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Objective and subjective cognitive enhancing effects of mixed amphetamine salts in healthy people

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ABSTRACT

Psychostimulants such as mixed amphetamine salts (MAS, brand name Adderall) are widely used for cognitive enhancement by healthy young people, yet laboratory research on effectiveness has yielded variable results. The present study assessed the effects of MAS in healthy young adults with an adequately powered double-blind cross-over placebo-controlled trial. We examined effects in 13 measures of cognitive ability including episodic memory, working memory, inhibitory control, convergent creativity, intelligence and scholastic achievement, with the goals of determining (1) whether the drug is at least moderately enhancing (Cohen's $d >= .5$) to some or all cognitive abilities tested, (2) whether its effects on cognition are moderated by baseline ability or COMT genotype, and (3) whether it induces an illusory perception of cognitive enhancement. The results did not reveal enhancement of any cognitive abilities by MAS for participants in general. There was a suggestion of moderation of enhancement by baseline ability and COMT genotype in a minority of tasks, with MAS enhancing lower ability participants on word recall, embedded figures and Raven's Progressive Matrices. Despite the lack of enhancement observed for most measures and most participants, participants nevertheless believed their performance was more enhanced by the active capsule than by placebo. We conclude that MAS has no more than small effects on cognition in healthy young adults, although users may perceive the drug as enhancing their cognition.

This article is part of a Special Issue entitled 'Cognitive Enhancers'.

1. Introduction

Cognitive enhancement refers to the use of neuropsychological drugs, most commonly psychostimulants such as amphetamine and methyphenidate, by cognitively normal, healthy people to improve cognitive function. Evidence suggests that enhancement is a common practice and may be gaining in popularity. A study on a large 2001 sample of undergraduate programs including institutions of different size, location, religious affiliation and private/public status, showed an almost 7% lifetime prevalence of nonmedical stimulant use (McCabe et al., 2005). Although this study did not distinguish between cognitive enhancement and other nonmedical uses, more recent surveys of college students have done so and indicate that cognitive enhancement is the primary motivation for most students using stimulants (e.g., DeSantis et al., 2008; see Smith and Farah, 2011; for a review). These more recent studies also indicate substantially larger proportions of students using prescription stimulants compared to the McCabe and colleagues' estimates, although the samples have been smaller and less representative. Aside from college students, enhancement use of stimulants has also been reported among professionals from various fields (e.g., lawyers, journalists, Madrigal, 2008; Maher, 2008; Tablot, 2009).

1.1. Stimulants' actual cognitive enhancement effects

One possible reason for the growing enhancement use of stimulants is that the drugs truly improve cognitive abilities such as learning and executive function, presumably through their effects on catecholamine neurotransmission (Meyer and Quenzer, 2005). Yet, in the aggregate, the evidence supporting stimulants' beneficial effects on healthy cognition is mixed. For example, Chamberlain et al. (2010) reviewed studies in which CANTAB tasks had been used to assess stimulant effects in patients and healthy control participants. They concluded that "acute doses of medication improved aspects of cognition, though findings were more consistent in subjects with ADHD than in healthy volunteers." Reviewing the literature on the cognitive effects of

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methylphenidate, Repantis et al. (2010) state that they were "not able to provide sufficient evidence of positive effects in healthy individuals from objective tests." Similarly, Hall and Lucke (2010) state that "There is very weak evidence that putatively neuro-enhancing pharmaceuticals in fact enhance cognitive function." An even stronger view was presented by Advokat (2010), whose reading of the literature led her to suggest that "studies in non-ADHD adults suggest that stimulants may actually impair performance on tasks that require adaptation, flexibility and planning."

Most recently, Smith and Farah (2011) surveyed more than fifty experiments on the effects of amphetamine and methylphenidate on a wide array of cognitive functions, including memory (episodic memory, procedural memory and probabilistic learning) and executive functions (working memory, cognitive control) in healthy young adults. They discovered a roughly even mixture of significant enhancement effects and null findings overall. Studies on episodic memory tended to show an enhancing effect of stimulants when retention intervals were longer than an hour, whereas evidence for enhancement of other functions was less clear. For executive functions (including inhibitory control, working memory and other executive functions) many studies reported significant enhancing effects but some did not. In addition, when found, these effects were sometimes qualified by complex interactions between the order of drug and placebo administration, participants' cognitive performance on placebo, and participants' genotypes. The possibility that other null results have been found but not published (publication bias, also known as the "file drawer effect") must be considered. In sum, a number of recent reviews have concluded that the cognitive enhancement potential of stimulants has not received firm empirical support.

Several factors may explain the inconsistency between users' beliefs that stimulants enhance cognition and the equivocal evidence for these effects. One possibility is that the assessment of enhancement effects in the laboratory has been impeded by problems such as unmeasured moderators, poor measurement of moderators or low statistical power. These would be especially serious challenges to research in this area if the effects of stimulants are small and dependent on individual differences. Another possibility is that stimulants create a subjective perception of enhancement, possibly more salient and wide-spread than the actual effects. The rest of this section will elaborate on these potential explanations.

1.2. Challenges in assessing the enhancing effects of stimulants

Among the challenges standing in the way of settling the question of stimulants' enhancement potential are the following four. The majority of published studies fail to meet any of these challenges, and no study has so far been designed to address all four. These challenges motivate the design of the present double-blind, placebo controlled, cross-over trial on the cognitive enhancement effects of mixed ampheramine salts (MAS, brand name Adderall).

1.2.1. Moderation of enhancement effects by individual differences

One reason why previous research may have failed to detect significant evidence for enhancement is that stimulants may be effective for some individuals but not for others. Thus, studies that have not measured or analyzed the effect of moderating individual differences may have erroneously concluded that the effects are small or nonexistent. One candidate moderator is individuals' endogenous dopamine activity. The relationship between dopamine activity and cognitive performance is believed to follow an inverted U-shaped curve, in which intermediate dopamine levels are optimal for cognitive performance, whereas low and high levels are detrimental (Robbins and Arnsten, 2009). Therefore, individuals at different starting points on this curve would benefit differentially from the increase of dopamine activity caused by a dose of stimulant. Individuals with sub-optimal baseline dopamine levels would be moved upward on the curve to higher cognitive performance. By contrast, individuals with high baseline dopamine, standing at the peak or on the downward-sloping portion of the curve, would move downward in cognitive performance.

Several studies have provided evidence for the moderation of stimulant effects by endogenous dopamine activity, as indexed by participants' Catechol *O*-methyltransferase (COMT) genotype. A common polymorphism of the COMT gene determines the activity of the COMT enzyme, which breaks down dopamine and norepinephrine. Hence, the COMT genotype influences the level of synaptic dopamine. Mattay et al. (2003) have shown that individuals whose COMT genotype is associated with higher endogenous dopamine show less enhancement by amphetamine and in certain tasks may actually perform worse on the drug.

