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Neuropsychological Functioning in College Students Who Misuse Prescription Stimulants

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Background and Objectives: Relatively little is known about the neuropsychological profiles of college students who misuse prescription stimulant medications.
Methods: Data presented are from college students aged 18–28 years who misused prescription stimulants prescribed for attention-deficit/hyperactivity disorder and controls (no prescription stimulant misuse). Students were assessed neuropsychologically using the self-report Behavioral Rating Inventory of Executive Functioning (BRIEF-A), the Cambridge Automated Neuropsychological Test and Battery (CANTAB), and other tests of cognitive functioning. The analyses included 198 controls (age 20.7 ± 2.6 years) and 100 prescription stimulant misusers (age 20.7 ± 1.7 years).
Results: On the BRIEF-A, misusers were more likely than controls to endorse greater dysfunction on 8 of 12 measures including Inhibition, Self Monitor, Initiation, Working Memory, and Plan/Organize, when adjusting for race and sex (all p's $< .05$). Similarly, when dichotomizing the BRIEF-A as abnormal (T score ≥ 65), misusers had more abnormalities on five of nine subscales, as well as all major indices (p's $< .05$). Misusers also performed worse on several subtests of the CANTAB and standardized cognitive battery (p's $< .05$). A proxy of prescription stimulant misuse frequency was positively correlated with greater executive dysfunction on the BRIEF-A.
Discussion and Conclusions: These data demonstrate elevated risk for neuropsychological dysfunction among students who misuse prescription stimulants compared to non-misusing peers. The presence of ADHD contributed significantly to these cognitive findings. Students who misuse prescription stimulants should be screened for neuropsychological dysfunction.
Scientific Significance: These data may better elucidate the neuropsychological profile of college-aged prescription stimulant misusers. (Am J Addict 2017;26:379–387)

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INTRODUCTION

Stimulant medications continue to be among the first line agents for attention-deficit/hyperactivity disorder (ADHD) in older adolescents, and young adults.[1] Many of the 4% to 5% of college students with ADHD[2] receive stimulants,[3] and stimulants are increasingly being diverted to those without a diagnosis of ADHD or a prescription.[4,5] Nonmedical use of prescription stimulants (eg, use without a prescription) has risen accordingly, and has become a public health concern.[6,7]

Several studies have shed light on the context of prescription stimulant misuse. For instance, data from McCabe et al.[8] suggest that stimulant misuse among high school students is associated with higher rates of alcohol and drug use. Similarly, investigations in older populations provide evidence that prescription stimulant misusers are more likely to meet full criteria for a substance use disorder (SUD).[9,10] In a 4-year prospective study, work by Arria et al.[9] demonstrated that the escalation of substance use problems was related to both declining class attendance and academic performance, as well as subsequent stimulant misuse. This association between academic difficulties and nonmedical prescription stimulant use is an outcome widely corroborated by others.[5,11–14]

Additional studies have shown that psychiatric disorders including depression[14,15] and ADHD[16] may be related to stimulant misuse. Arria et al.[17] reported significantly higher levels of ADHD symptoms among individuals with persistent, nonmedical prescription stimulant use throughout college, compared to both non-users of drugs or persistent marijuana users. Similarly, using blinded structured interviews, we recently reported a twofold risk for broad ADHD—inclusion of both subthreshold and threshold symptoms—associated with stimulant misuse in a college sample.[18]

These emerging data show compelling associations between stimulant misuse, ADHD symptomatology, SUD, academic decline, and other categorical psychiatric

diagnoses.[5,9,16,19] Prior work has focused on the potential cognitive enhancement of stimulants among healthy adults, but there is a paucity of data on the occurrence and nature of cognitive dysfunction in prescription stimulant misusers. Despite speculation of "self medication" associated with prescription stimulant misuse,[20] relatively few data exist on the subjective and objective neuropsychological functioning—particularly executive functioning—in traditional college-aged students who report misusing stimulants. One study ($N = 305$) in a college setting showed a positive association between self-reported executive dysfunction and prescription stimulant misuse.[21] While useful, this thesis on a small sample of actual stimulant misusers ($N = 58$) necessitates replication with larger samples and more sophisticated definitions for neuropsychological functioning.

To this end, we now report on a controlled study of stimulant misuse in college students. The current investigation represents a planned, primary analysis of cognitive functioning among prescription stimulant misusing college students compared to their non-misusing peers. Based on past findings of higher ADHD rates[17,18,20] and lower academic performance[5,9,16] in stimulant misusers, we hypothesized that stimulant misusers would endorse higher rates of both cognitive dysfunction in general and executive dysfunction specifically, compared to college students who do not misuse stimulants. Furthermore, we hypothesized that stimulant misusers would exhibit greater deficits on both subjective, self-report measures and objective tests of neuropsychological functioning. We also sought to replicate findings of lower academic performance in misusers compared to their non-misusing peers.

