Vigilance**

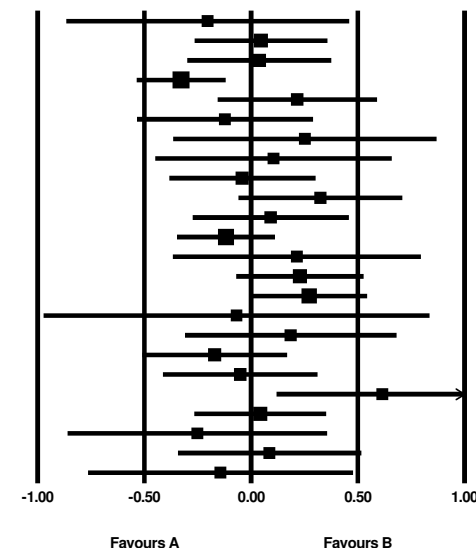
Data were extracted from 24 studies that investigated the neurocognitive effects of prescription stimulants on vigilance, or sustained and focused attention. Data from a total of 624 participants were extracted from studies that examined the effects of AMP ( $k = 5$ ), MPH ( $k = 17$ ), LDX ( $k = 1$ ), and ATX ( $k = 1$ ) on vigilance among adults with ( $k = 9$ ) and without ( $k = 15$ ) ADHD. Table 18 displays the descriptive data and effect size estimates (Hedge's  $g$ ) from each of the 24 studies. Under the random effects model, the studies generated a mean effect size of  $g = 0.037$  that was not significantly different than zero ( $SE = 0.047$ , 95% CI[-0.055, 0.128],  $p = .434$ ), with effect sizes ranging from  $g = -0.327$  to  $g = 0.615$ . A fixed effects model yielded similar results ( $g = 0.016$ ,  $SE = 0.038$ , 95% CI[-0.057, 0.090],  $p = .664$ ). Significant heterogeneity of variance was not revealed by the homogeneity analysis, ( $Q [23] = 32.218$ ,  $p = .096$ ).

Table 18

ADHD Medication Neurocognitive Effects on Vigilance Study and Mean Results

### Meta Analysis

Study name	ADHD	Comparison	Outcome	Statistics for each study						Hedges's g and 95% CI	
				Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
Agay et al. (2010)	Yes	MPH vs. PBO TOVA		-0.204	0.337	0.113	-0.863	0.456	-0.605	0.545	
Agay et al. (2014)	Yes	MPH vs. PBO TOVA		0.046	0.157	0.025	-0.262	0.354	0.294	0.769	
Barkley et al. (2005)	Yes	MPH vs. PBO CPT		0.039	0.171	0.029	-0.296	0.373	0.226	0.822	
Boonstra et al. (2005)	Yes	MPH vs. PBO CPT		-0.327	0.105	0.011	-0.533	-0.122	-3.127	0.002	
Bron et al. (2014)	Yes	MPH vs. PBO CPT; TOVA		0.216	0.189	0.036	-0.154	0.587	1.146	0.252	
Chamberlain et al. (2007)	Yes	ATX vs. PBO RVIP		-0.122	0.209	0.044	-0.532	0.287	-0.585	0.559	
Coons et al. (1981)a	No	MPH vs. PBO CPT		0.252	0.313	0.098	-0.362	0.865	0.804	0.421	
Coons et al. (1981)b	No	MPH vs. PBO CPT; Oddball		0.105	0.281	0.079	-0.446	0.656	0.374	0.708	
Costa et al. (2013)	No	MPH vs. PBO Go/No-Go		-0.041	0.174	0.030	-0.381	0.299	-0.236	0.813	
DuPaul et al. (2012)	Yes	LDX vs. PBO CPT		0.325	0.194	0.038	-0.056	0.706	1.672	0.094	
Elliott et al. (1997)	No	MPH vs. PBO RVIP		0.092	0.185	0.034	-0.271	0.455	0.497	0.619	
Fleming et al. (1995)	No	AMP vs. PBO CPT		-0.117	0.115	0.013	-0.343	0.109	-1.015	0.310	
Hink et al. (1978)	No	MPH vs. PBO Auditory Attention		0.215	0.295	0.087	-0.363	0.793	0.730	0.465	
Kollins et al. (2015)	No	MPH vs. PBO CPT		0.229	0.151	0.023	-0.066	0.524	1.521	0.128	
Kratz et al. (2009)	No	MPH vs. PBO Go/No-Go		0.273	0.137	0.019	0.005	0.540	1.994	0.046	
Levin et al. (2001)	Yes	MPH vs. PBO CPT		-0.068	0.460	0.211	-0.969	0.834	-0.147	0.883	
Rapoport et al. (1980)	No	AMP vs. PBO CPT		0.186	0.252	0.063	-0.307	0.679	0.739	0.460	
Silber et al. (2006)	No	AMP vs. PBO DV		-0.171	0.171	0.029	-0.506	0.165	-0.996	0.319	
Sofuoglu et al. (2008)	No	AMP vs. PBO SART		-0.051	0.183	0.034	-0.410	0.308	-0.278	0.781	
Strauss et al. (1984)	No	MPH vs. PBO CPT		0.615	0.251	0.063	0.122	1.108	2.447	0.014	
Theunissen et al. (2009)	No	MPH vs. PBO Mackworth Clock		0.043	0.156	0.024	-0.263	0.349	0.275	0.783	
Turner et al. (2003)	No	MPH vs. PBO RVIP		-0.252	0.309	0.095	-0.857	0.354	-0.815	0.415	
Turner et al. (2005)	Yes	MPH vs. PBO RVIP		0.086	0.218	0.047	-0.340	0.513	0.397	0.692	
Whiting et al. (2008)	No	AMP vs. PBO RVIP		-0.144	0.315	0.099	-0.761	0.474	-0.456	0.649	



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### Meta Analysis

Notes. AMP = Amphetamine; ATX = Atomoxetine; CPT = Continuous Performance Task; DV = Digit Vigilance; LDX = Lisdexamfetamine Dymesylate; MPH = Methylphenidate; PBO = Placebo; RVIP = Rapid Visual Information Processing; SART = Sustained Attention to Response Test; TOVA = Test of Visual Attention.

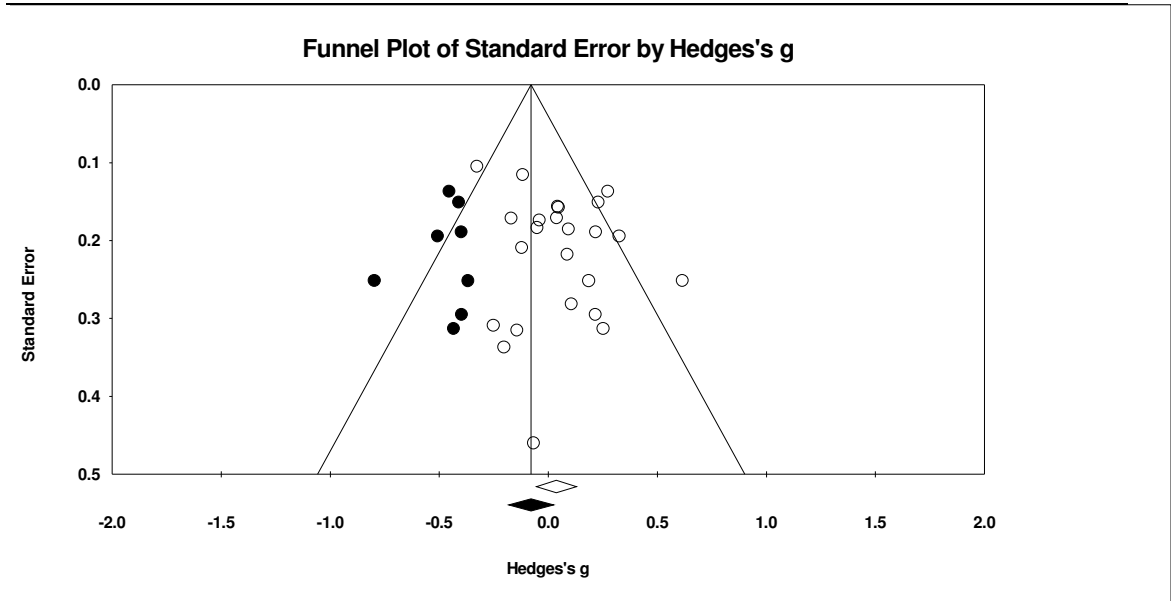
### **Outlier Evaluation**

Studies with effect sizes falling outside 3 standard deviations ( $SD = 0.230$ ) of the mean ( $g < -0.654$  or  $g > 0.728$ ) were examined as potential outliers. No studies met these criteria. Therefore, analyses were conducted maintaining effect sizes from all of the studies.

### **Publication Bias**

Analysis of publication bias indicated minimal risk with a Rosenthal's  $N$  of 24 to lead to a  $p$ -value at or above an alpha of .05 an Orwin's  $N$  of 64 to reduce the measure of effect to  $g = 0.01$  (this effect size was chosen to represent an estimate approaching zero considering the minimal effect size,  $g = 0.037$ , the studies generated). Trim and fill analysis suggested the imputation of 8 studies to account for positive bias resulting in a mean effect size that signified small negative effects ( $g = -0.079$ , 95% CI [-0.183, 0.025]) and Egger's regression just missed significance ( $B = 1.086$ ,  $SE = 0.711$ ,  $t(22) = 1.529$ , 95% CI [-0.387, 2.560],  $p = .070$ ) (see Figure 8). These findings indicated the likelihood of positive publication bias within this analysis.

Figure 8  
*Funnel Plot with Observed Studies for Vigilance*



### Moderator Analyses

Because the homogeneity analysis revealed a  $Q$  statistic that approached significance ( $p = .096$ ), moderator analysis was conducted for variables identified *a priori* and for additional moderating variables. ANOVA analog revealed significant differences for participant characteristics,  $Q(2) = 7.233$ ,  $p = .027$ . Follow-up two-group ANOVA analogs revealed significantly larger effect sizes found among studies with adult students ( $k = 4$ ;  $g = 0.320$ ,  $SE = 0.119$ , 95% CI [0.087, 0.553]) compared to studies that included other adults ( $k = 19$ ;  $g = -0.002$ ,  $SE = 0.046$ , 95% CI [-0.092, 0.088]),  $Q(1) = 6.358$ . Significant differences were not revealed between any of the other groups, although differences between studies with student populations and studies with elderly adult populations ( $k = 1$ ;  $g = -0.252$ ,  $SE = 0.042$ , 95% CI [-0.857, 0.354]) approached significance,  $Q(1) = 2.979$ ,  $p = .084$ . Interpretation of these differences is limited by the small sample size. The homogeneity of variance analysis

did not reveal significant heterogeneity for adults,  $Q(18) = 22.157, p = .225$  or students,  $Q(3) = 2.247, p = .523$ .

Similar results were found for participant recruitment characteristics,  $Q(5) = 11.932, p = .036$ , findings that are likely confounded with participant characteristics. Follow-up analyses with two-group ANOVA analogs revealed significantly larger effect sizes for studies conducting recruitment within university settings ( $k = 4; g = 0.320, SE = 0.119, 95\% CI [0.087, 0.553]$ ) compared to studies where recruitment was conducted within communities ( $k = 7; g = -0.048, SE = 0.062, 95\% CI [-0.169, 0.074]$ ),  $Q(1) = 7.507, p = .006$ , and also compared to studies that conducted recruitment within clinical settings ( $k = 6; g = -0.026, SE = 0.337, 95\% CI [-0.863, 0.456]$ ),  $Q(1) = 4.606, p = .032$ . Significant differences were also revealed between studies that did not report recruitment settings ( $k = 5, g = 0.205, SE = 0.090, 95\% CI [0.029, 0.381]$ ) and studies that recruited participants within communities,  $Q(1) = 5.364$ . None of the other recruitment variables showed significant differences; however, analyses were not conducted comparing military settings or community settings that were combined with other settings considering their small sample sizes. Homogeneity analyses did not reveal significant differences within participant recruitment groups.

Meta-regression revealed significant effects for age ( $k = 21; B = -0.019, SE = 0.005, 95\% CI [-0.029, -0.008], p = .001, R^2 \text{ analog} = 1.0$ ) and gender distribution ( $k = 22; B = -0.005, SE = 0.002, 95\% CI [-0.010, -0.000], p = .032, R^2 \text{ analog} = 0.52$ ) on measures of vigilance. Figures 9 and 10 show trends where a decrease in study effect size related to an increase in mean age and decrease in representation of females. A

significant trend was also revealed for cognitive baseline ( $k = 8$ ;  $B = 0.010$ ,  $SE = 0.004$ , 95% CI [0.002, 0.017],  $p = .014$ ,  $R^2 \text{ analog} = 1.00$ ). As can be seen in Figure 11, larger effect sizes associated with higher baseline scores of cognitive functioning. Finally, although lower numbers of days on medication was significantly related to higher effect sizes across studies ( $k = 24$ ;  $B = -0.013$ ,  $SE = 0.006$ , 95% CI [-0.025, -0.001],  $p = .034$ ,  $R^2 \text{ analog} = 0.63$ ), this finding should be interpreted with caution given only 4 studies administered medication for more than one day. No other significant continuous or categorical variables were revealed by meta-regression or ANOVA analog.

Figure 9  
*Scatter Plot with Observed Studies for Vigilance and Age*

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Figure 10  
Scatter Plot with Observed Studies for Vigilance and Percent Female

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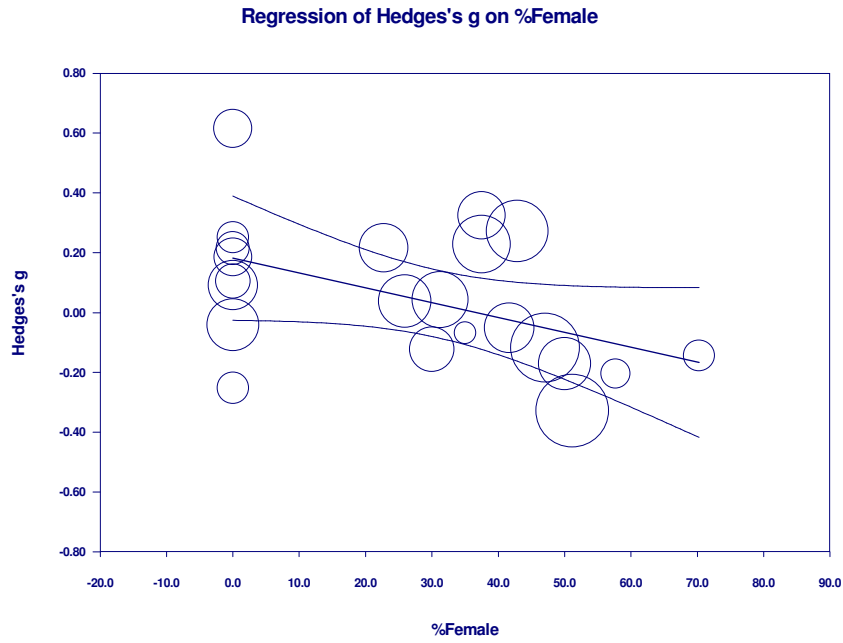
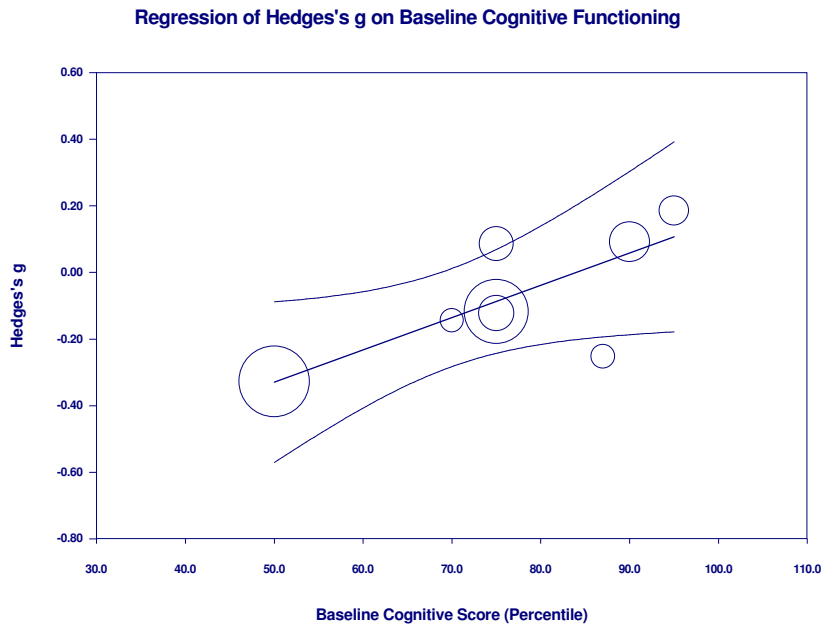


Figure 11  
Scatter Plot with Observed Studies for Vigilance and Baseline Cognitive Functioning

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### **Missing Data**

Eleven studies with insufficient data to calculate effect sizes were excluded from the analysis involving the effects of ADHD medication on neurocognitive enhancement of vigilance (see Appendix C). Four studies reported non-significant findings, 5 studies reported significant, positive effects, 1 study reported mixed findings, and 1 study did not provide enough information to report.

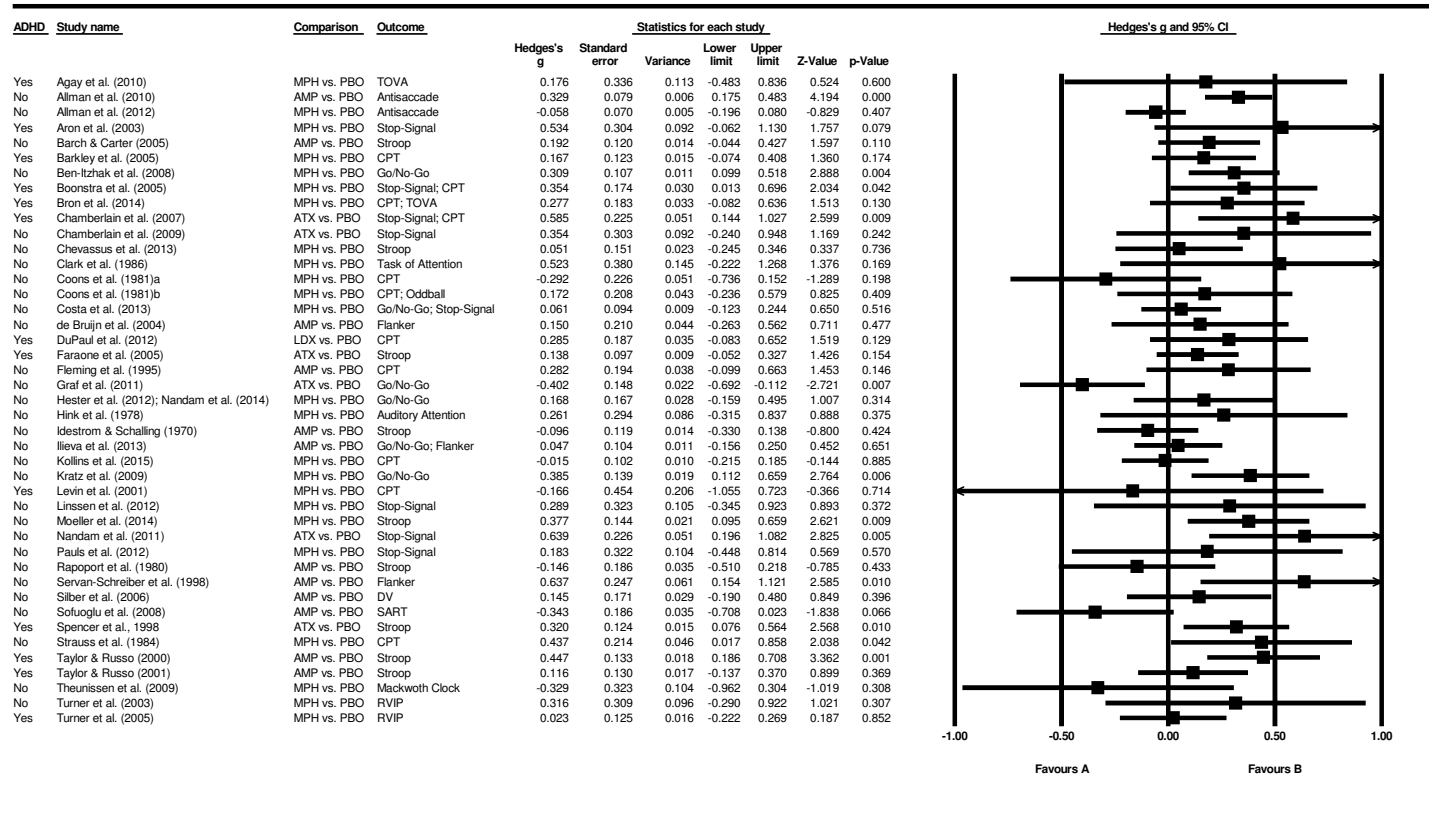
### **Neurocognitive Enhancement of Inhibitory Control**

Data were extracted from 43 studies that investigated the neurocognitive effects of ADHD medication on inhibitory control, including 1,495 participants. These studies examined the neurocognitive effects of AMP ( $k = 12$ ), MPH ( $k = 25$ ), LDX ( $k = 1$ ), and ATX ( $k = 5$ ) on inhibitory control on adults with ( $k = 13$ ) and without ( $k = 30$ ) ADHD. Table 19 displays the descriptive data and ES estimates (Hedge's  $g$ ) from each of the 43 studies. The random effects model analysis resulted in a statistically significant mean effect size of  $g = 0.164$  ( $SE = 0.036$ , 95% CI [0.094, 0.235],  $p < .001$ ), with effect sizes ranging -0.402 to 0.639. Under the fixed effects model, the mean effect size was slightly reduced to  $g = 0.145$  ( $SE = 0.036$ , 95% CI [0.101, 0.189],  $p < .001$ ). The heterogeneity of variance analysis yielded a significant  $Q$  statistic,  $Q(42) = 89.308$ ,  $p < .001$ .



Table 19  
ADHD Medication Neurocognitive Effects on Inhibitory Control and Mean Results

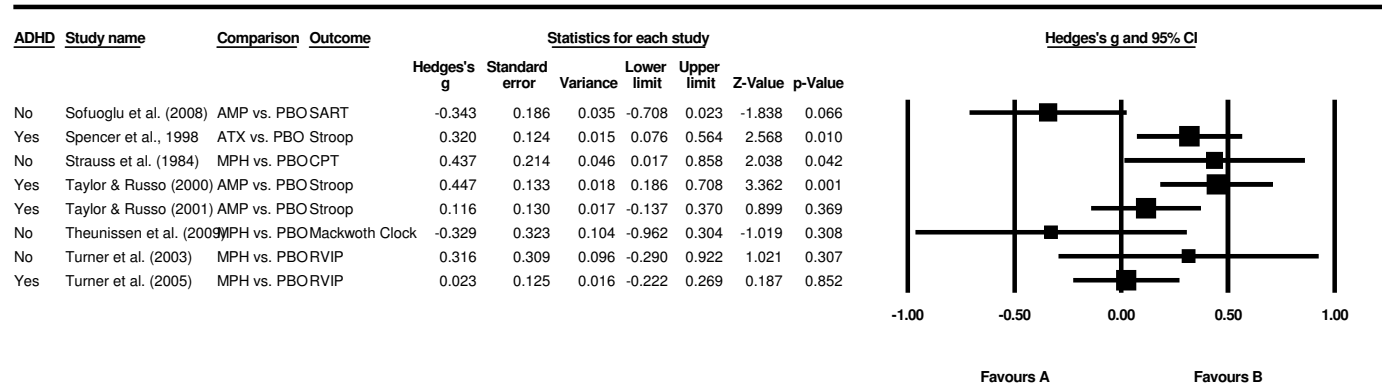
## Meta Analysis



Meta Analysis

Table 19 (continued)

## Meta Analysis



### Meta Analysis

Notes. AMP = Amphetamine; ATX = Atomoxetine; CPT = Continuous Performance Task; DV = Digit Vigilance; LDX = Lisdexamfetamine Dymesylate; MPH = Methylphenidate; PBO = Placebo; RVIP = Rapid Visual Information Processing; SART = Sustained Attention to Response Test; TOVA = Test of Visual Attention.