Another possible moderator of amphetamine's cognitive enhancing effects is cognitive ability. Several studies have found that participants who perform worse than average when on placebo are more likely to be enhanced by stimulants (Farah et al., 2008; de Wit et al., 2000, 2002; Mattay et al., 2000; Mehta et al., 2000). Findings of both COMT-moderated and performance-moderated enhancement suggest that some of the null results in literature may result from a mixture of true enhancing effects for some individuals and absent or even reversed effects for others. Measurement of these two potential moderating factors is therefore crucial for determining the true enhancement potential of stimulant drugs. In the present study we measure both.

1.2.2. Regression to mean and measurement of baseline performance

Baseline performance, as a moderator of enhancement, has typically been indexed by performance on placebo. This measure is problematic because of the phenomenon of regression to the mean. To the extent that there is measurement error in the data, participants who score well in the placebo condition would be expected to score less well on average in a different session, and participants who score poorly in the placebo condition would be expected to score somewhat better on average in a different session. Consequently, even in the absence of moderation by baseline, placebo scores may appear to moderate the difference between drug and placebo purely due to regression to the mean. For this reason, we obtain a measure of baseline ability that is independent from participants' performance on drug and placebo.

1.2.3. Moderation by order of drug administration

Some previous within-subjects trials on the effects of stimulants on cognition have unexpectedly revealed a third moderator of enhancement effects. In particular, significant enhancement effects on three different tasks have been observed when the drug was administered before placebo, but not after (Elliott et al., 1997). Such moderation is difficult to interpret; it might reflect a specificity of stimulant effects to novel tasks, or a specificity to more difficult tasks, or it may be a type II error. If order is not controlled and analyzed in within-subjects studies, the effects of stimulants could be inflated or diluted. Between-subjects studies are not free of this problem, as all participants effectively receive the drug or placebo first. If stimulant effects are fleeting, then single-session between-subjects studies would overestimate the effectiveness of the drug. Accordingly, in the present study we control for the order of drug administration both experimentally (i.e., by counterbalancing the variable between participants) and statistically.

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1.2.4. Statistical power

Insufficient statistical power to detect practically significant effects has been a major obstacle to discovering stimulants' cognitive enhancing properties. Most of the experiments reviewed by Smith and Farah (2011) used samples of fewer than 40 participants, many with between-subjects designs. The present within-subject study's sample size of 46 was chosen to give us 95% power to detect a medium-size effect (Cohen's $d = .5$) on any single measure.

1.3. Perceptions of enhancement

Another way to explain the discrepancy between the rising enhancement use and the inconclusive empirical evidence for its effectiveness would be to hypothesize an inconsistency between stimulants' perceived and actual effects on healthy cognition. Specifically, people may use stimulants for cognitive enhancement because they feel that the drugs improve their performance, even in the absence of actual effects. For this to be the case, two conditions need to be satisfied: first, participants must perceive their own performance as higher; second, they must attribute this higher performance to the drug.

Addressing the former condition, a number of studies have asked whether self-estimation of performance increases as a function of stimulants. This idea was first considered by researchers in the middle of the 20th century, motivated in part by concerns about amphetamine's effect on the judgment of military personnel. For example, Davis (1947) summarized his experience with British soldiers in World War II by writing that "the subject who has taken amphetamine usually judges the effects more favorably than the experimenter." Experimental evidence has provided converging support for this finding (Smith et al., 1964; Hurst et al., 1967; despite a null finding in Baranski and Pigeau, 1997). In Smith & Beecher's (1964) double-blind, placebo-controlled trial on amphetamine, participants took a calculus test. Although they overestimated their performance in both conditions, the magnitude of overestimation was significantly greater in the amphetamine group. In a recent study with modafinil, a nontraditional stimulant, Baranski et al. (2004) reported a trend toward more positive evaluation of performance with modafinil compared to placebo in a battery of cognitive tests. The idea that drug effects on subjective assessment of performance may interfere with our ability to judge drug effectiveness for cognitive enhancement was raised more recently by Hall and Lucke (2010) who pointed out that, when taken by healthy people, stimulants may inflate self-confidence, while failing to improve actual performance. Although previous research has reported some evidence for amphetamine's effects on self-evaluation, no research study, to our knowledge, has assessed whether participants specifically attribute this improved performance to the drug. Only if this is the case can the subjective drug effects explain the growing stimulant enhancement use in the absence of firm evidence for actual effects. For this reason, in addition to measuring the objective effects of the MAS on cognitive performance, we also obtained rating of subjective perceptions of the effects of the ingested pills.

1.4. The present study

The purpose of the present double-blind, placebo-controlled, crossover study was to examine the actual and perceived cognitive enhancing effects of MAS on healthy young adults who were not sleep-deprived. MAS is equivalent to the brand name drug Adderall, which has been characterized as the "drug of choice" for cognitive enhancement among college students (Desantis et al., 2009). We predicted that, relative to placebo, Adderall would improve performance on a wide range of cognitive functions, including episodic and working memory, inhibitory control and creativity, as well as performance on tasks based on standardized tests. We further expected that low cognitive performers, as well as carriers of the *val–val* variant of the COMT gene would benefit from the drug more that high performers and *met–met* carriers, respectively. An alternative hypothesis was that MAS might evoke a subjective perception of enhancement, more salient than the drug's actual enhancing effects. If substantiated, either of these predictions would provide a possible explanation of the growing psychostimulant use among healthy people.

2. Materials and methods

2.1. Participants

Participants were 46 Caucasian native English speakers (22 male and 24 female), aged 21–30 (M age = 24, $SD = 2.88$), who responded to advertisements posted in the area of Drexel University and the University of Pennsylvania, as well as to email announcements at the University of Pennsylvania, inviting participation in tests of memory, creativity, intelligence and personality. Participants were excluded if they reported a history of medical conditions contraindicated for stimulant use, including any neurological or psychiatric disease, seizure disorder, high blood pressure, glaucoma, gastrointestinal blockage, heart disease, or thyroid problems. Also excluded were participants using any other stimulants or substances that could interact with amphetamine, including addictive, psychoactive, neurological and blood-pressure drugs; anti-histamines; non-prescription dietary supplements; weight-loss pills; and caffeine consumption estimated to exceed 700 mg/day. Off-drug blood pressure measured to exceed 140/90 at the beginning of the study was another exclusion criterion because of the likelihood that the drug would increase blood pressure further. Women who were pregnant or likely to become pregnant were not allowed to participate. We also excluded potential participants who had previously used psychostimulant drugs to rule out sensitization (Paulson and Robinson, 1995) as an explanation for enhancement effects and tolerance (Schenk and Partridge, 1997) as an explanation for a lack of such effects.

2.2. Drug

20 mg of mixed amphetamine salts (sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and D, L-amphetamine aspartate monohydrate, with D-amphetamine and L-amphetamine in 3:1 ratio) and placebo were administered in visually indistinguishable capsules. The selected dose is within the range of doses used in the enhancement literature, with some studies using lower doses, some higher, and some equivalent (Smith and Farah, 2011). The test drug was supplied by the University of Pennsylvania Investigational Drug Service.

