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Neurocognitive enhancement or impairment? A systematic meta-analysis of prescription stimulant effects on processing speed, decision-making, planning, and cognitive perseveration

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Experimental and Clinical Psychopharmacology

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Neurocognitive Enhancement or Impairment? A Systematic Meta-Analysis of

Prescription Stimulant Effects on Processing Speed, Decision-Making, Planning,

and Cognitive Perseveration

Abstract

Increasing numbers of adults, particularly college students, are misusing prescription stimulants primarily for cognitive/academic enhancement, so it is critical to explore whether empirical findings support neurocognitive benefits of prescription stimulants. Previous meta-analytic studies have supported small benefits from prescription stimulants for the cognitive domains of inhibitory control and memory; however, no meta-analytic studies have examined the effects on processing speed or the potential impairment on other domains of cognition, including planning, decision-making, and cognitive perseveration. Therefore, the present study conducted a meta-analysis of the available literature examining the effects of prescription stimulants on specific measures of processing speed, planning, decision-making, and cognitive perseveration among healthy adult populations. The meta-analysis results indicated a positive influence of prescription stimulant medication on processing speed accuracy, with an overall mean effect size of g = 0.282 (95% CI 0.077, 0.488; $n = 345$). Neither improvements nor impairments were revealed for planning time, planning accuracy, advantageous decision-making, or cognitive perseveration; however findings are limited by the small number of studies examining these outcomes. Findings support that prescription stimulant medication may indeed act as a neurocognitive enhancer for accuracy measures of processing speed without impeding other areas of cognition. Considering that adults 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, the establishment of public policies informed by interdisciplinary research surrounding this issue, whether restrictive or liberal, is of critical importance.

Public Health Significance:

Misuse of prescription stimulants, which hold a high abuse potential, is a growing problem among student and non-student adults for enhancement of academic functioning and work productivity. By investigating the cognitive effects of prescription stimulants, the present meta-analytic study informs potential interventions and policy development surrounding prescription stimulant misuse and diversion.

Disclosures and Acknowledgments

Introduction

The efficacy of prescription stimulant 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 misuse for cognitive enhancement, as opposed to ADHD symptom management, is a growing problem among adults and college students with and without ADHD (Benson, Flory, Humphreys, & Lee, 2015; Weyandt et al., 2013; Weyandt et al., 2014). College students consistently report enhancing academics as their primary motivation for misusing stimulant medication (Benson et al., 2015; Weyandt et al., 2009; Weyandt et al., 2013), and adults with ADHD have indicated productivity as a motivation for stimulant misuse (Novak, Kroutil, Williams, & Van Brunt 2007). Although the widespread misuse of prescription stimulants for cognitive enhancement highlights the need for public policy addressing this issue, a number of questions remain about how best to approach such policy. Policy development requires in-depth understanding of a) the ethical and legal implications associated with prescription stimulant misuse, b) the cognitive behavioral effects of these medications in populations with and without ADHD, c) the underlying pharmacological mechanisms of these effects, and d) potential genetic and neurodevelopmental variation across cognitive and behavioral effects. Although it is beyond the scope of the present study to answer all of these questions, by elucidating the potential effects of prescription stimulant medications for particular domains of cognitive enhancement, we hope to contribute to an interdisciplinary dialogue spanning behavioral,

cognitive, and developmental psychology, as well as clinical neuroscience, behavior genetics, and pharmacology in order to help inform public policy.

Two previous reviews have assessed the effect of prescription stimulants on cognition in adults with and without ADHD, concluding that the effects of stimulant medications on cognitive enhancement vary according to population and task (Advokat, 2010; Smith & Farah, 2011). These reviews, however, 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). In their meta-analysis examining prescription stimulant efficacy for ADHD symptoms, Faraone, Biederman, Spencer, and Aleardi (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, accounting for medication type, medication dose, participant demographics and study design, would greatly contribute to the existing literature.

One meta-analytic study (Ilieva, Hook, & Farah, 2015) has explored the effects of prescription stimulant medication on cognition among adults. Findings from this study supported small but significant effects of methylphenidate and amphetamine on working memory ($g = 0.13$), episodic memory ($g = 0.20$) and inhibitory control ($g = 0.20$), and moderate effects on delayed memory ($g = 0.45$). The researchers speculated that larger

effects may be found among other domains of cognition related to learning (e.g.,

processing speed). An additional question that has been raised in the literature (Advokat,

2010; Ilieva, Boland, & Farah, 2013; Smith & Farah, 2011; Weyandt et al., 2013;

Weyandt et al., 2014) queries that even if positive benefits are associated with

prescription stimulant use in some areas of cognition, could these stimulants also be

associated with *impairments* of other components of cognition such as planning,

decision-making and perseveration?

To date, no meta-analyses have been conducted concerning the effects of

prescription stimulant medication on processing speed accuracy, planning time and

accuracy, advantageous decision-making, or cognitive perseveration. 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, the present meta-analytic study examined whether prescription

stimulants play a role in these specific behaviors of cognition among healthy adults.