METHODS

Details of the study are presented elsewhere.[18] Briefly, we recruited 100 subjects who were not currently receiving prescription stimulants therapeutically, but endorsed misusing a stimulant medication (*misusers*), and 200 subjects who similarly were not being treated with stimulant medication, and had never misused prescription stimulants (*controls*). A prior diagnosis of ADHD was not exclusionary for either group. For the purpose of this report, stimulant misuse was defined as the procurement and illicit use of another individual's prescription stimulant medication, or past misuse of one's own legal prescription (eg, using more than prescribed). Misusers and controls were categorized appropriately following a pre-screening questionnaire, in addition to specific prompts on the MGH Medication Misuse Assessment that queried for misuse of a legal stimulant prescription, or misuse of another individual's stimulant prescription. Of note, only a single incident of misuse was needed to categorize an individual as a misuser. Additionally, we were only concerned with those stimulants with FDA indications for ADHD, and did not investigate the misuse of modafinil, armodafinil, methamphetamine or other sympathomimetic amines (eg, cocaine, MDMA) or the misuse of non-stimulant ADHD medications.[22]

Subjects from both misuse and control groups were full-time undergraduate college students (18 and 28 years) in the Boston metropolitan area recruited by way of internet advertisements (eg, craigslist.com, myspace.com, etc.). Eligible individuals were contacted to complete a direct interview and self-report questionnaires. All subjects completed an informed consent to participate in the study. We obtained a federal release of confidentiality, and all aspects of the study were approved by the institutional review board.

Assessments

Neuropsychological Functioning

To assess clinical evidence of executive functioning, we used the Behavior Rating Inventory for Executive Function-Adult Version (BRIEF-A).[23] The BRIEF-A is a standardized self-report measure for adults 18–90 years that captures the behavioral manifestations of executive dysfunction across nine different subscales: Inhibit, Shift, Emotional Control, Self Monitor, Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials. The first four of the aforementioned nine scales comprise the higher-level Behavioral Regulation Index (BRI), which is a measure of an individual's ability to appropriately regulate behavioral and emotional responses. The remaining five scales comprise the Metacognition Index (MI), which assesses an individual's effective use of planning and organization to problem solve. When combined, the BRI and MI map onto the Global Executive Composite (GEC). Higher scores on any of the nine subscales, or the indices, are indicative of more severe executive dysfunction.

The BRIEF-A is a self-report scale comprised of 75 questions that are answered with a "Never," "Sometimes," or "Often" response. For example, the Self-Monitor subscale assesses aspects of interpersonal and social awareness and prompts the reader to answer how frequently he/she talks at inappropriate times, has difficulty reading others' feelings, does not understand why others might be upset, or says things without thinking, etc. Although there are nine subscales, questions are interspersed throughout and lack a visible demarcation indicating which subscale a question belongs to (eg, Self-Monitor draws from questions: 13, 23, 37, 50, 64, 70). The BRIEF-A has demonstrated reliability and validity across the major indices and composite subscales when assessing executive functioning in college students.[24]

Neuropsychological Assessment

For our neuropsychological assessment battery, we used The Cambridge Neuropsychological Test Automated Battery (CANTAB),[25] which is a computerized test system that assesses a range of executive functioning abilities: decision making and response control, attention, visual memory, semantic/verbal memory, and cognitive flexibility and planning. The CANTAB has demonstrated reliability when assessing cognitive functioning in substance-using patients.[26]

Subtests included the following: Spatial Working Memory (SWM), Verbal Recognition Memory (VRM), Stockings of Cambridge (SOC), Intra-Extra Dimensional Set Shifting (IED), Rapid Visual Information Processing (RVP), Affective Go/No-go (AGN), and Reaction Time (RTI).

For IQ, subjects completed the Wechsler Abbreviated Scale of Intelligence (WASI-II):[27] Vocabulary and Matrix Reasoning. Additional cognitive tests included the Wechsler Adult Intelligence Scale (WAIS-IV),[28] Wide Range Achievement Test (WRAT-III Math),[29] the Test of Word Reading Efficiency (TOWRE-II),[30] and the Delis–Kaplan Executive Functions Scale (DKEFS).[31] In total, administration time of the BRIEF-A, CANTAB, IQ testing, structured interview, and other self-report measures averaged between two and a half to four hours.

