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Effects of d-amphetamine upon psychosocial stress responses

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Abstract

Psychostimulant drugs alter the salience of stimuli in both laboratory animals and humans. In animals, stimulants increase rates of responding to conditioned incentive stimuli, and in humans, amphetamine increases positive ratings of emotional images. However, the effects of stimulants on real-life emotional events have not been studied in humans. In this study, we examined the effect of d-amphetamine on responses to acute psychosocial stress using a public speaking task. Healthy volunteers (N=56) participated in two experimental sessions, one with a psychosocial stressor (the Trier Social Stress Test) and one with a non-stressful control task. They were randomly assigned to receive d-amphetamine (5 mg n=18, 10 mg n=20) or placebo (n=18) on both sessions under double blind conditions. Salivary cortisol, subjective mood, and vital signs were measured at regular intervals during the session. Subjects also provided cognitive appraisals of the tasks before and after their performances. Amphetamine produced its expected mood and physiological effects, and the Trier Social Stress Test produced its expected effects on cortisol and mood. Although neither dose of amphetamine altered cardiovascular or hormonal responses to stress, amphetamine (10 mg) increased participants' pre-task appraisals of how challenging the task would be, and it increased post-task ratings of self-efficacy. Paradoxically, it also increased ratings of how stressful the task was, and prolonged aversive emotional responses. These findings suggest that amphetamine differentially affects stress response components: it may increase participants' appraisals of self-efficacy without dampening the direct emotional or physiological responses to the stress.

Keywords

d-amphetamine, cortisol, stress, emotion, cardiovascular

Introduction

While the abuse liability of psychoactive drugs is often attributed to the drugs' pleasurable subjective effects, recent evidence suggests that drugs may also alter reactivity to contextual stimuli in ways that may contribute to their abuse potential. For example, psychostimulants increase responses to pleasant stimuli and possibly also decrease reactions to negative stimuli, actions that may add to their appeal for nonmedical use (Bedi et al., 2009; Hysek et al., 2012; Wardle and de Wit, 2014). Surprisingly, few studies have investigated how drugs of abuse influence emotional or physiological responses to real-life emotional stimuli. In this study, we examined the effects of d-amphetamine (0 mg, 5 mg, 10 mg) upon appraisal of, and responses to, a stressful emotional experience.

Studies in our laboratory have shown that drugs of abuse can alter responses to simulated emotional stimuli, using the perception of emotional images, as well as subjective, psychophysiological and brain reactivity to emotional stimuli. For example, amphetamine increased the positive valence of emotional stimuli and improved recognition of standardized images of facial emotions (Ballard et al., 2012; Wardle and de Wit, 2012). Both delta-9-tetrahydrocannabinol (THC) and 3,4-methylenedioxymethamphetamine (MDMA) selectively impaired recognition of negative facial emotions (Bedi et al., 2010; Kirkpatrick et al., 2014; Wardle et al., 2012). Further, MDMA enhanced striatal response to positive expressions and both MDMA and THC attenuated amygdala responses to negative expressions (Bedi et al., 2009; Phan et al., 2008). Finally, MDMA reduced the negative emotional effects of simulated social rejection (Frye et al., 2014). Thus, these drugs influence positive and negative responses to emotional stimuli such as images and faces, suggesting that they may also alter in vivo aversive events such as an acutely stressful public speaking task.

Acute stress is an everyday life occurrence, and stress is integrally related to drug use and relapse (Sinha, 2001). For example, self-medication theories of drug abuse posit that certain individuals use drugs such as alcohol or benzodiazepines to relieve the aversive effects of stress. It is not clear whether, or how, stimulant drugs interact with acute stress to affect drug-seeking. Amphetamine potently increases positive mood (de Wit et al., 1986), which could offset negative emotional effects of stress. Indeed, Corr and Kumari (2013) showed that amphetamine attenuated startle responses potentiated by aversive images. Further, stimulant drugs improve cognitive performance as well as judgments of 'agency', or feelings of control (e.g. attention (Silber et al., 2006), learning and memory (Hart et al., 2002), reversal of vigilance and tracking performance decrements caused by sleep deprivation (Wiegmann et al.,

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1996), metacognition of agency (Kirkpatrick et al., 2008)). However, amphetamine may also increase responses to negative emotional stimuli. In one study we found that amphetamine magnified psychophysiological responses to negative emotional stimuli (Wardle et al., 2012) and Hariri et al. (2002) found that amphetamine potentiated amygdala responses to fearful and angry faces. Another stimulant drug, methylphenidate, administered at a relatively high dose (60 mg), increased the ability to detect sad and fearful expressions (Hysek et al., 2014). Early studies suggested that amphetamine and other stimulants increased fear and anxiety, although this effect may occur mainly at higher doses (Angrist and Gershon, 1970; Ellinwood et al., 1973; Hall et al. 1988). Amphetamine could either alleviate or worsen responses to acute stress, or it may have different effects on the separate components of the stress response. Like stress, amphetamine activates the sympathetic nervous system and increases cortisol (Knych and Eisenberg, 1979; Ostrander et al., 2003), suggesting that the effects may be additive. In rats, single doses of amphetamine increase stress-induced corticosterone and catecholamine release (Schmidt et al., 2001; Vogel et al., 1984) and there is cross-sensitization between amphetamine and acute stress (Antelman et al., 1980). To assess the effect of amphetamine on responses to a stressful emotional experience, we investigated its influence upon responses to an acute laboratory-based stressor that closely resembles a real-life aversive emotional event.

We examined the effect of low doses of the dopaminergic psychostimulant d-amphetamine (0 mg, 5 mg, 10 mg) upon appraisal of and responses to a standardized laboratory stressor, the Trier Social Stress Test (TSST; Kirschbaum et al., 1993). Healthy young adults received placebo or d-amphetamine (5 or 10 mg) 90 min before the TSST or a non-stressful control task. We measured effects of the amphetamine and tasks upon self-reported mood, cardiovascular measures and salivary cortisol. We hypothesized that amphetamine would attenuate negative appraisals of and mood responses to the stressful task, but would enhance cardiovascular and salivary cortisol responses.