These particular cognitive behaviors were selected because a) to date, no meta-analytic

studies have examined the effects of prescription stimulants on these cognitive behaviors;

b) these particular cognitive behaviors will proffer important implications for academic

enhancement; and c) a pilot search of the literature indicated these areas have been

adequately studied across neuropsychological research.

Previous research supports the potential for prescription stimulants to benefit

processing speed and impede cognitive flexibility; however, the potential for positive or

negative effects from stimulants on planning and decision-making remains less clear.

Processing speed has been described to rely on cognitive processes that involve attention and response speed (Lezak, Howieson, Bigler, & Tranel, 2012) and previous research has supported prescription stimulant benefits to these areas (Riccio, Waldrop, Reynolds, & Lowe, 2001; Schlösser et al., 2009). Further, an increase in error rates on tests of cognitive flexibility and set-shifting has been found to associate with prescription stimulants (Advokat, 2010; Dyme, Sahakian, Golinko, & Rabe, 1982; Rogers et al., 1999). Studies examining the effects of prescription stimulants on tasks of decision-making and planning, however, have mainly reported null effects (Agay, Yechiam, Carmel, & Levkovitz, 2010; Agay, Yechiam, Carmel, & Levkovitz, 2014; Elliott et al., 1997; Linssen,Sambeth, Vuurman, & Riedel , 2012; Turner et al., 2003). Considering that both planning and decision-making have been described to involve working memory, impulse control and sustained attention (Lezak et al., 2012), and previous research has demonstrated that prescription stimulants may result in small boosts in these areas of cognition (Ilieva et al., 2015; Koelega, 1993; Riccio et al., 2001), it is possible that prescription stimulants will also enhance planning and decision-making. Therefore, the primary hypothesis of the present study is that among healthy adults without ADHD, prescription stimulant medications will enhance performance on measures of processing speed accuracy, planning time and accuracy, and advantageous decision-making, and impair performance on measures of cognitive perseveration.

Methods

Literature search

The 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 that examined amphetamine or methylphenidate effects on

processing speed, planning, decision-making and cognitive perseveration conducted at

any time. The final search and retrieval process was conducted in January 2016 and

included a comprehensive search of PsycINFO and PubMed. A combination of the

following keyterms were used: *"Prescription stimulant", amphetamine, Adderall,*

methylphenidate, Ritalin, or *Concerta,* and *"processing speed", "psychomotor*

performance", planning, "decision making", "cognitive flexibility", "Digit Symbol

Substitution Task", "Iowa Gambling Task", "Spatial Planning Task", "Set Shift

Task", or *"Wisconsin Card Sorting Task".* Studies were also searched within a larger

pilot study that investigated the effects of prescription stimulants and prostimulants on

multiple domains of cognition, as well as the following review articles: Advokat, (2010),

Linssen, Sambeth, Vuurman, and Riedel (2014), Smith and Farah, (2011), and Repantis,

Schlattmann, Laisney, and Heuser, (2010). Titles, abstracts, and full articles were

examined to assess if studies met eligibility criteria, described in the following section.

Study Selection

Studies were selected for review based on the following criteria:

A. The study investigated the effects of oral ingestion of amphetamine or

methylphenidate on processing speed accuracy, planning time, planning

accuracy, advantageous decision-making, or cognitive perseveration using the

Digit Symbol Substitution Test (DSST), the Iowa Gambling Task (IGT), the

Tower of London (TOL) or New Tower of London (NTOL) Tasks, the

Wisconsin Card Sorting Task (WCST), or the Intra-Extra Dimensional Set-

shift Task (IDED); if the study investigated additional drugs or measures, only

data involving the stimulants listed previously and placebo were included.

B. The study was published in English.

C. The study used a double blind placebo-controlled design.

D. The sample included human subjects only, at least 18 years of age; if the study

included special groups, only data involving healthy controls were included.

E. The sample size was greater than one; single case studies were excluded.

F. The procedure did not limit sleep for participants; studies investigating sleep

deprivation or studies that deprived participants of sleep were excluded.

G. Studies that used drug discrimination learning procedures, i.e., teaching

participants to discriminate between drugs or doses of drugs, were excluded in

order to minimize confounds associated with these learning tasks.

Data extraction

Once all studies were identified and retrieved, data were extracted and coded

independently by two researchers according to a standardized coding manual. To measure

coder consistency, we calculated percent agreement (94.07%) based on established

guidelines (Lipsey & Wilson, 2001; Yeaton & Wortman, 1993) and disagreements were

resolved by discussion and consensus between coders. A comprehensive coding system

included basic descriptive statistics (sample size, reported effect size statistics, effect

direction and raw data to recalculate effect size), sample descriptors, study design and

study, stimulant medication descriptors, dependent constructs and measures of cognition, and the following moderators:

(1) Stimulant type (methylphenidate vs. amphetamine): Differences between methylphenidate (MPH) and amphetamine (AMP) were examined to determine if type of stimulant impacted cognitive neuroenhancement.