Frequency of Stimulant Misuse

Due to the heterogeneity of the misuse group (ie, some individuals may have only misused once or twice, while others may have misused many times) we were interested in comparing neuropsychological functioning of misusers with varying frequencies of stimulant misuse. Unfortunately, we did not have a question that specifically queried for lifetime frequency of stimulant misuse across our entire misuse sample. Instead, we derived *estimated* frequency of stimulant misuse using a single item from the previously described MGH Medication Misuse and Diversion Assessment.[18,32] The single item read; "On how many occasions have you bought or traded prescription ADHD medication that was not prescribed to you?" Subjects were demarcated based on lifetime frequency of misuse categorized as either: 1–5 times, 6–20 times, or 20+ times.

Statistical Analyses

We used the Student's *t*-test for continuous outcomes, the Wilcoxon rank-sum tests for SES, and Pearson's χ^2 for binary outcomes. Fisher's exact test was used in the event of small numbers. Linear and logistic regression were used to analyze the BRIEF-A and CANTAB. To determine whether sex affected the relationship between misusers and the endorsement of psychiatric disorders and SUD, we included the interaction term, misuse status-by-sex, in all models. If the interaction was not significant, we removed it from the analyses and collapsed the results; if it was significant we reported the results by sex. All statistical analyses were conducted using Stata 12.0. All tests were two-tailed with an alpha level set at .05 unless noted otherwise. Data are presented as mean ± standard deviation (SD) unless otherwise specified.

RESULTS

Clinical Characteristics of the Sample

As described previously,[18] our final sample included 100 stimulant misusers (age 20.7 ± 1.7 years) and 198 controls (age 20.7 ± 2.6 years)—a total of two controls from the originally recruited 200 were dropped a priori from the analysis due to incomplete data. There were no significant differences between misusers and controls in age, socioeconomic status (SES; 2.0 ± 1.0 vs $1.9 \pm .9$; $z = -.58$; $p = .57$), or gender (47% vs 41% male; $\chi^2 = .84$; $p = .36$). There were also no significant differences between misusers and controls regarding the repeating of a grade, special class accommodations, or extra help. We did find however, that misusers were more likely to be Caucasian than controls (84% vs 68%; $\chi^2 = 8.53$; $p = .03$). As a result, we adjusted for race across all analyses.

Clinical Evidence of Executive Functioning (BRIEF-A)

We first examined T-scores on the self-reported BRIEF-A, and found that stimulant misusers were more likely to endorse higher scores indicative of greater dysfunction in executive cognitive operations. Specifically, misusers endorsed a higher GEC ($p = .02$) when adjusting for race and sex (Table 1A). Misusers also manifested more dysfunction than controls on the BRI ($p = .03$) and MI ($p = .02$). Of the nine subscales that contribute to the GEC, misusers scored higher than controls on the following: Inhibition, Self Monitor, Initiation, Working Memory, and Plan/Organize (all p values $< .05$). When ADHD was included in the model, two indices (BRI, GEC) and three subscales (Self-Monitor, Initiation, Plan/Organize) lost statistical significance.

We next examined clinically relevant abnormalities on the BRIEF-A (ie, T scores ≥ 65). As seen in Table 1B, misusers were more likely to manifest clinical evidence of executive dysfunction than controls in multiple domains. More misusers than controls endorsed a T score ≥ 65 for the overall GEC, BRI, and MI (all p's $\leq .02$). Upon examination of the nine BRIEF-A subscales, more misusers than controls had clinically and statistically significant abnormalities (T score ≥ 65) for Inhibition, Initiation, Working Memory, Plan/Organize, and Task Monitor (all $p < .05$). When ADHD was included in the model, two indices (BRI, GEC) and two subscales (Working Memory, Task Monitor) on the BRIEF-A lost statistical significance.

Objective Neuropsychological Functioning (CANTAB)

We utilized the CANTAB to examine objective neuropsychological differences between stimulant misusers and controls. For the CANTAB, we found a significant sex interaction effect for Stockings of Cambridge (SOC): problems solved in minimum moves and Rapid Visual Information Processing (RVP) A' (Table 2). For the SOC, male misusers performed significantly worse compared to male controls, when adjusting for race ($p = .046$). When ADHD was added to the model, this subtest lost significance. Similarly, when adjusting for race, male misusers performed worse than male controls on the RVP

TABLE 1. Evaluation of clinically significant executive functioning on the Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) for prescription stimulant misusers versus controls