2.3. Tasks

There were three versions of each task, to avoid repetition of items or trial orders across baseline, placebo and MAS conditions. The three versions were of moderate and comparable difficulty as determined by pilot testing. One version was consistently used for the baseline condition while the other two versions were used equally often in the MAS and placebo conditions. The 13 measures are listed in Table 1 and are described here.

2.3.1. Memory

The consolidation of information into memory is central to learning and hence to academic and life success. Two tasks assessed memory with measures of verbal and visual recognition and verbal recall.

2.3.1.1. Face memory. In this test of episodic memory participants saw a sequence of 20 briefly flashed face images. Each stimulus was presented for 2250 ms, with an inter-trial interval of 750 ms. Encoding was followed by approximately 2 h of cognitive testing, after which participants completed a recognition test. This test consisted of the 20 previously presented targets intermixed with 20 new faces. Presentation duration and inter-trial interval at test were the same as those at the encoding phase. Our main dependent measure was number correct (total number correct out of total number of trials presented).

2.3.1.2. Word memory (two measures). Another test of episodic memory, this task presented participants with 25 words shown for 3 s each with no intertrial interval. After approximately 2 h performing other cognitive tasks, two measures of word memory were then obtained. In *word recall*, participants freely recalled as many words as possible. Performance was measured as number recalled. A *word recognition* test followed, in which participants viewed the 25 earlier words intermixed

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with 25 new words, presented in the same way as during encoding. The dependent measure in this case was number correct.

2.3.2. Working memory

Working memory is an aspect of executive function that involves active short-term maintenance of information and is essential for many forms of thinking and problem-solving. Two tasks assessed verbal and visual working memory.

Table 1
Drug Effect and Interactions, resulting from a series of 2 (Drug: MAS; Placebo) × 2 (Drug Order: MAS first; Placebo first) × 2 (Test Version Order: Version 1 first; Version 2 first) mixed-model ANOVAs with repeated measures on the first factor. The dependent variables were scores for 13 measures listed below.

Test (Measure)	Main/Interaction Effects	*df*[a]	*F*	*p*, uncorrected
Face Recognition (number correct)	Drug	1, 40	.78	.38
	Drug × Drug Order	1, 40	.00	.95
	Drug × Version Order	1, 40	.25	.62
	Drug × Drug Order × Version Order	1, 40	16.01	<.01
	Drug Order	1, 40	.01	.91
	Version Order	1, 40	3.83	.06
	Drug Order × Version Order	1, 40	.51	.48
Word Recall (number correct)	Drug	1, 40	.10	.76
	Drug × Drug Order	1, 40	1.03	.32
	Drug × Version Order	1, 40	.10	.76
	Drug × Drug Order × Version Order	1, 40	.04	.85
	Drug Order	1, 40	3.24	.08
	Version Order	1, 40	.28	.60
	Drug Order × Version Order	1, 40	.33	.57
Word Recognition (number correct)	Drug	1, 40	.82	.37
	Drug × Drug Order	1, 40	1.46	.23
	Drug × Version Order	1, 40	1.67	.20
	Drug × Drug Order × Version Order	1, 40	1.15	.29
	Drug Order	1, 40	1.88	.18
	Version Order	1, 40	6.15	.02
	Drug Order × Version Order	1, 40	.27	.61
Digit Span Backward (number correct)	Drug	1, 38	.25	.62
	Drug × Drug Order	1, 38	.00	.99
	Drug × Version Order	1, 38	2.00	.17
	Drug × Drug Order × Version Order	1, 38	.01	.92
	Drug Order	1, 38	.18	.67
	Version Order	1, 38	.37	.55
	Drug Order × Version Order	1, 38	3.92	.06
Digit Span Forward (number correct)	Drug	1, 38	.10	.75
	Drug × Drug Order	1, 38	2.43	.13
	Drug × Version Order	1, 38	1.04	.31
	Drug × Drug Order × Version Order	1, 38	.29	.59
	Drug Order	1, 38	.16	.69
	Version Order	1, 38	.50	.49
	Drug Order × Version Order	1, 38	.56	.46
Object-2-Back (omissions)	Drug	1, 41	1.13	.74
	Drug × Drug Order	1, 41	.28	.60
	Drug × Version Order	1, 41	.98	.33
	Drug × Drug Order × Version Order	1, 41	.11	.74
	Drug Order	1, 41	.03	.86
	Version Order	1, 41	.00	1.00
	Drug Order × Version Order	1, 41	.89	.35
Go/No-go (commissions)	Drug	1, 38	.54	.47
	Drug × Drug Order	1, 38	.28	.60
	Drug × Version Order	1, 38	.28	.60
	Drug × Drug Order × Version Order	1, 38	.12	.74
	Drug Order	1, 38	.18	.67
	Version Order	1, 38	.29	.59
	Drug Order × Version Order	1, 38	.34	.56
Flanker (inhibition cost)	Drug	1, 39	.20	.66
	Drug × Drug Order	1, 39	.13	.72
	Drug × Version Order	1, 39	.00	.98
	Drug × Drug Order × Version Order	1, 39	4.76	.04
	Drug Order	1, 39	.05	.83
	Version Order	1, 39	.05	.83
	Drug Order × Version Order	1, 39	.17	.68
Remote Associations (number correct)	Drug	1, 42	2.56	.12
	Drug × Drug Order	1, 42	.01	.94
	Drug × Version Order	1, 42	2.10	.16
	Drug × Drug Order × Version Order	1, 42	8.44	.01
	Drug Order	1, 42	.13	.72
	Version Order	1, 42	.14	.72
	Drug Order × Version Order	1, 42	.00	.95
Embedded Figures (number correct)	Drug	1, 32	.57	.46
	Drug × Drug Order	1, 32	.01	.93
	Drug × Version Order	1, 32	.34	.56
	Drug × Drug Order × Version Order	1, 32	10.68	<.01
	Drug Order	1, 32	1.83	.19
	Version Order	1, 32	.21	.65
	Drug Order × Version Order	1, 32	.88	.35
Raven (number correct)	Drug	1, 33	.01	.91
	Drug × Drug Order	1, 33	.05	.80
	Drug × Version Order	1, 33	1.92	.18
	Drug × Drug Order × Version Order	1, 33	.05	.83
	Drug Order	1, 33	.01	.93
	Version Order	1, 33	1.28	.27
	Drug Order × Version Order	1, 33	2.26	.14
SAT Math (number correct)	Drug	1, 41	1.16	.29
	Drug × Drug Order	1, 41	.55	.46
	Drug × Version Order	1, 41	1.79	.19
	Drug × Drug Order × Version Order	1, 41	4.56	.04
	Drug Order	1, 41	.10	.75
	Version Order	1, 41	2.24	.14
	Drug Order × Version Order	1, 41	1.02	.32
SAT Verbal (number correct)	Drug	1, 41	.47	.49
	Drug × Drug Order	1, 41	2.23	.14
	Drug × Version Order	1, 41	.37	.55
	Drug × Drug Order × Version Order	1, 41	.00	.98
	Drug Order	1, 41	.16	.69
	Version Order	1, 41	.24	.63
	Drug Order × Version Order	1, 41	2.02	.16

[a] *df* differed between tests due to differences in the number of excluded or missing data points per test.