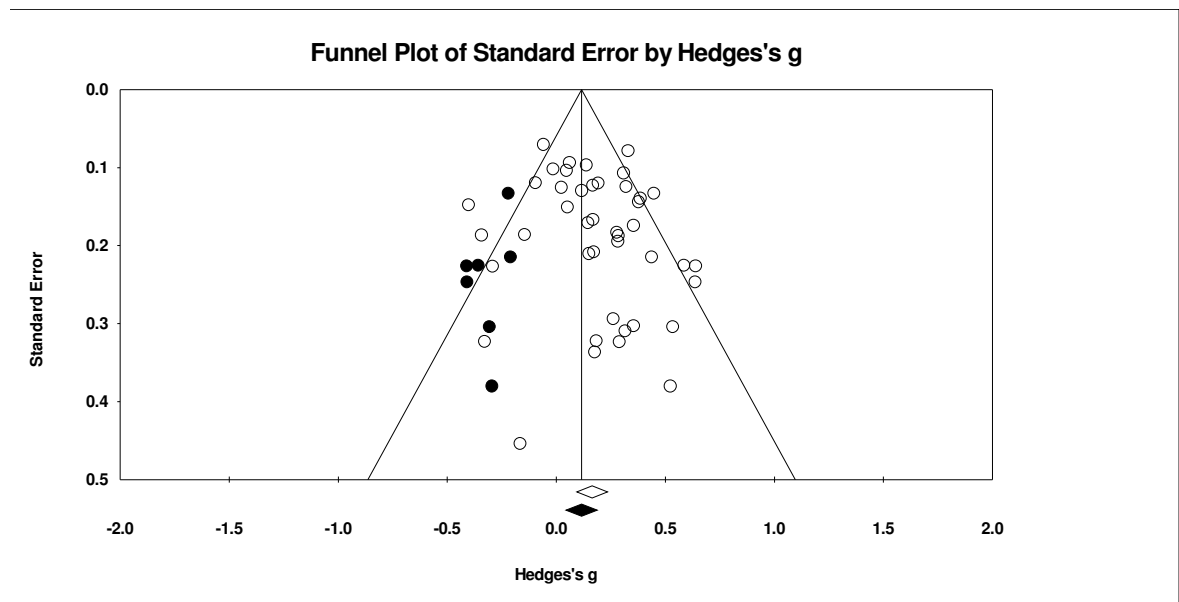
## Outlier Evaluation

Studies with effect sizes falling outside 3 standard deviations ( $SD = 0.236$ ) of the mean ( $g < -0.544$  or  $g > 0.872$ ) were examined as potential outliers. No studies met these criteria. Therefore, analyses were conducted maintaining effect sizes from all of the studies.

## Publication Bias

Analysis of publication bias indicated minimal risk with a Rosenthal's  $N$  of 454 to lead to a  $p$ -value at or above an alpha of .05 and Orwin's  $N$  of 27 to reduce the measure of effect to  $g = 0.10$ . Trim and fill analysis suggested the imputation of 7 studies resulting in a reduction in the mean effect size to  $g = 0.116$ , 95% CI [0.044, 0.188] (see Figure 12). Egger's regression approached significance ( $B = 0.710$ ,  $SE = 0.540$ ,  $t(41) = 1.316$ , 95% CI [-0.380, 1.801],  $p = .098$ ) indicating some risk for publication bias.

Figure 12  
*Funnel Plot with Observed Studies for Inhibitory Control*



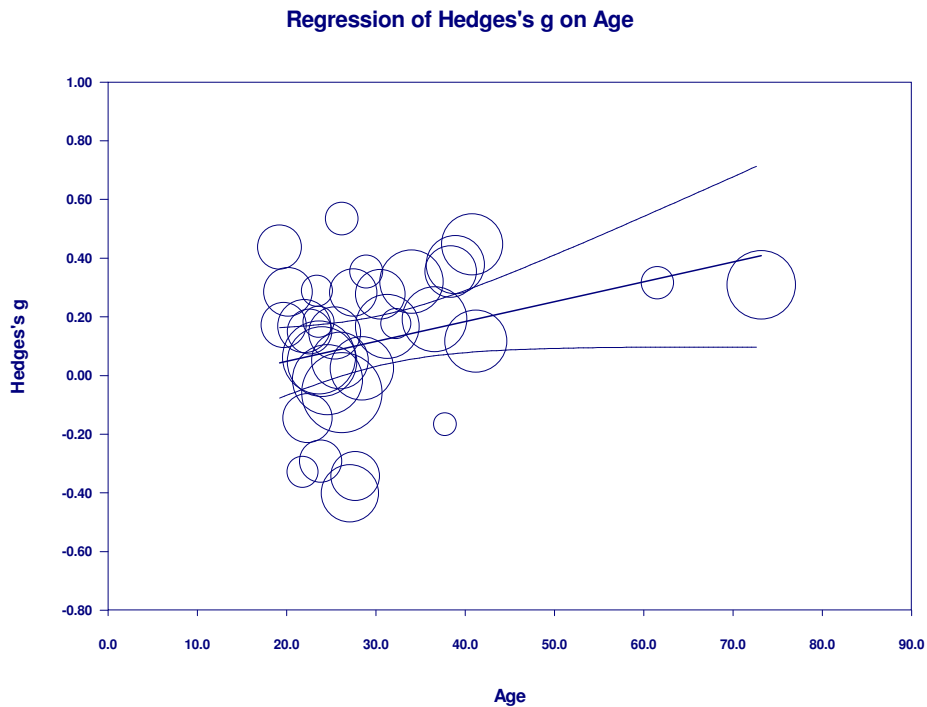
## Moderator Analyses

Moderator analyses were conducted given the between-study variability indicated by the significant homogeneity of variance analysis. ANOVA analog did not reveal any significant moderator variables. However, differences between studies administering low and high doses approached significance,  $Q(1) = 3.414, p = .065$ , where low doses ( $k = 31, g = 0.206, SE = 0.041, 95\% CI [0.125, 0.287]$ ) resulted in larger mean effect sizes than high doses ( $k = 12, g = 0.060, SE = 0.068, 95\% CI [-0.073, 0.192]$ ). Timing of dose activation also approached significance,  $Q(3) = 7.388, p = .061$ , so follow-up two-group ANOVA analogs were conducted to examine differences between individual groups. Results indicated significantly smaller effect sizes among studies that administered medication that was active prior to learning ( $k = 5, g = 0.011, SE = 0.066, 95\% CI [-0.119, 0.141]$ ) compared to studies where medication was active during learning ( $k = 29, g = 0.175, SE = 0.047, 95\% CI [0.083, 0.267]$ ),  $Q(1) = 4.077, p = .043$ , and also compared to studies where medication activation timing was not reported ( $k = 5, g = 0.264, SE = 0.032, 95\% CI [0.090, 0.217]$ ),  $Q(1) = 6.972, p = .008$ . Significant differences were not revealed for any other variables concerning timing of medication activation including studies reporting medication activation timing that was active following learning ( $k = 4, g = 0.155, SE = 0.126, 95\% CI [-0.091, 0.401]$ ). Homogeneity analyses indicated significant between-study variability for studies reporting medication activation during learning,  $Q(28) = 65.587, p < .001$ . Significant between-study variance was not revealed for any of the other variables related to medication activation timing.

As shown in Figure 13, a significant trend was revealed where age demonstrated a positive association with effect sizes ( $k = 34$ ,  $B = 0.007$ ,  $SE = 0.003$ , 95% CI [0.001, 0.012],  $p = .020$ ,  $R^2$  analog = 0.33). Although not significant, a trend ( $p < .10$ ) was revealed for higher number of sessions relating to smaller effect sizes ( $k = 43$ ,  $B = -0.043$ ,  $SE = 0.023$ , 95% CI [-0.088, 0.003],  $p = .066$ ,  $R^2$  analog = 0.11). Meta-regression and ANOVA analog did not reveal any other significant moderator variables.

Figure 13  
*Scatter Plot with Observed Studies for Inhibitory Control and Age*

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### Missing Data

A total of 11 studies investigating the effects of ADHD medication on inhibitory control that met the study's eligibility criteria did not have sufficient data to calculate effect sizes (see Appendix C). Four studies reported non-significant results, 2

studies reported mixed results, 2 studies reported positive and significant findings, and 2 studies did not report the findings related to inhibitory control.

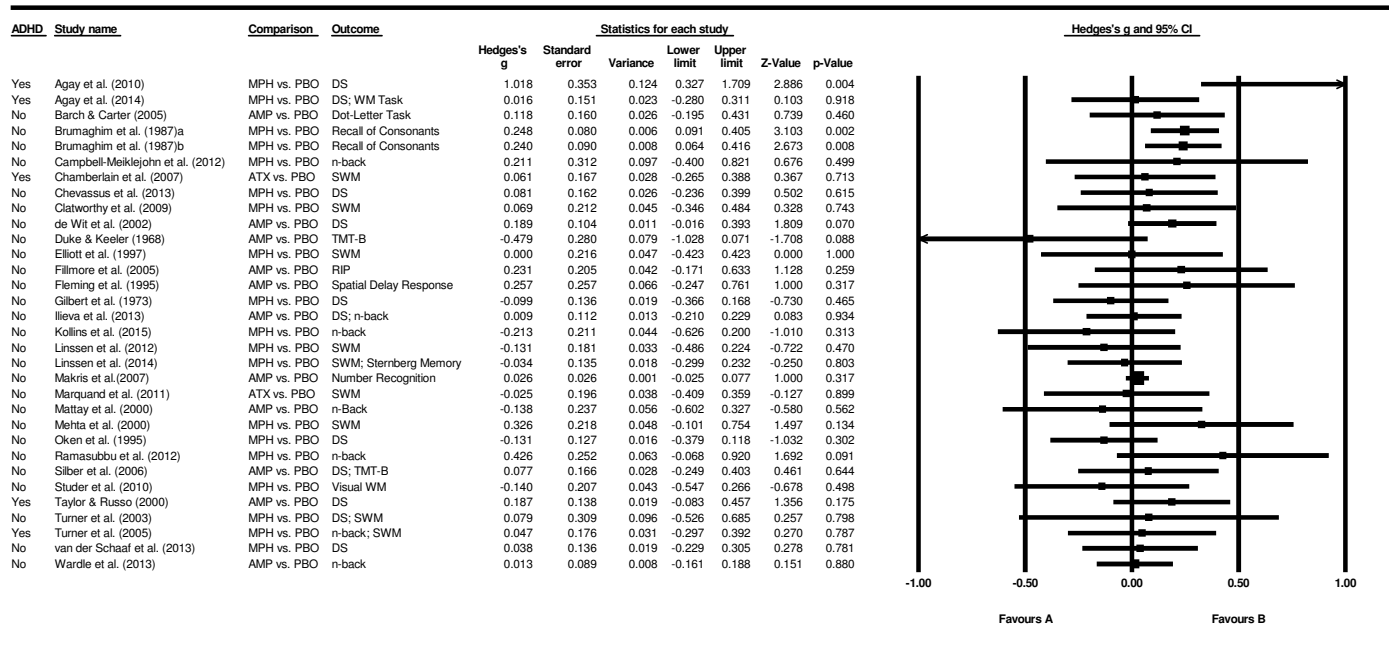
### **Neurocognitive Enhancement of Working Memory**

Data were extracted from 32 studies (895 participants) that investigated the neurocognitive effects of prescription stimulants on working memory. These studies explored the effects of AMP ( $k = 11$ ), MPH ( $k = 20$ ), and ATX ( $k = 1$ ) among adults with ( $k = 5$ ) and without ( $k = 27$ ) ADHD. Table 20 displays the descriptive data and effect size estimates (Hedge's  $g$ ) from each of the 32 studies. The studies generated a statistically significant mean effect size of  $g = 0.068$  ( $SE = 0.028$ , 95% CI[0.014, 0.123],  $p = .014$ ), with effect sizes ranging -0.479 to 1.018. A fixed effects model yielded a similar average mean effect ( $g = 0.054$ ,  $SE = 0.019$ , 95% CI[0.017, 0.090],  $p = .004$ ). The homogeneity of variance analysis did not reveal yield a significant  $Q$  statistic,  $Q(31) = 39.284$ ,  $p = .146$ , indicating minimal variability between studies.

Table 20

ADHD Medication Neurocognitive Effects on Working Memory Study and Mean Results

## Meta Analysis



### Meta Analysis

Notes. AMP = Amphetamine; ATX = Atomoxetine; DS = Digit Span; MPH = Methylphenidate; PBO = Placebo; RIP = Rapid Information Processing Task; SWM = Spatial Working Memory; TMT = Trail-Making Task; WM = Working Memory.

## Outlier Evaluation

Studies with effect sizes falling outside 3 standard deviations ( $SD = 0.158$ ) of the mean ( $g < -0.407$  or  $g > 0.543$ ) were examined as potential outliers. Two studies met these criteria: Duke & Keeler (1968),  $g = -0.479$  and Agay et al. (2010),  $g = 1.018$ . Table 21 displays the mean effect sizes with the inclusion of all studies, with each of these studies removed, and with the removal of both studies.

*Table 21*  
Outlier Summary of ADHD Medication and Working Memory

Analysis	$k$	Model	$g$	95% CI		$p$	$Q$ ( $df$ )
				LCL	UCL		
All studies	32	Fixed	0.054	0.017	0.090	.004	39.284 (31)
		Random	0.068	0.014	0.123	.014	
Duke & Keeler (1968) removed	31	Fixed	0.056	0.019	0.093	.003	35.661 (30)
		Random	0.073	0.021	0.125	.006	
Agay et al. (2010) removed	31	Fixed	0.051	0.014	0.088	.007	31.787 (30)
		Random	0.059	0.014	0.104	.010	
Both studies removed	30	Fixed	0.053	0.016	0.090	.005	28.202 (29)
		Random	0.053	0.016	0.090	.005	

*Notes.* \*  $p < .01$ ; \*\*  $p < .001$ .

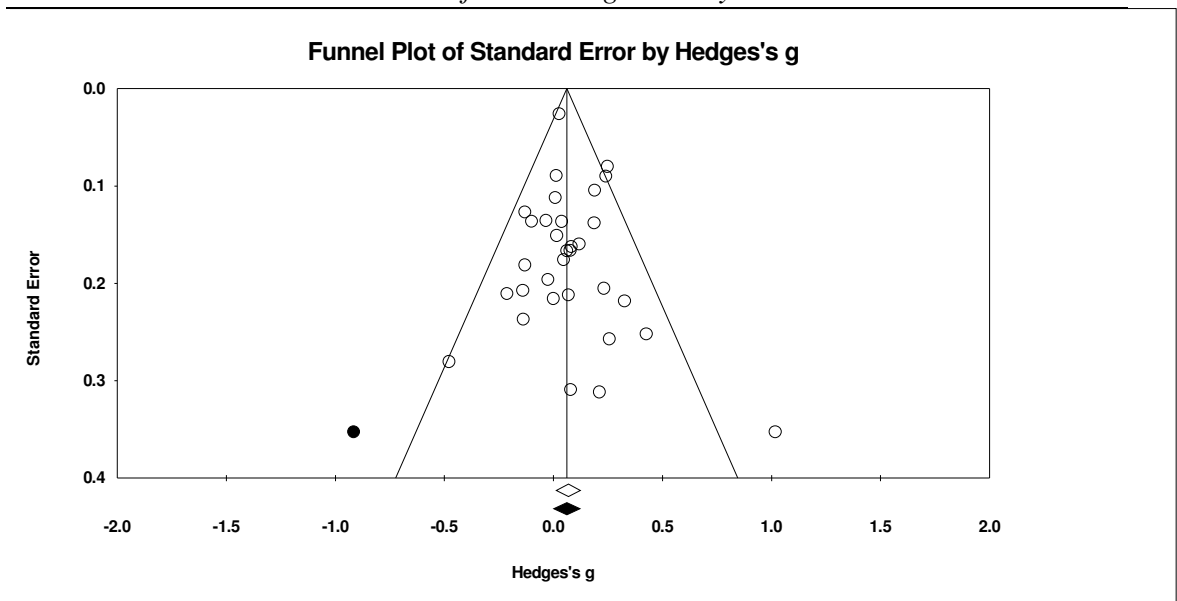
Duke & Keeler's (1968) study was described as a potential outlier in previous analyses; this study's removal resulted in a minimal increase in the mean effect size to  $g = 0.073$  from  $g = 0.068$ . Agay et al. (2010) examined the effects of MPH on adults with and without ADHD in a parallel design study, reporting significant positive effects for working memory as measured by DS. A decision to maintain both studies in the subsequent analyses was made considering their minimal effects on mean effect sizes.



## Publication Bias

Analysis of publication bias indicated minimal risk with a Rosenthal's  $N$  of 31 to lead to a  $p$ -value at or above an alpha of .05 and Orwin's  $N$  of 185 to reduce the effect size to  $g = 0.01$ . Trim and fill analysis suggested the imputation of 1 study, resulting in a slight reduction of the mean effect size to  $g = 0.062$ , 95% CI[0.001, 0.121] (see Figure 14). Egger's regression was not significant [ $B = 0.237$ ,  $SE = 0.309$ ,  $t(30) = 0.766$ , 95% CI [-0.394, 0.868],  $p = .225$ ). Therefore, risk of publication bias appeared to be minimal for working memory.

Figure 14  
*Funnel Plot with Observed Studies for Working Memory*



## Moderator Analyses

Because the homogeneity variance analysis did not indicate significant heterogeneity between studies, only variables identified *a priori* concerning the present study's hypotheses were explored as potential moderators. ANOVA analog and meta-regression did not reveal significance for ADHD status, activation timing of

learning, medication activation type, or baseline cognitive functioning (measured with intelligence tests and years of education).

### **Missing Data**

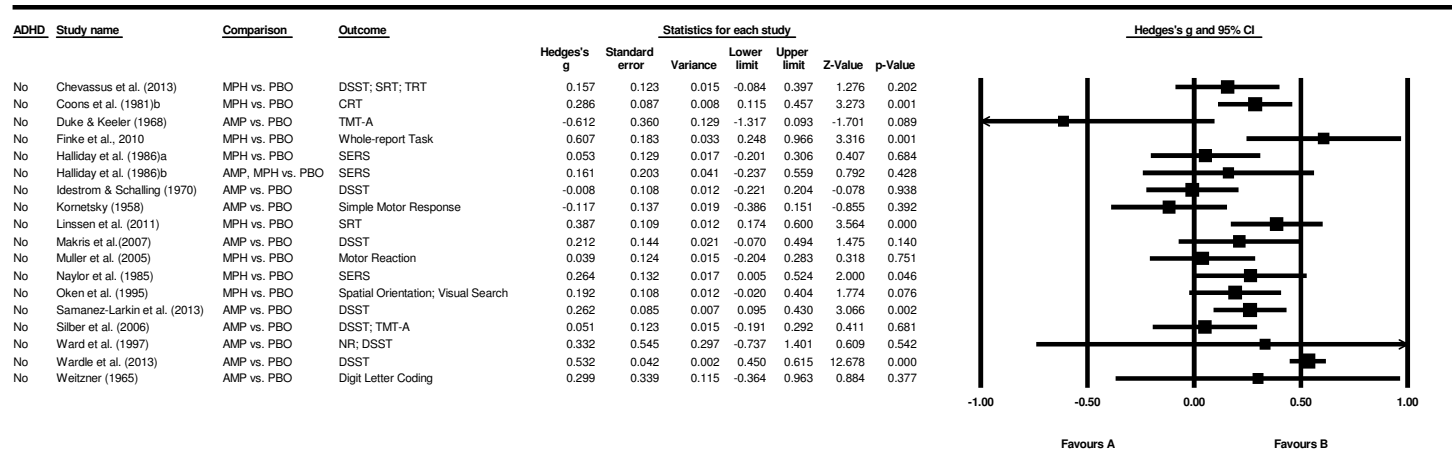
Eleven studies involving the effects of ADHD medication on neurocognitive enhancement of working memory were excluded from the analysis due to insufficient data for calculating effect sizes (see Appendix C). Six of the studies reported non-significant findings and five reported significant benefits of ADHD medication for working memory.

### **Neurocognitive Enhancement of Processing Speed**

Data were extracted from 18 studies that investigated the neurocognitive effects of ADHD medication on processing speed, resulting in a total of 558 participants. Effect sizes resulted from studies examining the effects of AMP ( $k = 9$ ), MPH ( $k = 8$ ), and ATX ( $k = 1$ ) on processing speed among adults without ADHD ( $k = 18$ ). Table 22 displays the descriptive data and effect sizes (Hedge's  $g$ ) from each of the 18 studies. Under the random effects model, the studies generated a statistically significant mean effect size of  $g = 0.195$  ( $SE = 0.060$ , 95% CI [0.077, 0.313],  $p = .001$ ), with effect sizes ranging -0.612 to 0.607. The fixed effects model yielded a much larger mean effect size of  $g = 0.306$ ,  $SE = 0.025$ , 95% CI [0.257, 0.355],  $p < .001$ ). The heterogeneity of variance analysis was significant,  $Q(17) = 73.499$ ,  $p < .001$ , indicating significant between-study variance.

Table 22  
*ADHD Medication Neurocognitive Effects on Processing Speed Study and Mean Results*

## Meta Analysis



### Meta Analysis

*Notes.* AMP = Amphetamine; CRT = Choice Reaction Time; DSST = Digit Symbol Substitution Task; MPH = Methylphenidate; NR = Number Recognition; PBO = Placebo; SERS = Stimulus Evaluation Response Selection; SRT = Simple Reaction Test; TMT = Trail-Making Task; TRT = Total Choice Reaction Test.

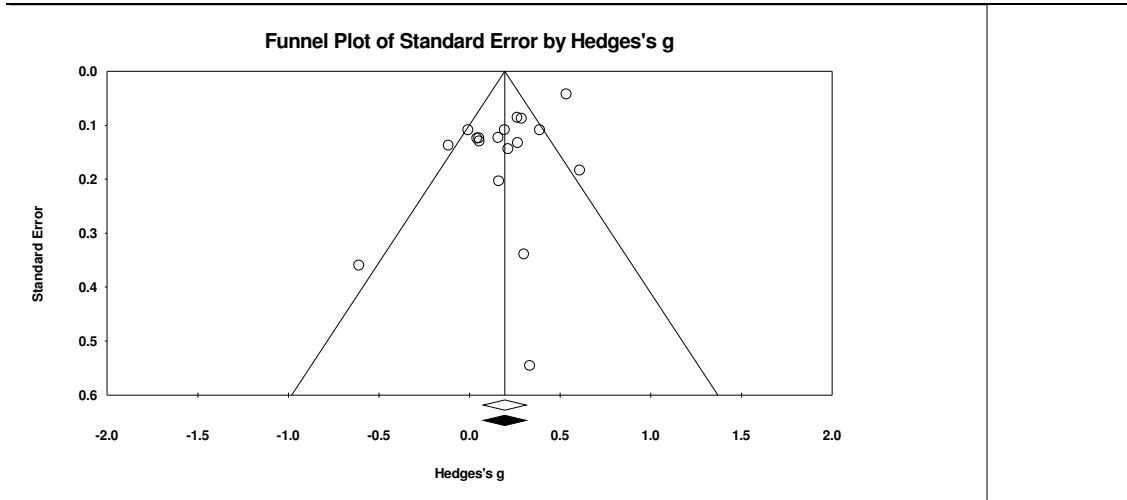
### **Outlier Evaluation**

Studies with effect sizes falling outside 3 standard deviations ( $SD = 0.256$ ) of the mean ( $g < -0.569$  or  $g > 0.959$ ) were examined as potential outliers. Only one study (Duke & Keeler, 1968) met these criteria with a mean effect size of  $g = -0.612$ . The removal of this study resulted in a slight increase in the mean effect size to  $g = 0.213$  ( $SE = 0.059$ , 95% CI [0.097, 0.328],  $p < .001$ ) from  $g = 0.195$ . Therefore, consistent to previous analyses, this study was maintained.

### **Publication Bias**

Analysis of publication bias indicated minimal risk with a Rosenthal's  $N$  of 270 to lead to a  $p$ -value at or above an alpha of .05 and an Orwin's  $N$  of 17 to reduce the measure of effect to 0.10. Although trim and fill analysis did not suggest the imputation of any studies to reduce positive bias, 8 studies were suggested for imputation to account for negative bias and resulted in an increase in the mean effect size to  $g = 0.382$ , 95% CI [0.260, 0.504]. Egger's regression was significant [ $B = -2.621$ ,  $SE = 0.780$ ,  $t(16) = 3.358$ , 95% CI [-4.276, -0.967],  $p = .002$ ) which is displayed visually in Figure 15. These findings suggest minimal risk of publication bias within analyses examining processing speed.

Figure 15  
*Funnel Plot with Observed Studies for Processing Speed*



### Missing Data

Fourteen studies were excluded due to insufficient data from the analysis involving the effects of ADHD medication on neurocognitive enhancement of processing speed (see Appendix C). Two studies reported mixed findings, 1 study reported a significant negative effect, 4 studies reported non-significant findings, and 7 studies reported significant and positive effects.

### Moderator Analyses

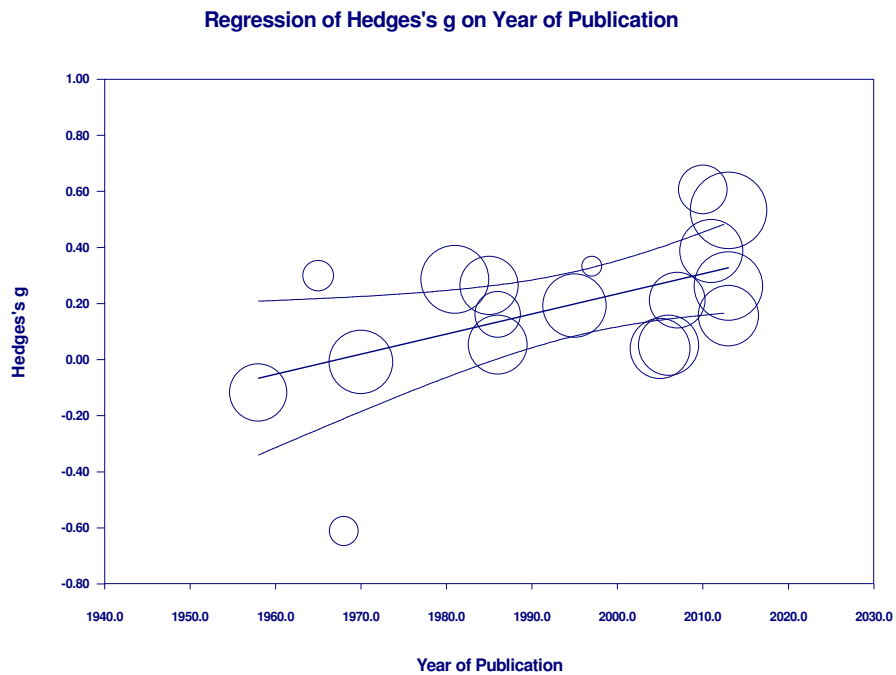
The significant  $Q$  statistic indicated between study variance so moderator analyses were conducted. ANOVA analog revealed significant differences for timing of dose activation,  $Q(3) = 7.873, p = .049$ ; however, when the one study that did not report timing of dose activation ( $k = 1, g = -0.612, SE = 0.360, 95\% \text{ CI } [-1.317, 0.093]$ ) was removed from this analysis, significant differences were not found,  $Q(2) = 3.047, p = .218$ .