(2) Dose (low vs. high): We examined the influence of dose level on stimulants for neurocognitive enhancement. Doses coded as "high" included the following: $\geq$ 20-mg (AMP), $\geq$ 40-mg (MPH). "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. One study (Elliott et al., 1997) only reported the collapsed findings from 20-mg ($n = 8$) and 40-mg ($n = 20$) of MPH because the researchers did not find significant differences between the doses. Considering the majority of participants received the highest dose, we coded effect sizes as "high."

(3) Sex Distribution: Percent female was coded as an estimate of sex distribution.

(4) Age of Sample: Mean age and age range were coded to determine the influence of participant age on prescription stimulant neuroenhancement.

(5) Study Design (crossover vs. parallel): Studies were coded as using either a crossover or within-subjects design or a parallel or between-subjects design.

(6) Inclusion of Non-Behavioral Measures (yes vs. no): For an additional assessment of publication bias, we followed a format similar to Ilieva et al. (2015) and differentiated studies that examined prescription stimulant effects

on behavioral tasks only and studies that examined prescription stimulant effects on behavioral tasks to better understand neurological or physiological outcomes. Studies that conducted cognitive assessments in conjunction with neurological (e.g., functional Magnetic Resonance Imaging [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.

(7) Timing of Dose Activation (during, prior, vs. after task): 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 short-acting amphetamine between 2-3 hours (Angrist, Corwin, Bartlett, & Cooper, 1987; Wachtel, ElSohly, Ross, Ambre, & de Wit, 2002) and short-acting methylphenidate between 1-2 hours (Kimko, Cross, & Abernethy, 1999; Volkow et al. 1998). 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."

Outcome performance measures and cognitive domains

Dependent performance measures and constructs were coded based on methods used by previous research and on theoretical constructs of cognition. In order to minimize measurement error, an a priori outcome selection strategy similar to that used by previous meta-analytic studies (Ilieva et al., 2015) was used whereby instruments and measures were limited based on reliability and validity and commonality across studies (see Table 1). The present meta-analysis focused on studies addressing the effects of prescription stimulants on the cognitive behaviors of processing speed accuracy, planning time, planning accuracy, advantageous decision-making, and cognitive perseveration because no meta-analyses have addressed these areas and because these areas proffer important implications for prescription stimulant misuse for academic enhancement. Specific instruments included: A) the Digit Symbol Substitution Task (DSST) to measure processing speed accuracy, B) the Iowa Gambling Task (IGT) to measure advantageous decision-making, C) the Tower of London Spatial Planning Task (TOL) and New Tower of London Spatial Planning Task (NTOL) to measure planning accuracy and time, and C) the Wisconsin Card Sorting Test (WCST) and the Intra-Extra Dimensional Set-shift Task (IDED) to measure cognitive perseveration.

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). Completed with paper and pencil or on the computer, the Digit Symbol Substitution Task (DSST) measures attention, motor performance, response speed and visuomotor coordination (Silber, Croft, Papafotiou, & Stough, 2006) and 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. 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). Although a number of additional measures of processing speed are available in the literature (e.g., continuous performance tests, trail making tasks, and reaction time), these tasks rely on a wide range of dimensions of performance. To minimize heterogeneity in cognitive processes, and because the DSST is used widely in the literature as a control measure of processing speed, accuracy measures of the DSST were selected to measure processing speed. Accuracy measures included number of trials correct in a specified amount of time (accuracy - total) or proportion of correct trials out of total trials attempted in a specified amount of time (accuracy - proportion).

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 may include gambling tasks and test of decision-making may include tower tests (Lezak et al., 2012).

Although a number of iterations of gambling tasks are available, a commonly used 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). The IGT presents four decks of cards of which half yield consistent large gains and larger losses and half yield consistent small gains and smaller losses (Agay et al., 2014). We prioritized number

of advantageous choices or probability of selecting most likely outcomes from the IGT to

measure the tendency to choose advantageously within decision-making. Note that the

number of disadvantageous choices was equal to the total number of choices minus the

number of advantageous choices (i.e., when added together, they sum to the total number

of opportunities); therefore, the number of disadvantageous choices was also used as a

negative representation of advantageous choices.

The Tower of London Spatial Planning Task (TOL) and the New Tower of

London Spatial Planning Task (NTOL) are the most commonly used versions of the

tower tasks. These tasks 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). The TOL requires participants to physically move the balls or discs

to come to the most efficient solution. The NTOL also requires participants to work out

the most efficient solution; however participants do not physically arrange the balls/discs

as they do in the TOL (Elliott et al., 1997). Both planning accuracy and planning time

were selected as measures of planning from the TOL and NTOL.

