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Mixed-amphetamine salts expectancies among college students: Is stimulant induced cognitive enhancement a placebo effect?

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ABSTRACT

Introduction: Non-medical use of prescription stimulants for cognitive enhancement in college students is increasing, despite evidence showing little benefit in non-clinical populations. The balanced placebo design (BPD) was used to independently evaluate the pharmacologic versus expectancy effects of mixed amphetamine salts on cognitive performance among a non-clinical sample of college-aged students.

Method: Participants were screened and excluded for ADHD and other psychopathologies. A non-clinical sample (N = 32) completed four two-hour laboratory sessions and were administered a neurocognitive battery in each session. Medication Assignment (10 mg mixed-amphetamine salt (Adderall™) versus placebo) was crossed with Instructional Set (deception versus truth). A within-subjects design was used, such that all participants experienced each of the four conditions of the BPD during one of the four laboratory sessions.

Results: Participants performed no better than chance in identifying whether they received stimulant or placebo (Belief about Medication Assignment; 47% agreement; $\kappa = -0.047$, $p = 0.590$). Participants showed improvement on only two of 31 subtests during active medication. Expecting and receiving stimulants was associated with improved cognitive performance. However, expecting placebo was associated with worse cognitive performance, regardless of the type of medication given.

Discussion: This study demonstrated that although non-medical use of stimulants does not enhance cognition, expectancies prominently influence cognitive performance. Participants who believed they received active medication both subjectively rated themselves as performing better and objectively performed better on a minority of subtests, independent of medication state.

1. Introduction

Non-medical use of prescription stimulant medications among student populations is increasing (Swanson and Volkow, 2008; Forlini and Racine, 2009). Youth exaggerate the cognitive enhancing value of prescription stimulants and overestimate the frequency with which fellow students use these medications (White et al., 2006). College students estimate that up to 70% of their fellow students currently use stimulants to augment academic performance when only approximately 4.1% report last year use and 2.1% last month use (McCabe, 2008; McCabe et al., 2005; White et al., 2006). Low performing students report the highest use of cognitive enhancing medications (Caviola and Faber, 2015; Repantis et al., 2011); however, positive cognitive improvement studies have shown limited benefits.

Comprehensive reviews of controlled trials exploring cognitive enhancement in healthy subjects dosed with methylphenidate or amphetamine salts found an equivalent degree of null findings and limited improvement on select measures (Ilieva et al., 2015; Repantis et al., 2011; Smiet and Farah et al., 2011; Franke et al., 2014). Similarly, cognitive enhancement studies have shown limited benefits on simple attention tasks, but no consistent benefit for complex learning tasks (Ilieva et al., 2015; Repantis et al., 2011; Linssen et al., 2014; Ilieva et al., 2013). Attention Deficit Hyperactivity Disorder (ADHD) was not carefully screened out in many of these studies and noted improvements may have been attributable to increased motivation and energy rather than enhanced episodic memory (Ilieva et al., 2015).

The use of stimulants among non-clinical students poses health risks (Franke et al., 2014; Linssen et al., 2014) and can even impair

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performance among high-performers (Finke et al., 2010; Mattay et al., 2000; Farah, 2015). Stimulant medications aggravate performance among individuals with adequate dopamine levels (Swanson et al., 2007; Pliszka 2005; Wilens, 2006). Cognitive enhancement by non-medical stimulant use may be a myth based on powerful peer-to-peer testimonies of students who are struggling academically or who have undiagnosed ADHD (Munro et al., 2017; van Rooij et al., 2015; Nigg et al., 2004; Keshavarzi et al., 2014; Reh et al., 2014; Rommelse et al., 2007) responding to accepted treatments (Overmeyer et al,. 2000; Swanson et al., 2007; Pliszka, 2005; Wilens, 2006).

The scientific community has not examined how stimulant-related expectancies influence cognitive enhancement in student populations (Franke et al., 2012). Studies of cognitive enhancement show a strong subjective belief in benefit of stimulant medication regardless of objective improvement on cognitive measures. A supra-therapeutic initial dose 20 mg of mixed-amphetamine salts showed no statistical benefit on 13 measures of cognitive ability on a SAT academic test, yet participants reported significant benefit (Ilieva et al., 2013). Looby and colleagues found enhancement of mood but no changes in cognitive performance in participants who were told they ingested a stimulant (Looby and Earleywine, 2011). Neuroimaging studies of placebo stimulant medication used in healthy individuals showed that the expectation of receiving a stimulant significantly modulated neurophysiological and neurochemical activity (Beauregard, 2007; Benedetti et al., 2005).