As shown in Figure 16, meta-regression revealed a significant trend for studies published more recently resulting in larger effect sizes ( $k = 18, B = 0.007, SE = 0.003,$

95% CI[0.002, 0.012],  $p = .008$ ,  $R^2 = 0.53$ ). No other significant variables were revealed by meta-regression; however, note that meta-regression could not be conducted for years of education or baseline cognitive functioning due to the low number of studies reporting them ( $k = 2$  and  $k = 0$ , respectively).

Figure 16  
*Scatter Plot with Observed Studies for Processing Speed and Year of Publication*

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### **Summary of Neurocognitive Enhancement of Narrow Constructs of Abilities of Focused Behavior**

Table 23 displays the mean effect sizes for ADHD medication on abilities of focused behavior overall, as well as on each underlying construct individually (vigilance, inhibitory control, working memory, and processing speed). Mean effect sizes were small for abilities of focused behavior overall, as well as for inhibitory control and processing speed, but they approached zero for vigilance and working memory.

Table 23

*Summary of ADHD Medication and Abilities of Focused Behavior Findings*

Outcome	<i>k</i>	Model	<i>g</i>	95% CI		<i>p</i>	<i>Q</i> ( <i>df</i> )
				LCL	UCL		
Overall	74	Fixed	0.148	0.115	0.181	<.001	120.770 <sup>**</sup>
		Random	0.140	0.094	0.186	<.001	(73)
Vigilance	24	Fixed	0.016	-0.057	0.090	.664	32.218
		Random	0.047	-0.055	0.128	.434	(23)
Inhibitory Control	43	Fixed	0.145	0.101	0.189	<.001	89.308 <sup>**</sup>
		Random	0.164	0.094	0.235	<.001	(42)
Working Memory	32	Fixed	0.054	0.017	0.090	.004	39.284
		Random	0.068	0.014	0.123	.014	(31)
Processing Speed	18	Fixed	0.306	0.257	0.355	<.001	73.499 <sup>**</sup>
		Random	0.195	0.077	0.313	.001	(17)

Notes. \*  $p < .01$ ; \*\*  $p < .001$ .

### Neurocognitive Enhancement of Narrow Constructs of Learning and Memory

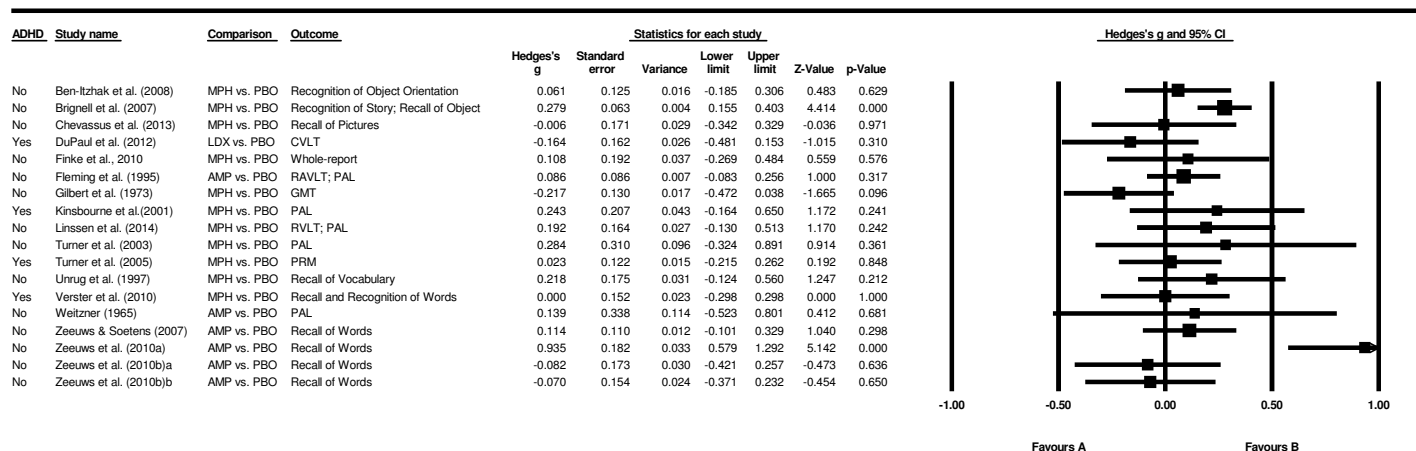
#### Neurocognitive Enhancement of Declarative Learning and Memory – Immediate

Data were extracted from 18 studies (567 participants) that investigated the neurocognitive effects of ADHD medication on declarative learning with immediate memory tests. Studies investigated AMP ( $k = 6$ ), MPH ( $k = 11$ ), and LDX ( $k = 1$ ) among adults with ( $k = 4$ ) and adults without ( $k = 14$ ) ADHD. Table 24 displays the descriptive data and ES estimates (Hedge's  $g$ ) from each of the 18 studies. The studies generated a mean effect size of  $g = 0.106$  that just missed significance ( $SE = 0.054$ , 95% CI [-0.000, 0.212],  $p = .051$ ) under the random effects model, with effect sizes ranging from  $g = -0.217$  to  $g = 0.935$ . A fixed effects model yielded similar findings that did reach statistical significance ( $g = 0.124$ ,  $SE = 0.031$ , 95% CI [0.063, 0.186],  $p < .001$ ). The heterogeneity of variance analysis yielded a significant  $Q$  statistic,  $Q(17) = 59.878$ ,  $p = .001$ .

Table 24

*ADHD Medication Neurocognitive Effects on Immediate Declarative Learning and Memory and Mean Results*

**Meta Analysis**



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**Meta Analysis**

*Notes.* AMP = Amphetamine; CVLT = California Verbal Learning Test; GMT = Guild Memory Test; LDX = Lisdexamfetamine Dymesylate; MPH = Methylphenidate; PAL = Paired Associates Task; PBO = Placebo; PRM = Pattern Recognition Memory Task; RVALT = Rey Verbal Auditory Learning Task.



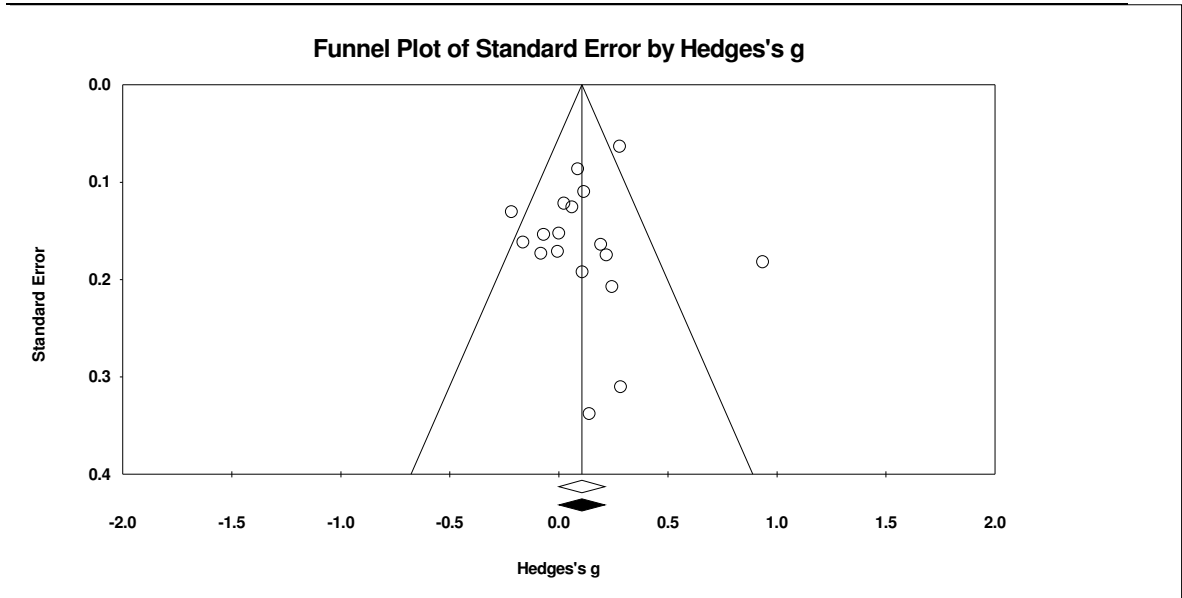
### **Outlier Evaluation**

Studies with effect sizes falling outside 3 standard deviations ( $SD = 0.229$ ) of the mean ( $g < -0.581$  or  $g > 0.793$ ) were examined as potential outliers. Only one study (Zeeuws et al., 2010a,  $p = .065$ ) met these criteria with a mean effect size of  $g = 0.935$ . The removal of this study resulted in a slight reduction in the mean effect size to  $g = 0.074$ ,  $SE = 0.040$ , 95% CI [-0.005, 0.153] from  $g = 0.106$ . Therefore, a decision to maintain this study was made, consistent to previous analyses.

### **Publication Bias**

Analysis of publication bias indicated minimal risk with a Rosenthal's  $N$  of 34 to lead to a  $p$ -value at or above an alpha of .05 and Orwin's  $N$  of 20 to reduce the measure of effect to  $g = 0.05$  (an estimate chosen to reflect a substantial decrease from the original mean effect size,  $g = 0.106$ ). Trim and fill analysis did not suggest the imputation of any studies to account for positive bias; however, 5 studies were suggested for imputation to account for negative bias resulting in an increase in the mean effect size to  $g = 0.190$ , 95% CI [0.086, 0.295]. Egger's regression was not significant ( $B = 0.523$ ,  $SE = 0.980$ ,  $t(16) = 0.534$ , 95% CI [-2.600, 1.554],  $p = .300$ ) as evidenced by the symmetry shown in the funnel plot (see Figure 17). Findings suggest minimal publication bias within the analysis of declarative memory measured immediately after learning.

Figure 17  
*Funnel Plot with Observed Studies for Immediate Declarative Learning and Memory*



### Moderator Analyses

Significant between study variability was present for studies exploring memory that measured immediately after learning, so moderator analyses were conducted. ANOVA analog revealed significant differences for stimulant administration type,  $Q(1) = 4.592, p = 0.032$ . Studies administering stimulant doses that were fixed ( $k = 16, g = 0.136, SE = 0.055, 95\% CI [0.028, 0.245]$ ) resulted in significantly larger mean effect sizes than studies administering titrated doses ( $k = 2, g = -0.123, SE = 0.108, 95\% CI [-0.333, 0.088]$ ); however, this finding was underpowered considering the low number of studies administering titrated doses. A similar finding was revealed on a trend level ( $p < .10$ ) for medication activation type,  $Q(1) = 2.790, p = 0.095$ , where studies administering short-acting medications ( $k = 17, g = 0.121, SE = 0.055, 95\% CI [0.014, 0.228]$ ) resulted in larger effect sizes than the one study administering long-acting stimulants ( $k = 1, g = -0.164, SE = 0.052, 95\% CI [-0.010, 0.193]$ ). These

findings do not appear to be clinically meaningful given the small number of studies investigating medication that was titrated and long-acting agents.

Differences between timing of medication activation approached significance,  $Q(3) = 7.681, p = 0.053$ . Similar to findings concerning medication activation and processing speed, however, when the one study that did not report medication activation timing was removed from this analysis ( $k = 1, g = -0.217, SE = 0.130, 95\% CI [-0.472, 0.038]$ ), results were not significant,  $Q(2) = 1.413, p = .493$ .

Meta-regression revealed a significant trend of higher number of days on medication relating to smaller effect sizes ( $k = 18, B = -0.021, SE = 0.010, 95\% CI [-0.039, -0.002], p = .030, R^2 = 0.32$ ). Similar to previous findings related to this variable, however, this finding reflects low variability across studies where only 3 studies reported more than 1 day of medication administration. No other significant variables were revealed by meta-regression or ANOVA analog. Furthermore education level and baseline cognitive functioning were not analyzed due to the low number of studies reporting these variables ( $k = 3$ ).

### **Missing Data**

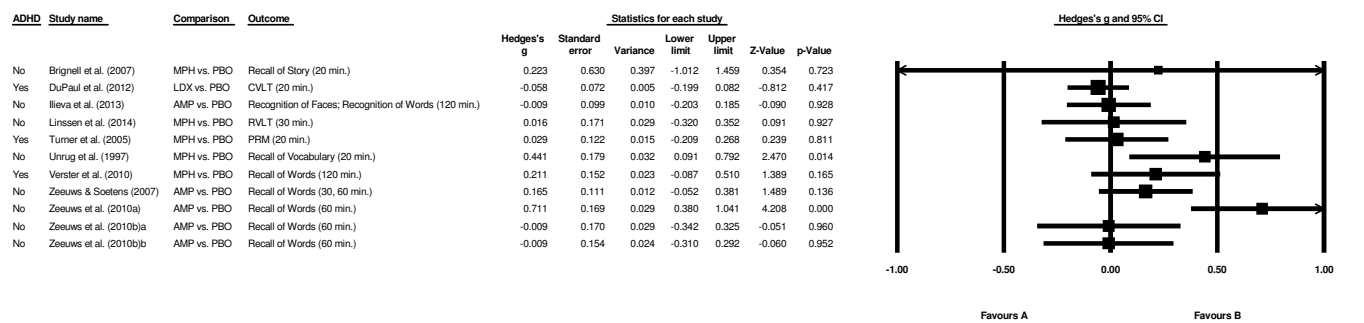
Fourteen studies with insufficient data to calculate effect sizes were excluded from the analysis involving the effects of ADHD medication on immediate declarative memory (see Appendix C). One study reported impairments on memory related to medication, 6 studies reported findings that were non-significant, 5 studies reported positive effects that were significant, and 2 studies did not report results for memory measured immediately after learning.

## Neurocognitive Enhancement of Declarative Learning and Memory – Delayed

Data were extracted from 11 studies that investigated the neurocognitive effects of ADHD medication on declarative learning with delayed assessment (20 minutes or longer but within the same day as learning) of memory. Taken together, these studies resulted in a total of 289 participants, investigating AMP ( $k = 5$ ), MPH ( $k = 5$ ), and LDX ( $k = 1$ ) effects among adults with ( $k = 3$ ) and without ( $k = 8$ ) ADHD. Table 25 displays the descriptive data and ES estimates (Hedge's  $g$ ) from each of the 11 studies. The studies resulted in a mean effect size of  $g = 0.126$  that approached statistical significance ( $SE = 0.067$ , 95% CI [-0.005, 0.256],  $p = .060$ ) under the random effects model, with effect sizes ranging from  $g = -0.058$  to  $g = 0.169$ . A fixed effects model yielded findings with a slightly reduced and statistically significant mean effect size ( $g = 0.077$ ,  $SE = 0.039$ , 95% CI [0.001, 0.153],  $p = .047$ ). The heterogeneity of variance analysis was significant,  $Q(10) = 24.861$ ,  $p = .006$ .

Table 25  
*ADHD Medication Neurocognitive Effects on Delayed Declarative Learning and Memory and Mean Results*

## Meta Analysis



## Meta Analysis

*Notes.* AMP = Amphetamine; CVLT = California Verbal Learning Test; LDX = Lisdexamfetamine Dymesylate; MPH = Methylphenidate; PBO = Placebo; RVALT = Rey Verbal Auditory Learning Task.

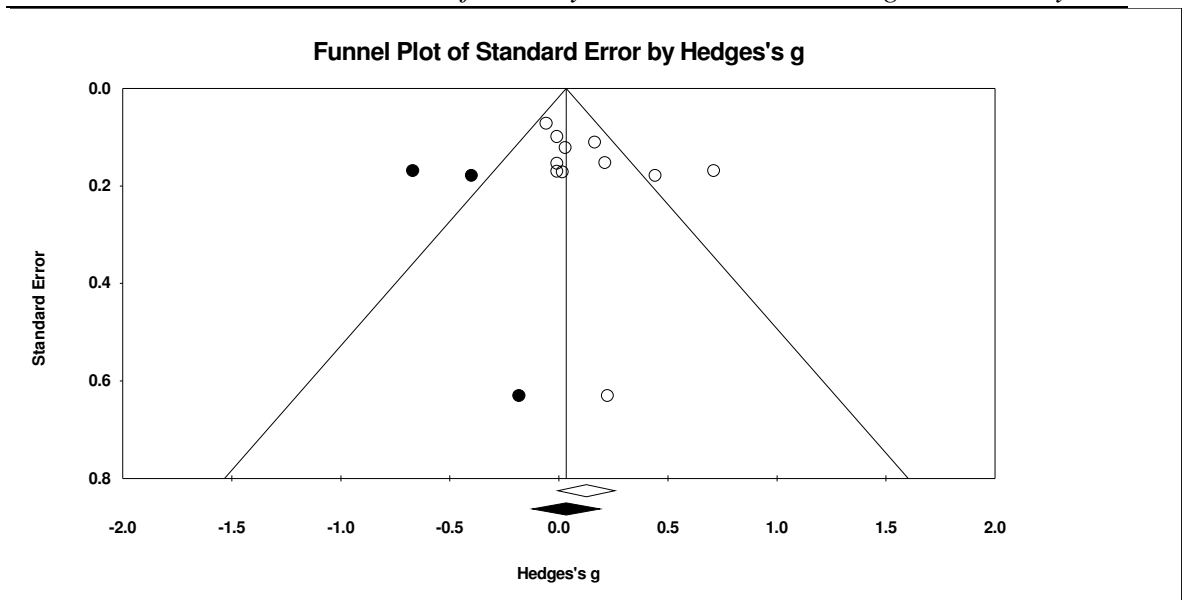
### Outlier Evaluation

Studies with effect sizes falling outside 3 standard deviations ( $SD = 0.222$ ) of the mean ( $g < -0.541$  or  $g > 0.793$ ) were examined as potential outliers. No studies met these criteria; therefore, effect sizes from all studies were maintained in the analyses concerning delayed assessment of declarative learning and memory.

### Publication Bias

Analysis of publication bias indicated minimal risk with a Rosenthal's  $N$  of 12 to lead to a  $p$ -value at or above an alpha of .05 and Orwin's  $N$  of 16 to reduce the measure of effect to 0.05 (this estimate was selected given the mean effect size was already approaching  $g = 0.10$ ). Trim and fill analysis suggested the imputation of 3 studies resulting in a reduction in the mean effect size to  $g = 0.034$ , 95% CI [-0.122, 0.189]. Egger's regression approached significance ( $B = 1.933$ ,  $SE = 1.134$ ,  $t(9) = 1.704$ , 95% CI [-0.633, 4.499],  $p = .061$ ) and the funnel plot (see Figure 18) indicated some positive bias prior to imputation.

Figure 18  
*Funnel Plot with Observed Studies for Delayed Declarative Learning and Memory*



### **Moderator Analyses**

Moderator analyses were conducted given the significant variability between studies indicated by the significant  $Q$  statistic. Significant differences were revealed for medication dose,  $Q(1) = 5.049$ ,  $p = .025$ , where studies that administered lower medication doses resulted in larger mean effect sizes ( $k = 7$ ,  $g = 0.207$ ,  $SE = 0.092$ , 95% CI[0.027, 0.387]) than studies that administered higher medication doses ( $k = 4$ ,  $g = -0.033$ ,  $SE = 0.055$ , 95% CI [-0.141, 0.074]). ANOVA analog also revealed trend level ( $p < .10$ ) differences for medication,  $Q(2) = 4.635$ ,  $p = .099$ ; however, when the only study examining LDX ( $k = 1$ ,  $g = -0.058$ ,  $SE = 0.072$ , 95% CI [-0.075, 0.390]) was removed from the analysis, significant differences were not found,  $Q(1) = 0.003$ ,  $p = .957$ . A similar finding was revealed for medication activation type, a variable that is confounded with medication, where a significant difference between short-acting ( $k = 10$ ,  $g = 0.156$ ,  $SE = 0.072$ , 95% CI [0.015, 0.298]) and long-acting ( $k = 1$ ,  $g = -0.058$ ,  $SE = 0.051$ , 95% CI[-0.051, 0.148]) medication was revealed,  $Q(1) = 4.445$ ,  $p = .035$ . Therefore, these findings do not reflect meaningful differences considering only one of the studies investigated a long-acting medication. ANOVA analog did not reveal any other significant variables.

No significant moderator variables were revealed by meta-regression. Note that meta-regression was not conducted for years of education and baseline cognitive functioning given only one study examined baseline cognitive functioning and no studies reported number of years of education.

### **Missing Data**

Due to insufficient data critical for calculating effect sizes, eleven studies meeting this study's eligibility criteria were excluded from the analysis involving the effects of ADHD medication on neurocognitive enhancement of delayed declarative memory (see Appendix C). Studies reported findings that were non-significant ( $k = 3$ ), as well as significant with positive effects ( $k = 7$ ). One study did not report enough information to interpret significance or direction of effects.

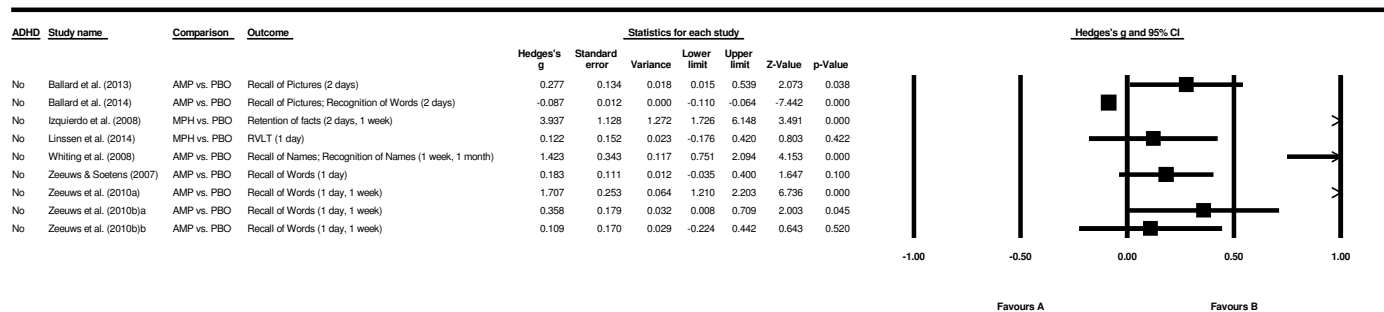
### **Neurocognitive Enhancement of Declarative Learning & Memory – Long-term**

Data were extracted from 9 studies that investigated the neurocognitive effects of ADHD medication on declarative learning with long-term delays of assessment (longer than one day and up to two weeks delay after learning). Data from a total of 236 participants represented studies investigating the effects of AMP ( $k = 7$ ) and MPH ( $k = 2$ ) among adults without ADHD ( $k = 9$ ). Table 26 displays the descriptive data and mean effect sizes (Hedge's  $g$ ) from each of the 9 studies. The studies resulted in statistically significant mean effect size of  $g = 0.499$  ( $SE = 0.161$ , 95% CI [0.183, 0.815],  $p = .002$ ) under the random effects model, with effect sizes ranging -0.087 to 3.937. A fixed effects model yielded mean effect sizes in the reverse direction compared to those found with the random effects model ( $g = -0.072$ ,  $SE = 0.011$ , 95% CI [-0.094, -0.049],  $p < .001$ ). The heterogeneity of variance analysis was significant,  $Q(8) = 103.264$ ,  $p < .001$ .



Table 26  
*ADHD Medication Neurocognitive Effects on Long-Term Declarative Learning Memory and Mean Results*

## Meta Analysis



## Meta Analysis

*Notes.* AMP = Amphetamine; MPH = Methylphenidate; PBO = Placebo; RVALT = Rey Verbal Auditory Learning Task.

### **Outlier Evaluation**

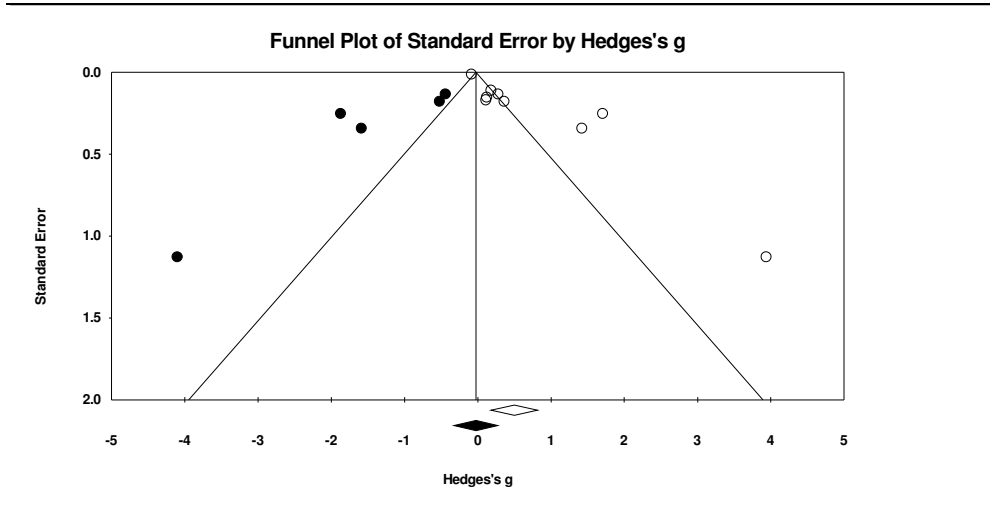
Studies with effect sizes falling outside of 3 standard deviations ( $SD = 0.222$ ) of the mean ( $g < -0.950$  or  $g > 1.948$ ) were examined as potential outliers. Only one study met these criteria (Izquierdo et al., 2008, described previously), with a mean effect size of  $g = 3.937$ . When this study was removed from the analysis, the mean effect size was slightly reduced to  $g = 0.429$  ( $SE = 0.154$ , 95% CI [0.127, 0.731],  $p = .005$ ) from the original mean effect size of  $g = 0.499$ . Therefore, a decision to maintain this study was made.