Materials and methods

Subjects

Healthy men and women (N=56) were recruited from the university and surrounding community by flyers and newspaper or online adverts without regard to race or ethnicity. Initial eligibility was assessed by telephone and suitable candidates attended the Human Behavioral Pharmacology Laboratory at the University of Chicago for an in-person interview, psychological and medical screening. To qualify, participants had to be in good health, aged 18–40 years, with a body mass index of 19–29 kg/m^2. They were excluded if they smoked more than 20 tobacco cigarettes a week, or if they had a serious medical condition, a current or past year diagnosis of a Major Axis I psychiatric disorder (American Psychiatric Association, 1994), a history of substance dependence (except nicotine), an abnormal electrocardiogram, used prescription medications including, in women, hormonal contraceptives, or worked night shifts. The University of Chicago Hospital's Institutional Review Committee for the use of human subjects approved the study protocol.

Procedure

Men and women were randomly assigned to one of three groups: placebo (N=18), 5 mg d-amphetamine (N=18) or 10 mg d-amphetamine (N=20). Women were tested only during the follicular phase of their cycle (White et al., 2002). Each subject attended two four-hour (h) sessions, separated by five days. The sessions were conducted from 13.00 to 17.00 hours in comfortable testing rooms with a sofa, easy chair, television, a desk and a computer for administration of questionnaires. Upon arrival, participants provided breath and urine samples to detect recent drug use. No one tested positive. Participants then relaxed in the testing room for 20 min before baseline measures were obtained (see Dependent measures section below). Then they consumed a capsule containing 0 mg, 5 mg or 10 mg d-amphetamine (see below) under double-blind conditions. These low doses were selected to be behaviorally active without producing pronounced subjective or cardiovascular effects, either alone or when combined with the stress task (Childs and de Wit, 2006; McCloskey et al., 2010). Participants then relaxed in the lab for 1 h and could read or watch movies. Physiological and subjective measures were obtained 60min after capsule administration. At 75 min (1.25 h) after capsule administration, the research assistant read instructions to the participant for the behavioral task scheduled for that day and then they were left alone for the 10 min preparatory period. At the end of this 10 min preparatory period, participants completed a questionnaire to assess cognitive appraisal of the task (see Dependent measures section). They were then escorted to a separate room for the TSST or to another (different) room for the control task. The task was scheduled to begin 1.5 h after capsule administration when d-amphetamine effects were expected to peak (Wachtel et al., 2002; White et al., 2007). Once subjects completed the task they were escorted back to their testing room where they completed post-task measures (including a post-task appraisal form) for a further 90 min before discharge. Five days after completing the session (i.e. at the second experimental session or during the final debriefing session), participants completed a task appraisal form (see Dependent measures section) on which they recalled their responses to the task completed at the previous session. The second session was the same as the first session except that they received the second condition (i.e. stress or no stress). Five days after the second experimental session, participants attended a debriefing session where they completed the task appraisal form, were debriefed about the drugs received and the purpose of the study, and they received payment.

Behavioral tasks. The order of the TSST and control tasks was counterbalanced among participants in each group. The TSST consists of a 5 min speech and 5 min arithmetic (serial subtraction) performed in front of two interviewers who are unknown to the participant and provide no positive feedback, except to prompt the participant to continue speaking or to inform them that their arithmetic answer is incorrect and that they must start again. A video camera projects the participant's image onto a television screen and is clearly visible to the participant during the task. The control task comprised a 5 min conversation with the research assistant about a favorite book, movie or television program, followed by a 5 min computer game (Solitaire), performed without a video camera. Participants were allowed 10 min to prepare for each task. During the preparatory period for

the TSST, a timer was visible to the participant which counted down the remaining time with an audible "ticking" and sounded an alarm when the preparatory period was complete.

Dependent measures

Subjective. Drug effects were assessed using the Addiction Research Center Inventory (ARCI; Martin et al.,1971) and the Drug Effects Questionnaire (DEQ; Johanson and Uhlenhuth, 1980) before and at 60 min after capsule administration and then at 30, 60 and 90 min after the tasks. Subjective responses to stress ("I feel stressed", "I feel tense" and "I feel insecure") were assessed using visual analog scales (VAS; Folstein and Luria, 1973; Morean et al., 2013), at −30, 0, 30, 60 and 90 min after each task. The VAS form was also completed during the tasks, between the first (speech) and second (mental arithmetic) components.

Physiological. Heart rate was measured continuously throughout the sessions (one reading per minute) using a Polar chest band and monitor (Mini-Logger, Mini Mitter/Respironics, Bend, OR, USA). Data were averaged over consecutive 10 min periods. Group numbers for heart rate data analysis were reduced due to equipment malfunction (0 mg N=12, 5 mg N=16, 10 mg N=15). Blood pressure was measured using a monitor (Critikon Dinamap Plus Vital Signs Monitor, GE Healthcare Technologies, Waukesha, WI, USA) before and at 60 min after capsule administration, and at 0, 30, 60 and 90 min after the tasks. Saliva samples were collected using Salivette® cotton wads (Sarstedt Inc., Newton, NC, USA) before and 60 min after capsule administration, and at 10, 20 and 60 min after the tasks. Samples were analyzed by the Core Laboratory at the University of Chicago Hospitals General Clinical Research Center for levels of cortisol (Salimetrics LLC, State College, PA, USA; sensitivity=0.003 µg/dL).