Cognitive Perseveration. Tasks of cognitive flexibility and the capacity to shift

require respondents to shift their thinking by changing the rules during the task (Lezak et

al., 2012). The Wisconsin Card Sorting Test (WCST) and the Intra-Extra Dimensional

Set-shift Task (IDED) are common tests of cognitive flexibility with performance

outcomes that measure cognitive perseveration (Lezak et al., 2012; Wild & Musser,

2014). The WCST is used to assess abstract concepts and set-shifting (Spreen & 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). An analog to the WCST,

Cambridge Neuropsychological Test Automated Battery's (CANTAB) IDED set shifting

test involves visual discrimination and attentional set formation (Barker, Pope, Smith,

Brown, & Hall, 2014; 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). We focused on perseveration as a measure of flexibility,

prioritizing the selection of perseverative errors and Extra-dimensional reversal shift

errors from the WCST and IDED, respectively.

Statistical Methods

Meta-analyses, which pool weighted estimates of effects into a common metric

across studies (Aloe, 2014; Lipsey & Wilson, 2001), were conducted on the retrieved

studies using the program Biostat's Comprehensive Meta-analysis (www.meta-

analysis.com) (Borenstein, Hedges, Higgins, & Rothstein, 2015). In total, 15 individual

meta-analyses were conducted that included five measures of cognition across three types

of medication dose (averaged, low, and high medication doses). Because results were

similar across meta-analyses conducted separately for high and low doses only the

averaged medication dose findings are presented here (see Supplementary Tables S1a and

S1b). 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 effect size distribution, analyses of publication bias, and

exploration of potential moderating variables.

Assessment of Effect Size. Effect sizes measuring post-treatment differences between placebo and control groups were calculated from a variety of statistics, including descriptive data, i.e., means and standard deviations, and inferential statistics, i.e., F (in cases of $df = 1$) and t. 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. Effect sizes were combined from studies that used both parallel and crossover designs. The appropriateness of synthesizing effect size data across parallel and crossover designs has been largely debated in the methodological literature (e.g., Elbourne et al., 2002; Lipsey & Wilson, 2001). Results from studies using crossover designs may be biased from carryover effects where the initial intervention effects may influence responses on subsequent interventions (Elbourne et al., 2002). In order to identify heterogeneity between study designs, the present study selected study design *a priori* as a moderator of interest.

Results were converted to the standardized mean difference (Hedge's *g*) for comparing across studies. 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 calculated by taking *d*, which is the difference of group means divided by the pooled within group standard deviation (Borenstein, Hedges, Higgins, & Rothstein, 2009; Hedges, 1981; Lipsey & Wilson, 2001), then multiplying by the coefficient *J*, a correction factor to account for small sample bias (Borenstein et al., 2009). Considering most of the included studies used a within-subjects or crossover design, it is important to note that the calculation of effect sizes from these studies require a different set of formulas 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). The particular equations used to

calculate Hedge's *g* for between-subjects or parallel designs and within-subjects or

crossover designs can be accessed in the Appendix (see Supplementary Tables S2a and

S2b).

   Assumption of Independence. Meta-analysis relies on the assumption that each

measure of effect is representative of independent studies. Most studies investigating

prescription stimulant effects reported findings from multiple outcomes, however,

yielding a potential for multiple effect size estimates. Therefore, a protocol to handle

studies with more than one effect size was used and guidelines can be found in the

appendix (Supplementary Table S3).

   Meta-analytic Technique. 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).

   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). A statistically significant *Q* is

indicative of a heterogeneous distribution, signaling the potential to test for moderators

(Lipsey & Wilson, 2001). The I^2 statistic is an index between 0 and 100% and is used as an estimate for the amount of statistical impact of heterogeneity on the total observed variation (Borenstein et al., 2009). Higgins, Thompson, Deeks, and Altman (2003) have suggested heterogeneity can be interpreted as low ($I^2 = 25\%$), moderate ($I^2 = 50\%$), or high ($I^2 = 75\%$).

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 (see Supplementary Tables S4a, S4b, S4c, and S4d). Note that for the present study, a decision to retain all studies in the subsequent analyses was made considering their minimal effects on mean effect sizes.

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 in which data were not available for effect size calculations were excluded from the final analysis. Case analysis for studies that did report moderator data was employed. A decision to omit data, as opposed to imputing data, was made given the limited number of studies examining prescription stimulant effects in the selected areas of cognition.

Finally, six different methods were used 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 (inclusion of non-behavioral measure) as a moderating variable.

      Statistical Tests of Moderators. Statistical tests of moderators were conducted for variables identified *a priori* as described previously, 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) using mixed effects models were run for tests of moderators.