2.3.2.1. Digit Span Forward and Backward (two measures). In this test of working memory, derived from a subtest of the Weschler Adult Intelligence Scale, the experimenter read digit sequences at a rate of approximately 1 digit per second and participants typed each sequence immediately after hearing it. In the Digit Span Forward task, 14 sequences were presented, with two each of lengths from 2 to 8. Participants reported the digits in the order they heard them. In the Digit Span Backward condition, 14 different sequences of length 2–8 were presented and participants reported the digits in reverse order. The digit sequences gradually increased in length (from two to eight digits). A response was counted as correct only if all the digits within a sequence were reported correctly and in the correct order (i.e., no partial credit). Number correct for Digit Span Forward is generally viewed as a simple measure of maintenance capacity and Digit Span Backward as a measure of ability to simultaneously maintain and process information (The Psychological Corporation, 2002).

2.3.2.2. Object-2-Back. Object-2-Back tests the ability to maintain and update information in working memory despite interference (Postle et al., 2005). Participants saw a sequence of 155 random polygons, each flashed briefly, for duration of

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1000 ms. Interstimulus interval was 500 ms. Participants had to press a button every time the currently presented object matched the object two shapes back. The dependent variable was the number of omission errors, which is associated specifically with working memory ability in n-back tasks (Oberauer, 2005).

2.3.3. Inhibitory control

The ability to withhold a habitual response or resist distraction by a salient stimulus is important for enabling us to act appropriately in many contexts. Two tasks assessed inhibitory control over responses and stimuli.

2.3.3.1. Go/No-go. Go/No-Go is a test of inhibitory control (see Braver et al., 2001), in which participants viewed a sequence of briefly flashed digits 1–9 (stimulus duration: 300 ms; interstimulus interval: 400 ms). Participants were asked to press a key as quickly as possible in response to all digits except for the digit 4. The digit 4 appeared on 15% of the 200 trials. For this task, the only opportunities for inhibitory control failure occur on the "4" trials and therefore the dependent measure was the number of commission errors (i.e., the number of trials on which participants failed to withhold a response to the "4"; Helmers et al., 1995).

2.3.3.2. Flanker. This test of inhibitory control (Eriksen and Eriksen, 1974) presented participants with 200 images of five horizontally aligned arrows. Participants were instructed to indicate as quickly and accurately as possible the direction (left or right) of the central arrow. In congruent trials, all arrows pointed in the same direction. In incongruent trials, the middle arrow pointed in a direction opposite to that of the peripheral arrows. The sequence consisted of an equal number of congruent and incongruent stimuli. Each stimulus remained on the screen until the participant responded; the response initiated a 1 s blank screen before the next stimulus appeared. The measure of inhibitory control, termed here inhibition cost, was the ratio of the median reaction time of incongruent trials to the median reaction time in response to congruent trials.

2.3.4. Creativity

Creativity is often defined as the ability to recombine familiar concepts in new and useful ways. It has been operationalized with tasks that require participants to find associations among disparate concepts and to view complex visual patterns in alternative ways. The two tasks used here were previously used by us in a study of the effects of MAS on creativity (Farah et al., 2008).

2.3.4.1. Remote associations test. In this test of convergent creativity (Mednick, 1962) participants must generate the word which associates a group of three other words. For example, presented with the stimulus triad "round – manners – tennis," they had to answer "table." The test included 15 triads, for each of which participants had 30 s to respond. The dependent measure was number correct.

2.3.4.2. Group embedded figures task. Another measure of convergent creativity (Noppe and Gallagher, 1977), this test presented participants with complex geometric designs and a smaller element from the design. Within each larger design participants had to find and trace the specified target element, which is "embedded," that is, not immediately apparent, given the overall visual gestalt of the design. An example is shown in Fig. 1. Participants completed 6 items within a 2-min time-limit for the whole test. The dependent measure was number correct.

2.3.5. Standardized tests

Among the many standardized tests of intelligence and achievement are Raven's Advanced Progressive Matrices, a nonverbal test of fluid intelligence, and the Scholastic Achievement Test (SAT), taken by college applicants in the US. The two tasks here were composed of individual items taken from these standardized tests.

2.3.5.1. Raven's Advanced Progressive Matrices. In this test of nonverbal intelligence (Raven, 1976) participants saw a series of abstract patterns, each of which had a missing piece. Participants had to choose the best fitting piece from 6 options. Each version of the test consisted of 12 items. Completion time for the whole test was limited to 10 min. The measure of interest was number correct.

2.3.5.2. Scholastic Achievement Test (SAT; two measures). This standardized test includes sections assessing "critical reading," "writing" and "mathematics." We selected questions from a book of practice tests and grouped them into two sections, "Verbal" and "Math." The former consisted of 48 multiple-choice questions completed under a 40-min time limit. Question types (and corresponding number of questions) were as follows: Sentence Completion (7), Reading Comprehension (26), Improving Sentences (9), Identifying Sentence Errors (6). The Math section consisted of 27 questions (19 in multiple-choice and 8 in free-response format) testing algebra, geometry and other miscellaneous high-school-level problems, to be completed under a 28-min time limit without the use of a calculator. The measures of interest for *SAT-Verbal* and *SAT-Math* were number correct.

2.3.6. Perceived drug effect

Perceived effect was examined through the following self-report prompt: "The following question refers to all tests completed TODAY. How and how much did the drug influence (either positively or negatively) your performance on the tests? Please use the scale below. You answer can be any number between 1 and 100." The scale referred to was a line, ranging from 1 to 100, and labeled as follows: 1 = "the drug impaired my performance extremely"; 25 = "the drug somewhat impaired my performance"; 50 = "the drug had no effect"; 75 = "the drug somewhat improved my performance"; 100 = "the drug improved my performance extremely."

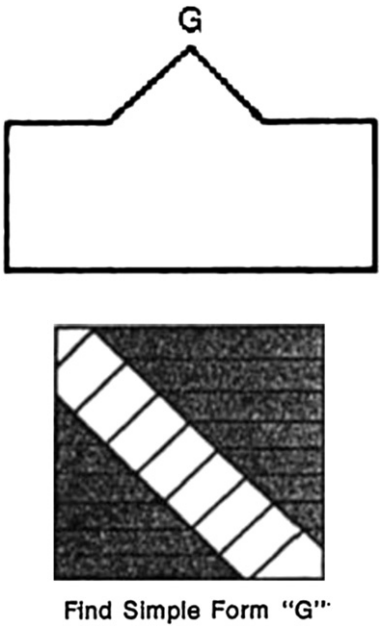

Fig. 1. Embedded figures task: An example stimulus.