Task appraisal. Task appraisals were assessed using the Primary Appraisal Secondary Appraisal rating scale (Gaab et al., 2005). Subjects completed this scale after the 10 min preparatory period, before the task began. This 16-item questionnaire assesses anticipatory cognitive appraisals. Subjects rate the extent to which they agree or disagree with statements regarding how threatening and challenging they perceive the task (Primary Appraisal) and their ability to perform the task and to control the task outcome (Secondary Appraisal). Subjects also completed a VAS appraisal questionnaire after the task ("I found the task stressful", "I found the task challenging", "I knew how to influence the task", "I was able to influence the task" and "I was satisfied with my performance").

TSST performance. Simple measures of the participants' performance during the TSST were obtained to assess any influence of d-amphetamine. During the speech portion, the number of pauses lasting >5 s and the total length of time for which subjects paused were recorded. During the arithmetic portion, the total number of correct and incorrect responses was recorded.

Other. To control for baseline between-group differences that may impact responses to stress, we used standardized questionnaires to obtain measures of trait anxiety (State Trait Anxiety Inventory; Spielberger, 1989), current stress levels (Perceived Stress Scale; Cohen et al., 1983) and perceived stress reactivity (Perceived Stress Reactivity Scale; Schlotz et al., 2011).

Drugs

d-amphetamine (Barr Laboratories, Pomona, NY, USA; 5 mg tablets) was placed inside opaque size 00 capsules with dextrose filler. Placebo capsules contained only dextrose filler.

Statistical analysis

Demographic characteristics, trait anxiety and levels of perceived stress were compared between groups using one factor (Group) analysis of variance (ANOVA) for continuous variables and chi-squared for categorical variables. Baseline measures were compared between groups using ANOVA before capsule administration to ensure that the groups did not differ.

Effects of d-amphetamine before the task. The effects of d-amphetamine upon physiological (cortisol, heart rate, blood pressure) and subjective (ARCI, DEQ) measures before the tasks were evaluated using the change score from pre- to post-capsule (–15 to 60 min) averaged across both testing sessions and compared between groups using ANOVA. As a secondary measure to examine drug effects that occurred after the task we also compared drug effects using three factor (Group*Task*Time) repeated measures ANOVA (rmANOVA) across the entire session. Participants' pre-task appraisals of the task were analyzed using one factor (Group) ANOVA.

Effects of d-amphetamine upon stress responses. The effect of drug on responses to the task were compared across the three groups using three factor (Group*Task*Time) rmANOVA. To take into account pre-task differences related to the effects of d-amphetamine, physiological and subjective measures during and after the task were calculated as a change from pre-task baseline score. Post-task appraisals were analyzed using one factor (Group) ANOVA. The effects of d-amphetamine on performance during the public speaking and mental arithmetic portions of the TSST were analyzed between groups using one factor ANOVA.

Analyses were performed using SPSS 22 for Windows. Throughout, we used planned contrasts to probe non-linear dose effects of amphetamine. Significant linear dose effects were further analyzed using post-hoc multiple comparisons tests. Effect sizes are reported throughout; Cohen's d for t tests (where 0.2, 0.5 and 0.8 represent small, medium and large effect sizes respectively) and eta-squared (η^2) or partial eta-squared ($\rho\eta^2$) for ANOVAs (where 0.01, 0.06 and 0.16 represent small, medium and large effect sizes respectively).

Results

Participant characteristics

Fifty-six participants completed testing in the study (50% female). The majority of participants were in their early 20s

Table 1. Demographic and drug use characteristics for participants in each group. Data represent mean ± SEM unless otherwise indicated. There were no significant differences between the groups.

	0mg	5mg	10mg	Statistics[a]
***N* (female)**	18 (9)	18 (10)	20 (9)	$\chi^2(2)=0.4$
Race, %				$\chi^2(4)=6.3$
European American	39	39	55	
African American	28	22	0	
Other	33	39	45	
Age, years	22.9 ± 1.0	24.5 ± 1.1	23.3 ± 1.2	$F(2,55)=0.5$
BMI, kg/m²	22.6 ± 0.4	22.7 ± 0.5	22.6 ± 0.5	$F(2,55)=0.0$
Full-time student, %	50	50	65	$\chi^2(2)=1.2$
Current drug use				
Caffeine, drinks/week	7.2 ± 1.8	7.6 ± 1.2	9.9 ± 2.2	$F(2,55)=0.7$
Alcohol, drinks/week	7.5 ± 1.1	7.9 ± 1.1	10.0 ± 2.2	$F(2,55)=0.7$
Marijuana, times/month	5.6 ± 2.7	2.0 ± 1.7	2.2 ± 1.1	$F(2,55)=1.1$
Recreational drug use history, % ever used				
Stimulants	39	28	25	$\chi^2(2)=0.9$
Opiates	17	22	15	$\chi^2(2)=0.4$
Cannabinoids	83	72	85	$\chi^2(2)=1.1$
Club drugs	28	17	20	$\chi^2(2)=0.7$
Hallucinogens	28	11	30	$\chi^2(2)=2.2$
Tranquilizers	6	6	15	$\chi^2(2)=1.4$
Inhalants	11	11	25	$\chi^2(2)=1.8$
Current Stress, PSS	11.9 ± 1.2	13.1 ± 1.4	10.6 ± 1.1	$F(2,55)=1.2$
Trait Anxiety, STAI	32.2 ± 2.0	35.1 ± 1.9	32.8 ± 1.8	$F(2,53)=0.6$
Stress Reactivity, PSRS	13.4 ± 1.6	17.4 ± 1.5	16.2 ± 1.3	$F(2,53)=1.9$

[a]Indicates results of one factor (Group) analysis of variance or Pearson's chi-squared analyses (all not significant).
χ^2: chi-squared; BMI: body mass index; PSS: Perceived Stress Scale; STAI: State Trait Anxiety Inventory: PSRS: Perceived Stress Reactivity Scale.