Results

Search results

      A total of 1,296 titles were initially identified via the bibliographic databases PsycINFO (257) and Pubmed (1039), including journal articles and book chapters (1273) and dissertations (23). A total of 21 studies met eligibility criteria of which 16 studies had sufficient data to calculate effect sizes met and were included in this study (see Table 2). Of these, 8 studies with a total of 345 participants examined prescription stimulant effects on processing speed, 5 studies with a total of 152 participants examined prescription stimulant effects on planning and decision-making, and 6 studies with a total of 337 participants examined cognitive perseveration. A total of 10 studies examined the effects of AMP and 6 studies examined the effects of MPH. Note that while eligibility criteria allowed for both short-acting and long-acting agents, all of the included studies examined short-acting agents.

Stimulant effects on processing speed accuracy

Data were extracted from 8 studies that investigated the neurocognitive effects of prescription stimulant medication on processing speed using a crossover design, resulting in a total of 345 participants (see Figure 1). When all doses were averaged together, under the random effects model, the studies generated a statistically significant mean effect size of g =0.282 (95% CI 0.077, 0.488, p = .007), with effect sizes ranging between g = −0.061 to g = 0.645. The heterogeneity of variance analysis was significant, Q (7) = 73.276 [I^2 = 90.447], p <.001, indicating significant between-study variance.

Analysis of publication bias indicated minimal risk with a Rosenthal's N of 218 to lead to a p-value at or above an alpha of .05 and an Orwin's N of 22 to reduce the measure of effect to 0.10. Under the random effects model, trim and fill analysis suggested the imputation of 4 studies to reduce *negative bias* resulting in an increased effect size of g = 0.518 (95% CI 0.310, 0.726) (see Supplementary Figure 1) and Egger's regression was significant [B = −5.305, SE = 1.918, $t(6)$ = 2.766, 95% CI −9.998, 0.612, p = .032]. Five studies were excluded from the analysis because they did not have sufficient data to calculate effect sizes. Findings from these studies were mixed; three studies reported null findings (Crabbe et al., 1983; Holdstock & de Wit, 2001; Kennedy, Odenheimer, Baltzley, Dunlap, & Wood, 1990), one study reported positive findings (Hamidovic, Dlugos, Palmer, & de Wit, 2010), and the final study reported negative findings (i.e., MPH was associated with a reduction in processing speed accuracy; Kollins, Rush, Pazzaglia, & Ali, 1998). These findings suggest minimal risk of positive publication bias within analyses examining processing speed.

The significant Q statistic indicated between study variance so moderator analyses were conducted. None of the moderators demonstrated significant differences through metaregression or ANOVA analog.

Stimulant effects on planning time, planning accuracy, and advantageous decision-making

Stimulant effects on tendency to choose advantageously. Data were extracted from 2 studies that investigated the neurocognitive effects of prescription stimulant medication on tendency to choose advantageously, resulting in a total of 44 participants (see Figure 2). When all doses were averaged together, under the random effects model, the studies generated a mean effect size of $g = -0.191$ (95% CI $-0.561, 0.180, p = .313$). The heterogeneity of variance analysis was not significant, $Q(1) = 0.204$ [$I^2 = 0.000$], $p =.656$, indicating minimal between-study variance. ANOVA analog did not reveal significant differences between the study using a parallel design ($g = -.045$; Agay et al., 2010) and the study using a crossover design ($g = -0.241$; Agay et al., 2014), $Q(1) = 0.204$, $p = .652$. Given the effect size for tendency to choose advantageously was not statistically significant and the small number of studies included in the analysis, analysis of publication bias and moderator analyses were not conducted.

Stimulant effects on planning accuracy. Data were extracted from 2 studies that investigated the neurocognitive effects of prescription stimulant medication on planning accuracy, resulting in a total of 79 participants (see Figure 3). When all doses were averaged together, under the random effects model, the studies generated a mean effect size of $g =0.048$ (95% CI $-0.194, 0.290$), $p = .698$) that was not statistically significant, with effect sizes ranging from $g = 0.024$ to $g = 0.146$. The heterogeneity of variance

analysis was not significant, Q (1) = 0.150 [I^2 = 0.000], p =.698, indicating minimal

between-study variance. ANOVA analog did not reveal significant differences between

effect sizes from the study using a parallel design (g = 0.146; Turner et al., 2003) and the

study using a crossover design (g = 0.024; Linssen et al., 2012), Q(1) = 0.150, p = .698.

Publication bias and further moderator analyses were not conducted due to the small

number of studies and minimal between-study variance.

Stimulant effects on planning time. Data were extracted from 3 studies that

investigated the neurocognitive effects of prescription stimulant medication on planning

time, resulting in a total of 107 participants (see Figure 4). When all doses were averaged

together, under the random effects model, the studies generated a mean effect size of g =

−0.140 (95% CI −0.383, 0.102, p = .257) that was not statistically significant, with effect

sizes ranging from g = -0.561 to g = 0.006. The heterogeneity of variance analysis was

not significant, Q (2) = 3.452 [I^2 = 42.062], p =.178.