2.4. Procedure

The study took place over seven sessions, which included consent and practice (Session 1), followed by the full battery of cognitive tasks, for the baseline (i.e., no pill), placebo and MAS conditions (Sessions 2–7). Baseline testing (Sessions 2–3) always preceded drug/placebo testing (Sessions 4–7) to minimize the influence of practice effects on data from the placebo and MAS conditions. During on-pill Sessions 4–7, the order of drug administration was counterbalanced, in a way that 24 participants received MAS in Sessions 3 and 4, and 22 participants received the drug in Sessions 6 and 7 The timeline of the study, including session sequence and timing, is presented in Fig. 2.

2.4.1. Session 1: intake interview, instructions and practice

The first session consisted of consent procedure, followed by practice versions of the actual tests. The practice tests were identical to the experimental versions, except for comprising of fewer trials and different items. At the end of the session, participants were instructed to abstain, for the rest of the study, from drugs containing stimulants or interacting with stimulants (or to notify the study personnel if they had to take such drugs). Participants were also asked to avoid heavy meals on test days.

2.4.2. Session 2 and 3: baseline testing

Sessions 2 and 3 provided a measure of unmedicated (off-drug, off-placebo) performance. The placebo condition was not used as a measure of baseline, so that regression to the mean would not be mistaken for moderation by cognitive ability.

After the initial blood pressure measurement, participants completed an SAT test (one Verbal and one Math section) or a battery of cognitive tests (described above), respectively in Session 2 and 3. These baseline tests were a version of the to-be-administered on-pill battery.

2.4.3. Sessions 4–7: testing on drug and placebo

The goal of these four sessions was to measure participants' cognitive performance on MAS and on placebo. At the onset of these sessions, participants reported the amount of sleep and caffeine consumption during the previous 24 h. They answered questions on their diet and medication intake to determine compliance with earlier instructions and had their blood pressure measured at the beginning and end of these sessions. Participants also underwent a urine drug test to corroborate self report and deter use of excluded drugs (amphetamine, cocaine, barbiturates, benzodiazepine, phencyclidine and tetrahydrocannabinol). Female

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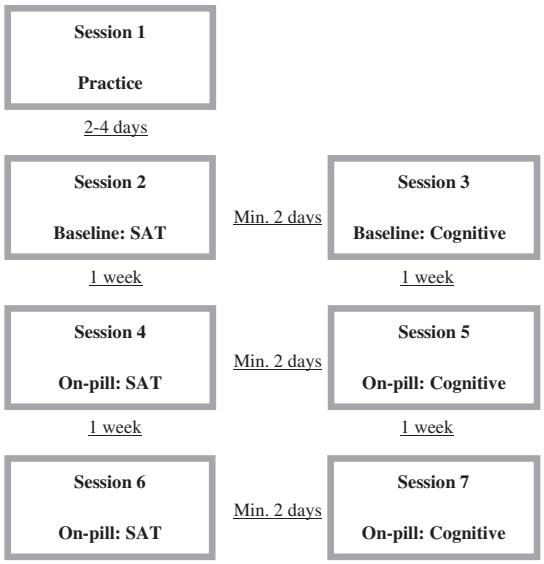

Fig. 2. Experimental procedure. Each box corresponds to an individual testing session, with the time intervals between sessions indicated. Baseline testing (Sessions 2–3) always preceded drug/placebo testing (Sessions 4–7) to minimize the influence of practice effects on data from the placebo and MAS conditions. Each individual participant's four on-pill sessions were scheduled at the same time of the day.

participants were administered a urine pregnancy test. Participants with positive results on any of these tests were excluded. After an initial blood pressure measurement (participants were excluded if the measurement exceeded 140/90), participants were randomly assigned to take either MAS (20 mg) or a visually indistinguishable placebo capsule in a double-blind manner. A 75-min waiting period followed. We chose this interval to ensure that the peak drug plasma level, which is reached 2–3 h after administration (Angrist et al., 1987) would occur during the testing. During the waiting time participants remained in the testing area and either read student periodicals or watched documentary DVDs (no homework or emotionally evocative movies were allowed). Five minutes before testing (70 min after drug intake), blood pressure was taken again and participants were excluded if the measurement exceeded 150/100. In sessions 4 and 6 the battery of tests included personality, mood and attributional style questionnaires (not relevant to cognitive enhancement and therefore not discussed further here) and test materials assessing verbal and mathematical abilities from the SAT. In sessions 5 and 7 the remaining cognitive tests were administered, in the same order for all participants. The two nonbaseline versions of the tasks were counterbalanced with both drug condition (MAS, placebo) and session order. After the cognitive battery (sessions 5 and 7) participants reported their perception of the pill's influence on their performance using the scale described earlier. At the end of each session, participants were reminded of the restriction on caffeine use and heavy-meal consumption for the rest of the study. If finishing the study, participants were thanked and paid.

2.5. Data analysis approach

2.5.1. Outlier removal

We removed outliers by excluding individual scores 3 *SD* above or below the mean of either the drug, placebo or baseline on each cognitive and subjective measure. If, on a particular measure, an individual participant's baseline, drug, or placebo score met the criterion for an outlier, we excluded all the data (i.e., MAS, Placebo *and* baseline) of this participant from analyses of that same task. This led to the exclusion of a total of 22 data points, or .85% of all data.

2.5.2. Missing data

143 task performance measures (or 5.55% of all data) were missing due to technical problems (50 data points), evidence of participants' failure to understand the task instructions (9 data points), or experimenter error (84 data points).

2.5.3. Statistical tests

In overview, our approach to statistical testing was based primarily on mixed model analysis of variance (ANOVA) with drug (MAS or placebo) as a within-subjects factor and drug order and test version order as between-subject factors. Multivariate analysis of variance (MANOVA) was used to assess the effects of drug across all 13 measures of cognitive ability and ANOVA to assess drug effects on each individual measure of cognitive ability and on ratings of perceived enhancement. Moderation of cognitive enhancement by baseline ability and COMT genotype was tested within the same framework. We also use multivariate regression and simple bivariate correlation in order to test two specific relations involving non-categorical factors (the moderating effect of COMT *val* load and the relation between perceived and actual enhancement). All analyses were conducted in SPSS 20. The significance threshold was set to the standard cutoff of .05. Results are reported without correction for multiple comparisons, a lenient approach that maximizes our ability to identify positive results at the risk of increasing possible false positive results.

3. Results

3.1. Effects of mixed amphetamine salts

Table 2 shows the means and standard deviations of performance in each task for the baseline, placebo and MAS conditions. To examine whether cognitive performance differed between MAS and Placebo sessions, we conducted a 2 (Drug: MAS; Placebo) × 2 (Drug Order: MAS first; Placebo first) × 2 (Test Version Order: Version 1 first; Version 2 first) mixed-model MANOVA with repeated measures on the first factor. The dependent variables were scores for 13 measures (listed in Table 1). On this test, the difference between MAS and placebo performance did not reach significance ($F(13, 13) = 1.71$, $p = .17$), indicating that there was no overall enhancing effect of MAS on cognitive performance in the tasks. We also failed to observe any significant two-way interaction between the drug conditions and either the drug order or the version order: ($F(13, 13) = .59$, $p = .83$; $F(13, 13) = 1.28$, $p = .33$, respectively). The absence of a Drug × Drug Order interaction indicates that MAS is no more or less enhancing when taken before

Table 2
Means and standard deviations of performance on each dependent measure for the baseline, placebo and mixed amphetamine salts condition.