(23.6±0.6 years) and 30% reported prior recreational use of stimulants. Table 1 shows demographic and drug use characteristics for participants in each treatment group; there were no differences between groups in any of the characteristics. The groups also did not differ at baseline on measures of mood, hormonal or cardiovascular function

d-amphetamine effects before the task

After capsule ingestion but before the task (i.e. from pre-capsule to 60 min post-capsule), amphetamine (AMP) significantly increased heart rate ($F(2,42)=4.17$ $p<0.05$ $\eta^2=0.17$) and this effect was sustained across the entire session (Group $F(2,40)=6.66$ $p<0.01$ $\rho\eta^2=0.25$; see Figure 1). Post-hoc tests revealed that 10mg AMP increased heart rate relative to both 0mg (mean difference=11.4 beats/min) and 5 mg AMP (mean difference = 7.5 beats/min).

AMP did not significantly increase blood pressure before the tasks began, although when data across the entire sessions were considered, 10mg AMP increased diastolic blood pressure overall in comparison with placebo (Group $F(2,53)=3.66$ $p<0.05$ $\rho\eta^2=0.12$; 10 mg>0mg $p<0.05$). AMP did not significantly influence cortisol levels before the tasks began. However, AMP 10mg significantly increased cortisol levels across both sessions in comparison with the 5mg dose (Group $F(2,27)=3.67$ $p<0.05$, $\rho\eta^2=0.21$, 10>5 mg $p<0.05$; Figure 2).

Neither dose of AMP increased ratings of mood and drug effects on the ARCI and DEQ before the tasks began, but across the entire session AMP (10 mg) increased scores of stimulant-like effects on the ARCI Amphetamine (Group $F(2,53)=3.29$ $p<0.05$ $\rho\eta^2=0.11$, 10>0 mg $p<0.05$) and Benzedrine scales (Group $F(2,53)=3.19$ $p<0.05$ $\rho\eta^2=0.11$, 10>0 mg $p<0.05$). Before the tasks began, AMP (10 mg only) increased ratings of feeling stressed (Group $F(2,55)=3.90$ $p<0.05$, 10 mg>0 mg $p<0.05$), tense (Group $F(2,55)=4.99$ $p=0.01$, 10mg>0mg $p<0.01$) and insecure (Group $F(2,55)=4.55$ $p<0.05$, 10 mg>0 mg $p<0.05$), and this effect was sustained throughout both sessions (Group $F(2,53)\geq 5.31$ $ps<0.01$ $\rho\eta^2\geq 0.17$).

On each session, subjects "appraised" the difficulty of the task before completing the task. On this measure, AMP 10 mg increased pre-task ratings of the TSST as challenging (Group $F(2,55)=3.46$ $p<0.05$ $\eta^2=0.12$).

The incidence of side effects among the groups was low but significantly greater after 10 mg AMP than after placebo (0 mg=0%, 5 mg=17%, 10 mg=30%; $F(2,53)=5.39$ $p<0.01$ $\rho\eta^2=0.17$, 10mg>0mg $p<0.01$). Reports of side effects did not differ between the TSST and control sessions. The most commonly reported adverse effects were headache (9%), stomachache (4%), fatigue (4%) and decreased appetite (4%).

Stress reactivity

The TSST had its expected effects on cardiovascular, hormonal and subjective ratings, and there were modest effects of AMP on certain measures. In comparison with the control task, the TSST

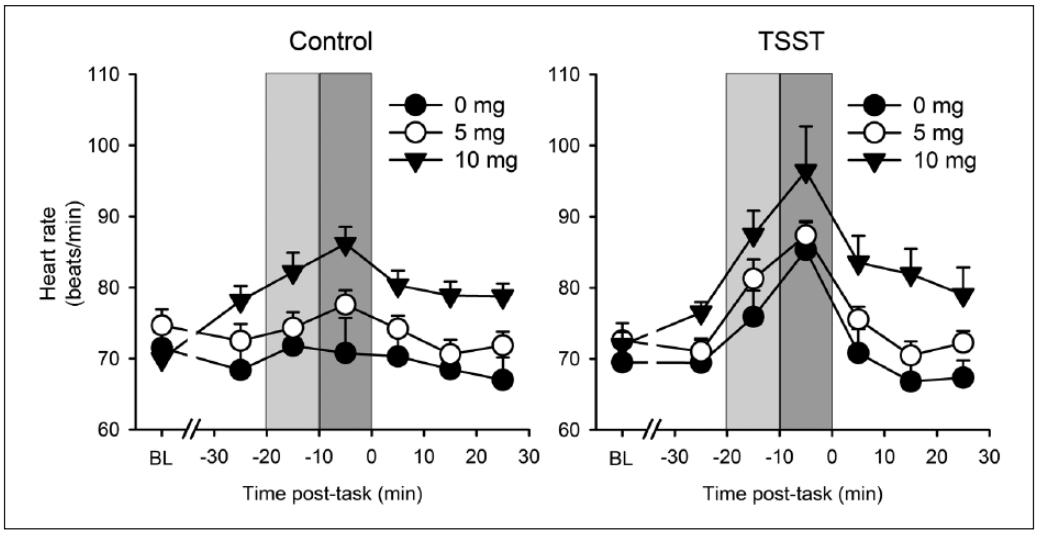

Figure 1. Changes in heart rate across sessions for participants treated with 0 mg, 5 mg or 10 mg d-amphetamine. Data represent mean ± SEM for participants in each group. BL (baseline) indicates measures taken before capsule administration. The light shaded bar represents the preparation phase of the task (between instructions and performance) and the dark shaded bar represents task performance. Amphetamine (10 mg) significantly increased heart rate overall in comparison with 0 mg, both before the tasks began and across both sessions.
TSST: Trier Social Stress Test.