### **Publication Bias**

Analysis of publication bias indicated minimal risk with a Rosenthal's  $N$  of 43 to lead to a  $p$ -value at or above an alpha of .05 and Orwin's  $N$  of 35 to reduce the effect size to  $g = 0.10$ . Trim and fill analysis indicated the imputation of five studies, resulting in the reversal of the effect size direction (i.e., negative) and reduction in the mean effect size ( $g = -0.025$ , 95% CI [-0.326, 0.274]). Furthermore, Egger's regression was significant ( $B = 3.401$ ,  $SE = 0.710$ ,  $t(7) = 4.793$ , 95% CI [1.723, 5.078],  $p < .001$ ), which is represented by the asymmetry shown in the funnel plot (see 19) indicating positive bias.

Figure 19

*Funnel Plot with Observed Studies for Long-term Declarative Learning and Memory*



### Moderator Analyses

Due to the small number of studies examining long-term declarative memory ( $k = 9$ ), analyses to test for moderator variables were underpowered. For a number of variables (e.g., ADHD status, study design, medication type) analyses could not be conducted because no variability concerning those variables between studies was present. As such, moderator variables were only conducted for variables that had at least 3 studies per group; these included the study design variables of counterbalancing and randomization. ANOVA analog did not reveal significant differences for either variable.

Meta-regression was also conducted for variables reported by at least 3 studies (year of publication, age, gender distribution, number of sessions, number of days between sessions, and days on medication). Year of publication was associated with effect sizes on a trend level ( $k = 9$ ,  $B = -0.124$ ,  $SE = 0.067$ , 95% CI [-0.255, 0.007],  $p = .064$ ,  $R^2 = 0.00$ ), where more recent publications were related to smaller effect sizes. No other significant variables were revealed by meta-regression.

### **Missing Data**

Eleven studies met eligibility criteria involving the effects of ADHD medication on neurocognitive enhancement of long-term declarative memory, but were excluded from the analysis due to insufficient data (see Appendix C). The majority of results from these studies indicated significant and positive effects of medication on long-term memory ( $k = 9$ ). The remaining studies reported non-significant findings ( $k = 1$ ) or did not report adequate information to interpret findings ( $k = 1$ ).

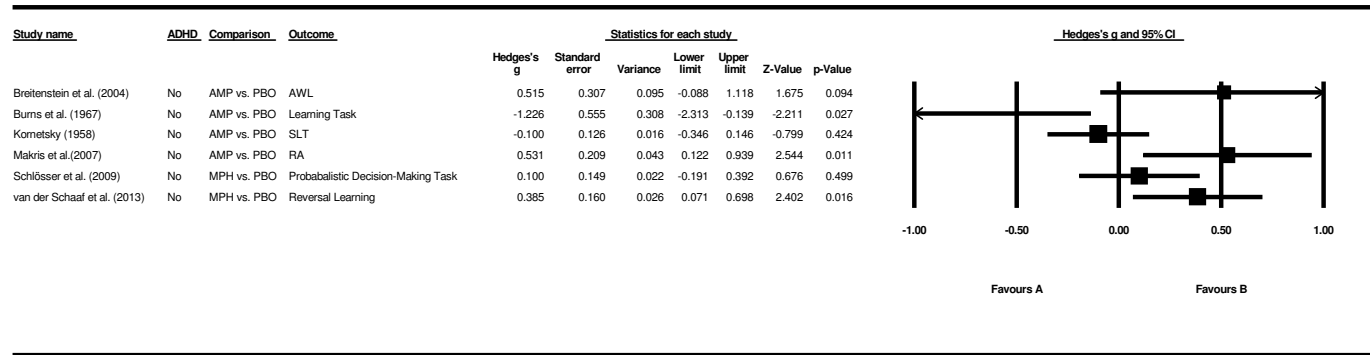
### **Neurocognitive Enhancement of Non-Declarative Learning and Memory**

Data were extracted from 6 studies that investigated the neurocognitive effects of ADHD medication on non-declarative learning and memory, resulting in a total of 120 participants without ADHD ( $k = 6$ ). Four studies investigated the effects of AMP and 2 studies investigated the effects of MPH on non-declarative learning and memory. Table 27 displays the descriptive data and ES estimates (Hedge's  $g$ ) from each of the 6 studies. The studies resulted in a mean effect size of  $g = 0.165$  that was not statistically different than zero ( $SE = 0.151$ , 95% CI [-0.131, 0.461],  $p = .277$ ), with effect sizes ranging from  $g = -1.226$  to  $g = 0.531$ . The fixed effects model yielded similar results ( $g = 0.145$ ,  $SE = 0.074$ , 95% CI [0.001, 0.290],  $p = .048$ ). The heterogeneity of variance analysis yielded a significant  $Q$  statistic,  $Q(5) = 17.128$ ,  $p = .004$ .

Table 27

ADHD Medication Neurocognitive Effects on Non-declarative Learning and Memory and Mean Results

### Meta Analysis



### Meta Analysis

Notes. AMP = Amphetamine; AWL = Associative Word Learning; MPH = Methylphenidate; PBO = Placebo; RA = Repeated Acquisition of Response Sequences Task; SLT = Simple Learning Task.

### **Outlier Evaluation**

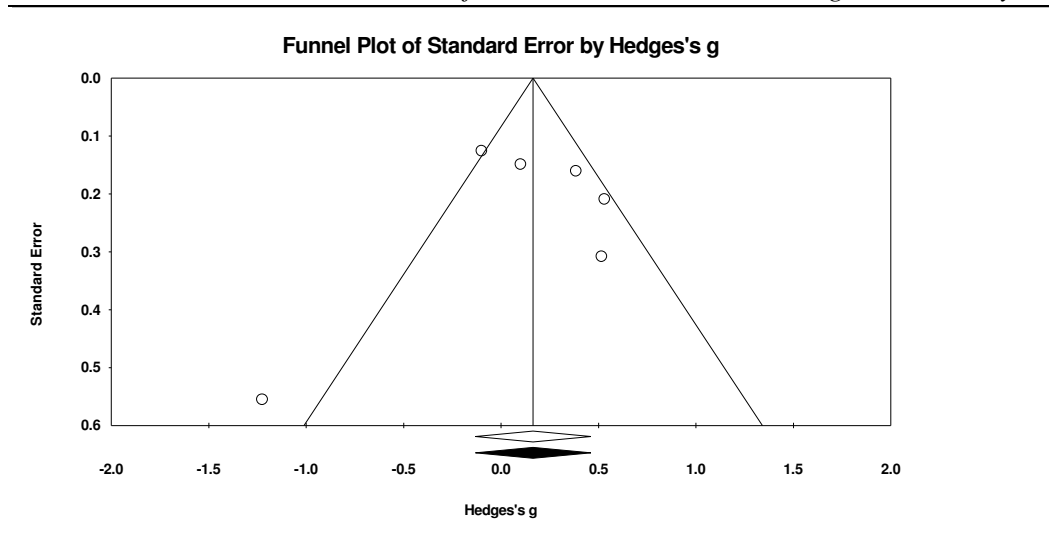
Studies with effect sizes falling outside 3 standard deviations ( $SD = 0.370$ ) of the mean ( $g < -0.945$  or  $g > 1.275$ ) were examined as potential outliers. Only one study met these criteria (Burns et al., 1967, described previously), with a mean effect size of  $g = -1.226$ . When this study was removed from the analysis, the mean effect size was increased to  $g = 0.237$  ( $SE = 0.130$ , 95% CI [-0.017, 0.492],  $p = .068$ ) from the original mean effect size of  $g = 0.165$ . Considering the low number of studies ( $k = 6$ ) investigating the effects of ADHD medication on non-declarative learning and memory, a decision to maintain this study was made.

### **Publication Bias**

Because the  $p$ -value for observed studies was not significant under the mixed effects model and approached  $p = .05$  under the fixed effects model, Rosenthal's  $N$  was calculated to be 0. Based on Orwin's  $N$ , 3 studies with effect sizes of  $g = 0.0$  would reduce the mean effect size to  $g = 0.10$ . Trim and fill analysis did not suggest the imputation of any studies. Egger's regression was not significant ( $B = -0.221$ ,  $SE = 2.224$ ,  $t(4) = 0.099$ , 95% CI [-6.397, 5.954],  $p = .463$ ) represented by the symmetry shown in the funnel plot (see Figure 20). These findings suggest minimal publication bias, but consistently small effect sizes.

Figure 20

*Funnel Plot with Observed Studies for Non-declarative Learning and Memory*



### **Moderator Analyses**

The small sample size included for non-declarative memory ( $k = 6$ ) precluded the investigation of moderators. Therefore, moderator analyses were not conducted.

### **Missing Data**

Two studies missing critical data for the calculation of effect sizes were excluded from the analysis involving the effects of ADHD medication on neurocognitive enhancement of non-declarative memory (see Appendix C). One study reported findings that were mixed and one study reported non-significant findings.

### **Summary of Neurocognitive Enhancement of Narrow Constructs of Learning and Memory**

Table 28 displays the mean effect sizes for ADHD medication on learning and memory immediate and delayed combined, as well as for each underlying construct individually (declarative memory that was measured immediately after learning, with short delays after learning or with long-term delays after learning, as well as non-declarative learning and memory). Results suggest that effect sizes for declarative and

non-declarative memory measured immediately after or with a short-delay after learning resulted in small effect sizes. Effect sizes for memory measured with long-term delays (between 1 day and 2 weeks), however, resulted in effect sizes considered medium in size according to Cohen's convention.

Table 28  
*Summary of ADHD Medication and Learning & Memory Findings*

Outcome	<i>k</i>	Model	<i>g</i>	95% CI		<i>p</i>	<i>Q</i> ( <i>df</i> )
				LCL	UCL		
Overall (Immediate & Delayed Only)	24	Fixed	0.082	0.023	0.192	.006	49.139*
		Random	0.104	0.015	0.192	.021	(23)
Declarative - Immediate	18	Fixed	0.124	0.063	0.186	<.001	59.878*
		Random	0.106	-0.000	0.212	.051	(17)
Declarative - Delayed	12	Fixed	0.077	0.001	0.153	.047	24.861*
		Random	0.126	-0.005	0.256	.060	(10)
Declarative - Long-term	9	Fixed	-0.072	-0.094	-0.049	<.001	92.253**
		Random	0.499	0.183	0.815	.002	(8)
Non-declarative	6	Fixed	0.145	0.001	0.290	.048	17.128*
		Random	0.165	-0.132	0.461	.277	(5)

Notes. \*  $p < .01$ ; \*\*  $p < .001$ .

### **Neurocognitive Enhancement of Narrow Constructs of Executive Function Neurocognitive Enhancement of Planning and Decision-Making**

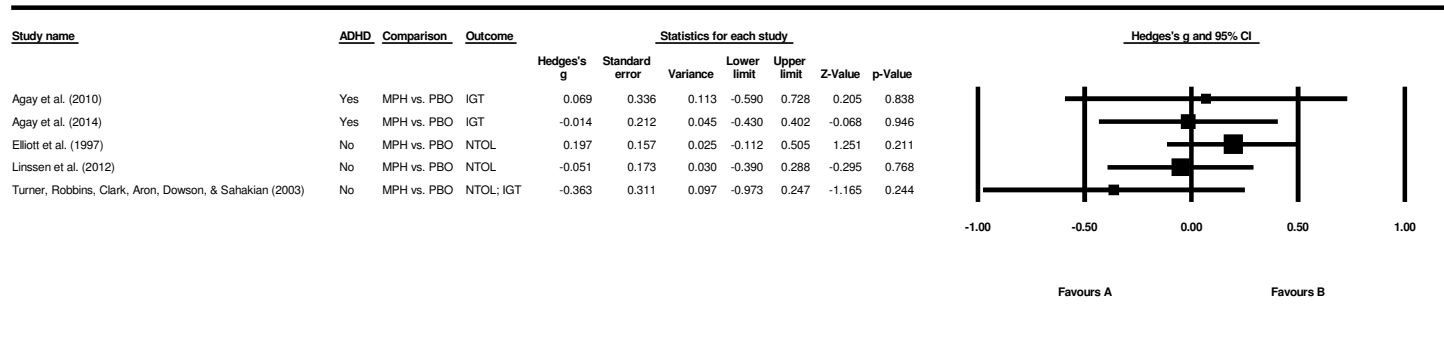
Data were extracted from 5 studies, resulting in a total of 153 participants, investigating the neurocognitive effects of ADHD medication on planning and decision-making. Studies explored the effects of MPH ( $k = 5$ ) among adults with ( $k = 2$ ) and without ( $k = 3$ ) ADHD. Table 29 displays the descriptive data and mean effect sizes (Hedge's  $g$ ) from each of the 5 studies. Both a fixed and random effects model resulted in a mean effect size of  $g = 0.024$  that was not significantly different than zero



( $SE = 0.093$ , 95% CI [-0.158, 0.207],  $p = .795$ ), with effect sizes ranging from  $g = -0.363$  to  $g = 0.197$ . The heterogeneity of variance analysis was not significant,  $Q(4) = 2.987$ ,  $p = .560$ .

Table 29  
*ADHD Medication Neurocognitive Effects on Planning and Decision-Making and Mean Results*

## Meta Analysis



## Meta Analysis

*Notes.* IGT = Iowa Gambling Task; MPH = Methylphenidate; PBO = Placebo; NTOL = Tower of London Spatial Planning Task.

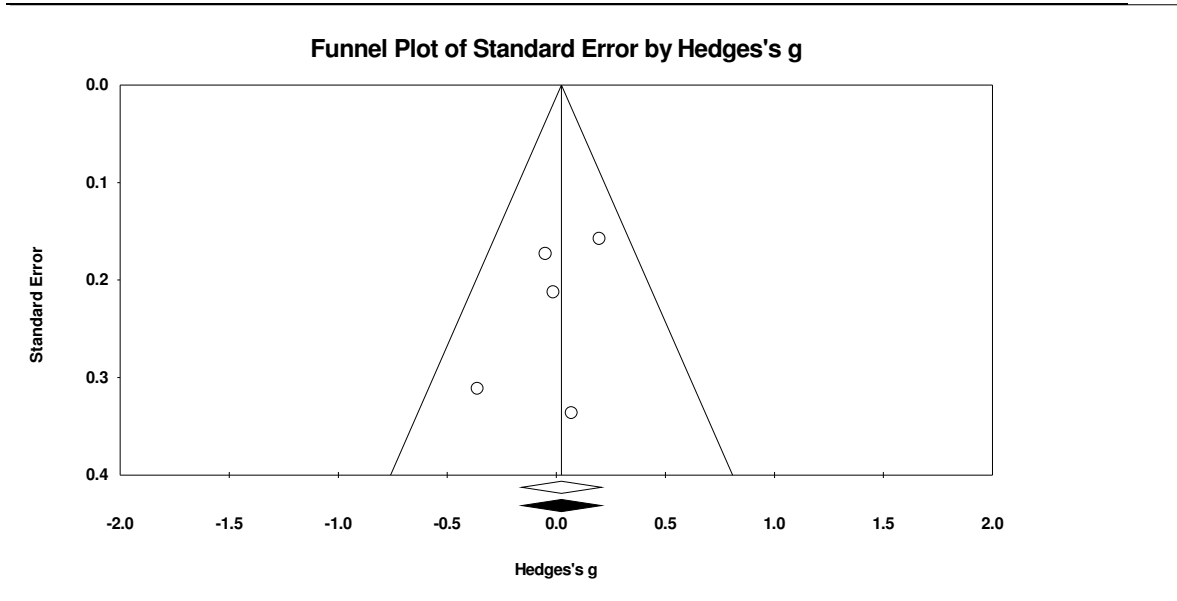
### **Outlier Evaluation**

Studies with effect sizes falling outside 3 standard deviations ( $SD = 0.208$ ) of the mean ( $g < -0.599$  or  $g > 0.648$ ) were examined as potential outliers. None of the studies met these criteria; therefore, effect sizes from all studies were maintained.

### **Publication Bias**

Because the mean effect size for planning and decision-making approached zero and the  $p$ -value for observed studies was not significant ( $p = .974$ ), Rosenthal's  $N$  was calculated to be 0. Based on Orwin's  $N$ , 7 studies with effect sizes of  $g = 0.0$  would reduce the mean effect size to  $g = 0.01$  (an estimate chosen given the mean effect size was approaching zero,  $g = 0.024$ ). Trim and fill analysis did not suggest the imputation of any studies to account for positive bias; however, 1 study was suggested for imputation to account for negative bias. Egger's regression was not significant ( $B = -1.602$ ,  $SE = 1.296$ ,  $t(3) = 1.236$ , 95% CI [-5.726, 2.523],  $p = .152$ ) represented by the symmetry shown in the funnel plot (see Figure 21). These findings suggest minimal publication bias, but consistently small effect sizes.

Figure 21  
*Funnel Plot with Observed Studies for Planning and Decision-Making*



### **Moderator Analyses**

The small sample size included for planning and decision-making ( $k = 5$ ), as well as the non-significant findings from the homogeneity of variance analysis, precluded the investigation of moderators. Therefore, moderator analyses were not conducted.

### **Missing Data**

No studies were excluded from the analysis involving the effects of ADHD medication on neurocognitive enhancement of planning and decision-making due to insufficient data.

### **Neurocognitive Effects of Self-Regulation**

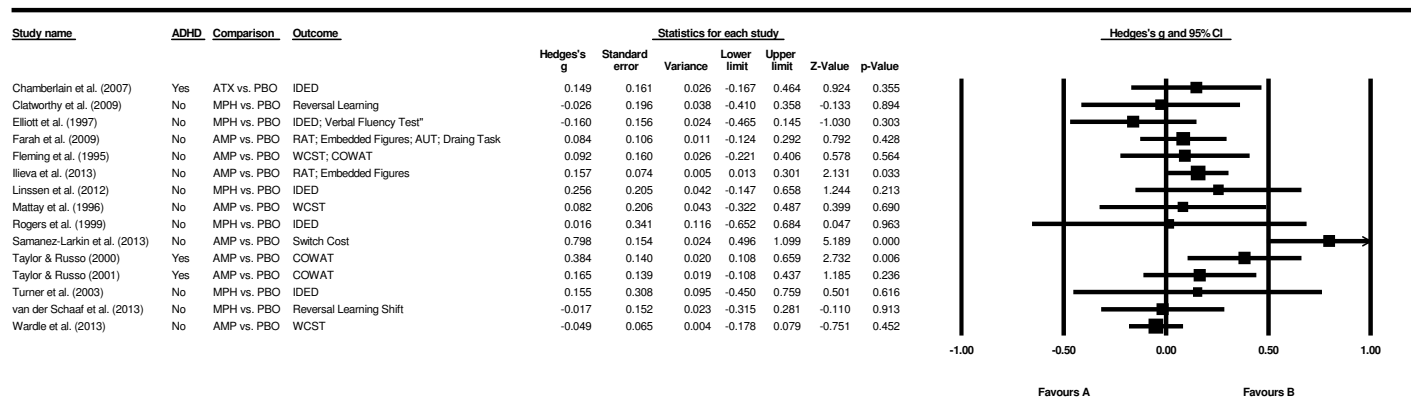
Data were extracted from 15 studies, including a total of 556 participants, that investigated the neurocognitive effects of ADHD medication on self-regulation.

Studies were conducted across populations of adults with ADHD ( $k = 3$ ) and without ADHD ( $k = 12$ ), examining the effects of AMP ( $k = 8$ ), MPH ( $k = 6$ ), and ATX ( $k =$

1). Table 30 displays the descriptive data and ES estimates (Hedge's  $g$ ) from each of the 15 studies. The studies generated a statistically significant mean effect size of  $g = 0.139$  ( $SE = 0.059$ , 95% CI [0.023, 0.254],  $p = .0019$ ) with effect sizes ranging from  $g = -0.160$  to  $g = 0.798$ . A fixed effects model yielded findings with a slightly reduced mean effect size ( $g = 0.108$ ,  $SE = 0.033$ , 95% CI [0.043, 0.173],  $p = .001$ ). The heterogeneity of variance analysis indicated significant between-study variance,  $Q [14] = 35.217$ ,  $p = .001$ .

Table 30  
*ADHD Medication Neurocognitive Effects on Self-Regulation and Mean Results*

### Meta Analysis



### Meta Analysis

*Notes.* AMP = Amphetamine; ATX = Atomoxetine; COWAT = Controlled Oral Word Association Test; IDED = Intra-Extra Dimensional Set-Shift Task; MPH = Methylphenidate; PBO = Placebo; RAT = Remote Associations Task; WCST = Wisconsin Card Sorting Test.

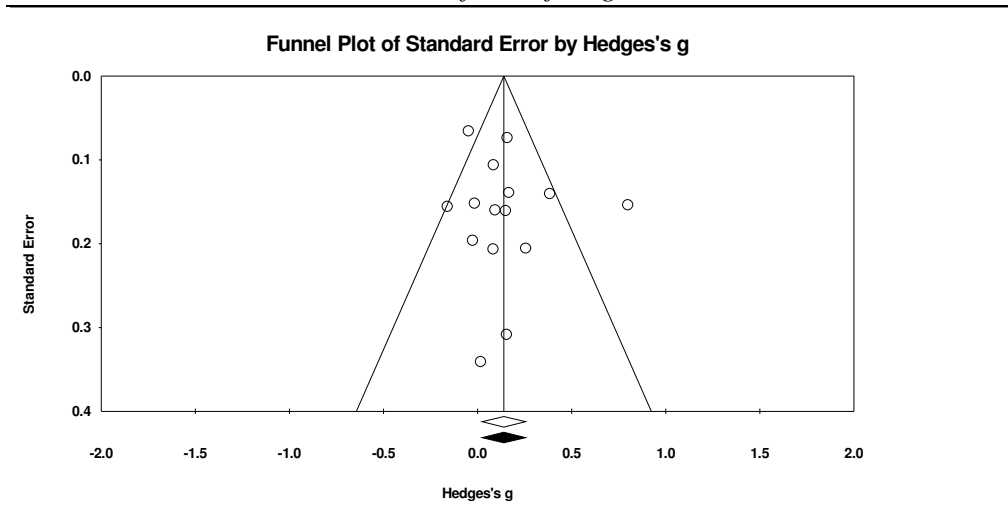
### Outlier Evaluation

Studies with effect sizes falling outside 3 standard deviations ( $SD = 0.228$ ) of the mean ( $g < -0.546$  or  $g > 0.824$ ) were examined as potential outliers. No studies met these criteria; therefore, effect sizes from all 15 studies were maintained in the analyses concerning self-regulation.

### Publication Bias

Analysis of publication bias indicated minimal risk with a Rosenthal's  $N$  of 34 to lead to a  $p$ -value at or above an alpha of .05 and Orwin's  $N$  of 5 to reduce the effect size to  $g = 0.10$ . Trim and fill analysis did not suggest the imputation of any studies and Egger's regression was not significant ( $B = 0.854$ ,  $SE = 0.973$ ,  $t(13) = 0.878$ , 95% CI [-1.248, 2.957],  $p = .198$ ). Additionally, the symmetry shown in Figure 22 suggests the risk for publication bias was minimal.

Figure 22  
*Funnel Plot with Observed Studies for Self-Regulation*



### Moderator Analyses

Because the homogeneity analysis was significant, moderator analyses including variables identified *a priori* were conducted. ANOVA analog revealed

differences on a trend level ( $p < .10$ ) between studies that utilized counterbalancing of treatment conditions ( $k = 5$ ,  $g = 0.035$ ,  $SE = 0.057$ , 95% CI[-0.078, 0.147]) and studies that did not report counterbalancing ( $k = 10$ ,  $g = 0.217$ ,  $SE = 0.086$ , 95% CI[0.048, 0.387]),  $Q(1) = 3.099$ ,  $p = .078$ . Homogeneity analyses indicated significant heterogeneity between studies that did not report counterbalancing treatment conditions,  $Q(9) = 20.855$ ,  $p = 0.013$ ; significant heterogeneity was not revealed for studies that did report counterbalancing methods,  $Q(4) = 6.234$ ,  $p = .182$ . No other significant moderator variables were revealed with ANOVA analog or meta-regression. Note that number of years of education was not analyzed in these analyses due the low number of studies reporting this variable ( $k = 2$ ).

### **Missing Data**

Three studies with insufficient data for calculation effect sizes were excluded from the analysis involving the effects of ADHD medication on neurocognitive enhancement of self-regulation (see Appendix C). Findings from these studies indicated results that were non-significant.

### **Summary of Neurocognitive Enhancement of Narrow Constructs of Executive Function**

Table 31 displays the mean effect sizes for the effects of ADHD medication on executive function overall, as well as its effects on the underlying constructs of executive function (planning and decision-making and self-regulation). Mean effect sizes resulting from measures of self-regulation were small, but mean effect sizes from measures of planning and decision-making approached zero.