Given the effect size for planning time was not statistically significant, analysis of

publication bias with Rosenthal's N and Orwin's N was not conducted. Trim and fill

analysis indicated the imputation of 2 studies to reduce *negative bias* resulting in an

effect size approaching 0, g = 0.006 (95% CI −0.237, 0.248) (see Supplementary Figure

2). Egger's regression was not significant [B = -3.386, SE = 1.020, t(1) = 3.319, 95% CI

−16.350, 9.578, p = .186]. These findings suggest minimal risk of publication bias within

analyses examining planning and decision time. ANOVA analog examining differences

between effect sizes from the study using a parallel design (g = -0.561; Turner et al.,

2003) and the two studies using a crossover design (g = -0.060; Elliott et al., 1997;

Linssen et al., 2012) was not significant, Q(1) = 2.808, p = .094. Given the small number

of studies available for analyses and the minimal heterogeneity between studies,

additional moderator analyses were not conducted.

Stimulant effects on cognitive perseveration

Data were extracted from 6 studies that investigated the neurocognitive effects of

prescription stimulants on perseveration, resulting in a total of 337 participants (see

Figure 5). When all doses were averaged together, under the random effects model, the

studies generated a mean effect size of $g = 0.003$ (95% CI $-0.095, 0.101$), $p = .949$) that

was not statistically significant, with effect sizes ranging from $g = -0.138$ to g $= 0.254$.

The heterogeneity of variance analysis was not significant, Q (5) $= 2.866$ [$I^2 = 0$], $p =$

.721.

Given the effect size for cognitive perseveration was not statistically significant,

analysis of publication bias with Rosenthal's *N* and Orwin's *N* was not conducted. Trim

and fill analysis indicated the imputation of 3 studies to reduce *negative bias* resulting in

a negative effect size of $g = -0.021$ (95% CI $-0.114, 0.072$) (see Supplementary Figure

3). Egger's regression was not significant [$B = 0.684$, $SE = 0.495$, $t(4) = 1.381$, 95% CI

$-0.691, 2.060, p = .239$]. These findings suggest minimal risk of publication bias within

analyses examining cognitive perseveration. ANOVA analog did not reveal significant

differences between effect sizes based on study design, $Q(1) = 1.206$, $p = .272$, in which

two studies used a parallel design ($g = 0.236$) and four studies used a crossover design (g

$= -0.010$). The overall Q statistic was not significant, indicating minimal between study

variance so additional moderator analyses were not conducted.

Discussion

The primary indications for ADHD prescription stimulant medication (e.g., Adderall, Ritalin, Dexedrine) are for the reduction of ADHD symptoms including impulsivity, hyperactivity, inattention. A, n increasing number of college students and non-student adults with and without ADHD, however, have reported misusing these medications to enhance their academic functioning or productivity. Previous research examining the effects of prescription stimulant medication on cognition has typically relied on small sample sizes and yielded mixed results. Therefore, the present study conducted 15 meta-analyses to explore the potential for prescription stimulant medication as a neurocognitive enhancer, as well as influencing factors associated with its neurocognitive effects.

Consistent with our primary hypothesis, prescription stimulant medication showed consistent and positive effects for increasing processing accuracy ($g = 0.282$). Study results for processing speed did not differ by dose level or across samples of varying ages or gender distributions. This finding is consistent with previous meta-analytic study findings that these medications have small and significant effects on other abilities of focused attention. Specifically, benefits from prescription stimulants in the areas of working memory ($g = 0.13$), inhibitory control ($g = 0.20$) (Illieva et al., 2015), and measures of vigilance (Riccio et al.,2001) have been reported in the literature.

Previous researchers have questioned if prescription stimulants are associated with *impairments* of other components of cognition such as cognitive flexibility or perseveration (Advokat, 2010; Smith & Farah, 2011; Weyandt et al., 2013). Contrary to our hypothesis, the present study did not support the association of prescription stimulants with impairments in the area of cognitive perseveration ($g = 0.003$). Results

also revealed non-significant effects for tendency to choose advantageously ($g = -0.191$),

planning accuracy ($g = 0.048$), and planning time ($g = -0.140$). It is important to note,

however, that the small number of studies investigating these outcomes limit the

interpretation of these findings. Indeed, the analysis examining the effects of MPH relied

on a combined sample size of $n = 44$ among only 2 studies and resulted in a small

negative effect size. One of these studies (Agay, 2014) also reported that participants

with low performance at baseline tended to improve and those with high performance

tended to demonstrate impairments. Unfortunately, due to the limited number of studies

examining the effects of prescription stimulants on planning time, planning accuracy, and

advantageous decision-making, analyses exploring moderator variables were not

conducted in the present study. Thus, adequately powered studies that also take into

accounts individual differences are needed to fully understand if prescription stimulants

truly cause impairments to decision-making.