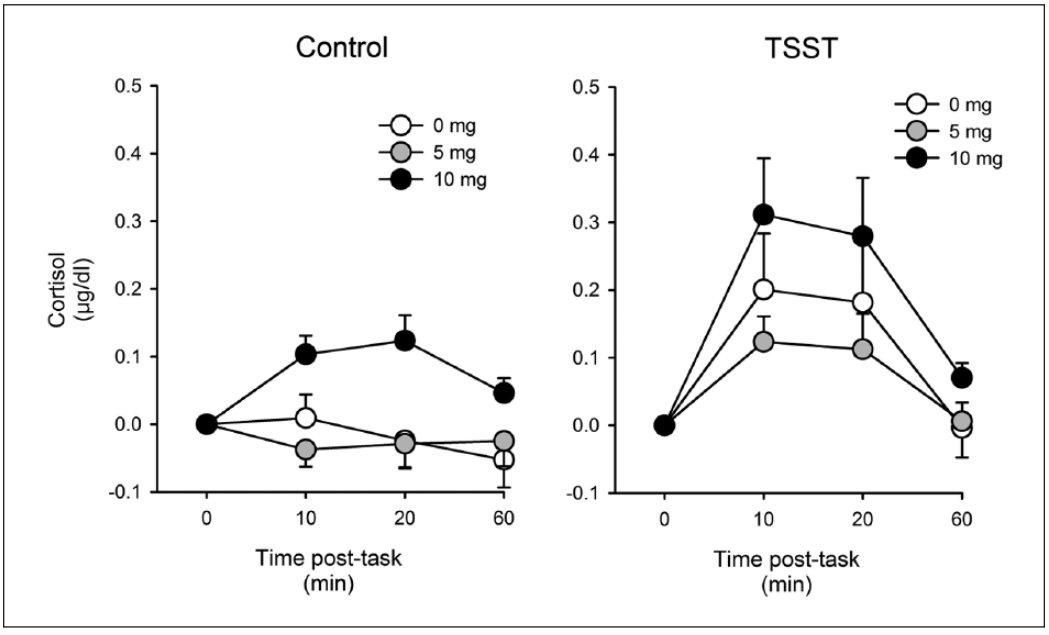

Figure 2. Changes in salivary cortisol across sessions after the TSST (right) or the control task (left). Data represent mean ± SEM for participants in each group. Amphetamine 10 mg increased cortisol after the tasks began across both sessions in comparison with the 5 mg dose.
TSST: Trier Social Stress Test.

significantly increased heart rate in all three groups (Task $F(1,40)=26.52$ $p<0.001$ $\rho\eta^2=0.40$; Figure 1), and increased systolic blood pressure (Task $F(1,53)=8.85$ $p<0.01$ $\rho\eta^2=0.14$), diastolic blood pressure (Task $F(1,53)=5.03$ $p<0.05$ $\rho\eta^2=0.09$) and cortisol (Task $F(1,27)=15.1$ $p=0.001$ $\rho\eta^2=0.36$; Figure 2). The TSST also significantly increased VAS ratings of feeling stressed (Task $F(1,53)=32.6$ $p<0.001$ $\rho\eta^2=0.38$), tense (Task $F(1,53)=73.2$ $p<0.001$ $\rho\eta^2=0.58$) and insecure (Task $F(1,53)=52.9$ $p<0.001$ $\rho\eta^2=0.50$). AMP significantly potentiated stress-induced increases in "I feel tense" (Group*Task $F(2,53)=5.18$ $p<0.01$ $\rho\eta^2=0.16$; Figure 3) and "I feel insecure" (Group*Task $F(2,53)=5.14$ $p<0.01$ $\rho\eta^2=0.16$).

To interpret the interactions between group and task, we performed separate analyses of participants' responses during the stress induction phase, using the area under the curve (AUC) from pre-task to immediately post-task, and the recovery phase, using the AUC from immediately post-task to the end of the session.

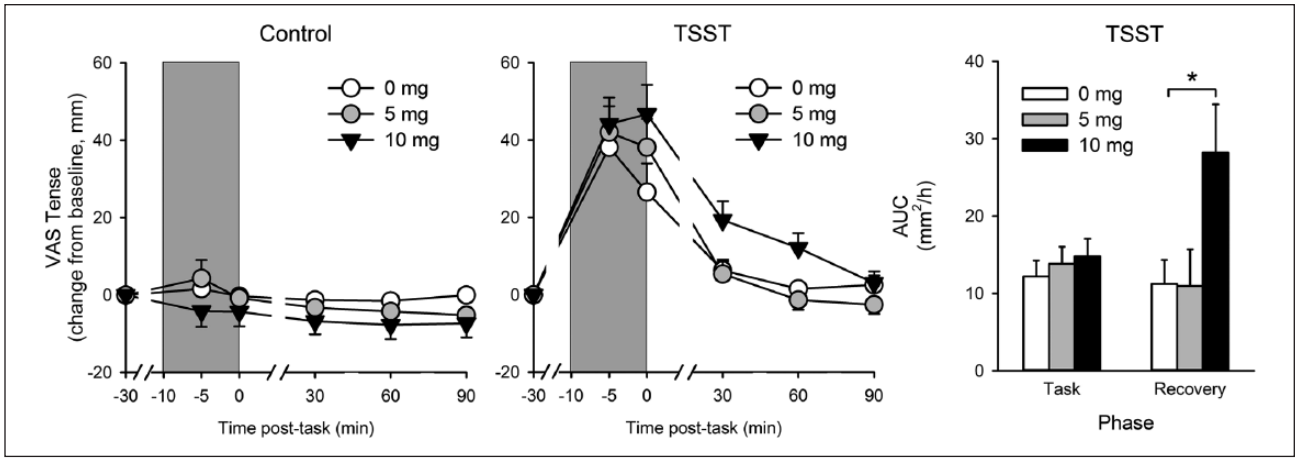

Figure 3. Changes in ratings of "I feel tense" across sessions after the TSST (middle) and control tasks (left). Right-hand graph shows area under the curve (AUC) for participants in each group. Data represent mean ± SEM for participants in each group. Amphetamine (10 mg) amplified TSST-induced increases in "I feel tense" in comparison with placebo 0 mg.
VAS: visual analog scale; TSST: Trier Social Stress Test.
*indicates a significant difference from 0mg.