Table 31  
*Summary of ADHD Medication and Executive Function Findings*

Outcome	<i>k</i>	Model	<i>g</i>	95% CI		<i>p</i>	<i>Q (df)</i>
				LCL	UCL		
Overall	17	Fixed	0.106	0.042	0.170	<.001	32.844* (16)
		Random	0.127	0.024	0.230	.005	
Planning and Decision Making	5	Fixed	0.024	-0.158	0.207	.795	2.987 (4)
		Random	0.024	-0.158	0.207	.795	
Self-Regulation	15	Fixed	0.108	0.043	0.173	<.001	35.217* (14)
		Random	0.139	0.023	0.254	.019	

Notes. \*  $p < .01$ ; \*\*  $p < .001$ .

### Summary of Neurocognitive Enhancement of All Cognitive Constructs

Table 32 displays the mean effect sizes resulting from the random effects model for all cognitive constructs. Mean effect sizes were small for cognition, as well as the broad cognitive constructs of abilities of focused behavior, learning and memory, and executive function. Small effect sizes were also found for inhibitory control, working memory, processing speed, declarative learning and memory (immediate and delayed), and self-regulation. Vigilance, non-declarative memory, and planning and decision-making resulted in mean effect sizes that were not significantly different from zero.

Table 32  
*Summary of ADHD Medication and All Cognitive Constructs Under Random Effects Model*

Outcome	<i>k</i>	<i>g</i>	95% CI		<i>p</i>
			LCL	UCL	
Cognition Overall	91	0.147	0.095	0.199	<.001
Abilities of Focused Behavior	74	0.140	0.094	0.186	<.001
Vigilance	24	0.047	- 0.055	0.128	.434
Inhibitory Control	43	0.164	0.094	0.235	<.001
Working Memory	32	0.068	0.014	0.123	.014
Processing Speed	18	0.195	0.077	0.313	.001
Learning & Memory (Immediate & Delayed Only)	24	0.104	0.015	0.192	.021
Declarative - Immediate	18	0.106	- 0.000	0.212	.051
Declarative - Delayed	12	0.126	- 0.005	0.256	.060
Declarative - Long-term	9	0.499	0.183	0.815	.002
Non-declarative	6	0.165	- 0.132	0.461	.277
Executive Function	17	0.127	0.024	0.230	.005
Planning and Decision Making	5	0.024	- 0.158	0.207	.795
Self-Regulation	15	0.139	0.023	0.254	.019

*Notes.* \*  $p < .01$ ; \*\*  $p < .001$ .

## **CHAPTER 6: Discussion**

The primary indications for ADHD prescription stimulant medication are for the reduction of ADHD symptoms (impulsivity, hyperactivity, inattention), for individuals diagnosed with ADHD. Yet, an increasing number of college students, both with and without ADHD, have reported misusing these medications to enhance their academic functioning. Previous research examining the effects of ADHD medication on cognition has typically relied on small sample sizes and yielded mixed results. Therefore, the present study conducted 14 meta-analyses ( $k = 91$ ) to explore the potential for ADHD medication as a neurocognitive enhancer, as well as influencing factors associated with its neurocognitive effects.

### **Summary of Predictions**

#### **Neurocognitive Enhancement Effects**

The first hypothesis that medications for the treatment of ADHD would demonstrate general positive effects on cognition was partially supported. When abilities of focused behavior (vigilance, inhibitory control, working memory, and processing speed), learning and memory (declarative and non-declarative), and executive function (planning and decision-making and self-regulation) were averaged together, a significant effect size for neurocognitive enhancement from ADHD medication was revealed ( $g = 0.15$ ). This effect size is considered small based on Cohen's convention and the effect sizes reported in the literature for ADHD medication efficacy. ADHD medication for neurocognitive enhancement among adults with and without ADHD, however, is not directly comparable to its use for ADHD symptoms. Although small, these effects are notable for their overall improvement in

cognitive performance, suggesting that ADHD medication may indeed enhance cognition in adults with and without ADHD. These overall general neurocognitive effects, however, appear to vary across cognitive constructs and may have been influenced by publication bias. Therefore, the findings suggest that ADHD medication may act as a neurocognitive enhancer for *some* but not all areas of cognition.

### **Abilities of Focused Behavior**

ADHD medication appears to have a small, positive effect on abilities of focused behavior ( $g = 0.15$ ). In particular, prescription stimulant medication showed consistent and positive effects for reducing impulsivity (inhibitory control,  $g = 0.16$ ) and increasing processing efficiency ( $g = 0.20$ ). Findings also revealed very small medication effects for improving working memory ( $g = 0.07$ ). These findings are similar to those reported by previous meta-analyses and reviews (Ilieva et al., 2015; Linssen et al., 2014; Smith & Farah, 2011). It is important to note, however, that symptoms of ADHD are not necessarily associated with processing speed or working memory (Lovett & Leja, 2015). Therefore, the finding that ADHD medication holds potential for enhancing processing speed memory is a benefit that may fall outside the scope of its indications as a treatment for ADHD symptoms.

The effects of ADHD medication on sustained attention, however, did not result in overall improvements ( $g = 0.03$ ). This finding is somewhat surprising considering the extensive literature base documenting the efficacy of ADHD medication for the reduction of ADHD symptoms that include attention and focus (e.g. Faraone, 2012; Faraone & Biederman, 2002; Faraone & Buitelaar, 2010; Faraone and Glatt, 2010). This finding may indicate that the neurocognitive benefits of ADHD

medication for focused behaviors may hinge on some of the former constructs, most likely inhibitory control. An alternative explanation, however, is that the minimal effects on sustained attention were the result of ceiling effects in the related tasks, something that has been suggested to occur on tests of attention and inhibition (Chamberlain et al., 2006; Chamberlain et al., 2007; Costa et al., 2013; Wöstman et al., 2013).

### **Learning and Memory**

ADHD medication resulted in small improvements in learning measured immediately or with a short delay following learning, with the present study revealing a significant and small effect size resulting from 23 studies ( $g = 0.10$ ). Although qualified by publication bias, results related to the narrow construct of long-term learning and memory indicated the potential for ADHD medication to improve memory retrieval days following medication administration and learning. In particular, findings from the present study support previous research (Advokat, 2010; Ilieva et al., 2015; Smith & Farah, 2011) that has found that stimulants are most effective for enhancing memory consolidation, as opposed to encoding or retrieval.

While declarative memory that was measured immediately after learning (i.e., within 20 minutes) or measured at a delayed time-point within the same day of learning (i.e., after 20 minutes within 1 day) resulted in small effects that approached statistical significance ( $g = 0.11$ ,  $g = 0.13$ , respectively), declarative memory that was measured longer than a day after learning resulted in a significant medium effect size ( $g = 0.50$ ). In sum, it appears that peak effects of ADHD medication may be especially beneficial for consolidation, resulting in improved retention in the days following

encoding; however, this finding should be interpreted cautiously given the high risk of publication bias.

Regarding non-declarative memory, i.e., procedural and probabilistic learning that was gradual and unconscious, the present study's findings support previous research (Smith & Farah, 2011) indicating mixed effects from ADHD medication. Unfortunately, few studies have explored non-declarative memory ( $k = 6$ ) and nearly all of them have relied on measures of learning rates or reaction times, as opposed to learning consolidation or accuracy. Only two studies (Schlösser et al., 2009; van der Schaaf et al., 2013) examined measures of error or accuracy. Schlösser et al. (2009) reported significant effects for RT but not error (calculated to  $g = 0.22$  and  $g = -0.02$ , respectively), implicating an improvement in processing speed, but not necessarily learning. The other study, conducted by van der Schaaf and colleagues (2013) resulted in a significant and small effect size ( $g = 0.21$ ) for accuracy. Although the present study's results suggested that ADHD medication has small effects ( $g = 0.16$ ) on non-declarative learning, this preliminary research may reflect small improvements in speed of processing. Furthermore, findings were not significantly different than an effect size of zero; however, this finding most likely reflects the small sample size ( $k = 6$ ) included for non-declarative learning and memory.

### **Executive Function**

A particularly interesting question that has been raised in the literature (Advokat, 2010; Smith & Farah, 2011) regarding prescription stimulants as neurocognitive enhancers is even if positive benefits are associated with prescription stimulant use in some areas of cognition, could they also be associated with

*impairments* of other components of cognition such as creativity and flexibility?

Results from the present study suggest that ADHD medication *does not* impair executive function, at least for the component of self-regulation (cognitive flexibility, verbal fluency, and creativity). Indeed, findings from the present study actually supported small benefits of ADHD medication for abilities of self-regulation ( $g = 0.14$ ).

The significant and small mean effect size concerning self-regulation provides preliminary support for Smith and Farah's (2011) conclusion that prescription stimulants have a positive effect on cognitive control, a similar construct to self-regulation that refers to regulation of cognitive processes in everyday situations that are not necessarily natural or intuitive. In particular, the authors explained that these effects were most robust for participants with lower overall scores, participants who had the catechol-*O*-methtransferase (*COMT*) genotype related to poorer executive function, or participants who reported difficulty with impulsivity. Similarly, Farah and colleagues (2009) reported that among healthy adults, those with lower baseline creativity actually received creative benefits from prescription stimulants. While the present study examined creativity in conjunction with other abilities of self-regulation, i.e., verbal fluency and cognitive flexibility, the results do support Farah's conclusion. In fact, only 3 of the 15 studies measuring self-regulation resulted in negative effect sizes, and only 1 of these studies utilized measures related to creativity; the other studies examined flexibility and verbal fluency.

A similar question concerns ADHD medication effects on planning and decision-making – do prescription stimulants lead to difficulty with planning or poorer

decision-making? Agay and colleague's (2010) findings shed some light on this question, where for adults with ADHD, MPH was shown to have minimal to no effects on planning and decision-making ( $g = 0.069$ ), but for adults without ADHD, MPH had negative effects ( $g = -0.240$ ). Agay et al.'s 2014 study also found effects for adults with and without ADHD that were close to zero; however, results indicated a negative effect for both groups ( $g = -0.014$  and  $g = -0.175$ , respectively). The present study also found that ADHD medication had minimal to no effects on planning and decision-making ( $g = 0.024$ ), although this finding is limited by the small number of studies examining this outcome ( $k = 5$ ). While these results do not implicate any benefits for planning and decision-making from ADHD medication, they are notable in that these medications do not appear to impair these abilities. This finding is significant for college students taking prescription stimulants for enhancement of studying material that may require more complex thoughts and decisions. It also has significant implications for students taking prescription stimulants to "party," "stay awake to party," or "get high," an additional motivation for stimulant misuse (Weyandt et al., 2013). These students may be engaging in other risky behaviors (e.g., drugs and alcohol) and it would be very concerning if these medications appeared to worsen their ability to make decisions.

### **Medication Dose**

To test the second hypothesis – that higher doses of ADHD medication would result in greater effects – doses were coded as either "low" or "high." Contrary to this hypothesis, dose level was not significant for the majority of analyses, indicating that variability of effects were not significantly influenced by level of medication dose.



Three exceptions to this finding, however, indicated differences between dose level for the narrow constructs of declarative learning and memory – delayed and inhibitory control, as well as the broad construct of abilities of focused behavior. Findings suggest that when there were differences between dose levels, *lower* doses of medication resulted in the *greatest* gains.

It is possible that dose level was not a significant variable in the majority of analyses due to the averaging of doses and effect sizes across studies investigating the neurocognitive enchaining effects of multiple doses of ADHD medication. Specifically, effect sizes were averaged across doses for 17 of the included studies (although 2 studies only reported results with doses averaged together), which may have mitigated some of the effects of higher medication doses compared to lower doses. To explore this possibility, effect sizes for each dose in studies reporting multiple doses were calculated for cognition. Ideally differences between dose levels reported in each study would be assessed with ANOVA analog; however, approximately half of the studies reported a range of doses that all fell within the category of “low” leaving only a small number of studies available for comparison. Instead, effect sizes are displayed in Table 33 according to study and results for each dose. Visual inspection indicates that differences between effect sizes by dose were mixed, some were larger for higher doses compared to lower ones (e.g., Ward et al., 1997; Wardle et al.), others were equivocal (e.g., Ballard et al., 2014), and a few were smaller for higher doses compared to lower ones (e.g., Idestrom & Schalling, 1970). When viewing only those studies that included low doses and high doses meeting

criteria for the current study's conventions of low and high doses (shown with an asterisk in Table 33), results still appear mixed.

Instead, this finding may support dose level effects following a U-shaped pattern, where the lowest and highest doses proffer the lowest effects and medium doses result in the most benefits. Indeed, a recent review indicated that for MPH, a U-shaped pattern emerged for effects on working memory (Linssen et al., 2014). Yet the same review indicated that the most effective dose levels varied according to cognitive outcome. Specifically, optimal doses of MPH for processing speed were the lowest doses, for verbal learning and memory optimal doses followed a linear trend, and for reasoning and problem solving they were the highest doses (Linssen et al., 2014).

A final, but related explanation for the equivocal findings across dose levels relates to variability across individuals. For example, medication is most effective when titrated according to individual assessment (Coghill et al., 2013) and *some* individuals appear to perform better with lower doses compared to higher ones. The same effect may be true for cognition.

Table 33  
*Study Effect Sizes by Dose(s)*

Study	Construct	Dose A			Dose B			Dose C			
		Dose	<i>g</i>	<i>SE</i>	Dose	<i>g</i>	<i>SE</i>	Dose	<i>g</i>	<i>SE</i>	
Ballard et al. (2013)	AMP*	L&M	10-mg	<b>0.260</b>	0.133	20-mg	<b>0.294</b>	0.134			
Ballard et al. (2014)	AMP*	L&M	10-mg	<b>-0.085</b>	0.117	20-mg	<b>-0.056</b>	0.117			
Barkley et al. (2005)	MPH	AFB	10-mg	<b>0.042</b>	0.146	20-mg	<b>0.164</b>	0.147			
DuPaul et al. (2012)	LDX*	AFB; L&M	30-mg	<b>0.087</b>	0.174	50-mg	<b>0.174</b>	0.177	70-mg	<b>0.052</b>	0.177
Fillmore et al. (2005)	AMP	AFB	7.5-mg	<b>0.266</b>	0.207	15-mg	<b>0.197</b>	0.204			
Ideström & Schalling (1970)	AMP	AFB; EF	5-mg	<b>-0.126</b>	0.147	15-mg	<b>-0.002</b>	0.145			
Kinsbourne et al. (2001)	MPH	L&M	5-mg	<b>0.311</b>	0.209	10-mg	<b>0.204</b>	0.206	20-mg	<b>0.213</b>	0.206
Kollins et al. (2015)	MPH*	AFB; EF	10-mg	<b>-0.048</b>	0.232	40-mg	<b>0.042</b>	0.231			
Kornetsky (1958)	AMP	AFB; L&M	5-mg	<b>-0.117</b>	0.133	10-mg	<b>-0.106</b>	0.133			
Linssen et al. (2011)	MPH*	PS	10-mg	<b>0.203</b>	0.105	20-mg	<b>0.357</b>	0.108	40-mg	<b>0.600</b>	0.113
Linssen et al. (2012)	MPH*	AFB; EF	10-mg	<b>0.014</b>	0.232	20-mg	<b>0.004</b>	0.228	40-mg	<b>0.092</b>	0.214
Makris et al. (2007)	AMP	AFB; L&M	0.035- mg/kg	<b>0.212</b>	0.146	0.07- mg/kg	<b>0.225</b>	0.150	0.14- mg/kg	<b>0.252</b>	<b>0.136</b>

Study	Construct	Dose A			Dose B			Dose C			
		Dose	g	SE	Dose	g	SE	Dose	g	SE	
Rapoport et al. (1980)	AMP*	AFB	0.25-mg/kg	<b>-0.24</b>	0.252	0.50-mg/kg	<b>0.164</b>	0.259			
Turner et al. (2003a)	MPH*	AFB; EF; L&M;	20-mg	<b>-0.026</b>	0.310	40-mg	<b>0.150</b>	0.310			
Ward et al. (1997)	AMP	AFB	5-mg	<b>0.661</b>	0.580	10-mg	<b>0.930</b>	0.600			
Wardle et al. (2013)	AMP*	AFB; EF	5-mg	<b>-0.042</b>	0.072	10-mg	<b>0.057</b>	0.072	20-mg	<b>0.141</b>	0.072

Notes. \* = Study included doses falling in both categories of “low” and “high” according to the present study’s conventions.

### **Timing of Medication Activation**

To investigate the third hypothesis – that the relationship between prescription stimulant, prostimulant, and nonstimulant ADHD medication and cognition would vary according to timing of dose, with activation of stimulant during learning processes yielding greater effects than activation at other times among adults with and without ADHD – studies were coded conducting assessments prior to, during, or after peak effects of medication would normally occur. Significant differences were not found among studies for timing of dose activation for the majority of cognitive constructs. For the narrow construct of inhibitory control, however, studies where medication was active prior to assessment resulted in significantly smaller effect sizes compared to studies where medication was active during assessment and studies that did not report the timing of activation. However, note that only 5 studies administered medication so it was active prior to learning that included inhibitory control as an outcome variable.

These findings are likely the result of low variability in timing of dose, which is related to the inclusion of studies with high quality research designs. The vast majority of studies ( $k = 54$ ) were coded as medication having peak effects during assessments. The other studies, 11 of which were coded as peak effects occurring after assessment and 17 of which prior to assessment, reported timing of learning and/or assessment that was close to being considered as occurring during peak effects. However, an additional explanation relates to the duration of stimulant effects. For example, although LDX demonstrates clinically significant effects within 2 hours, it

has been shown to be effective for as long as 13 hours (Biederman et al., 2007; Heal, Cheetham & Smith, 2009).

### **Medication Activation Type**

Findings from the present study support the hypothesis that the relationship between prescription stimulant, prostimulant, and nonstimulant ADHD medication and cognition would be consistent across medication activation types (short-acting, medium-acting, or long-acting medications) among adults with and without ADHD. No differences that were clinically relevant were found between studies investigating short-acting ( $k = 83$ ) compared to studies investigating medium or long-acting ( $k = 8$ ) medication effects on cognition in general, or for abilities of focused behavior, learning and memory, and executive function. This finding is consistent with the literature examining the efficacy of ADHD medication, which suggests that a variety of medication activation types offer significant effects (Kooij et al., 2010). It should be noted, however, that the vast majority of studies investigated the cognitive effects of short-acting agents, limiting the validity of these findings.

### **Baseline Cognitive Functioning**

The hypothesis that prescription stimulant, prostimulant, and nonstimulant medication ADHD effects on cognition would demonstrate a negative relation with baseline cognitive functioning of adults with and without ADHD was not supported in the present study. However, it is important to note that this hypothesis was more difficult to test than other hypotheses in the present study and merits further investigation. Only 3 of the 91 studies included in this study presented results separately for groups demonstrating lower and higher performance on cognitive

outcomes prior to medication administration. The results from these studies suggested that adults with lower cognitive baseline scores may experience more cognitive benefits from ADHD medication compared to adults with higher scores. Faraone and colleagues (2005) examined the effects of ATX on executive function in adults with ADHD over a ten-week treatment period and reported significant differences between placebo and treatment for adults with ADHD scoring below the normative mean for the Stroop-color word test at baseline, but not for adults with ADHD who scored above the mean at baseline. These differences resulted in effect sizes of  $g = 0.160$  and  $g = -0.064$ , respectively. Finke et al. (2010) also assessed differences between adults scoring low and high at baseline, in this case examining the effects of MPH and modafinil on healthy adult's visual processing speed. Participants scoring below the sample's median were categorized as "low" and those scoring above the median were categorized as "high." Similar to the previous study, significant differences were only found for the participants considered to be low at baseline between placebo and medication and not for participants considered to be high at baseline. Unfortunately, data were only reported for significant results so effect sizes between the two groups could not be compared; however effect sizes that were large in size for visual processing speed ( $g = 1.214$ ) and small for visual short-term memory ( $g = 0.215$ ) were calculated for participants performing low at baseline.

A number of additional studies did not report sufficient descriptive data for the calculation of effect sizes, but investigated the differing effects of prescription stimulants for cognition taking into account participant cognitive baseline functioning. Although data were not reported separately for participants with low and high

cognitive baseline scores, Agay et al. (2014) also found that adults with and without ADHD who scored lower at baseline received the greatest benefits from MPH. Additionally, the effect of MPH on associative learning showed impairments for participants with high baseline working memory and benefits for participants with low baseline working memory in another study (van der Schaaf et al., 2013). Whiting et al. (2008), however, reported that improved word recognition and recall occurred for participants irrespective of baseline neuropsychological performance.

Implications from a recent study using PET scans to measure the effects of MPH on brain glucose metabolism supported these findings and may help explain their mechanism of action. Findings suggested that MPH intake was associated with attenuated brain metabolism increases instigated by cognitive tasks, i.e. facilitating the focus of attentional resources during cognitive task, and that the largest effects were found for participants demonstrating the lowest brain metabolism at baseline. Participants with the lowest metabolic activation at baseline (indicating “optimal focusing”), however, made the fewest cognitive gains (Volkow et al., 2008). These results suggest that MPH may proffer the greatest benefits to individuals with baseline impairments or attention problems.

Studies investigating the influence of genetic variants related to the val158met polymorphism of the catechol-*O*-methtransferase (*COMT*) genotype gene on ADHD medication cognitive effects have provided further insight on differences in cognitive baseline, but have demonstrated mixed results (Mattay et al., 2003; Wardle et al., 2013). Findings from Mattay et al. (2003) also support a U inverted hypothesis where individuals with the *COMT* met/met gene appeared to exhibit higher baseline function,



resulting in impairments related to AMP, compared to individuals with the *COMT* val/val gene who exhibit lower baseline function and may benefit most from AMP. Similar to Volkow et al. (2008), this study found that for individuals with the val/val gene, AMP improved cognitive efficiency as evidenced by a reduced activity in brain regions associated with working memory. A replication of this study (Wardle et al., 2013), however, did not support this finding and reported no significant interaction between *COMT* and AMP effects on performance on the WCST and *n*-back.

Because baseline functioning specific to each cognitive variable was not available to test as a moderator, global measures of cognitive functioning at baseline were tested as potential moderators to further examine this hypothesis. Eighteen studies reported results that included a global measure of cognitive functioning prior to medication administration, but meta-regression did not reveal overall cognitive functioning as a significant moderator variable for cognition in general or for any of the broad constructs of cognition. Among the 8 studies reporting global intelligence scores that examined a measure of the narrow construct of vigilance, however, a significant trend was revealed where larger effect sizes were associated with higher scores of cognitive functioning. This finding may have occurred because of the limited variability among studies reporting of cognitive functioning, i.e., mean scores fell at or above the 70<sup>th</sup> percentile for all studies and many studies excluded participants with mean scores falling below average or low average.

Future research should explore group differences between adults with lower baseline scores compared to those with higher baseline scores on tests of cognition. If only adults scoring low receive cognitive benefits from ADHD medication the vast

majority of college students misusing prescription stimulants for academic purposes may not actually receive any neurocognitive benefits. This finding would be important for developing interventions to prevent and intervene in prescription stimulant misuse on college campuses.

### **ADHD Status**

The present study's findings did not support the final hypothesis that the relationship between prescription stimulant, prostimulant, and nonstimulant ADHD medications and cognition would result in greater benefit for adults with ADHD compared to adults without ADHD. Differences between studies examining adults with ADHD compared to those examining adults without ADHD were not significant for cognition, or when analyzed separately for abilities of focused behavior, learning and memory, and EF.

Considering that ADHD's defining characteristics include clinically elevated levels of inattention and impulsivity, in addition to hyperactivity, the finding that effect sizes were equivocal for adults with and without ADHD for abilities of focused behavior (encompassing vigilance and inhibitory control) is particularly surprising. Yet, even studies exploring differences between adults with and without ADHD *without* medication on other measures of executive function have reported mixed results (Advokat, 2010). Specifically, a review investigating the cognitive effects of stimulants in adults with ADHD (Advokat, 2010) found that while some studies reported no differences between adults with and without ADHD on the NTOL (Gropper and Tannock, 2008; Riccio, Wolfe, Romine, Davis & Sullivan, 2004), other studies reported deficits among adults with ADHD (McLean et al., 2004; Young,

Morris, Toone, & Tyson, 2007). Furthermore, a meta-analysis (Boonstra et al., 2005) examining studies comparing differences between adults with ADHD and adults without ADHD on measures of executive function did not reveal significant differences on measures of vigilance (CPT attentiveness), inhibitory control (CPT errors of commission, Stroop Interference scores), processing speed (TMT-A), or working memory (TMT-B and DS forwards and backwards). However, adults with ADHD performed significantly worse on measures of verbal fluency ( $d = 0.62$ ) and Stroop-Color Word score ( $d = 0.89$ ), which the present study used to measure inhibitory control, but demonstrated significantly lower caution in response style on the CPT ( $d = -0.22$ ). The findings from Boonstra's study may indicate that differences between adults with and without ADHD are even more specific than the constructs used in the present study.

It is also possible that differences between these two populations were confounded with differences between studies in general, requiring a more explicit examination of the differing neurocognitive effects of ADHD medication for adults with and without ADHD. Two studies included in the present study did compare the neurocognitive effects of ADHD medication on adults with and without ADHD. Specifically, Agay et al. (2010; 2014) included a sample of adults with ADHD and a sample of healthy controls in their study investigating the effects of MPH on vigilance, working memory and decision-making. While the present study included the results from the ADHD group only, when comparing individual results of medication effects on cognitive constructs, results appear mixed (see Table 33). Indeed, findings specific to Agay et al.'s most recent (2014) study were that regardless

of ADHD status, adults with lower cognitive baseline scores proffered the most cognitive effects from MPH. Conclusions about direct comparisons between adults with and without ADHD based on two studies are premature and further research is warranted to investigate any differences for the neurocognitive effects of ADHD medication between the two groups.