A. BRIEF-A (continuous)

	Misusers ($N = 100$)	Controls ($N = 197$)	
Subscale	T score ± SD	T score ± SD	Statistics
Inhibition	55.3 ± 12.2	50.9 ± 10.6	Beta: 4.5; 95% Confidence Interval (CI): 1.7, 7.2; $p = .001^{**}$
Shifting	51.7 ± 11.3	50.8 ± 10.3	Beta: 1.1; 95%CI: −1.5, 3.7; $p = .4$
Emotional control	48.4 ± 10.5	47.6 ± 10.3	Beta: 1.3; 95%CI: −1.2, 3.7; $p = .3$
Self monitor	49.3 ± 10.7	46.3 ± 9.9	Beta: 3.2; 95%CI: .7, 5.7; $p = .01^{*}$
Initiation	54.0 ± 12.2	51.4 ± 10.5	Beta: 2.8; 95%CI: .1, 5.5; $p = .04^{*}$
Working memory	56.0 ± 12.5	52.8 ± 10.7	Beta: 3.6; 95%CI: .8, 6.4; $p = .01^{**}$
Plan/organize	54.1 ± 12.3	50.6 ± 10.3	Beta: 3.3; 95%CI: .6, 6.0; $p = .02^{*}$
Task monitor	55.6 ± 12.3	53.0 ± 11.1	Beta: 2.8; 95%CI: −.07, 5.6; $p = .056$
Organization of material	52.5 ± 11.6	50.1 ± 10.9	Beta: 1.9; 95%CI: −.8, 4.6; $p = .18$
Index			
Metacognition (MI)	52.5 ± 10.5	49.6 ± 8.9	Beta: 2.9; 95%CI: .6, 5.2; $p = .02^{**}$
Behavioral Regulation (BRI)	49.1 ± 9.2	47.0 ± 8.0	Beta: 2.2; 95%CI: .2, 4.3; $p = .03^{*}$
Global Executive Composite (GEC)	50.9 ± 9.9	48.3 ± 8.4	Beta: 2.6; 95%CI: .4, 4.8; $p = .02^{*}$

B. BRIEF-A (dichotomous, >=65)[a]

	Misusers ($N = 100$)	Controls ($N = 197$)	
Subscale	N (%)	N (%)	Statistics
Inhibition	22 (22)	19 (10)	Odds Ratio (OR) = 2.7; 95% Confidence Interval (CI): 1.4, 5.3; $p = .005^{**}$
Shifting	14 (14)	18 (9)	OR: 1.8; 95%CI: .8, 3.8; $p = .15$
Emotional control	10 (10)	19 (10)	OR: 1.1; 95%CI: .5, 2.5; $p = .8$
Self monitor	10 (10)	10 (5)	OR: 2.1; 95%CI: .8, 5.4; $p = .1$
Initiation	21 (21)	19 (10)	OR: 2.5; 95%CI: 1.3, 5.1; $p = .008^{**}$
Working memory	24 (24)	31 (16)	OR: 1.9; 95%CI: 1.01, 3.5; $p = .05^{*}$
Plan/organize	25 (25)	20 (10)	OR: 2.7; 95%CI: 1.4, 5.2; $p = .003^{**}$
Task monitor	22 (22)	26 (13)	OR: 1.9; 95%CI: 1.0, 3.6; $p = .05^{*}$
Organization of material	17 (17)	21 (11)	OR: 1.6; 95%CI: .8, 3.2; $p = .2$
Index			
Metacognition (MI)	14 (14)	7 (4)	OR: 4.7; 95%CI: 1.8, 12.4; $p = .002^{**}$
Behavioral Regulation (BRI)	8 (8)	4 (2)	OR=4.9; 95%CI: 1.4, 17.5; $p = .01^{*}$
Global Executive Composite (GEC)	10 (10)	6 (3)	OR: 3.4; 95%CI: 1.2, 9.8; $p = .02^{*}$

[a]One subject did not complete the BRIEF.

$^{*}p$-value $> .05$ when ADHD was included in the model.

$^{**}p$-value $< .05$ when ADHD was included in the model.

test ($p = .007$) and significance remained after ADHD was added to the model.

Analyses focusing on the remaining tasks of the CANTAB revealed that misusers, compared to controls, were more likely to have a higher score for the median correct latency variable of the Affective Go/No-Go (AGN), when adjusting for race and gender ($p = .01$). We found no other significant associations (all p values $> .05$).