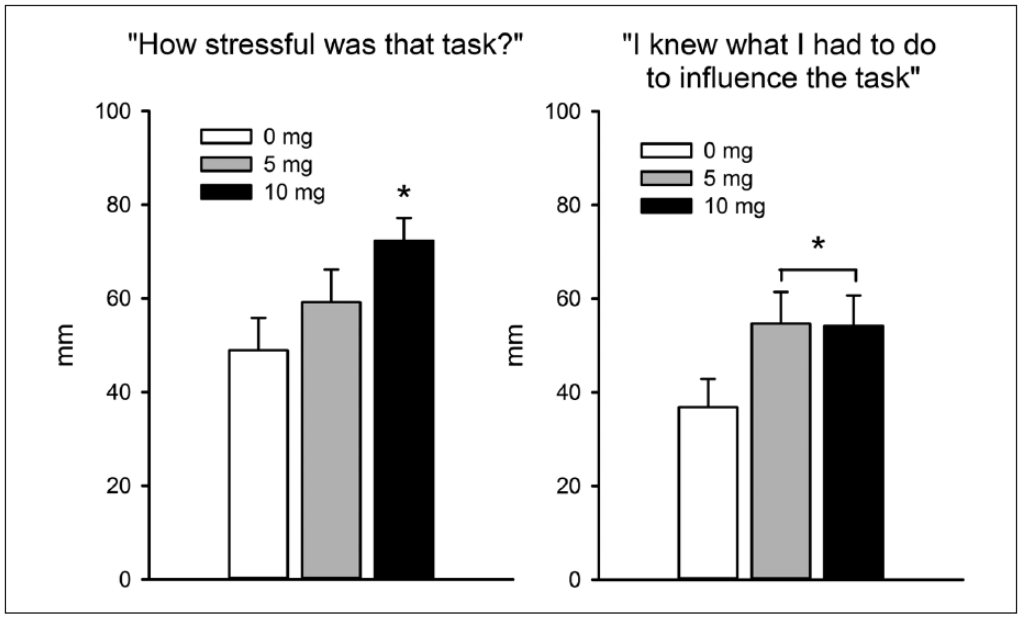

Figure 4. Influence of d-amphetamine upon post-task appraisals of the Trier Social Stress Test. Data represent mean ± SEM. Amphetamine (5 and 10 mg) increased ratings of participants' self-efficacy, yet 10 mg also increased ratings of the task as stressful.
*indicates a significant difference from 0mg.

During the stress induction phase, the three groups reported similar increases in feeling tense (Group*Task $F(2,53)=1.27$ $p>0.1$) and insecure (Group*Task $F(2,53)=0.64$ $p>0.1$). However, during the recovery phase, subjects who received 10 mg AMP reported feeling tense (Group*Task $F(2,53)=6.12$ $p<0.01$ $\rho\eta^2=0.19$, 10>0mg $p<0.05$) and insecure (Group*Task $F(2,53)=7.16$ $p<0.01$ $\rho\eta^2=0.21$) for a longer period of time than the other two groups.

Task appraisals and performance

After completing the TSST, participants treated with 10mg AMP rated the task as significantly more stressful (Group $F(2,55)=3.62$ $p<0.05$ $\eta^2=0.12$), but at the same time they rated themselves as being more able to influence the TSST (Group $F(2,55)=3.61$ $p<0.1$ $\eta^2=0.08$; Figure 4). Planned contrasts revealed that both AMP doses significantly increased participants' confidence in their ability to influence the task ($t(53)=2.21$ $p<0.05$). AMP did not influence appraisals of the control task.

In comparison with placebo, AMP increased the percentage of time spent talking during the speech component of the TSST (planned contrast AMP *vs*. placebo $t(46)= -2.08$ $p<0.05$; mean difference= −15.3 ± 7.3%). The drug did not affect performance on the mental arithmetic component of the task.

Discussion

This study assessed the effects of low doses of a stimulant drug on responses to a simulated real-life stressful situation in healthy young adults. Despite their well-known sympathomimetic effects (Heal et al., 2013), stimulant drugs also improve cognition and ratings of confidence (Kirkpatrick et al., 2008), both of which might reduce the stress of a challenging public speaking task. We found that the low doses of AMP tested here produced their expected subjective and cardiovascular effects in these healthy young adults, and the stressful task was effective. AMP did not reduce either the subjective or physiological indices of stress on most measures, either before the task or after it. However, after completing the task, participants pretreated with 10 mg AMP reported both that the task was more stressful, and at the same time, that they were more able to influence their performance on the task, consistent with an increase in confidence and self-efficacy. The only other effect of AMP on responses to the task was a prolongation of subjective responses to acute stress, without a concurrent prolongation of physiological and hormonal responses.

The present study provided little support for the idea that AMP reduces either the perception of challenging tasks, or the emotional or physiological responses to acute social stress. On one hand this may be expected, based on its profile of sympathomimetic effects including increased arousal, heart rate and blood pressure, and perhaps even cortisol. These effects are similar to the effects of acute stress, and thus the two treatments might be expected to be additive. On the other hand, AMP also increases attention and feelings of confidence and control, which may protect against some of the adverse effects of an unanticipated social stressor, as we had in this study. We observed little evidence that the drug improved either the perception of the stressor, or physiological responses to it. The one measure that fits with the idea of improved confidence was the post-task appraisal rating, where subjects treated with AMP reported that they were more able to influence the task, even though the drug had little effect on their performance.