Overall, studies attributing cognitive enhancing properties to stimulants in non-clinical populations are limited (Advokat, 2010; Bagot and Kaminer, 2014; Ilieva et al., 2015; Smith and Farah, 2011). No previous studies have distinguished whether the partial cognitive benefits observed with stimulants arise from placebo expectation from the medication or true pharmacologically-induced performance enhancement. The balanced placebo design (BPD) has been utilized to separate the pharmacological effects versus expectations (Rohsenow and Marlatt, 1981; Juliano and Brandon, 2002; Kelemen and Kaighobadi, 2007). The BPD consists of four conditions in which drug dose (active vs. placebo) is crossed with instructional set (deception vs. truth). This results in two conditions in which participants are told the truth (given placebo/told placebo and given active/told active) as well as two conditions where participants are deceived (given placebo/told active and given active/told placebo). Due to the strong enhancement perceptions held by youth, the BPD will be especially useful to separate physiological versus expectancy effects from mixed-amphetamine salts. The added deception condition that goes beyond a traditional placebo design (i.e., told placebo but, given active) allows for the examination of physiological effects in the absence of any positive expectancies, and possibly in the presence of negative expectations. Therefore, the utilization of BPD with mixed-amphetamine salts will provide a novel examination with more complete separation between physiology versus expectation.

In the present study, the BPD was used to independently evaluate the pharmacological effects of mixed-amphetamine salts versus stimulant-related expectancies on cognitive performance among a non-clinical sample of college-aged students with vigorous efforts to exclude subclinical ADHD. We hypothesized that positive expectation of benefit and/or presence of stimulant would improve performance on attention measures, but that higher level cognitive functions will be unaffected by the presence of stimulant or stimulant-related expectancies. Additionally, we explored whether expectancies moderated instructional set for the cognitive enhancing properties of stimulants.

2. Methods

2.1. Participants

Thirty-nine participants were recruited from the University of Alabama at Birmingham campus. The inclusion criteria included: age 19–30-years-old, willingness to reduce caffeine intake to less than 100 mg on testing days in heavy caffeine users, adequate birth control, and at least average IQ. Exclusion criteria included: pregnancy; breast feeding; history of psychiatric conditions including ADHD or first degree relatives with ADHD; substance use disorders, prescription stimulant use or illicit stimulant use within one year; sleep disorders; contraindications to stimulants (i.e., tics, Tourette's, cardiac disease, hypertension); uncontrolled medical illnesses; or active contagious infection. This study received approval from the University of Alabama at Birmingham Institutional Review Board.

2.2. Measures

2.2.1. Demographics

A questionnaire assessed demographic information including race, age, gender, education level, socioeconomic status, and medical history

2.2.2. Psychopathology

ADHD symptomology was assessed with the ADHD Rating Scale-IV (ADHD-RS) using the appropriate adult prompts. The ADHD-RS is an 18-item, provider-administered questionnaire to diagnose ADHD symptom criteria derived from the DSM-IV (Spencer et al., 2010). (DSM-IV criteria are more rigourous for ADHD than DSM-5 criteria). Other psychological disorders were assessed with the MINI International Neuropsychiatric Interview (Lecrubier et al., 1997), which is a short semi-structured interview designed to screen for psychiatric disorders.

2.2.3. Stimulant expectancies

Participants' expectations regarding prescription stimulants were assessed with the Prescription Stimulant Expectancy Questionnaire II (PSEQ II). The PSEQ-II is a 45–item questionnaire and consists of four subscales: Cognitive Enhancement, Anxiety and Arousal, Social Enhancement, as well as Guilt and Dependence (Looby and Earleywine, 2010).

2.2.4. Cognitive measures

The Wechsler Test of Adult Reading (WTAR) was administered as an estimate of intellectual ability that correlates highly with standard tests of intelligence (Venegas and Clark, 2011). Verbal fluency was measured with the Controlled Oral Word Association Test (COWAT). The COWAT measures spontaneous production of words belonging to the same category or beginning with some designated letter. Memory was assessed with the California Verbal Learning Test-II (CVLT-II) and Wechsler Digit Span. The two versions (A and B) of the CVLT-II were administered on alternate weeks to assess short- and long-term memory.

Several measures were used to assess various components of attention. The Connors Continuous Performance Task (CPT) was administered to measure sustained and selective attention. The Stroop test measured selective attention cognitive processing speed, through inhibition of autonomic verbal processing. Trails A and B assessed executive functioning including attention, visual scanning, shifting set and cognitive flexibility, and psychomotor speed.

2.2.5. Subjective improvement

Participants were asked to rate their global impression and improvement based on perceived drug effect. The Clinical Global Impression-Improvement form consists of 2 items and each item is rated on a scale ranged from 1 (*much improved*) to 7 (*very much worse*).

2.2.6. Manipulation check

Belief about medication assessment was measured through a single question administered at the end of each testing period asking whether the patient believed they received a stimulant or placebo.