Task (Measure)	Condition	*N*	*M*	*SD*
Face Recognition (number correct)	Baseline	44	29.05	3.25
	Placebo	44	27.61	4.25
	MAS	44	28.05	4.78
Word Recall (number correct)	Baseline	44	4.25	2.69
	Placebo	44	4.50	4.05
	MAS	44	4.59	3.36
Word Recognition (number correct)	Baseline	44	35.16	4.21
	Placebo	44	34.93	5.65
	MAS	44	34.39	5.04
Digit Span Backward (number correct)	Baseline	42	9.57	2.51
	Placebo	42	10.05	2.70
	MAS	42	10.17	2.80
Digit Span Forward (number correct)	Baseline	42	11.83	1.77
	Placebo	42	12.24	1.59
	MAS	42	12.17	1.67
Object-2-Back (omissions)	Baseline	45	10.38	4.90
	Placebo	45	8.98	4.59
	MAS	45	8.84	5.06
Go/No-go (commissions)	Baseline	42	13.95	5.24
	Placebo	42	15.12	6.20
	MAS	42	14.55	5.50
Flanker (inhibition cost)	Baseline	43	1.16	.05
	Placebo	43	1.16	.06
	MAS	43	1.16	.05
Remote Associations (number correct)	Baseline	46	8.35	2.10
	Placebo	46	7.89	2.50
	MAS	46	8.48	2.18
Embedded Figures (number correct)	Baseline	36	2.88	1.79
	Placebo	36	3.25	1.87
	MAS	36	3.39	1.78
Raven (number correct)	Baseline	37	7.27	1.87
	Placebo	37	8.19	2.16
	MAS	37	8.11	1.84
SAT Math (number correct)	Baseline	45	12.98	5.39
	Placebo	45	13.76	6.48
	MAS	45	13.07	6.18
SAT Verbal (number correct)	Baseline	45	29.42	6.68
	Placebo	45	30.73	7.25
	MAS	45	30.29	7.51

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or after the placebo session. However, given the inclusion of a Baseline condition before all MAS and placebo conditions, these results do not rule out the possibility that MAS could enhance performance with novel tasks. A marginally significant three-way (Drug × Drug Order × Version Order) interaction was observed (F (13, 13) = 2.14, p = .09). This interaction, which indicates differential drug effects on different versions of the tasks depending upon the order in which they were performed, does not lend itself to any obvious interpretation. The possibility that the versions differed in difficulty, and the order in which they were encountered synergistically compounded these difficulty differences, is not supported by a comparison of performance across versions from placebo conditions.

Although we began by testing the multivariate hypothesis that MAS would enhance overall performance across tasks, we also had a priori hypotheses about MAS effects on each of the 13 measures obtained in the project. We therefore followed up the MANOVA with a series of univariate 2 (Drug: MAS; Placebo) × 2 (Drug Order) × 2 (Test Version Order) mixed-model ANOVAs with repeated measures on the first factor. These analyses tested the effect of MAS on each of the 13 cognitive measures listed in Table 1. Again, these analyses revealed no effects of MAS and no two-way interactions between drug and order or drug and version for any of the 13 measures. The three-way interaction trend noted above emerged as significant (without correction for multiple comparisons) for five of the thirteen measures: Face Recognition, Flanker, Remote Associations, Embedded Figures, SAT Math. All main effects and interactions are shown in Table 1.

Faced with null results for the effect of MAS on cognitive performance in these tasks, we asked whether differences in participants' sleep prior to the MAS and placebo test days could have obscured the drug's enhancing effect. Self-reported sleep duration did not differ significantly between the sessions (t (41) = .91, p = .37 for neurocognitive testing sessions; t (45) = .74, p = .47 for SAT sessions), and showed a trend in the opposite direction to that hypothesized here, toward more sleep before MAS test sessions (M = 7.12, SD = 1.26 for neurocognitive testing sessions; M = 7.15, SD = 1.30 for SAT sessions) than placebo (M = 6.89 h, SD = 1.53 for neurocognitive testing sessions; M = 6.98, SD = 1.45 for SAT testing sessions).

3.2. Moderation of MAS effect by baseline performance

To determine whether MAS enhances cognition for some people, with an effect that is moderated by baseline cognitive performance, we first separated participants into two groups according to whether their baseline performance was above or below the median and then conducted a series of 2 (Drug: MAS; Placebo) × 2 (Baseline Performance: Below-Median; Above-Median) × 2 (Drug Order) × 2 (Test Version Order) mixed-model ANOVAs with repeated measures on the first factor for each of the 13 cognitive performance measures (MANOVA was not carried out because different participants fall in the upper and lower groups for different measures). Significant interactions between drug and baseline performance emerged on two measures: Word Recall (F (1, 36) = 4.78, p = .04) and, replicating our earlier study of MAS effects on this task (Farah et al., 2008), Embedded Figures (F (1, 28) = 8.48, p < .01). There was also a marginal trend toward significance for Raven's Progressive Matrices (F (1, 29) = 2.83, p = .10). In all three cases, the pattern of means was consistent with the prediction, based on the literature discussed earlier, of relatively more enhancement for the lower performing participants. As shown in Fig. 3, MAS tended to improve performance for the below-median baseline performers, while acting in the opposite direction for the above-median performers.