AMP did influence one index of response to acute stress: it prolonged the subjective responses to stress after 10 mg AMP. After AMP (10 mg) and stress, subjects' ratings of "tense" and "insecure" remained elevated until the end of the session, whereas the drug did not increase tension ratings on the control session. This suggests that the mild sympathomimetic effects of the AMP added to the perceived psychological effects of the psychosocial stressor. There are numerous examples of similar cases of "misattribution" of physiological arousal, in which participants attribute mild residual arousal from one source to current environmental contexts (Cantor et al., 1975; Dutton and Aron, 1974; Schachter and Singer, 1962).

The present study had several limitations. First, the doses of amphetamine were low. The 5 mg dose produced marginal effects on any measure, and the 10 mg dose produced modest effects on typical stimulant-like responses. We selected low doses because of the possibility that there might be additive or more than additive effects between AMP and stress, but this was not the case. Therefore, it remains to be determined whether a higher dose of AMP might dampen either the perception of public speaking or acute mood responses to the task. A second limitation was that the participants were highly functioning healthy individuals. It is possible that stimulant drugs preferentially improve performance or confidence in individuals with low baseline levels. Thus, a future study might examine the effect of a stimulant drug in individuals with social anxiety or anxiety in public speaking settings.

The present results add to a growing literature on the effects of psychoactive drugs or hormones on response to acute stress. The neuropeptides oxytocin and vasopressin have stress-dampening effects (McRae-Clark et al., 2013; Shalev et al., 2011), as does the neurosteroid allopregnanolone (Childs et al., 2010). Het and Wolf (2007) reported that pretreatment with cortisol also dampened responses to the TSST. Alcohol reduces some aspects of acute stress (Childs et al., 2011). Finally, the benzodiazepine alprazolam dampens both psychological and physiological responses to the TSST (Fries et al., 2006), and we recently reported that the opioid partial agonist buprenorphine reduces both hormonal and threat appraisal responses to the TSST (Bershad et al., 2015, 2016). The effects of drugs or hormones on the perception of stress, the ability to perform under stressful conditions, and the mood or physiological responses to stress may reveal psychological processes that increase the value of the drug to certain, at-risk individuals.

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Declaration of Conflicting Interests

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References

American Psychiatric Association (2000) *Diagnostic and Statistical Manual of Mental Disorders* (4th ed, text rev). Washington, DC: American Psychiatric Association.

Angrist BM and Gershon S (1970) The phenomenology of experimentally induced amphetamine psychosis – preliminary observations. *Biol Psychol* 2: 95–107.

Antelman SM, Eichler AJ, Black CA, et al. (1980). Interchangeability of stress and amphetamine in sensitization. *Science* 18: 329–331.

Ballard M, Bedi G and de Wit H (2012) Effects of delta(9)-tetrahydrocannabinol on evaluation of emotional images. *J Psychopharmacol* 26; 1289–1298.

Bedi G, Hyman D and de Wit H (2010) Is ecstasy an 'empathogen'? MDMA increases social feelings but blunts identification of negative emotions in others. *Biol Psychiatry* 68: 1134–1140.

Bedi G, Phan KL, Angstadt M, et al. (2009) Effects of MDMA on sociability and neural response to social threat and social reward. *Psychopharmacology* 207: 73–83.

Bershad AK, Jaffe JH, Childs E and de Wit H (2015) Opioid partial agonist buprenorphine dampens responses to psychosocial stress in humans. *Psychoneuroendocrinology* 52: 281–288.

Bershad AK, Seiden JA and de Wit H (2016) Effects of buprenorphine on responses to social stimuli in healthy adults. *Psychoneuroendocrinology* 63: 43–49.

Cantor JR, Zillmann D and Bryant J (1975) Enhancement of experienced sexual arousal in response to erotic stimuli through misattribution of unrelated residual excitation. *J Pers Soc Psychol* 32: 69–75.

Childs E and de Wit H (2006) Subjective, behavioral, and physiological effects of acute caffeine in light, nondependent caffeine users. *Psychopharmacology (Berl)* 185: 514–523.

Childs E, O'Connor S and de Wit H (2011) Bidirectional interactions between acute psychosocial stress and acute intravenous alcohol in healthy men. *Alcohol Clin Exp Res* 35: 1794–1803.

Childs E, Van Dam NT and de Wit H (2010) Effects of acute progesterone administration upon responses to acute psychosocial stress in men. *Exp Clin Psychopharmacol* 18: 78–86.

Childs E, Vinci LM and de Wit H (2006). Responses to the Trier Social Stress Test (TSST) in single versus grouped participants. *Psychophysiology* 43: 366–371.

Cohen S, Kamarck T and Mermelstein R (1983) A global measure of perceived stress. *J Health Soc Behav* 24: 385–396.

Corr PJ and Kumari V (2013) Effect of D-amphetamine on emotion-potentiated startle in healthy humans: Implications for psychopathy and antisocial behaviour. *Psychopharmacology (Berl)* 225: 373–379.

De Wit H, Uhlenhuth EH and Johanson CE (1986) Individual differences in the reinforcing and subjective effects of amphetamine and diazepam. *Drug Alcohol Depend* 16: 341–360.

Dutton DG and Aron AP (1974) Some evidence for heightened sexual attraction under conditions of high anxiety. *J Pers Soc Psychol* 30: 510–517.

Ellinwood EH, Jr, Sudilovsky A and Nelson LM (1973) Evolving behavior in the clinical and experimental amphetamine (model) psychosis. *Am J Psychiatry* 130: 1088–1093.

Folstein MF and Luria R (1973) Reliability, validity, and clinical application of the Visual Analogue Mood Scale. *Psychol Med* 3: 479–486.

Fries E, Hellhammer DH and Hellhammer J (2006) Attenuation of the hypothalamic-pituitary-adrenal axis responsivity to the Trier Social Stress Test by the benzodiazepine alprazolam. *Psychoneuroendocrinology* 31: 1278–1288.