Implications

Even with findings supporting significant effects of prescription stimulant

medication on processing speed accuracy, the question remains as to how meaningful

these effects are in settings outside of the laboratory. In particular, are these effects

meaningful for college students engaging in illicit stimulant misuse for academic

purposes and non-student adults misusing stimulants for productivity? The included

studies conducted cognitive assessments in research laboratories, providing an

environment quite unlike one in which college students and other adults would normally

work, study, read or write. In fact, research accumulated over the past three decades has

suggested prescription stimulant medication results in minimal to no effects on the

overall academic achievement in children with ADHD, even though it may increase

attention and improve productivity, (Advokat, 2010; Lakhan & Kirchgessner, 2012).

Studies that directly investigate the neurocognitive effects of prescription stimulant

medication on academic tasks and work productivity will help shed light on how

meaningful the effects found in the present study are regarding prescription stimulant

misuse.

Another important consideration is the wide range of medication doses included

in the present study that may not reflect the levels of medication college students and

other adults are misusing. The literature on prescription stimulant misuse does not

provide an indication of the typical dose being misused; however, 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. If varying

doses also result in cognitive impairments (or worse, adverse health outcomes), college

students and other adults would benefit from safety information and efficacy information

regarding prescription stimulant medication dose. Future studies investigating

prescription stimulant effects on tasks involving actual academic assignments (e.g., essay

composition, calculus problems) or work productivity, comparing doses optimal for

behavior improvement to lower doses in adult populations would shed light on this issue

(Weyandt et al, 2013; Weyandt et al., 2014).

Of note, there are a number of interventions being explored for their potential as

cognitive neuroenhancers for processing speed that could serve as an alternative to

prescription stimulant medication, including video games (between $d = 0.48$ to $d = 1.47$;

Dye, Green, & Bavelier, 2009), and exercise ($d = 0.091$;Chang, Labban, Gapin, & Etnier,

2012). Although the present study's findings revealed smaller effect sizes from prescription stimulant medication for processing speed enhancement than the previously described video game 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.

Methodological Considerations

The present study has a number of strengths that support its contribution towards uncovering the potential of prescription stimulant medication as a neurocognitive enhancer. 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 prescription stimulant medication on cognitive perseveration, planning and decision-making. Importantly, a major strength of the present study involved the well-established methodology applied to calculate mean effect sizes and test for moderator variables. It is particularly important to emphasize that previous studies examining the neurocognitive effects of prescription stimulant medication have relied on sample sizes that were likely underpowered. Indeed, the 16 studies included in the present study relied on small sample sizes (mean $n = 35$) 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, contributes substantially to the literature.

A number of limitations are also important to note, however, relating to the study's design and methodology and studies investigating the cognitive effects of prescription stimulant 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, 1998). For example, the inclusion of one study (Turner et al., 2003) that focused on healthy elderly males may represent findings relevant only to elderly populations and limits the generalizability of this study. Additionally, meta-analysis is plagued by issues of limited power for moderator variable detection (Hedges & Pigott, 2004). The absence of significant moderator variables in the present study may reflect a lack of power as opposed to lack of variability.

A related issue that is often raised regarding meta-analyses is the potential influence of publication bias on meta-analytic findings. Because methods to measure and minimize publication bias may require a larger number of studies than included in the present study, we utilized a wide range of techniques (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) to account for this limitation. Findings from publication bias analyses suggested that in general the included studies tended towards negative bias. In other words, the present study may have overrepresented smaller and more negative effects in the literature as opposed to larger and positive effects, which are typically associated with publication bias. Still, a concern regarding the exclusion of missing data should be noted.

Previous meta-analyses examining the efficacy of prescription stimulant 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 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.

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, Mollica, Maruff, & Snyder, 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. In order to account for variability, the present study only included studies meeting more rigid criteria (e.g., specific measures only).

Finally, although meta-analysis is a powerful method that may help uncover the true effect of an 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). Although the present study used specific inclusion criteria to select studies meeting standards of quality, a wide variety of study designs and study methodology were included. It is important to note that study design was selected *a priori* as a moderator variable and differences in effect sizes across parallel and crossover studies were not found; however, the small number of included studies also limited these analyses.

Finally, a critically important limitation in this literature was the omission of reporting participant ethnicity across most studies. It is unclear why so few studies investigating the cognitive effects of prescription stimulant medication reported participant ethnicity, but it will be important for future research to include more ethnically diverse populations.

Future Research

The present findings suggest that prescription stimulant medication may act as a neurocognitive enhancer of processing speed without impeding other domains of cognition such as flexibility. 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 prescription stimulant 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 prescription stimulant medication for cognitive enhancement. The potential for moderating effects of participant characteristics, particularly baseline cognitive functioning and related genotype variability, need to be clarified. If only adults with

lower baseline cognitive functioning scores or those homozygous to a particular genotype receive neurocognitive benefits from prescription stimulants many adults misusing prescription stimulants are taking unnecessary risks with minimal results. Or worse, if prescription stimulant medication actually impairs cognitive functioning in certain individuals, some adults may actually be worsening their ability to engage in higher-level learning.