Additional Cognitive Battery

In addition to the CANTAB, a cognitive battery drawing from various standardized assessments was used to objectively assess neuropsychological performance (Table 3). There were no significant differences between misusers and controls regarding Full Scale IQ; however, misusers were more likely to score lower on the Digit Span ($p = .03$), and Letter Number Sequencing ($p = .01$) subtests, as well as the cumulative Working Memory

TABLE 2. Comparative performance of prescription stimulant misusers versus controls on the Cambridge Neuropsychological Test Automated Battery (CANTAB)[a]

	Misusers $N = 100$	Controls $N = 197$	
	Mean ± SD	Mean ± SD	Statistics
Verbal recognition memory (VRM)			
Free recall—total correct (immediate)	7.1 ± 1.9	7.4 ± 2	Beta: −.3; 95% Confidence Interval (CI): −.8, .1; $p = .16$
Recognition—total correct (immediate)	23.0 ± 1.1	23.2 ± 1.1	Beta: −.2; 95% CI: −.5, .1; $p = .16$
Recognition—total correct (delayed)	22.7 ± 1.5	22.8 ± 1.5	Beta: −.1; 95% CI: −.5, .2; $p = .44$
Spatial working memory (SWM)[b]			
Between errors	16.2 ± 12.9	15.4 ± 14.3	Beta: 2.4; 95% CI: −.9, 5.6; $p = .2$
Between errors z score	.9 ± .5	.9 ± .6	Beta: −.8; 95% CI: −.2, .5; $p = .2$
Strategy	27.8 ± 8.3	28.8 ± 7.1	Beta: −.4; 95% CI: −2.3, 1.4; $p = .6$
Strategy z score	.8 ± .9	.7 ± 1.0	Beta: −.5; 95% CI: −.3, .2; $p = .7$
Stockings of Cambridge (SOC)			
Male			
Problems solved in minimum moves	9.5 ± 1.7	10.1 ± 1.7	Beta: −.6; 95% CI: −1.3, −.01; $p = .046^{*}$
Problems solved in minimum moves z score	.7 ± .8	1.0 ± .8	Beta: −.3; 95% CI: −.6, −.005; $p = .046^{*}$
Female			
Problems solved in minimum moves	9.5 ± 1.8	9.0 ± 2.0	Beta: .5; 95% CI: −.1, 1.1; $p = .13$
Problems solved in minimum moves z score	.7 ± .9	.4 ± 1.0	Beta: .3; 95% CI: −.7, .6; $p = .13$
Intra-Extra Dimensional Set Shift (IED)			
Total errors (adjusted)	20.3 ± 18.1	21.7 ± 24.7	Beta: .03; 95% CI: −5.5, 5.6; $p = 1.0$
Total errors (adjusted) z score	.3 ± .5	.3 ± .7	Beta: −.0; 95% CI: −.2, .2; $p = 1.0$
Affective Go/No-Go (AGN)[c]			
Correct latency—median—positive	502 ± 63.4	485.2 ± 58	Beta: 18.7; 95% CI: 3.8, 33.6; $p = .01^{**}$
Correct latency—median—negative	503.4 ± 58.2	493.3 ± 62.8	Beta: 12; 95% CI: −3.4, 27.4; $p = .13$
Rapid Visual Information Processing (RVP)			
Response latency—median	397.2 ± 70.3	402.9 ± 94	Beta: −3.6; 95% CI: −25.1, 18; $p = .7$
Response latency—median z score	1.0 ± .7	.9 ± .9	Beta: .04; 95% CI: −.2, .2; $p = .7$
Male			
A'[d]	.89 ± .1	.94 ± .05	Beta: −.05; 95% CI: −.09, −.01; $p = .007^{**}$
A' z score	.12 ± .9	.37 ± .9	Beta: −.3; 95% CI: −.7, −.03; $p = .04^{**}$
Female			
A'[c]	.92 ± .07	.93 ± .05	Beta: −.005; 95% CI: −.02, .01; $p = .59$
A' z score	.24 ± .7	.18 ± .9	Beta: .05; 95% CI: −.2, .3; $p = .7$
Reaction Time (RTI)			
Five-choice reaction time—median	330.7 ± 79.2	327.5 ± 46.7	Beta: 6.6; 95% CI: −7.9, 21.1; $p = .4$
Five-choice reaction time—median z score	.5 ± 1.3	.6 ± .8	Beta: −.1; 95% CI: −.3, .1; $p = .4$
Simple reaction time—median	306.8 ± 66.4	304.2 ± 50	Beta: 5.1; 95% CI: −8.5, 18.7; $p = .5$
Simple reaction time—median z score	.3 ± .8	.3 ± .6	Beta: −.6; 95% CI: −.2, .1; $p = .5$
Five-choice error score—all	.1 ± .4	.1 ± .4	Beta: .005; 95% CI: −.1, .1; $p = .9$
Simple error score—all	.2 ± 1.0	.2 ± .6	Beta: −.01; 95% CI: −.2, .2; $p = .9$