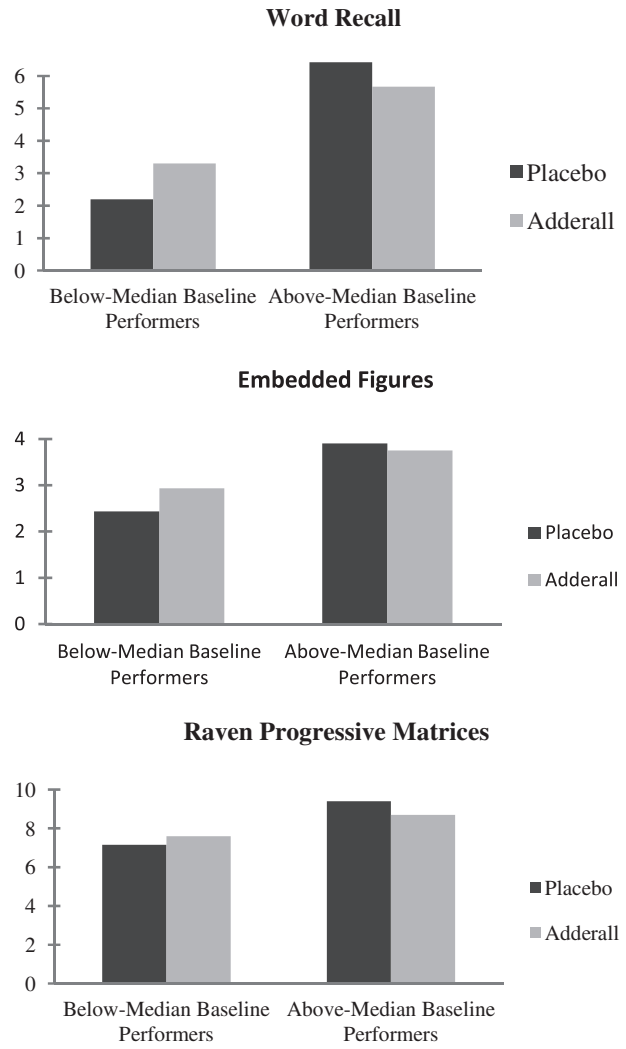

Fig. 3. Mean performance of participants whose overall baseline performance was below and above the median on Word Recall, Embedded Figures and Raven's Progressive Matrices. Conventional error bars are not shown because the comparisons are within subjects.

In addition to comparing the effects of MAS between higher and lower performing participants, we can also ask whether low performers, the subgroup exclusively expected to benefit from the drug, shows enhancement. This question was addressed by a series of 2 (Drug: MAS; Placebo) × 2 (Drug Order: MAS first; Placebo first) × 2 (Test Version Order: Version 1 first; Version 2 first) mixed-model ANOVAs with repeated measures on the first factor for each of the 13 measures only among the subsample performing below the median on baseline. The effect of the drug was significant on Word Recall (F (1, 16) = 6.71, p = .02), Embedded Figures (F (1, 12) = 8.41, p = .01); and Raven's Progressive Matrices (F (1, 16) = 5.36, p = .03). None of the remaining measures showed evidence of enhancement for the lower performing participants. See Supplementary Table 1 for other results which, because extraneous to our prediction, are not discussed further.

3.3. Moderation of MAS effect by COMT genotype

Given the findings reviewed earlier of moderation of amphetamine enhancement effects by COMT genotype, we divided participants into three groups depending on whether they had *val*–*val*, *val*–*met*, or *met*–*met* alleles of COMT. Because a MANOVA

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using genotype as a 3-level factor would not capture the ordering among the three groups we instead employed three alternative sets of analyses.

First, we conducted a regression analysis, which included *val* load, drug order and version order to predict a composite of the differences between MAS and placebo. The overall model was not significant, $p = .28$. Second, we carried out thirteen additional regressions to examine the effects of *val* load, drug order and version order on MAS effect (i.e., drug minus placebo score) on each separate measure. Overall regression models for SAT Math and Verbal were marginally significant ($F(3, 43) = 2.52$, $p = .07$; $F(3, 43) = 2.25$, $p = .10$, respectively). On SAT Math, the effect of COMT was significant ($b = .35$, $t = 2.38$, $p = .02$); this effect was near significant on SAT Verbal ($b = .24$, $t = 1.64$, $p = .11$). The patterns of means complied with the prediction that people with *val–val* genotype are more susceptible to enhancement than those with *met–met* genotype (see Fig. 4).

Third, we used MANOVA to contrast the effects of MAS on the two groups of homozygous participants with a 2 (Drug: MAS; Placebo) × 2 (COMT genotype: *val–val*; *met–met)* × 2 (Drug Order) × 2 (Test Version Order) mixed-model MANOVA, as well as with corresponding ANOVAs for each of the 13 measures. Neither the multivariate test for COMT moderation was significant ($F(5, 1) = .64$, $p = .73$), nor any of the univariate tests, $p > .26$ in all cases, with the exception of a significant Drug × COMT interaction on SAT Math ($F(1, 11) = 13.06$, $p < .00$) which again complied with the predicted pattern of relatively greater enhancement for homozygous *val* than homozygous *met* participants (see Fig. 4). Additionally, a significant drug effect emerged on SAT Math: $F(1, 11) = 5.63$, $p = .04$, although as shown Fig. 4, this main effect of drug was an overall impairing effect. Main effects of COMT genotype were found for Word Recognition ($F(1, 10) = 5.42$, $p = .04$), along with borderline significant effects for Word Recall ($F(1, 10) = 4.65$, $p = .06$), SAT Verbal ($F(1, 11) = 4.24$, $p = .06$) and Object-2-Back Omissions ($F(1, 10) = 4.22$, $p = .07$). The *met–met* genotype was associated with better performance than the *val–val* in all three cases.

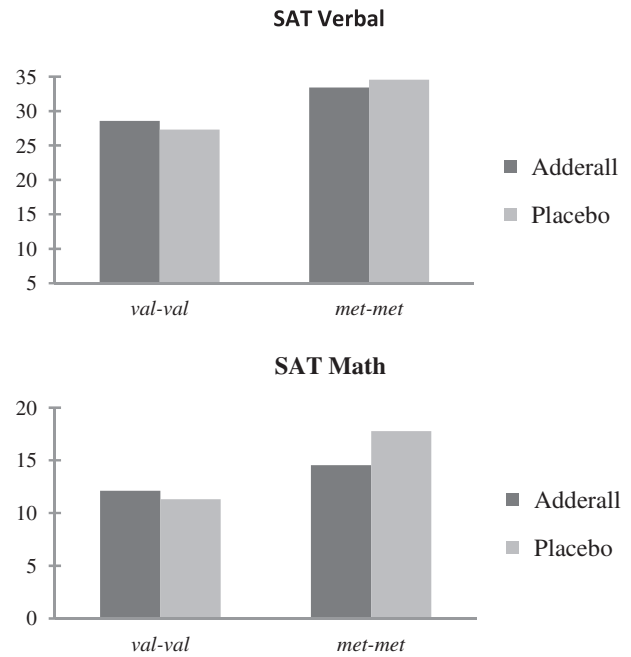

Fig. 4. Mean performance of participants homozygous for the *val* and *met* allele of the COMT gene on SAT Math and SAT Verbal. Conventional error bars are not shown because the comparisons are within subjects.

As with the analyses of baseline performance moderation, we followed up these analyses of genotype moderation with direct comparisons of drug and placebo performance in just the subjects for whom the drug would be expected, a priori, to be more helpful. We first carried out a 2 (Drug: MAS; Placebo) × 2 (Drug Order: MAS first; Placebo first) × 2 (Test Version Order: Version 1 first; Version 2 first) mixed-model MANOVA with repeated measures on the first factor and the 13 performance measures as the dependent variables. The effect of MAS did not reach significance ($F(2, 1) = .27$, $p = .81$), nor did other effects or interactions, $p > .49$ in all cases. We then ran a series of 2 (Drug: MAS; Placebo) × 2 (Drug Order: MAS first; Placebo first) × 2 (Test Version Order: Version 1 first; Version 2 first) mixed-model ANOVAs with repeated measures on the first factor for each of the 13 measures only among the subsample homozygous for the *val* allele. The effect of the drug did not reach significance on any of the measures (all *p's* > .24). See Supplementary Table 1 for other results which, because extraneous to our prediction, are not discussed further.