Although the present study's findings are clinically and empirically important, limitations related to the external validity of the included measures limit the finding's generalizability to populations in academic settings. More specifically, research examining representative populations of college students will directly inform the potential enhancement or impairments associated with prescription stimulant misuse during late adolescence and early adulthood. Considering the neurodevelopmental changes that occur during late adolescence and early adulthood, findings from the present study that included adults across a range of ages may not adequately represent the manner in which prescription stimulant misuse impacts cognition in college aged populations.

The present study addressed cognitive constructs not previously studied, but additional areas of cognition should also be investigated in relation to prescription stimulant medication. For example, prescription stimulant 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). Additional measures of processing speed (e.g., continuous performance tasks, response time for item recognition tasks) should also be examined to validate the present study's findings that prescription stimulants may proffer benefits for

processing speed accuracy. Furthermore, the finding that prescription stimulant medication did not result in effect sizes significantly different than zero on tasks of planning time and accuracy, advantageous decision-making, and cognitive perseveration 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 prescription stimulant medication on neurocognitive enhancement. Sample sizes of the studies included in the present investigation ranged from $n = 6$ to $n = 192$; however, the vast majority of studies ($k = 11$, 68.75%) 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 prescription stimulant medication have been greatly underpowered. Given this serious limitation in the literature, future studies should reference findings from existing meta-analyses as guides when determining required sample sizes.

Future Directions

A number of ethical and social issues related to prescription stimulant medication as a neurocognitive enhancer have garnered attention in the literature (e.g., Dubljević, 2013; Farah, 2004; Goodman, 2010). 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 academic dishonesty are analogous to 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. Yet, pharmacological enhancement is not unique to the area of cognition as it is already being used to control mood, sleep, appetite and sex (Farah, 2004; Farah et al., 2004).

The present study's findings, in conjunction with previous research, indicate that prescription stimulant medication provides small, but significant cognitive effects across multiple domains of cognition, i.e., cognitive neuroenhancement. Irrespective of peoples' ethical and professional views on the issue, prescription stimulants are being used illegally for the purpose of cognitive neuroenhancement and at high rates across many college campuses. Therefore, the establishment of public policies surrounding this issue, whether restrictive or liberal, is of critical importance. An important policy consideration concerns the abuse potential of prescription stimulants among healthy college students and non-student adults. Evidence supports that both AMP and MPH hold a high abuse potential for physiological and/or psychological dependence, but instances of abuse among ADHD populations are actually rare (Kollins, 2007). To date, the literature on prescription stimulant misuse has largely focused on prevalence rates and adult characteristics associated with misuse. Research examining the potential for psychological and physical abuse of these drugs among healthy adults is sorely needed to inform the development of public policy concerning this issue. As Farah and colleagues (2004) 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). The answer to this question needs to be informed by collaborative efforts across the sciences. The interdisciplinary nature of this public policy issue is clear, as cognitive effects and potential for abuse from prescription stimulants likely depend on the interplay of individual characteristics (i.e., genetic variability), pharmacological mechanisms and actions, and cognitive effects encompassing behavioral science and behavioral neuroscience.

Conclusion

The present study supports the effectiveness of prescription stimulant medication for neurocognitive enhancement of processing speed accuracy in the adult population. While preliminary findings also indicate prescription stimulant medication does not appear to impair nor enhance planning, decision-making or cognitive perseveration, it is important to note that only a small number of studies addressed these outcomes. The present findings suggest that college students misusing prescription stimulants for academics and non-student adults misusing prescription stimulants for productivity may actually receive meaningful benefits. Further research is warranted, however, to investigate whether enhancement of tasks of cognition translate to boosts in academic grades in the college setting or increased productivity in the workplace. Public policy informed by collaborations across the sciences that addresses the use of prescription stimulant medication for neurocognitive enhancement is needed given the interdisciplinary nature of this topic.

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Figure Legends

Figure 1. Overview of meta-analysis of processing speed accuracy. Eight studies examining effects of amphetamine on processing speed accuracy; Summary Cohen's *d* calculated with random effects model.

Figure 2. Overview of meta-analysis of tendency to choose advantageously. Two studies examining effects of methylphenidate effects on tendency to choose advantageously; Summary Cohen's *d* calculated with random effects model.

Figure 3. Overview of meta-analysis of planning accuracy. Two studies examining effects of methylphenidate effects on planning accuracy; Summary Cohen's *d* calculated with random effects model.

Figure 4. Overview of meta-analysis of planning time. Two studies examining effects of methylphenidate effects on planning time; Summary Cohen's *d* calculated with random effects model; RT = response time.

Figure 5. Overview of meta-analysis of cognitive perseveration. Six studies examining effects of amphetamine and methylphenidate effects on cognitive perseveration; Summary Cohen's *d* calculated with random effects model; ED = Extra dimensional.