Table 33  
*Effect Sizes from Studies Including Adults with and without ADHD*

Construct	Adults with ADHD		Adults without ADHD	
	Agay et al. (2010)	Agay et al. (2014)	Agay et al. (2010)	Agay et al. (2014)
WM	$g = 1.018$	$g = 0.016$	$g = 0.227$	$g = 0.250$
V	$g = -0.002$	$g = 0.062$	$g = 0.062$	$g = 0.170$
PD	$g = 0.069$	$g = 0.014$	$g = -0.240$	$g = -0.175$

*Notes.* WM = Working Memory; V = Vigilance; PD = Planning and Decision-Making.

### Additional Moderator Variables

Even though there was a high degree of variability present among study effects – where ADHD medication demonstrated large, positive effects ( $g = 3.94$ ) and large, negative effects ( $g = -1.23$ ) on cognition – very few of the study’s potential moderating variables were significant across cognitive constructs. In particular, *none* of the variables explored as moderator variables for the effects of ADHD medication on cognition as a broad category were significant. This finding is consistent with previous research that has failed to uncover gender distribution or dose level effects across studies examining AMP and MPH effects on inhibitory control and episodic memory (Ilieva et al., 2015). When moderator variables were analyzed separately for the broad and narrow constructs of cognition, however, a number of meaningful variables were significant, shedding light on some of the between-study variability.

## **Study Descriptors and Research Design**

Significant differences were not found for the majority of variables related to research design (study design, number of wash-out days between sessions, learning or practice effects, and inclusion of non-behavioral measures). In particular, the finding that non-behavioral assessments (e.g., fMRI, PET) did not influence the present study's effects is important to consider when comparing results from future studies, considering some meta-analyses and reviews (e.g., Coghill et al., 2013) have excluded studies with non-behavioral assessments to minimize additional confounding variables related to environment.

Randomization of treatment groups, however, was associated with larger effect sizes for abilities of focused behavior. This finding may suggest differences between quality of studies. Furthermore, counterbalancing was associated with smaller effect sizes for self-regulation, which may reflect the importance of counterbalancing treatment conditions for accurate results. However, considering differences between counterbalancing status were only found among effect sizes of self-regulation, this finding could be an artifact of the small sample sizes within groups.

It is also important to note that for some of the cognitive constructs (learning and memory as a broad construct, as well as declarative learning and memory – long-term and processing speed), studies that were published more recently resulted in larger effect sizes. Indeed, two of the three extreme negative effect sizes identified by outlier examinations resulted from studies that were conducted prior to 1970 (Burns et al., 1967; Duke & Keeler, 1968). Whether this trend reflects an increase in publication bias or an improvement in study quality over the years is unclear.

## **Medication**

The majority of variables related to medication, including number of doses administered, medication type, and dose type, were not revealed as significant moderators. Note that differences between medication types (stimulant, pro-stimulant, or non-stimulant) could not be analyzed in the most analyses due to the low number of studies examining pro-stimulants ( $k = 1$ ) and non-stimulants ( $k = 5$ ).

There was some indication, however, for an association between studies that administered medication for fewer number of days and larger effect sizes for the broad construct learning and memory, as well as the narrow categories of vigilance and declarative memory measured immediately after learning. However, these findings were limited by low variability (only 10 studies administered medication more than one day) precluding conclusions about the effect of prolonged medication use. If further research supports the finding that greater medication effects for neurocognitive enhancement are associated with single administration methods, college students who report misusing ADHD medication for academic reasons may actually benefit from infrequent and sporadic use of medication to enhance studying and increase performance.

Regarding the inclusion of other drugs, studies that examined ADHD medication alone resulted in larger mean effect sizes for abilities of focused behavior than studies that included other drugs (e.g., MPH and psilocybin). This finding has meaningful implications for future research investigating the neurocognitive effects of prescription stimulants on abilities of focused behavior, suggesting such studies

should limit their investigation to ADHD medication. However, significant differences between these studies were not shown for any of the other constructs of cognition.

### **Recruitment**

For cognition in general, studies that utilized recruitment methods employed within the community resulted in larger mean effect sizes than studies that recruited participants from universities or clinics for cognition (note that differences only approached statistical significance  $p < .10$ ). However, because this finding was not replicated across the broad and narrow level constructs of cognition, these differences do not appear meaningful. Interestingly, the reverse finding was true for participant and recruitment characteristics' association with effect sizes pertaining to the narrow construct of vigilance. Here, studies that included adult student samples and studies that employed recruitment strategies targeting universities resulted in *larger* effect sizes than studies examining other adult populations and studies recruiting within community or clinical settings. This finding may be the artifact of inadequate power considering the small number of studies examining students and reporting university recruitment ( $k = 4$ ). It is also possible, however, that college and university students were less influenced by the ceiling effect associated with tests of attention, i.e., students may have had lower baseline scores than other participants. Indeed, the mean effect size for vigilance when including all studies was not significant, but the mean effect size for vigilance among studies that included students was significant ( $g = 0.320, p = .007$ ). It is therefore possible that neurocognitive benefits for vigilance, or sustained attention, are unique to college students who may have a higher degree of distractions in their environments.

## **Participant Demographics**

For cognition in general, and among the broad constructs of cognition, results did not differ by samples of varying ages or gender distributions. These findings suggest that prescription stimulants may provide cognitive benefits across populations varying in age and gender. However, findings regarding tasks of sustained attention suggest that ADHD medication may have greater neurocognitive benefits for younger adult males in academic settings. Interestingly, for inhibitory control, older populations appeared to benefit more from ADHD medication than younger populations. Although definitive conclusions about these findings are precluded by the limited variability of age and gender within studies, it is possible these findings also reflect differences in baseline functioning.

Finally, although number of years of education did not emerge as a modifying variable for any cognitive constructs, findings were limited by the small number of studies reporting this variable ( $k = 15$ ) and for some of the constructs (e.g., learning and memory) this variable could not be included in the meta-regression.

## **Implications**

The present study revealed small effect sizes for studies investigating the effects of ADHD medication on cognition, but how meaningful are these effect sizes in settings outside of the laboratory? In particular, are these effects meaningful for college students engaging in illicit stimulant misuse for academic purposes? While results from this study cannot directly answer this question, it seems likely that the larger effects related to long-term learning and memory indicate these effects could be meaningful for college students. In particular, college students taking prescription



stimulants 1-3 hours prior to memory consolidation, are probably receiving the greatest benefit.

The consistent and small effect sizes found for ADHD medication effects on inhibitory control also suggest that students who struggle with impulsivity may benefit from prescription stimulants. This finding is consistent with the literature base (Moeller et al., 2001) on characteristics of college students engaging in misuse of prescription stimulants, that has found those students more likely to take prescription stimulants illegally are also more prone to risk-taking behaviors (e.g., using other illegal drugs). It is surprising, however, that effects for inhibitory control were not more robust as ADHD medications are well known for yielding behavioral improvements associated with reductions in impulsivity, with meta-analyses revealing mean effect sizes between  $g = 0.31$  and  $g = 0.74$  for adults with ADHD (Faraone & Glatt, 2010). Yet, the present study found only small effects for inhibitory control that did not differ across studies investigating populations with and without ADHD.

Less certainty exists regarding the clinical and educational relevance of some of the other variables of cognition, such as working memory, processing speed, and self-regulation. While tests of learning and memory are directly comparable to tests within academic settings, tests of focused behavior and executive function may be less comparable to tasks relevant to academics. The included studies conducted cognitive assessments in research laboratories, providing an environment quite unlike one in which college students would normally attempt to study, read or write. In fact, research accumulated over the past three decades has suggested ADHD medication results in minimal to no effects on the overall academic achievement in children with

ADHD, even though ADHD medication may increase attention, improve productivity, and boost some areas of academic performance (e.g., quizzes, homework completion) (Advokat, 2010; Lakhan & Kirchgessner, 2012). For example, among children with ADHD there is evidence to suggest prescription stimulant medication is associated with improvements in school performance productivity (i.e., permanent product measures) (Wigal et al., 2011), but improvements may only result in a 15% increase in academic achievement for medicated students compared to unmedicated students with ADHD (Gadow, 1983 as cited in Advokat, 2010). Researchers (Gadow, 1983 as cited in Advokat, 2010; Swanson et al., 1991 as cited in Advokat, 2010) have hypothesized that “cognitive toxicity” may explain the relative improvement in behavior compared to the minimal effects on academics, where the optimal doses for behavior improvements may be higher than that for academic enhancement and actually *impair* academics. In the college setting, however, preliminary research *does not* support the explanation of “cognitive toxicity,” with studies indicating comparable GPA performance of medicated college students with ADHD and unmedicated college students with ADHD (Advokat et al., 2011). Instead, research suggests that positive study habits, as opposed to ADHD medication, have shown promise for overcoming achievement gaps in college students with ADHD compared to those without ADHD (Advokat et al., 2011).

While less is known about the optimal dose of ADHD medication for cognitive enhancement, previous research (Linssen et al., 2014) has suggested that for MPH, it may vary according to the specific type of cognition. Further, efficacy research examining ADHD medication for symptom management suggests it varies across

individuals and requires optimization of dose (Coghill et al., 2013; Vitiello, 2008). Although findings from the present study did not indicate significant differences between low and high doses of ADHD medication for most constructs of cognition, the limited variability of medication doses included in the present study precludes any definitive conclusions. Furthermore, medication doses included in the present study may not reflect the levels of medication college students are misusing. The literature on prescription stimulant misuse does not provide an indication of typical dose students misuse, but if higher doses could result in cognitive impairments (or worse, adverse health outcomes), college students would benefit from safety information and efficacy information regarding ADHD medication dose. Future studies investigating prescription stimulant effects on tasks involving actual academic assignments (e.g., essay composition, calculus problems), comparing doses optimal for behavior improvement to lower doses in adult populations would shed light on this issue.

It is also worth noting that there are a number of interventions being explored for their potential as cognitive neuroenhancers that could serve as an alternative to ADHD medication. Among these are video games that have shown promise for enhancing processing speed (between  $d = 0.48$  to  $d = 1.47$ ; Dye, Gree, & Bavelier, 2009) and computerized training programs tailored to improve cognitive abilities (e.g., Gist training, employed to improve abstract reasoning and generalize it to everyday life and Luminosity, a computerized brain game) (Chapman & Mudar, 2014; Hardy, Drescher, & Sarkar, 2011). Exercise has also been shown to benefit enhancement of cognition, with a recent meta-analysis revealing significant effect sizes for information processing ( $d = 0.091$ ), attention ( $d = 0.416$ ) and executive function ( $d = 0.189$ )

(Chang, Labban, Gapin, & Etnier, 2012). Furthermore, mindfulness practice has been demonstrated to relate to improvements in cognitive performance within school settings, with studies resulting in large mean effect sizes ( $g = 0.80$ ) for measures of cognition that included attention, creativity, and academic grades (Zenner, Herrnleben-Kurz, & Walach, 2014). In light of these findings, some researchers (Moreau & Conway, 2013) have even called for the use of “specifically-designed sports” that combine movement and cognitive challenges to enhance cognition. While the present study’s findings revealed smaller effect sizes from ADHD medication for cognitive enhancement than these alternative interventions, the ease of taking a medication compared to long-term trainings and programs should not be overlooked. Even a small boost in enhancement may be meaningful when applied to an increase in a grade for college students (Ilieva et al., 2015), especially considering it can result in near immediate effects.

### **Physiological Implications**

The present study suggests that prescription stimulants are neurocognitive enhancers that proffer *small* effects. The mechanism by which neurocognitive enhancement occurs, however, remains an empirical question. Stimulant use has been shown to associate with the normalization of brain activation patterns for adults with ADHD and an increase in efficiency of attentional resources for adults with and without ADHD (Weyandt et al., 2013). One study hypothesized that the association between MPH-induced dopamine increases and mathematical task motivation among healthy adults may lead to improvements in attention and performance, suggesting *task motivation* as a mechanism for cognitive benefits (Volkow et al., 2004).

Although studies investigating the morphological effects of stimulants among humans are scarce, studies conducted on animal models have reported findings that may indicate the potential for damage as a result of stimulant use (Weyandt et al., 2013). For example, studies have reported oxidative brain damage in rats (Urban, Warehouse, & Gau, 2012) and synaptic alterations of thalamic nuclei and GABA transmission in mice (Goitia et al., 2013; Weyandt et al., 2013). One study (Schouw et al., 2013) found that oral administration of MPH was associated with reductions in DATS in the striatum, as well as blunted hemodynamic responses, in recreational users of d-AMP, indicating that recreational use of d-AMP may lead to DA dysfunction. These findings highlight the importance of considering the risk associated with prescription stimulant use for cognitive neuroenhancement; even if college students misusing prescription stimulants are receiving small neurocognitive benefits, they may also be vulnerable to associated dysfunctions.

Numerous studies have also reported on the extensive side effects and potential for adverse outcomes related to ADHD medication (e.g., Heal & Pierce, 2006; Heal et al., 2009). The most common side effects induced by ADHD medication may include insomnia, appetite loss and anorexia, emotional lability, abdominal cramps, nausea and vomiting, dizziness, and nervousness, as well as changes in blood pressure and heart rate (Heal & Pierce, 2006; Weyandt et al., 2014). Of particular concern, a meta-analysis examining appetite suppression as a side effect of MPH (Schachter, Pham, & King, 2001) reported that across 62 studies, appetite suppression was observed by 45% of parents and teachers (Heal & Price, 2006). Given the significant difficulties college students experience with healthy eating (Kelly, Mazzeo, & Bean, 2013), the

side effect of appetite suppression could have cumulative negative consequences for college students. Finally, in a review exploring cardiovascular outcomes related to ADHD medication, nearly half of the studies reported significant effects (Rapport & Moffit, 2002) suggesting serious risk associated with ADHD medication misuse. Indeed, the potential for negative side effects and adverse outcomes from ADHD medication is concerning when considering its role as neurocognitive enhancers.

### **Social and Ethical Implications**

Recently, a number of ethical and social issues related to ADHD medication as a neurocognitive enhancer have garnered attention in the literature (e.g., Dubljević, 2013; Farah, 2004; Goodman, 2010). For example, critics of cognitive neuroenhancers have compared cognitive neuroenhancement to cheating, arguing that gains made under neuroenhancement cannot be claimed as the user's own (Goodman, 2010). However, a recent survey of German students revealed only small correlations between the use of cognitive neuroenhancers and the acts of plagiarism and fabrication (Dubljević, Sattler, & Racine, 2014), suggesting users may not necessarily perceive cognitive neuroenhancement to be as unethical as acts generally considered to be cheating. Arguments about the equivalence of cognitive neuroenhancement to cheating resemble debates about the use of anabolic steroids and human growth hormone performance among professional athletes – that are now generally considered to be illegal in most professional sports leagues.

Regarding the ethical implications related to research, concerns have been raised for neurocognitive enhancement research given the potential for only minimal benefits, impacting a select (academic, i.e., privileged) population (Farah, 2004). Even

more concerning, however, is the distinction between neuroenhancement and “neurocorrection,” which could be used as a way of coercing individuals holding less power (i.e., prison populations, children) (Farah, 2004, p. 423). For example, the use of prescription stimulants for neuroenhancement in children and adolescents without a diagnosis of a neurological disorder has been considered “unjustifiable” by some (Graf et al., 2013, p. 1258), considering the fiduciary responsibility of physicians and the potential for coercion within child populations, among other reasons. Indeed, considering previous research has concluded ADHD medication largely controls children with ADHD’s behavior and does not yield any academic benefits (Advokat, 2010), coercion is a concern even for children diagnosed with ADHD.

On the other hand, proponents of cognitive neuroenhancers that have weighed the relative risks associated with medication advocate for the regulation of extended-release stimulants as neuroenhancers, with lower abuse potential and less severe side effects (Dubljević, 2013; Greely, 2013). Considering the present study’s findings that ADHD medication provides small, but significant cognitive effects across multiple domains of cognition, there does appear to be justification for prescriptions stimulants use as cognitive neuroenhancers. Irrespective of peoples' views on the issue, however, prescription stimulants are already being used illegally for the purpose of cognitive neuroenhancement at high rates. Therefore, the establishment of public policies surrounding this issue, whether restrictive or liberal, is of critical importance. As Farah aptly explained, “The question is therefore not whether we need policies to govern neurocognitive enhancement, but rather what kind of policies we need” (p. 424).

## **Limitations**

The present study has a number of strengths that support its contribution towards uncovering the potential of ADHD medication as a neurocognitive enhancer. At present, this study is the only systematic meta-analysis examining the effects of ADHD medication including stimulant, pro-stimulant, and non-stimulants, on a wide-range of cognitive outcomes for adults with and without ADHD. Studies were searched for and retrieved from multiple bibliographic databases in order to capture as much data as possible and minimize publication bias. This study was the first meta-analysis to explore the effects of ADHD medication on executive function tasks addressing self-regulation (creativity, cognitive flexibility, and verbal fluency), as well as planning and decision-making. Unique to the present study was the inclusion of multiple moderator variables that have not been previously explored, such as participant ADHD status, timing of medication activation, and number of washout days between sessions in studies. Finally, a major strength of the present study involved the well-established methodology applied to calculate mean effect sizes and test for moderator variables, which allowed for standardized comparisons and a high level of power to test hypotheses. It is particularly important to emphasize that previous studies examining the neurocognitive effects of ADHD medication have relied on sample sizes that were likely underpowered. Indeed, the 91 studies included in the present study relied on small sample sizes (mean  $n = 30.53$ ) and resulted in small effect sizes. Therefore, this meta-analytic study, which pooled weighted estimates of effects and resulted in more power than individual studies, contributed greatly to the literature.



A number of limitations are also important to note, however, relating to the study's design and methodology, as well as the theoretical foundations guiding the coding of cognitive data, and related to studies investigating the cognitive effects of ADHD medication in general. First, a limitation concerning meta-analysis methodology concerns its potential to overlook important individual variation by focusing on between-study variance (Egger & Smith, 1998b). Meta-analysis is plagued by issues of limited power for moderator variable detection (Hedges & Pigott, 2004). For example, findings from the present study that indicate most of the potential moderator variables were not significant may reflect a lack of power as opposed to lack of variability. Even when moderator variables are significant, however, they are often confounded with other variables that are difficult to untangle from one another. Other criticisms of meta-analysis have included its reliance on published studies that may not reflect cultural diversity found in research conducted in less developed countries, as well as its potential for inclusion bias stemming from predetermined study selection criteria that may be influenced by existing literature (Egger & Smith, 1998a).

A related issue that is often raised regarding meta-analyses is the potential influence of publication bias on meta-analytic findings. While the present study utilized a number of methods to measure and minimize publication bias (Egger's regression index, the funnel plot, Duval and Tweedie's trim and fill, Orwin's adapted version of Rosenthal's *fail-safe* N, and an assessment of publication bias as a moderating variable), a concern regarding the exclusion of missing data should be noted. One method for handling studies that report findings as "non-significant" is to

record a dummy variable with the effect size set to zero. Although the present study used this method for studies that included at least enough data to calculate one effect size within the outcome measures of one instrument, using this method for all missing data would have provided a more conservative estimate of effect sizes. Still, considering the large number of studies that provided data that revealed negative and minimal effects, the present study's findings appear to be representative of both significant and non-significant study findings.

Previous meta-analyses examining the efficacy of ADHD medication for improvements in ADHD symptoms have found significant differences between studies using change scores, i.e. studies comparing baseline scores, and post-treatment (or endpoint scores), i.e. studies comparing changes between placebo and medication scores, as measurement outcome (Faraone et al., 2006). Because all but one of the studies included in the present study reported data to calculate endpoint scores, findings in the present study were based on differences between placebo and medication scores unless only change scores were available (the case for only two studies, Gilbert, 1973 and Naylor et al., 1985, which reported on differences between change scores in placebo versus medication samples). Some studies reported data to allow for calculation of effect sizes for both change scores and endpoint scores (21 of the 91 studies included here), but considering that nearly all studies reported data to calculate effect sizes from endpoint scores, the present study did not calculate effect sizes from change scores.

Another important consideration is the susceptibility of meta-analysis to overlook important influences, such as the social context of the study, the quality of

the study, and theoretical influences/implications (Lispey & Wilson, 2001). For example, in their meta-analysis assessing stimulant effects on ADHD symptomatology, Faraone & Glatt (2010) suggested that the systematic variability across methodology between classes of drugs may have produced misleading results. On the other hand, two recent reviews exploring the cognitive effects of prescription stimulant medication in children (Pietrzak et al., 2006) and in adults (Linssen et al., 2014) suggested that the use of meta-analysis for these investigations would be inappropriate due to the variability across study methodology, participant characteristics, treatment conditions and neuropsychological instruments used across studies. Indeed, it is likely that clearer patterns would have emerged if the present study only included studies meeting more rigid criteria (e.g., specific measures only).

One potential criticism of the null findings regarding differences between adults with and without ADHD is the present study's decision to group all ADHD participants together, as opposed to investigating the differences between subtypes of ADHD (predominantly hyperactive/impulsive, predominantly inattentive, and combined). A natural expectation would be that adults with predominantly hyperactivity/impulsivity would receive the greatest benefits for inhibitory control and adults with ADHD predominantly inattentive would receive the greatest benefits in the area of vigilance, although with considerable overlap. Unfortunately, studies investigating the cognitive effects of ADHD medication on samples of adults with ADHD did not provide descriptive data for subtypes separately, so the present study could not explore this hypothesis. Future research might focus on these differences in

order to clarify the magnitude of neurocognitive effects from ADHD medication according to ADHD subtype.

Finally, although meta-analysis is a powerful method that may help uncover the true effect of an intervention (Kraemer et al., 1998), results are limited by the quality of available published studies. Many criticisms of meta-analysis stem from the decision to either maintain open inclusion criteria (leading to a variety of studies that may not be comparable) or to adopt rigid inclusion criteria (resulting in less meaningful findings because of the exclusion of potentially meaningful studies) (Kraemer et al., 1998). Although the present study utilized inclusion criteria to select studies meeting standards of quality, a wide variety of study designs and study methodology were included. Publications also varied in the amount of detail provided regarding study design and participants characteristics. Of particular importance was the lack of report of participant ethnicity in most studies. It is unclear why so few studies investigating the cognitive effects of ADHD medication reported participant ethnicity, but considering that those that did report participant ethnicity relied on predominantly white samples (e.g., Halliday et al., 1986; Halliday et al., 1994; Rapoport, Buschman, & Weingartner, 1980; Zeeuws, Deroost, & Soetens, 2010), it will be important for future research to include more ethnically diverse populations.

Another important limitation related to studies investigating the cognitive effects of ADHD medication relates to the tests used to measure cognition. As described previously, there is a considerable amount of overlap between cognitive constructs, and the instruments designed to measure them are just one way of conceptualizing cognitive outcomes. A potential criticism of the present study is the

subjective nature of the coding of cognitive instruments and measures. For example, inhibitory control was categorized as an underlying construct of Abilities of Focused Behavior, but an argument could be made to categorize it as an Executive Function considering the overlap between response inhibition and self-regulation. Likewise, outcome variables from the WCST, which have been used to measure inhibitory control in other studies (e.g., Ilieva et al., 2015) were categorized as self-regulation in the present study. Similar issues concerning the ranking of specific measures within instruments exist. For example, previous meta-analysis has implicated the format of the Stroop task (computer versus card) as affecting effect sizes among populations with Schizophrenia (Westerhausen et al., 2011). Although the present study attempted to select the measures most pertinent to each cognitive construct, an abundance of measures were available across constructs and it is possible that the present study only captured some of the important findings in the literature. Fortunately, the present study attempted to account for categorization errors and construct overlap by analyzing the constructs across three levels ranging in scope from broad to narrow.

It is interesting to note that when compared to the effect sizes resulting from a web-based cognitive training, the effect sizes in the present study appear minimal. Specifically, Hardy et al. (2011) investigated the cognitive effects of Luminosity, a web-based cognitive training, and reported that after 30 sessions of 20 minutes participants scored significantly higher on measures of divided attention, spatial working memory, and letter memory than at pretest. Compared to a small control group, effect sizes were  $g = 1.128$ ,  $g = 0.377$ , and  $g = 0.113$ , respectively. Although impressive in size (particularly for divided attention), these effect sizes may have little

to no clinical utility given participants were being trained and tested with the same cognitive exercises. In other words, these effect sizes likely indicate that Luminosity is beneficial for improving scores on Luminosity and little else. Likewise, it is possible that many of the included studies examining the cognitive effects of prescription stimulants are measuring improvements in tests of cognition that do not relate to cognitive abilities most applicable to the motivations for cognitive neuroenhancement.

### **Future Directions**

The present findings suggest that ADHD medication may act as a neuroenhancer across a range of cognitive constructs that include abilities of focused behavior, learning and memory, and executive function. These effects, although small, appear to be significant for adults of varying ages and may be comparable for men and women. Still, a number of questions remain unanswered about the effects of ADHD medication for cognition among varying populations that may help elucidate their mechanism of action.