[a]One subject was dropped from the analysis due to a missing test.
[b]Two subjects were dropped due to scores outside of the range of normal.
[c]Two subjects were dropped due to scores outside of the range of normal.
[d]Ten subjects were dropped due to scores outside of the range of normal.
$^{*}p$-value $> .05$ when ADHD included in the model.
$^{**}p$-value $< .05$ when ADHD included in the model.

index of the WAIS-IV, when adjusting for race and sex. All of the aforementioned differences on the WAIS-IV remained statistically significant after ADHD was added to the model. We found no other significant associations on the remaining subtests of the WRAT-III, TOWRE-II, and DKEFS (all p values $> .05$).

Frequency of Stimulant Misuse

We further examined a subset of 83 misusers who were divided into three groups based on lifetime frequency of buying or trading prescription stimulants: 1–5 times ($N = 53$), 6–20 times ($N = 23$), or 20+ times ($N = 7$). There was a significant, positive correlation between greater frequency of buying or trading prescription stimulants and self-reported executive dysfunction on all subscales and indices of the BRIEF-A ($p < .05$) (Table 4), excluding Task Monitor.

DISCUSSION

Our current data support our hypothesis that despite similar intelligence, college-aged stimulant misusers have more evidence of neuropsychological dysfunction in general, and clinical executive dysfunction specifically, compared to their non-misusing peers. The amount of misuse appears connected to the severity of executive functioning difficulties. Due to the cross-sectional nature of the sample and high rates of confounders such as ADHD and SUDs—independently linked to neuropsychological dysfunction[33,34]—the directionality or mechanism(s) of risk of cognitive deficits are outside of the scope of this study and need to be further examined.

Our finding of more executive dysfunction in stimulant misusers compared to controls supports prior work conducted with a smaller sample,[21] in addition to extending the work of others who have shown ADHD symptomatology, academic decline and performance issues related to stimulant misuse.[5,9,16,18] In fact, the twofold risk for broad ADHD among misusers previously reported in this sample (misusers 27% vs controls 16%), combined with the loss of significance for a range of subtests when covarying by ADHD, suggests that ADHD symptomatology contributed substantially to the neuropsychological dysfunction among misusers. Irrespective of the origin of the observed neuropsychological deficits (eg, due to ADHD, SUD, other psychopathology) these data are among the first to report simultaneously on subjectively and objectively derived cognitive dysfunction in young adults who engage in the misuse of prescription stimulants used for the treatment of ADHD.

Self-reported levels of dimensionally rated executive dysfunction were significantly greater among stimulant misusers compared to controls on the three major indices of the BRIEF-A (ie, GEC, BRI, and MI), and five of the nine subscales (Table 1A). Elevated scores on the BRI for this sample suggest stimulant misusers are more likely to suffer from an impaired ability to both monitor the self and situation for what are considered to be acceptable social behaviors and to inhibit impulsive reactions. Elevated scores on the MI, which remained significant even when covarying by ADHD, suggest that when stimulant misusers are presented with a problem, they are less adept at maintaining and organizing information in working memory, strategically planning and executing a response, and making necessary changes based on the outcome. The breakdown of stimulant misusers versus controls with abnormal threshold of executive dysfunction (eg, T-scores ≥ 65) provides further insight into the self-perceived differential functioning between the two groups. Misusers not only scored dimensionally higher than controls on the aforementioned scales (Table 1A), but were also more likely to exhibit dysfunction at severe, clinically relevant levels ($T \geq 65$) (Table 1B).

TABLE 3. Scaled scores denoting cognitive functioning on the Wechsler Abbreviated Scale of Intelligence (WASI-II) and Wechsler Adult Intelligence Scale (WAIS-IV) for stimulant misusers versus controls