In sum, as with the analysis of moderation by baseline performance, we found mixed evidence for the moderation by COMT: little evidence supported the predicted moderation but when such moderation was observed, it was generally consistent with the hypothesis of relatively greater enhancement in carriers of the val allele.

3.4. Perceived enhancement

We examined MAS's effect on perceived enhancement through a 2 (Drug: MAS; Placebo) × 2 (Drug Order) × 2 (Test Version Order) ANOVA, with repeated measures on the first factor. A main effect of drug ($F(1, 40) = 4.09$, $p = .05$) indicated that participants perceived MAS ($M = 55.18$, $SD = 14.87$) as slightly more beneficial for cognitive performance than placebo ($M = 50.25$, $SD = 3.95$).

Although the earlier analyses demonstrate that MAS did not enhance cognition by any of the measures examined, it is nevertheless possible that subjective perceptions of enhancement are related to degree of true enhancement. To test this, we correlated the difference in perceived enhancement between MAS and placebo, on the one hand, and the corresponding difference scores on each of our 11 cognitive performance measures (no measure of perceived enhancement was administered during SAT Math and Verbal sessions). Ten of the 11 correlations did not reach statistical significance. A significant correlation emerged between perceived and actual enhancement on Go/No-go ($r = .33$, $p = .04$). To assess the relation between subjective perceptions and performance on all of the tasks together, we also created a composite of the differences between MAS and placebo sessions from each measure. This composite score did not correlate significantly with perceived enhancement: $r = -.06$, $p = .76$. In sum, on average participants believed that the MAS had enhanced their cognitive performance more than placebo. This perception stands in contrast to the reality: There was no actual enhancement on average nor were participants who felt more enhanced by the MAS more likely to show a true enhancement effect.

4. Discussion

4.1. Conclusions and relation to wider enhancement literature

Does MAS enhance cognition in healthy young adults? Our study was designed to overcome several challenges that have hampered previous attempts to answer this question. It had sufficient power to detect a medium-size effect for any one measure of cognitive performance. We nevertheless failed to find enhancement with any of the 13 measures we used. Of course, a different

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drug or a different dose of MAS might have led to a different finding. Nevertheless, we can state that a standard clinical dose of a drug that is commonly used for cognitive enhancement did not enhance cognition in an adequately powered study. The most straightforward interpretation of these results is that MAS is not a powerful cognitive enhancer. If it does enhance cognition in healthy and adequately-rested young adults, the effects are likely to be small.

These findings raise the question of why many published studies find large effects of amphetamine on cognitive performance with tests of memory, executive function and other cognitive processes. We believe that the answer is related to a set of problems, specifically low study power, flexibility in specific outcomes to be tested and publication bias against null results, which bedevil all branches of science, as explained in Ioannidis's (2005) provocatively titled article, "Why most published research findings are false." The impact of these problems on psychology and neuroscience research, in the absence of any intentional malfeasance has been discussed by Ioannidis (2011), Lehrer (2010) and Simmons et al. (2011) among others. Research on cognitive enhancement is not particularly susceptible to these problems, compared to other research topics, but neither is it immune to them. As a result, it is difficult to estimate the true robustness and effect size of cognitive enhancement with MAS and other stimulant medications by surveying the published literature.

On the assumption that the enhancing effects are real but are too small to be reliably captured in studies with sample sizes in the range typically used, one would expect a mix of positive and null results to be obtained. Of course, those effects that are found would show relatively large effect sizes, because only those results that by chance err on the large side would achieve significance. This is the pattern that we have seen in the literature, particularly regarding the effects of amphetamine on executive functions (Smith and Farah, 2011).

In the present study we also tested the hypotheses that MAS is enhancing for subsets of healthy young adults, specifically those who are less cognitively capable or who are homozygous for the *val* allele of the COMT gene. Here too we generally failed to support these hypotheses, although a minority of specific statistical tests showed the predicted patterns.

Finally, we found a small but reliable effect of MAS on judgments of enhancement, reminiscent of Davis's (1947) observations of soldiers in World War II quoted earlier. Participants believed themselves to be more enhanced by the pill when given MAS compared to placebo. Although not apparent for every individual participant, the overall tendency was for participants to feel that their cognitive performance has been enhanced by MAS. This may in part explain MAS's popularity as a cognitive enhancer.

4.2. Limitations of the present study

The present study was carefully designed to sample a wide array of cognitive abilities, to have adequate power and to measure potential moderators. In other respects, however, its design leaves some important questions unanswered. Most importantly, like most published studies in the enhancement literature (Smith and Farah, 2011), we did not vary drug dose and cannot know whether a higher or lower dose of the drug might have produced different results. Similarly, we did not test the cognitive enhancing potential of other enhancers, such as methylphenidate and modafinil, leaving open the possibility that these drugs may significantly improve healthy people's cognitive performance. We did not measure bioavailability of the drug (e.g., plasma amphetamine) and so cannot quantify how this varied across participants and sessions, for example as a function of individual differences in drug metabolism or food consumed before a session. Different or more frequent assessments of the perceived effects of MAS might have revealed more nuanced results or measured perceived enhancement more reliably. Our participants were not representative of the general population; in addition to the restricted age range, they met a number of health and lifestyle criteria for inclusion, including never having used prescription stimulants and being low or moderate consumers of caffeine. Perhaps different results would have been obtained with people who have already self-selected to use stimulants or who enjoy large daily doses of caffeine.

4.3. Implications for neuroethics

The present results have several implications for the neuroethics of cognitive enhancement. We believe that the issues of fairness, freedom and agency, discussed so extensively in the neuroethics literature (e.g., Farah et al., 2004) are not moot despite the present results. It is of course true that the most thoughtful and incisive ethical analysis is pointless if applied to an inaccurate representation of the empirical facts of the matter. But we believe that Hall and Lucke (2010) are too dismissive of the realities of cognitive enhancement when they write "Guidelines for enhancement prescription are … premature. More skepticism needs to be expressed about neuroenhancement claims for pharmaceuticals and bioethicists should be much more cautious in … making proposals that will facilitate such use." (p. 2042). The present results suggest only that the effects of one currently available enhancement drug are small when measured in laboratory tests of memory, executive function and tests of intellectual aptitude. These results leave many questions unanswered.

Among the important open questions are: How helpful might a small enhancement effect be over time? Might the effects be larger when measured under real-world conditions (e.g., with distractions in the environment or for longer and hence more tedious tasks than the typical memory or executive function experiment) or in a different state (e.g., after sleep deprivation)? Does MAS exert a larger effect on other processes, such as motivation to work, which are not captured by laboratory studies of memory and executive function but which nevertheless impact academic and other cognitive work? Or are users primarily attracted to this drug because of the illusory perception of enhancement our participants reported? These are important questions for future research, which will furnish the needed empirical basis for discussions of enhancement ethics and policy.

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Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.neuropharm.2012.07.021.

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