Research is warranted to further investigate a number of areas related to ADHD medication for cognitive enhancement. The potential for moderating effects of participant characteristics, particularly baseline cognitive functioning, COMT genotype variability, and ADHD status, need to be clarified. If only adults with lower baseline cognitive functioning scores, and/or adults with the *COMT* val/val, receive neurocognitive benefits from ADHD medication many college students misusing prescription stimulants are taking unnecessary risks with minimal results. Or worse, if ADHD medication actually impairs cognitive functioning for some adults, some college students may actually be worsening their ability to engage in higher-level

learning and thinking tasks. The variability in effect sizes across studies found in the present study suggests that ADHD medication may have differential effects that appear to be relatively unexplored.

Furthermore, adults and children with ADHD have consistently demonstrated impairments on many of the tests used to measure cognition, in particular those that rely heavily on focused attention such as tasks of focused behavior and Stroop interference measures (Advokat, 2010). It is therefore plausible that low baseline performance scores and ADHD characteristics are confounding variables, so that if one group benefits from ADHD medication both groups will benefit. Based on these findings it will also be important to understand if college students who report misusing prescription stimulants for academic purposes are also more likely to have higher levels of ADHD symptoms and/or lower levels of baseline cognitive functioning. For example, one explanation proposed by researchers is that a proportion of prescription stimulant misusers may actually be self-medicating for undiagnosed attention difficulties (Weyandt et al., 2013; Peterkin, Crone, Sheridan, & Wise, 2010). If this is the case, these students may benefit from prescription stimulant medication for the purpose of reducing ADHD symptoms and should be encouraged to consult with their medical providers.

Studies that directly investigate the neurocognitive effects of ADHD medication on academic tasks, including essay composition, high level math calculations, and tests of learning and memory relevant to college courses will help shed light on how meaningful the effects found in the present study are for prescription stimulant misuse. Although the present study's findings are indeed

meaningful, limitations related to the external validity of the included measures limit the finding's generalizability to populations in academic settings.

Although the present study attempted to include as many constructs of cognition as possible, there are many other areas that should be investigated in relation to ADHD medication. For example, the construct of Executive Function encompasses much more than simple tasks of cognitive flexibility, verbal fluency and decision-making tasks. ADHD medication may offer greater benefits for other areas of cognition, such as volition and motivation, the latter of which has been suggested to be a mechanism of prescription stimulants for neuroenhancement (Volkow et al., 2008). Furthermore, the finding that ADHD medication did not result in effect sizes significantly different than zero on tasks of non-declarative memory and planning and decision-making was based on a small number of studies, requiring further examination.

Finally, further research is warranted to better understand the underlying statistical power of studies that have examined the effects of ADHD medication on neurocognitive enhancement. Sample sizes of the studies included in the present investigation ranged from  $n = 6$  to  $n = 536$ ; however, the vast majority of studies ( $k = 72, 79.12\%$ ) relied on sample sizes that included less than 30 participants. Considering the consistently small effect sizes found in the present study, it is likely that these and previous studies examining cognition and ADHD medication have been greatly underpowered. Given this serious limitation in the field, a power analysis addressing these studies would inform future research and provide further clarity concerning the variability within the present study's findings.



## Conclusion

The present study supports the potential for using ADHD medication for neurocognitive enhancement in particular domains of cognition for both adults with ADHD and adults without ADHD. Specifically, ADHD medication appears to have enhancing effects on inhibitory control, working memory, processing speed, immediate and delayed memory, and self-regulation, supported by small and significant effect sizes in each domain. Most notably, peak effects of ADHD medication may be especially beneficial for memory consolidation, resulting in improved retention in the days following encoding, supported by a significant, moderate mean effect size for long-term declarative learning and memory. ADHD medication had little to no effects on tasks measuring planning and decision-making and non-declarative learning and memory; however, this finding was limited by the small number of studies addressing these outcomes. Finally, ADHD medication does not appear to influence tasks requiring sustained attention when examined separately from inhibitory control, suggesting that improvements in attention may relate to improvements in impulsivity.

These findings have significant implications for the ethical debate regarding prescription stimulants for cognitive neuroenhancement. The fact that ADHD medication can boost long-term memory and efficiency indicates that the large number of college students misusing prescription stimulants for academics may actually be receiving meaningful benefits. Still, further research is warranted to investigate the academic implications of prescription stimulant misuse, i.e., does enhancement of tasks of cognition translate to boosts in academic grades in the college setting? Still,

findings indicate the need for public policy addressing the use of prescription stimulant medication for neurocognitive enhancement is needed, especially considering the medical risks associated with prescription stimulant misuse.

## APPENDICES

### Appendix A: Article Coding Scheme

Variable Name	Description/Instructions
<b>Study Descriptors</b>	
Name of Study	Enter full APA reference of study.
Country of Researcher	Enter country(ies) where authors are located.
Year of Publication	Enter 4 digit number of year of publication.
<b>Sample Descriptors</b>	
Targeted Sample	1 = Adults 2 = University Students 3 = Elderly 4 = Adults & University Students NR = Not Reported
Recruitment Type	Select: 1 = Community 2 = University 3 = Clinic 4 = Military 5 = Community & Clinic 6 = Community & University NR = Not Reported
Sample Size	Enter study sample size.
Mean Age	Enter mean age of all participants.
Standard Deviation of Age	Enter standard deviation of age of all participants.
Age Range	Enter age range of participants.
Ethnicity Distribution	Record ethnicity distribution of participants in percent.
Gender Distribution	Enter percent female of participants.
Years of Education	Enter mean number of years of education.
Measure of Cognitive/Intellectual Abilities	Record name of instrument used to measure cognitive abilities and mean standard score reported.
ADHD Status	Select: 1 = Yes 2 = No
Special Groups	Record any additional special groups examined in the study.
<b>Methods and Procedures</b>	
Type of Outcome Score	Select: Change Score / Post treatment Score
Study Design	Select: Parallel / Crossover
Counterbalanced	For crossover studies, were treatment and placebo groups counterbalanced? 1 = Yes 2 = No NR = Not Reported NA = Not Applicable
Randomized	Was participant selection randomized for

Variable Name	Description/Instructions
	treatment and placebo groups? 1 = Yes 2 = No NR = Not Reported
Number of Sessions	For crossover studies, record number of sessions administered.
Washout Days	For crossover studies, record number of washout days between sessions.
Pretreatment Training or Practice Session	Select: 1 = Yes 2 = No
Pretest	Select: 1 = Yes 2 = No
Non-behavioral Measures	Record inclusion of fMRI, PET, EEG, etc. and select: 1 = Yes 2 = No
<b>ADHD Medication Descriptors</b>	
Medication Administration Type	Select: 1 = Fixed 2 = Titrated
Medication Administration Days	Record number of days participants were administered medication.
Medication	Select: 1 = AMP ( <i>d</i> -AMP, MAS) 2 = MPH 3 = LDX 4 = ATX 5 = AMP & MPH
Medication Type	Select: 1 = Short-Acting 2 = Medium or Long-Acting
Number of Doses Administered	Record number of doses administered within study.
Dose Level	Record exact dose(s) administered. For doses reported per kg, calculate dose by multiplying dose by 62kg.
Mean Dose Level	Average dose levels and then code based on the following criteria: 1 = Low (AMP < 20mg, MPH < 40mg, LDX < 50mg, ATX < 70mg) 2 = High (AMP ≥ 20mg, MPH ≥ 40mg, LDX ≥ 50mg, ATX ≥ 70mg)
Timing of Dose Relative to Assessment	Record number of minutes dose was administered prior to learning. Then code based on the following criteria: 1 = Activated Before Learning (AMP < 2hrs,

Variable Name	Description/Instructions
	MPH < 1hr, LDX < 2hrs, ATX < 1hr) 2 = Activated During Learning (AMP 2-3hrs, MPH 1-2hrs, LDX 2-4hrs, ATX 1-2hrs) 3 = Activated After Learning (AMP > 3hrs, MPH > 2hrs, LDX > 4hrs, ATX > 2hrs)
Timing of Dose Relative to Delayed Assessment for Memory and Learning	If memory and learning was measured, also record # of minutes dose administered prior to memory test
Inclusion of Other Drugs	Enter if study examined additional drugs to AMP, MPH, LDX, and ATX select: 1 = Yes 2 = No
<b>Results</b>	
Reported Both Significant and Non-significant Results	Enter if study reported results for all measures, both significant and non-significant: 1 = Yes 2 = No

*Notes.* AMP = Amphetamine; APA = American Psychological Association; ATX = Atomoxetine; fMRI = functional Magnetic Resonance Imaging; *d*-AMP = Dextro-amphetamine; EEG = Electroencephalogram; LDX = Lisdexamfetamine Dymethylate; MAS = Mixed Amphetamine Salts; MPH = Methylphenidate; PET = Positron Emission Tomography.

## Appendix B: Test-Retest Reliability Coefficients by Construct and Measure

### *Test-Retest Reliability Coefficients by Construct and Measure*

Task	Measure	Reliability (measure)	Reference
<b>Vigilance and Inhibitory Control</b>			
Antisaccades	Antisaccade error	.92 (error rate)	Wöstmann et al. (2013)
Change Task (extension of Stop-Signal Task)	RT (stop-signal)* Mean RT (stop-signal, change response)* RT SD (stop-signal, change response)*	.50 (SST, mean go RT)	Wöstmann et al. (2013)
<i>Continuous Performance Task (CPT)</i>	Omission	.20 (omission)	Buchsbaum & Sostek (1980)
	Detectability/attentiveness (d')	.76 (d')	Connors (2000)
	Commission	.59 (commission)	Buchsbaum & Sostek (1980)
	Hit RT	.95* (hit RT)	Connors (2000)
	Interstimulus interval Vigilance decrement	.85 (interstimulus interval)	Buchsbaum & Sostek (1980)
	Variability/SE	.66* (Variability)	Connors (2000)
<i>Digit Vigilance Test</i>	Accuracy Commission	.66 (error scores)	Kelland & Lewis (1996)
	RT	.91 (total time)	Kelland & Lewis (1996)
<i>Flanker</i>	Difference/ratio between congruent and incongruent accuracy/error Incongruent accuracy/error	.65 (incongruent-congruent accuracy)	Wöstmann et al. (2013)
Go/No-Go	No-Go Accuracy Commissions	.84 (commission)	Wöstmann et al. (2013)
Oddball Task	Omission	.20 (CPT omission)	Buchsbaum & Sostek (1980)

*Test-Retest Reliability Coefficients by Construct and Measure*

Task	Measure	Reliability (measure)	Reference
	Commission	.59 (CPT commission)	Buchsbaum & Sostek (1980)
<i>Mackworth Clock Test</i>	Accuracy	.76 (CPT d')	
<i>Rapid Visual Information Processing (RVIP)</i>	Detectability/target sensitivity (A')	.49 (A')	Syväoja et al. (2014)
	Commission Omission (B')	.83 (CPT B')	Connors (2000)
	RT Latency	.73 (TOVA RT)	Llorente et al. (2001)
Stop-Signal Task	P(Response) SSRT	.03 (SSRT)	Wöstmann et al. (2013)
<i>Stroop Task</i>	Interference errors Interference RT Incongruent score/errors	.82 (median interference)	Wöstmann et al. (2013)
<i>Sustained Attention to Response Test (SART)</i>	Errors RT	.76 (commission)	Robertson et al. (1997)
<i>Test of Variables of Attention (TOVA)</i>	Omission	.51 (omission)	Llorente et al. (2001)
	Commission Accuracy over time (d')	.71 (commission)	Llorente et al. (2001)
	RT	.73 (RT)	Llorente et al. (2001)
Miscellaneous Tasks of Attention	Sensitivity (d') Error Bias ( $\beta$ )	.20 (CPT omission)	Buchsbaum & Sostek (1980)
	RT variability	.75 (RT variability)	Llorente et al. (2001)
<b>Working Memory</b>			
<i>Digit Span (DS)</i>	Standard score Longest span	.79 (SS)	Calamia, Markon, & Tranel, (2013)
<i>Dot-Letter Task</i>	Accuracy Positive fit Span length	.68 (SWM errors)	Lowe & Rabbit (1998)

*Test-Retest Reliability Coefficients by Construct and Measure*

Task	Measure	Reliability (measure)	Reference
	Omissions Between-search Within-search Absolute RT Latency of response		
<i>n</i> -back	Accuracy Omission Commission	.519 (0-Back Accuracy) .493 (1-Back Accuracy) .538 (2-Back Accuracy) .732 (3-Back Accuracy)	Hockey & Geffen (2004)
	RT	.857 (0-Back RT) .787 (1-Back RT) .691 (2-Back RT) .806 (3-Back RT)	Hockey & Geffen (2004)
<i>Spatial Delay Response</i>	Accuracy	.68 ( <i>SWM</i> errors)	Lowe & Rabbit (1998)
Spatial Location	Accuracy RT	.68 ( <i>SWM</i> errors)	Lowe & Rabbit (1998)
<i>Spatial Working Memory (SWM)</i>	Accuracy Strategy score Positive fit Between error Within error Total error Absolute error	.68 (errors)	Lowe & Rabbit (1998)
<i>Spatial Span (SS)</i>	Span length Errors	.64 (span)	Lowe & Rabbit (1998)
<i>Sternberg Memory Task</i>	Accuracy RT RT variability	.93 (RT)	Neubauer, Rieman, Mayer, & Angleitner (1997)
<i>Trail Making Test-B (TMT-B)</i>	RT	.56 (RT)	Neyens & Aldenkamp (1996)
Visual Working Memory Task	Accuracy	.68 ( <i>SWM</i> errors)	Lowe & Rabbit (1998)
Processing Speed			



*Test-Retest Reliability Coefficients by Construct and Measure*

Task	Measure	Reliability (measure)	Reference
Choice Reaction Time Tests: -SERS -Choice Visual Attention -Choice Reaction Time Test	Accuracy Omission Commission Standard score RT	.911 (RT)	May et al. (1986)
Digit Symbol Substitution Task (DSST)	Standard score	.851 (SS)	Calamia et al. (2013)
	AUC	.851 (SS)	Calamia et al. (2013)
Simple Reaction Time Tests : -CNV Stop Light Task -CNV Lines Task -SERS -Simple Motor Response -Motor Reaction Task -Simple Reaction Time Test -Visual Search Task -Spatial Orienting Task	RT SD Distraction time Errors	.881 (RT)	May et al., 1986
Trail Making Test-A (TMT-A)	RT	.33 (RT)	Neyens & Aldenkamp, 1996
<i>Declarative Learning &amp; Memory</i>			
California Verbal Learning Test (CVLT)	Level of recall trials 1-5	.749 (trials 1-5 total)	Calamia et al. (2013)
	Level of delayed free recall short delay	.652 (short delay free recall)	Calamia et al. (2013)
	Short delay retention	.621 (recognition)	Calamia et al. (2013)
Paired Associates Learning Test (PAL)	Accuracy (mean, maximum) Errors	.57 (memory score)	Lowe & Rabbit (1998)

*Test-Retest Reliability Coefficients by Construct and Measure*

Task	Measure	Reliability (measure)	Reference
	Total trials	.75 (average trials to success)	Lowe & Rabbit (1998)
<i>Pattern Recognition Memory Task</i>	Accuracy Response Latency*	.84 (shape recognition)	Lowe & Rabbit (1998)
Recall of Words, Pictures, Stories, Objects Recognition of Words, Pictures, Stories, Objects	Recall Recognition Sensitivity (d') Commission Intrusions Confabulations Response Bias (C)	.77 (word retention)	Murdock (1960)
<i>Rey Verbal Auditory Learning Task (RVALT)</i>	Trial Score A' (Sensitivity)	.344 (Trial 1) .481 (Trial 5)	Uchiyama et al. (1995)
	Error	.414 (intrusion errors)	Uchiyama et al. (1995)
<b>Non-Declarative Learning and Memory</b>			
Probabilistic Learning	Accuracy Perseverative errors	.74 (reversal error)	Freyer et al. (2009)
	Mean errors to criterion	.23 (spontaneous error)	Freyer et al. (2009)
	Feedback sensitivity	.03 (strategy change after probabilistic error)	Freyer et al. (2009)
	RT* Latency of response*	.90 (RT for first correct response)	Freyer et al. (2009)
Repeated Acquisition of Response Sequences Task (RA)	Correct response rate Incorrect response rate	.74 (probabilistic learning, reversal error)	Freyer et al. (2009)
Learning Tasks	RT*	.90 (Probabilistic learning, RT for	Freyer et al. (2009)

*Test-Retest Reliability Coefficients by Construct and Measure*

Task	Measure	Reliability (measure)	Reference
		first correct response)	
Reversal Learning Tasks	Reward accuracy	.03 (probabilistic learning, strategy change after probabilistic error)	Freyer et al. (2009)
	Punishment accuracy Errors	.74 (probabilistic learning, reversal Error)	Freyer et al. (2009)
<b>Planning and Decision Making</b>			
<i>Iowa Gambling Task (IGT)</i>	Probability of accuracy Advantageous choices Disadvantageous choices Mean Attempt of moves Deliberation time* Latency of RT*	.47 (fifth deck)	Cardoso et al. (2010)
<i>Tower of London Spatial Planning Task (NTOL)</i>	Accuracy Mean attempt of moves Latency* RT*	.70 (total score)	Schnirman et al. (1998)
<b>Self-Regulation</b>			
<i>Alternative Uses Task</i>	Mean score	.883 (number of figures correctly identified)	Kepner & Neimark (1984)
<i>Controlled Oral Word Association Test (COWAT)</i>	Fluency score	.794 (score)	Calamia et al. (2013)
<i>Drawing Task from the Abbreviated Torrance Test for Adults</i>	Total score	.93	Kim (2006)

*Test-Retest Reliability Coefficients by Construct and Measure*

Task	Measure	Reliability (measure)	Reference
<i>Group Embedded Figures Task</i>	Accuracy	.883 (number of figures correctly identified)	Kepner & Neimark (1984)
<i>Intra-Extra Dimensional Set-shift Task (IDED)</i>	Accuracy Total Extra dimensional Perseverative Discrimination Reversal Latency* RT*	.70 (total errors to ED shift)	Lowe & Rabbit (1998)
Probabilistic Learning	Accuracy Perseverative errors	.74 (reversal error)	Freyer et al. (2009)
	Mean errors to criterion	.23 (spontaneous error)	Freyer et al. (2009)
	Feedback sensitivity	.03 (strategy change after probabilistic error)	Freyer et al. (2009)
	RT* Latency of response*	.90 (RT for first correct response)	Freyer et al. (2009)
<i>Remote Association Task</i>	Accuracy	.883 (number of figures correctly identified, Embedded Figures Task)	Kepner & Neimark (1984)
Switch Cost and Switch Setting Tasks	Switch cost score RT*	.616 (WCST, perseverative errors)	Calamia et al. (2013)
<i>Verbal Fluency Test</i>	Fluency	.74 (phonemic fluency)	Tombaugh, Kozak & Rees (1999)
<i>Wisconsin Card Sorting Test (WCST)</i>	Accuracy Fluency Failures Perseveration errors	.616 (perseverative errors)	Calamia et al. (2013)

*Test-Retest Reliability Coefficients by Construct and Measure*

Task	Measure	Reliability (measure)	Reference
	Number of categories	.88 categories sorted	Tate et al. (1998)

*Notes.* \* indicates split-half reliability; AUC = Area Under the Curve; SD = Standard Deviation; SE = Standard Error; RT = Reaction Time; SSRT = Stop-Signal Reaction Time; SS = Spatial Span; SWM = Spatial Working Memory.

## Appendix C: Studies Excluded Due to Insufficient Data

### *Studies Excluded Due to Insufficient Data*

Study	Design	ADHD Status	N	Medication (Dose)	Instrument (Construct)	Findings
Aman, Vamos, & Werry (1984)	Crossover	No	12	MPH (0.3-mg/kg)	Short Term Memory (STM) task (DM-D) CPT (V, IC)	Fewer commission errors under MPH compared to the placebo were found for the CPT. Omission errors were not significantly different across MPH and placebo groups, although there was a trend for better performance under MPH. Ceiling effects were present for the STM task; therefore, findings for that task were not reported.
Anderer, Saletu, Semlitsch, & Pascual-Marqui (2002)	Crossover	No	20	MPH (20-mg)	NR	NR
Asghar, Tanay, Baker, Greenshaw, & Silverstone (2003)	Crossover	No	25	AMP (25-mg)	SRT (PS)	AMP significantly decreased reaction times at 30, 60, 90, 150 and 210 minutes compared with placebo.
Ballard (2013)	Crossover	No	NR	AMP (10, 20-mg)	Memory Retrieval (DM-L)	AMP administered before retrieval testing showed no affect on memory and increased false recognition, but it improved preferential emotional memory when administered prior to learning without increasing false recognition.
Bernard, Penelaud, Mocaer, & Donazzolo (2011)	Crossover	No	18	MPH (40-mg)	CRT (PS)	MPH was associated with decreased recognition RT compared to PBO, but significant differences were not found for total RT or the difference between recognition RT and total RT.
Brumaghim, & Klorman (1998)	Crossover	No	22	MPH (0.3-mg/kg)	PAL (DM-I)	MPH did not significantly reduce the number of errors during learning or enhance recall. Further, MPH was not found to significantly affect reaction and motor times; however, the task design required participants to wait until submitting their response, not optimal for evaluating drug effects on RT.
Bullmore et al. (2003)	Parallel	No	24	MPH (20-mg)	Object-Location Learning task (WM)	No significant differences were found between the MPH and PBO group.
Bullmore et al. (2001)	Crossover	No	12	MPH (40-mg)	PAL (DM) <i>n</i> -choice motor reaction (PS)	NR
Bye, Munro-Faure, Peck,	Crossover	No	12	AMP (2.5, 5, 7.5-mg)	Auditory Vigilance Test (V)	No significant differences were reported for errors of omission or signal detection (sensitivity) between AMP and PBO groups; however, mean

*Studies Excluded Due to Insufficient Data*

Study	Design	ADHD Status	N	Medication (Dose)	Instrument (Construct)	Findings
& Young (1973). Callaway (1983)	Crossover	No	16	MPH (5, 10, 20-mg)	RT task (PS)	values indicated better performance scores for the AMP group.  Among the young women only, RT was speeded under 10 and 20 mg of MPH relative to placebo (not among the older women). Vigilance task perceptual sensitivity (an estimate of hit and false alarm rates) and conservatism in reporting occurrence of target were not significantly different across the MPH and placebo groups. Vigilance RT was significantly lower in the MPH group compared with the PBO group at the 2.5-hour time point. No significant PBO-MPH group differences in delayed-immediate free recall performance were observed. Selective reminding test sum performance, however, was improved in the MPH relative to the PBO group (other SRT measures were non-significant). No significant effects of MPH were found for Total Free Recall or Forced-Choice Pairwise-Recognition test performance for either the Free Recall or Selective Reminding Test tasks.
Camp-Bruno & Herting (1994)	Parallel	No	31	MPH (20-mg)	Recall of Verbal Learning (DM-I, D) Selective Reminding Test (SRT) (DM-I, D) Vigilance Task (V, IC)	ATX was found to enhance SSRT response times relative to placebo, but no significant differences were found for median Go response times. For probabilistic learning, no significant differences between ATX and placebo were found.  Increases in both error rate and target detection rates were found for measures of divided, but not focused attention, in the MPH condition compared to the PBO. Significant differences were not found for discrimination or response time.
Chamberlain et al. (2006)	Parallel	No	60	ATX (60-mg)	SSRT (IC) probabilistic learning task (NDL)	RT and number of omissions significantly decreased with increasing MPH dose.
Clark, Geffen, & Geffen (1986b)	Crossover	No	10	MPH (0.65-mg/kg)	Task of Attention (V)	There were no significant differences between AMP and PBO groups on measures of DS or DSST.
Cooper et al. (2005)	Crossover	No	32	MPH (5, 15, 45-mg)	Working Memory Task (WM) CPT (V)	AMP did not significantly affect the % of failed stop trials nor stop RT. "Slow stoppers", however, compared with "fast stoppers" (median split of group), demonstrated increased stop RT speed on AMP compared with PBO. This effect was not observed in the faster group. MPH did not have significant effects for number of consecutive errors preceding a switch (perseverative errors) or the probability of switching after erroneous feedback.
Crabbe, Jarvik, Liston, & Jenden (1983)	Crossover	No	12	AMP (10-mg)	DS (WM) DSST (PS)	On tasks of spatial orientation AMP showed improvements compared to PBO, but for perceptual speed significant differences were not found between AMP and PBO.
de Wit, Crean, & Richards (2000)	Crossover	No	20	AMP (10, 20-mg)	Stop-Go (IC)	
Dodds et al. (2008)	Crossover	No	20	MPH (60-mg)	Reversal Learning (SR)	
Evans & (1964)	Parallel	No	60	AMP (10-mg)	Guilford Test of Memory Span (WM) Guilford Test of Perceptual Speed (PS)	

*Studies Excluded Due to Insufficient Data*

Study	Design	ADHD Status	N	Medication (Dose)	Instrument (Construct)	Findings
Fisch, Groner, Groner, & Menz (1983)	Crossover	No	12	MPH (5, 10-mg)	Letter identification (WM)	MPH did not significantly affect the identification of rapidly presented strings of letters.
Fitzpatrick, Klorman, Brumaghim, & Keefover (1988)	Crossover	No	20	MPH (17.5 - 25.0- mg)	Item Recognition (WM)	RTs were speeded by MPH. MPH was associated with decreased non-responses; however, a drug*session order interaction was found wherein errors decreased more if PBO was administered first than if MPH was administered first.
Frankenhaeuser & Post (1966)	Crossover	No	30	AMP (15-mg)	SRT (PS)	Performance speed was significantly improved by AMP compared to PBO.
Halliday et al. (1990)	Crossover	No	16	AMP (10-mg)	SERS (PS)	AMP speeded mean RT relative to placebo and did not interact with response or stimulus complexity. When RT was decomposed into processing (PT) and distraction time (DT), AMP decreased PT for hard responses, but for easy response, D-AMP decreased distraction time (TDT). When those effects were combined to simulate mean RT, they cancelled each other and the differential effects disappeared.
Halliday et al. (1994)	crossover	No	13	AMP (10-mg)	SERS (PS)	AMP was associated with positive effects for response processing, stimulus evaluation and preprocessing.
Hamidovic, Dlugos, Palmer, & de Wit (2010)	crossover	No	152	AMP (5, 10-mg)	DSST (PS)	AMP was associated with "typical" effects on the DSST
Hermens et al. (2007)	Crossover	No	32	MPH (5, 15, 45-mg)	Oddball (IC) CPT (V) Mackworth Clock (V) Verbal Memory Recall (DM-I, D) Switching of attention (SR) Paced auditory serial addition test (PS)	Oddball RT: significant arithmetic trend of decreasing RT to correctly identified stimuli with increasing MPH. CPT-RT: significant decreasing ordinal trend with increasing dose of MPH. CPT-Total Errors and CPT-FN errors: significant logarithmic trends, where errors decreased with increasing dose of MPH. Mackworth Clock Task: increasing MPH dose was associated with an ordinal trend of decreased RT Variability, Total Errors, and FNs. Serial test: ordinal decreasing trend with increasing MPH. MPH had "virtually no impact on words recalled." Results not reported for other tasks.
Honey et al. (2003)	Crossover	No	23	MPH (20-mg)	Object-location learning (WM)	No significant effects of MPH on accuracy or response latency were found.
Kennedy, Odenheimer, Baltzley, Dunlap, & Wood (1990)	Crossover	No	16	D-AMP (10-mg)	Grammatical Reasoning (SR) Code Substitution (PS) Short-term Memory (WM)	Grammatical Reasoning and Code Substitution were not significantly affected by AMP. AMP significantly improved performance on the Short-Term Memory Test.