	Misusers ($N = 100$)	Controls ($N = 198$)	
WASI-II	Mean ± SD	Mean ± SD	Test statistics, p-value
Vocabulary scaled score	12.9 ± 2.1	13.2 ± 2.5	Beta: −.5; 95% Confidence Interval (CI): −1.1, .09; $p = .10$
Matrix scaled score	11.7 ± 1.8	11.5 ± 2.2	Beta: .1; 95% CI: −.4, .6; $p = .66$
Full scale IQ	113.0 ± 8.9	113.5 ± 11.2	Beta: −1.1; 95% CI: −3.7, 1.4; $p = .38$
WAIS-IV			
Digit span scaled score	10.8 ± 2.5	11.5 ± 3.0	Beta: −.8; 95% CI: −1.5, −.09; $p = .03$**
Arithmetic scaled score	12.1 ± 2.3	12.1 ± 2.5	Beta: −.1; 95% CI: −.7, .4; $p = .64$
Letter number scaled score	11.2 ± 2.3	11.9 ± 2.9	Beta: −.9; 95% CI: −1.5, −.2; $p = .01$**
Digit symbol scaled score	11.1 ± 2.6	11.5 ± 2.9	Beta: −.5; 95%CI: −1.2, .1; $p = .1$
Symbol search scaled score	12.7 ± 2.5	12.8 ± 3.2	Beta: −.2; 95% CI: −.9, .5; $p = .64$
Working memory	107.7 ± 11.3	110.7 ± 14.1	Beta: −3.9; 95% CI: −7.1, −.7; $p = .02$**
Processing speed	110.6 ± 12.9	111.9 ± 15.7	Beta: −1.9, 95% CI: −5.5, 1.6; $p = .3$

**p-value $< .05$ when ADHD was included in the model.

TABLE 4. Relationship between frequency of buying/trading prescription stimulants and clinical executive functioning measured by the Behavior Rating Inventory of Executive Functioning-Adult Version (BRIEF-A)

	1–5 times ($N=53$)	6–20 times ($N=23$)	20+ times ($N=7$)	F statistic, p-value
Subscale				
Inhibition	53.4 ± 11.3	56.7 ± 12.6	65.3 ± 13.6	$F=3.3$; $p=.041$
Shifting	50.5 ± 9.2	51.3 ± 12.5	61.4 ± 14.9	$F=3.2$; $p=.046$
Emotional control	45.5 ± 8.2	52.4 ± 12.7	56.1 ± 14.6	$F=6.0$; $p=.004$
Self monitor	48.3 ± 9.1	51.0 ± 12.1	60.7 ± 11.8	$F=4.7$; $p=.01$
Initiation	51.0 ± 9.9	54.6 ± 12.6	68.7 ± 11.8	$F=8.4$; $p<.001$
Working memory	54.9 ± 11.7	55.1 ±12.5	66.9 ± 13.4	$F=3.1$; $p=.049$
Plan/organize	51.4 ± 9.8	54.0 ± 13.2	69.4 ± 11.2	$F=8.4$; $p<.001$
Task monitor	54.7 ± 11.6	55.0 ± 12.9	63.6 ± 13.5	$F=1.7$; $p=.2$
Organization of material	50.8 ± 11.8	53.3 ± 9.9	63.1 ± 9.1	$F=3.9$; $p=.02$
Index				
Metacognition	50.5 ± 9.1	52.4 ± 10.5	64.7 ± 9.4	$F=6.9$; $p=.002$
Behavioral regulation	47.0 ± 7.4	51.2 ± 10.5	58.4 ± 12.3	$F=6.1$; $p=.004$
Global executive composite	48.9 ± 8.3	51.7 ± 10.1	62.4 ± 11.3	$F=7.1$; $p=.002$

Among misusers only ($N=83$) who answered the prompt, "On how many occasions have you bought or traded prescription ADHD medication that was not prescribed to you?" a linear association between prescription stimulant diversion frequency and T-score on the BRIEF-A subscales was observed.

Although we found relatively fewer major differences between misusers and controls on the objective CANTAB and IQ/cognitive tests, several measures were significant. For instance, in SOC in males, spatial planning difficulties were noted that have been related to frontal lobe dysfunction.[25,35,36] Prior work has linked frontal lobe dysfunction to cognitively impaired decision-making, response inhibition, planning, and memory.[37,38] Other objective findings indicated a decreased capacity for vigilance and sustained attention (male misusers), processing biases, and working memory difficulties in misusers—also substantiated by self report on the BRIEF-A. These findings have been linked to neuropsychological dysfunction, SUD,[39] risk for substance use in adolescence,[40,41] and affective disorders.[42,43]

Similar to Rabiner et al.,[16] we previously reported higher rates of ADHD among stimulant misusers in this sample.[18] The current data further suggest that misusers are at higher risk for deficits in attention and executive functioning—both of which have been independently related to SUD and academic underachievement in older adolescents and young adults.[44–46] While the directionality of the association remains unclear in our study, executive dysfunction appears linked to stimulant misuse. Due to the high rates of alcohol and drug use disorders among stimulant misusers in the current sample,[18] SUD may be contributory in part to the observed neuropsychological dysfunction. Further studies might aim to better elucidate the relative contributions of ADHD and SUD to the neuropsychological dysfunction of college-aged stimulant misusers.

