Neuropharmacology 64 (2013) 496–505

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

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

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ARTICLE INFO

Article history:
Received 4 June 2012
Received in revised form
7 July 2012
Accepted 9 July 2012

Keywords:
Cognitive enhancement
Amphetamine
Adderall
Memory
Working memory
Inhibitory control
Creativity
Intelligence
COMT

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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http://dx.doi.org/10.1016/j.neuropharm.2012.07.021

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.