*Studies Excluded Due to Insufficient Data*

Study	Design	ADHD Status	N	Medication (Dose)	Instrument (Construct)	Findings
Klorman et al. (1984)a	Crossover	No	NR	MPH (20-mg)	CPT (V, IC)	No significant effects of MPH on test performance or response time were found.
Klorman et al. (1984)b	Crossover	No	NR	MPH (20-mg)	CPT (V, IC)	MPH did not significantly affect response time or number of errors; however, for errors of omission a significant decrease in the MPH group was found.
Klorman et al. (1984)c	Crossover	No	NR	MPH (20-mg)	CPT (V, IC)	MPH was found to significantly reduce the rate of omissions. Rate of commission errors was also lower under MPH although this difference was not statistically significant. RT was also speeded under MPH.
Kollins, Rush, Pazzaglia, & Ali (1998)	Crossover	No	10	MPH-IR, MPH-SR (20-mg)	DSST (PS) Circular Lights task (PS)	IMPH-IR (20mg) was associated with significant increases in the number of circular lights responses and MPH-SR (20mg) was associated with significant decreases in correct trials on the DSST; however, MPH-SR (40mg) resulted in significant increases in the number of Circular Lights task responses.
Kumari et al. (1997)	Crossover and Parallel	No	60	AMP (5-mg)	Procedural Learning Task (NDL)	Mean procedural learning scores were not significantly different between placebo and AMP groups; however, RT was significantly reduced in the AMP group.
Kupietz, Richardson, Gadow, & Winsberg (1980)	Crossover	No	9	MPH (5, 10-mg)	Verbal Learning of 96 Chinese characters (DM)	Lower dose of MPH reduced the number of total errors for the simultaneous instruction method only. Both doses of MPH reduced the numbers of errors made in reaching item criterion under the simultaneous instruction method but not under progressive instruction, but no significant differences across doses were found. Errors made in achieving two-trial list criterion were significantly reduced with low dose of MPH compared to PBO but not the high dose of MPH.
Martin, Corcoran, Zhang, & Katic (2014)	Crossover	Yes	18	LDX (50-mg/day) AMP-IR (20-mg/day)	Power of Attention (V)	Composite Power of Attention scores for both LDX and AMP-IR were improved relative to placebo at all post-administration time points (except for 2 hours post admin for LDX and 1 hour post admin for AMP-IR)
Mintzer & Griffiths (2007)	Crossover	No	18	AMP (20, 30-mg/70kg)	Episodic memory/meta-memory (DM-D) n-back (WM) Sternberg (WM) DSST (PS)	AMP (30 only) significantly improved performance on the DSST (number attempted) but did not significantly affect working memory or episodic memory but did increase d' on the recognition memory test (AMP 30 only).
Mulligan (2002)	Crossover	Yes	16	MPH (0, 0.2, 0.4-mg/kg)	n-back (WM)	Results indicated significant group differences in accuracy and RT increased with greater WM load. Under PBO, the control group outperformed the ADHD group in accuracy performance at 2-back and in reaction time at 3-back. Group differences under PBO disappeared with administration of 0.4 mg/kg of MPH, and this dose was associated with improved performance for the ADHD group at low (1-back) to moderate (2-back) levels of WM load. Findings suggest that 0.4 mg/kg dose of MPH improves the working memory performance of ADHD adults at low to

*Studies Excluded Due to Insufficient Data*

Study	Design	ADHD Status	N	Medication (Dose)	Instrument (Construct)	Findings
Rush, Essman, Simpson, & Baker (2001)	Crossover	No	8	AMP (10, 20-mg) MPH (20, 40-mg)	DSST (PS)	moderate levels of WM load. Significant effects on DSST performance were not found for the drug conditions.
Slattum (1992).	Crossover	No	8	D-AMP (5, 10, 20-mg)	CPT (V, IC)	NR
Soetens et al. (1995)a	Crossover	No	12	D-AMP (10-mg)	Word recall (DM-I, DM-D, DM-L)	AMP significantly improved recall performance for both 1 sec and 4 sec word presentation time conditions, relative to PBO.
Soetens et al. (1995)b	Crossover	No	18	D-AMP (10-mg)	Word recall - (DM-I, DM-L)	Recall of words was enhanced with AMP.
Soetens et al. (1995)c	Crossover	No	14	AMP (10-mg)	Word recall (DM-I, DM-D, DM-L)	AMP interacted with session order, with the strongest effects in sessions 2 and 3. Additionally, an interaction between AMP and moment of administration emerged, with AMP administered before learning improving performance but not when administered after learning.
Soetens et al. (1995)d	Crossover	No	12	AMP (10-mg; injected intramuscularly)	Word recall (DM-I, DM-D, DM-L)	AMP significantly improved performance at 1-day delay recall.
Soetens et al. (1995)e	Crossover	No	12	AMP (10-mg)	Word recall (DM-I, DM-D, DM-L)	AMP significantly improved recognition performance compared with placebo at the 1-week retest (non-significant for immediate and 1-day delayed recognition).
Soetens et al. (1993)a	Crossover	No	18	AMP (10-mg)	Free recall of words (DM-I, L)	Significant increases in recalled words were found for memory tested a day after learning, and non-significant increases were shown immediately after learning.
Soetens et al. (1993)b	Crossover	No	18	AMP (10-mg)	Free recall of words (DM-I, D, L)	Significant increases in recalled words were found with a 1-hour and 1-day delay, but no significant improvements were found for immediate recall.
Soetens et al. (1993)c	Crossover	No	12	AMP (10-mg)	Free recall of words (DM-I, D, L)	Significant effects were found for recall after a 1, 2 and 3 days delayed.
Tipper et al. (2005)	Parallel	No	17	AMP (2, 5, 12.5-mg)	SMT (WM)	There was no significant difference in RT between AMP and PBO groups, but significant memory load and session results were consistent with difficulty and practice effects, respectively. For PAL, when learning occurred before drug administration, acquisition was identical on placebo and MPH. Retention 24 hours later was not affected by MPH. When PAL learning occurred after drug administration, MPH resulted in poorer recall during early acquisition trials but not later ones, presumably due to a ceiling effect. Picture recognition was not significantly affected by MPH. For Story recall, when learning occurred prior to drug infusion, no significant differences between MPH and PBO were found. When learning occurred after drug administration, MPH
Wetzel et al. (1981)a	Crossover	No	12	MPH (0.5-mg/kg)	PAL (DM-I, DM-L) Picture recognition (DM-I, DM-L) Story recall (DM-I, DM-L)	

*Studies Excluded Due to Insufficient Data*

Study	Design	ADHD Status	N	Medication (Dose)	Instrument (Construct)	Findings
Wetzel et al. (1981)b	Crossover	No	12	MPH (0.1, 0.25-mg/kg)	PAL (DM-I) Picture recognition (DM-I) Story recall (DM-I)"	impaired recall. PAL retention was not significantly affected when learning occurred either prior to or after infusion of MPH. Picture recognition and story recall was not significantly affected by MPH, either before or after learning.
Zhu et al. (2013)	Crossover	No	18	MPH (20-mg)	Go/No-Go Task (IC)	Significant effects were not found between the MPH and PBO groups on Go or No-Go accuracy.

*Notes.* ADHD = Attention-Deficit/Hyperactivity Disorder; AMP = Amphetamine; AMP-IR = AMP Immediate Release; ATX = Atomoxetine; CPT = Continuous Performance Task; CRT = Choice Reaction Test; DM = Declarative Memory; DM-I = Declarative Memory – Immediate; DM-D = Declarative Memory – Delayed; DM – L = Declarative Memory – Long-term; DS = Digit Span; DSST = Digit Symbol Substitution Task; IC = Inhibitory Control; MPH = Methylphenidate; MPH-IR = MPH Immediate Release; MPH-SR = MPH Sustained Release; NDL = Non-Declarative Learning; NR = No Report; PAL = Paired Associates Learning Task; PBO = Placebo; PS = Processing Speed; RT = Reaction Time; SERS = Stimulus Evaluation Response Selection; SMT = Sternberg Memory Task; SR = Self-Regulation; SRT = Simple Reaction Test; STM = Short Term Memory Task; V = Vigilance; WM = Working Memory.

## Appendix D: Measures by Study and Narrow Cognitive Construct

Study	Instrument	Measure(s)
<i>Vigilance</i>		
Agay et al. (2010)	TOVA	Omissions
Agay et al. (2014)	TOVA	Weighted average of RT, RT errors and performance quality over time
Barkley et al. (2005)	CPT	Omissions
Boonstra et al. (2005)	CPT	Sensitivity
Bron et al. (2014)	CPT	Omissions
	TOVA	Discriminative ability
Chamberlain et al. (2007)	RVIP	Proportion of targets detected
Coons et al. (1981)a	CPT	Omissions
Coons et al. (1981)b	CPT (and oddball)	Omissions
Costa et al. (2013)	Go/No-Go	Go accuracy Oddball accuracy
DuPaul et al. (2012)	CPT	Omissions, detectability
Elliott et al. (1997)	RVIP	Accuracy
Fleming et al. (1995)	CPT	Omissions
Hink et al. (1978)	Auditory Attention	Correct positive hits
Kollins et al. (2015)	CPT	Omissions
Kratz et al. (2009)	Go/No-Go	Hit Rate
Levin et al. (2001)	CPT	Omissions, composite measure of attentiveness
Rapoport et al. (1980)	CPT	Omission Errors
Silber et al. (2006)	DV	Accuracy
Sofuoglu et al. (2008)	SART	Omissions
Strauss et al. (1984)	CPT	Omissions, Sensitivity of detection
Theunissen et al. (2009)	Mackworth Clock	Hits
Turner et al. (2003)	RVIP	Sequence detection
Turner et al. (2005)	RVIP	Target sensitivity
Whiting et al. (2008)	RVIP	Hit rate
<i>Inhibitory Control</i>		
Agay et al. (2010)	TOVA	Commissions
Allman et al. (2010)	Antisaccade	Antisaccade Error
Allman et al. (2012)	Antisaccade	Antisaccade Error
Aron et al. (2003)	Stop-Signal	SSRT
Barch & Carter (2005)	Stroop	Incongruent Errors
Barkley et al. (2005)	CPT	Commissions
Ben-Itzhak et al. (2008)	Go/No-Go	Go/No Go Accuracy
Boonstra et al. (2005)	Stop-Signal	SSRT
	CPT	Commissions
Bron et al. (2014)	CPT	Commissions
	TOVA	Commissions
Chamberlain et al. (2007)	Stop-Signal	SSRT
	RVIP	Commissions
Chamberlain et al. (2009)	Stop-Signal	SSRT
Chevassus et al. (2013)	Stroop	Stroop-Color word T

Study	Instrument	Measure(s)
Clark et al. (1986a)	Task of Attention	Error Rate
Coons et al. (1981)a	CPT (2 versions)	Commissions
Coons et al. (1981)b	CPT (and oddball)	Commissions
Costa et al. (2013)	Go/No-Go	No-Go errors
	Stop-Signal	SSRT
de Bruijn et al. (2004)	Flanker	Errors
	Go/No-Go	Commissions
		Total correct
DuPaul et al. (2012)	CPT	Commissions
Faraone et al. (2005)	Stroop	Interference
Fleming et al. (1995)	CPT	Commissions
Graf et al. (2011)	Go/No-Go	Commissions on no-go
		incongruent
Hester et al. (2012);	Go/No-Go	No-Go accuracy
Nandam et al. (2014)		
Hink et al. (1978)	Auditory Attention	False positives
Idestrom & Schalling (1970)	Stroop	Incongruent RT
Ilieva et al. (2013)	Go/No-Go	Commissions
	Flanker	Inhibition Cost
Kollins et al. (2015)	CPT	Commissions
Kratz et al. (2009)	Go/No-Go	Impulsivity Errors
Levin et al. (2001)	CPT	Commissions
Linssen et al. (2012)	Stop-Signal	SSRT
Moeller et al. (2014)	Stroop	Interference
Nandam et al. (2011)	Stop-Signal	SSRT
Pauls et al. (2012)	Stop-Signal	SSRT (two versions)
Rapoport et al. (1980)	Stroop	Commissions
Servan-Schreiber et al. (1998)	Flanker	Incongruent Errors
Silber et al. (2006)	DV	False Alarms
Sofuoglu et al. (2008)	SART	Commissions
Spencer et al., 1998	Stroop	Interference T
Strauss et al. (1984)	CPT	Commissions
Taylor & Russo (2000)	Stroop	Stroop-Color Word T
Taylor & Russo (2001)	Stroop	Interference
Theunissen et al. (2009)	Mackworth Clock	Stop RT
Turner et al. (2003)	RVIP	False Alarms
Turner et al. (2005)	RVIP	Response Bias
<i>Working Memory</i>		
Agay et al. (2010)	DS	DS Forward
		DS Backward
Agay et al. (2014)	DS; WM Task	DS Forward
		DS Backward
		SWM Errors
		SWM Strategy Score
Barch & Carter (2005)	Dot-Letter Task	Accuracy
Brumaghim et al. (1987)a	Recall of Consonants	Error rate
Brumaghim et al.	Recall of	Error rate

Study	Instrument	Measure(s)
(1987)b	Consonants	
Campbell-Meiklejohn et al. (2012)	<i>n</i> -back	Hits Misses False Alarms
Chamberlain et al. (2007)	SWM	Total Between-Search Errors Strategy Score
Chevassus et al. (2013)	DS	DS
Clatworthy et al. (2009)	SWM	SWM Errors
de Wit et al. (2002)	DS	DS
Duke & Keeler (1968)	TMT-B	RT
Elliott et al. (1997)	SWM	Strategy Score
Fillmore et al. (2005)	RIP	RIP Score
Fleming et al. (1995)	Spatial Delay Response	Accuracy
Gilbert et al. (1973)	DS	DS
Ilieva et al. (2013)	DS	DS Backward DS Forward
	<i>n</i> -back	Omissions
Kollins et al. (2015)	<i>n</i> -back	Accuracy
Linssen et al. (2012)	SWM	Accuracy Absolute Errors Positive Fit
Linssen et al. (2014)	SWM	Accuracy Absolute Errors Positive Fit
Makris et al.(2007)	Number Recognition	Accuracy
Marquand et al. (2011)	SWM	Accuracy for Rewarded Accuracy for Nonrewarded
Mattay et al. (2000)	<i>n</i> -back	Accuracy
Mehta et al. (2000)	SWM	Between-search errors Within-search errors
	<i>n</i> -back	Hit rate False alarm rate Sensitivity
Oken et al. (1995)	DS	DS Forwards DS Backwards
Ramasubbu et al. (2012)	<i>n</i> -back	Accuracy Errors Misses
Silber et al. (2006)	DS	DS Forwards DS Backwards
	TMT-B	RT
Studer et al. (2010)	Visual WM	Accuracy
Taylor & Russo (2000)	DS	DS Forward DS Backward
Turner et al. (2003)	DS	DS Forward DS Backward
	SWM	Strategy Score Between-search errors

Study	Instrument	Measure(s)
		Within-search errors
	SSP	Span length
Turner et al. (2005)	SWM	Total errors
		Strategy score
		Between errors
		Within errors
	<i>n</i> =back	Span length
		Total errors
van der Schaaf et al. (2013)	DS	DS Forward
		DS Backward
Wardle et al. (2013)	<i>n</i> -back	Accuracy
<i>Processing Speed</i>		
Chevassus et al. (2013)	DSST	DSST score
	SRT	RT
	CRT	RT
Coons et al. (1981)b	CRT	Omissions
		Commissions
		RT
Duke & Keeler (1968)	TMT-A	RT
Finke et al., 2010	Whole-report Task	Rate
Halliday et al. (1986)a	SERS	RT
Halliday et al. (1986)b	SERS	RT
Idestrom & Schalling (1970)	DSST	DSST score
Kornetsky (1958)	Simple Motor Response	RT
Linssen et al. (2011)	SRT	Accuracy
		RT
Makris et al.(2007)	DSST	Accuracy
		Trial Rate
	DSST	Number attempted
		Proportion correct
Muller et al. (2005)	Motor Reaction	Errors
Naylor et al. (1985)	SERS	RT
Oken et al. (1995)	Spatial Orientation	RT
	Visual Search	Errors
Samanez-Larkin et al. (2013)	DSST	DSST score
Silber et al. (2006)	DSST	DSST Score
	TMT-A	RT
Ward et al. (1997)	NR	Latency
	DSST	Trial Rate
		Accuracy Rate
Wardle et al. (2013)	DSST	AUC
Weitzner (1965)	Digit Letter Coding	Errors
<i>Immediate Declarative Learning and Memory</i>		
Ben-Itzhak et al. (2008)	Recognition of object orientation	Accuracy

Study	Instrument	Measure(s)
Brignell et al. (2007)	Recognition of story; Recall of object	Accuracy Confabulations Errors Recognition
Chevassus et al. (2013) DuPaul et al. (2012)	Recall of pictures CVLT	Recall Level of Recall Trial 1-5 Total Short Delay Retention
Finke et al., 2010 Fleming et al. (1995)	Whole-report RAVLT	Rate Trial 1 Trials 1-5
		AB trial 1 AB trials 1-3 AC trial 1 AC trials 1-3 AB-AC
Gilbert et al. (1973)	GMT	Paragraphs Paired Associates Designs
Kinsbourne et al.(2001) Linssen et al. (2014)	PAL RVALT PAL	Accuracy Mean score Maximum Mean
Turner et al. (2003)	PAL	First trial memory score Total errors Total trials
Turner et al. (2005) Unrug et al. (1997)	PRM Recall of vocabulary	Accuracy Recall
Verster et al. (2010)	Recall and recognition of words	Recall Recognition
Weitzner (1965) Zeeuws & Soetens (2007)	PAL Recall of words	Trials to criterion Recall accuracy Number of intrusions (errors)
Zeeuws et al. (2010a)	Recall of words	Sensitivity Response Bias
Zeeuws et al. (2010b)a	Recall of words	Response Bias Hits False Alarms
Zeeuws et al. (2010b)b	Recall of words	Response Bias Hits False Alarms
<i>Delayed Declarative Learning and Memory</i>		
Brignell et al. (2007)	Recall of story (20	Recall



Study	Instrument	Measure(s)
DuPaul et al. (2012)	min.) CVLT (20 min.)	Level of Recall Long-Delay Free Long-Delay Retention
Ilieva et al. (2013)	Recognition of faces; Recognition of words (120 min.)	Recall accuracy Recognition accuracy
Linssen et al. (2014)	RVALT (30 min.)	Mean Score Recall Sensitivity
Turner et al. (2005) Unrug et al. (1997)	PRM (20 min.) Recall of vocabulary (20 min.)	Accuracy Recall
Verster et al. (2010)	Recall of words (120 min.)	Recall Recognition
Zeeuws & Soetens (2007)	Recall of words (30, 60 min.)	Recall accuracy Number of intrusions (errors)
Zeeuws et al. (2010a)	Recall of words (60 min.)	Sensitivity Response Bias
Zeeuws et al. (2010b)a	Recall of words (60 min.)	Response Bias Hits False Alarms
Zeeuws et al. (2010b)b	Recall of words (60 min.)	Response Bias Hits False Alarms
<i>Long-term Declarative Learning and Memory</i>		
Ballard et al. (2013)	Recall of pictures (2 days)	Hit Rate False Alarm Rate
Ballard et al. (2014)	Recall of pictures; Recognition of words (2 days)	Recall Recognition
Izquierdo et al. (2008)	Retention of facts (2 days, 1 week)	Retention
Linssen et al. (2014)	RVALT (1 day)	Recall RT Sensitivity
Whiting et al. (2008)	Recall of names; Recognition of names (1 week, 1 month)	Recognition
Zeeuws & Soetens (2007)	Recall of words (1 day)	Recall accuracy Number of intrusions (errors)
Zeeuws et al. (2010a)	Recall of words (1 day, 1 week)	Sensitivity Response Bias
Zeeuws et al. (2010b)a	Recall of words (1 day, 1 week)	Hits False Alarms Response Bias
Zeeuws et al. (2010b)b	Recall of words (1 day, 1 week)	Hits False Alarms Response Bias

Study	Instrument	Measure(s)
<i>Measures by Study and Instrument of Non-Declarative Learning and Memory</i>		
Breitenstein et al. (2004)	AWL	Learning Curve
Burns et al. (1967)	Learning Task	Learning Rate
Kornetsky (1958)	SLT	RT
Makris et al.(2007)	RA	Response rate Accuracy
Schlösser et al. (2009)	Probabalistic Decision-Making Task	Probability RT
van der Schaaf et al. (2013)	Reversal Learning	Accuracy
<i>Measures by Study and Instrument of Planning and Decision-Making</i>		
Agay et al. (2010)	IGT	Number of advantageous choices
Agay et al. (2014)	IGT	IGT dis FPGT dis
Elliott et al. (1997)	NTOL	Movement rate Accuracy rate
Linssen et al. (2012)	NTOL	Accuracy RT
Turner et al. (2003)	NTOL	Move attempts Latency
	IGT	Probability of selecting most likely outcome Deliberation time
<i>Measures by Study and Instrument of Self-regulation</i>		
Chamberlain et al. (2007)	IDED	Total errors Total reversal errors ED shift errors
Clatworthy et al. (2009) Elliott et al. (1997)	Reversal Learning	Errors
	IDED	Perseverative errors
	Verbal Fluency Test	Letter Fluency Category Fluency
Farah et al. (2009)	RAT	Accuracy
	Embedded Figures	Accuracy
	AUT	Mean score
	Drawing Task	Mean score
Fleming et al. (1995)	WCST	Number of categories Perseverative responses Failures
	COWAT	Fluency
Ilieva et al. (2013)	RAT	Accuracy
	Embedded Figures	Accuracy
Linssen et al. (2012)	IDED	Accuracy
Mattay et al. (1996)	WCST	Conceptual level Accuracy Number of categories

Study	Instrument	Measure(s)
Rogers et al. (1999)	IDED	Perseveration error Errors Accuracy
Samanez-Larkin et al. (2013)	SCT	RT Switch Cost
Taylor & Russo (2000)	COWAT	COWAT score
Taylor & Russo (2001)	COWAT	COWAT score
Turner et al. (2003)	IDED	Total errors ED errors
van der Schaaf et al. (2013)	Reversal Learning (shifting)	Accuracy
Wardle et al. (2013)	WCST	Perseverative errors

*Notes.* AUC = Area Under the Curve; AUT = Alternative Uses Test; AWL = Associative Word Learning; COWAT = Controlled Oral Word Association Test; CPT = Continuous Performance Task; CRT = Choice Reaction Test; CVLT = California Verbal Learning Test; DVT = Digit Vigilance Task; DS = Digit Span; DSST = Digit Symbol Substitution Task; GMT = Guild Memory Test; IDEED = Intra-Extra Dimensional Set-Shift Task; IGT = Iowa Gambling Task; PAL = Paired Associates Learning Task; PRM = Pattern Recognition Memory Task; RA = Repeated Acquisition of Response Sequences Task; RAT = Remote Associations Task; RIP = Rapid Information Processing Task; RT = Reaction Time; RVALT = Rey Verbal Auditory Learning Task; RVIP = Rapid Visual Information Processing; SART = Sustained Attention to Response Test; SCT = Switch Cost Task; SERS = Stimulus Evaluation Response Selection; SLT = Simple Learning Task; SRT = Simple Reaction Test; SSP = Spatial Span Task; SSRT = Stop-Signal Reaction Time; SWN = Spatial Working Memory; NTOL = Tower of London Spatial Planning Task; TOVA = Test of Visual Attention; TMT = Trail-Making Task; WCST = Wisconsin Card Sorting Test; WM = Working Memory

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