We speculate that the cognitive impairment in this population likely represents a preexisting condition that misusers may attempt to reconcile by misusing prescription stimulants. The positive correlation in the current report between our proxy of stimulant misuse frequency and level of executive dysfunction, appears to support this supposition. Given the inherent pressures to perform academically in college, it is not altogether surprising that the nonmedical use of prescription stimulants represents one of the few substance use behaviors that is more prevalent among traditional-age college students relative to their same-age young adult peers not attending college.[6] Our findings, in conjunction with the literature, lend credibility to the notion that stimulant misusing college students may be self-medicating attentional difficulties, executive dysfunction, and academic impairment.

There are a number of limitations in the current report. Although the overwhelming majority of findings consistently trended in the direction predicted by our hypotheses, the risk for Type I error must be acknowledged due to the number of (sub)tests on the BRIEF-A, CANTAB and our cognitive battery. Statistical corrections were not conducted because of the cross-sectional nature of the study and in order to prevent the introduction of Type II error. The heterogeneous nature of our misuse group (ie, single misuse and 20+ incidents of lifetime misuse grouped together) likely resulted in an underestimation of effect sizes. Students were derived from the metropolitan Boston area and may not generalize to other regions. While the overall sample size was modest ($N=298$), the cell sizes in specific groups were relatively small, thus limiting our Power. Since we relied on self-report for some of our measures, our subjects may not have completed their questionnaires fully, and/or may have underreported their pathology. Additionally, we did not instruct misusers to abstain from nonmedical use of stimulants on the day of neuropsychological testing, although a minority of misusers reported current nonmedical use of prescription stimulants by way of self-report and scheduled interview. We did not account for the higher risk for ADHD in misusers versus controls; however, for these analyses, we were focused on cognitive dysfunction relative to stimulant misuse status and

not the role of ADHD. Our proxy of frequency of stimulant misuse was based on a single item from a questionnaire that indirectly evaluated this issue. Lastly, our data are cross-sectional, and as such, are associative in nature.

Despite these limitations, the current controlled study provides new information on the high rates of neuropsychological dysfunction in general, and executive dysfunction more specifically, in college students who misuse prescription stimulant medications. Our findings add to previous work linking high rates of ADHD and executive dysfunction to misuse of prescription stimulants, and highlight the need to clinically and scientifically further assess neuropsychological functioning in college students who misuse prescription stimulant medications.

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Declaration of Interest

Dr. Timothy Wilens receives or has received grant support from the following sources: NIH(NIDA). Dr. Timothy Wilens is or has been a consultant for: Euthymics/Neurovance, NIH(NIDA), Ironshore, Sunovion, TRIS; US National Football League (ERM Associates), U.S. Minor/Major League Baseball; Bay Cove Human Services and Phoenix House (Clinical Services). Dr. Timothy Wilens has a published book: *Straight Talk About Psychiatric Medications for Kids (Guilford Press)*; and co/edited books *ADHD in Children and Adults (Cambridge Press)*, *and Massachusetts General Hospital Comprehensive Clinical Psychiatry (Elsevier)*. Dr. Wilens is co/owner of a copyrighted diagnostic questionnaire (Before School Functioning Questionnaire). Dr. Wilens has a licensing agreement with Ironshore (BSFQ Questionnaire). Dr. Wilens is Chief, Division of Child and Adolescent Psychiatry and (Co) Director of the Center for Addiction Medicine at Massachusetts General Hospital. Dr. Amy Yule received grant support from the American Academy of Child and Adolescent Psychiatry Pilot Research Award for Junior Faculty supported by Lilly USA, LLC in 2012. She received grant support from the Massachusetts General Hospital Louis V. Gerstner III Research Scholar Award from 2014 to 2016. Dr. Yule is currently receiving funding through the American Academy of Child and Adolescent Psychiatry Physician Scientist Program in Substance Abuse K12DA000357-17. Dr. Ronna Fried is currently receiving research support from Lundbeck. In 2015, Dr. Fried received honoraria from the MGH Psychiatry Academy for tuition-funded CME course. During previous years, she received research support from the National Institutes of Health and Shire. The authors (Nicholas W. Carrellas, MaryKate Martelon, Rayce Anselmo, and Dr. Sean E. McCabe) report no conflict of interest.

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