Frye C, Wardle MC, Norman GJ, et al. (2014) MDMA decreases the effects of simulated social rejection. *Pharmacol Biochem Behav* 117: 1–6.

Gaab J, Rohleder N, Nater UM, et al. (2005) Psychological determinants of the cortisol stress response: The role of anticipatory cognitive appraisal. *Psychoneuroendocrinology* 30: 599–610.

Hall RC, Popkin MK, Beresford TP, et al. (1988) Amphetamine psychosis: Clinical presentations and differential diagnosis. *Psychiatr Med* 6: 73–79.

Hariri AR, Mattay VS, Tessitore A, et al. (2002). Dextroamphetamine modulates the response of the human amygdala. *Neuropsychopharmacology* 27: 1036–1040.

Hart CL, Haney M, Foltin RW, et al. (2002). Effects of the NMDA antagonist memantine on human methamphetamine discrimination. *Psychopharmacology* 164: 376–384.

Heal DJ, Smith SL, Gosden J, et al. (2013). Amphetamine, past and present – a pharmacological and clinical perspective. *J Psychopharmacol* 27: 479–496.

Het S and Wolf OT (2007) Mood changes in response to psychosocial stress in healthy young women: Effects of pretreatment with cortisol. *Behav Neurosci* 121: 11–20.

Hysek CM, Domes G and Liechti ME (2012) MDMA enhances "mind reading" of positive emotions and impairs "mind reading" of negative emotions. *Psychopharmacology* 222: 293–302.

Hysek CM, Simmler LD, Schillinger N, et al. (2014) Pharmacokinetic and pharmacodynamic effects of methylphenidate and MDMA administered alone and in combination. *Int J Neuropsychopharmacol* 17: 371–381.

Johanson CE and Uhlenhuth EH (1980) Drug preference and mood in humans: d-amphetamine. *Psychopharmacology (Berl)* 71: 275–279.

Kirkpatrick M, Lee R, Wardle M, et al. (2014) Effects of MDMA and intranasal oxytocin on social and emotional processing. *Neuropsychopharmacology* 39: 1654–1663.

Kirkpatrick MG, Metcalfe J, Greene MJ, et al. (2008) Effects of intranasal methamphetamine on metacognition of agency. *Psychopharmacology (Berl)* 197: 137–144.

Kirschbaum C, Pirke KM and Hellhammer DH (1993) The 'Trier Social Stress Test' – a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology* 28: 76–81.

Knych ET and Eisenberg RM (1979) Effect of amphetamine on plasma corticosterone in the conscious rat. *Neuroendocrinology* 29: 110–118.

McCloskey M, Palmer AA and de Wit H (2010) Are attention lapses related to d-amphetamine liking? *Psychopharmacology (Berl)* 208: 201–209.

McRae-Clark AL, Baker NL, Maria MM, et al. (2013) Effect of oxytocin on craving and stress response in marijuana-dependent individuals: A pilot study. *Psychopharmacology* 228: 623–631.

Martin WR, et al. (1971) Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. *Clin Pharmacol Ther* 12: 245–258.

Morean ME, de Wit H, King AC, et al. (2013) The drug effects questionnaire: Psychometric support across three drug types. *Psychopharmacology* 227: 177–192.

Ostrander MM, Richtand NM and Herman JP (2003). Stress and amphetamine induce Fos expression in medial prefrontal cortex neurons containing glucocorticoid receptors. *Brain Res* 990: 209–214.

Phan KL, Angstadt M, Golden J, et al. (2008) Cannabinoid modulation of amygdala reactivity to social signals of threat in humans. *J Neurosci* 28: 2313–2319.

Schachter S and Singer JE (1962) Cognitive, social, and physiological determinants of emotional state. *Psychol Rev* 69: 378–399.

Schlotz W, Yim IS, Zoccola PM, et al. (2011) The Perceived Stress Reactivity Scale: Measurement invariance, stability, and validity in three countries. *Psychol Assess* 23: 80–94.

Schmidt ED, Schoffelmeer AN, De Vries TJ, et al. (2001) A single administration of interleukin-1 or amphetamine induces long-lasting increases in evoked noradrenaline release in the hypothalamus and sensitization of ACTH and corticosterone responses in rats. *Eur J Neurosci* 13: 1923–1930.

Shalev I, Israel S, Uzefovsky F, et al. (2011) Vasopressin needs an audience: Neuropeptide elicited stress responses are contingent upon perceived social evaluative threats. *Horm Behav* 60: 121–127.

Silber BY, Croft RJ, Papafotiou K, et al. (2006) The acute effects of d-amphetamine and methamphetamine on attention and psychomotor performance. *Psychopharmacology (Berl)* 187: 154–169.

Sinha R (2001) How does stress increase risk of drug abuse and relapse? *Psychopharmacology (Berl)* 158: 343–359.

Spielberger CD (1989). *State-Trait Anxiety Inventory: Bibliography*. 2nd ed. Palo Alto, CA: Consulting Psychologists Press.

Vogel WH, Miller J, DeTurck KH, et al. (1984) Effects of psychoactive drugs on plasma catecholamines during stress in rats. *Neuropharmacology* 23: 1105–1108.

Wachtel SR, Ortengren A and de Wit H (2002) The effects of acute haloperidol or risperidone on subjective responses to methamphetamine in healthy volunteers. *Drug Alcohol Depend* 68: 23–33.

Wardle MC and de Wit H (2012) Effects of amphetamine on reactivity to emotional stimuli. *Psychopharmacology* 220: 143–153.

Wardle MC and de Wit H (2014) MDMA alters emotional processing and facilitates social interaction. *Psychopharmacology* 231: 4219–4229.

Wardle MC, Garner M, Munafo M, et al. (2012) Amphetamine as a social drug: Effects of d-amphetamine on social processing and behavior. *Psychopharmacology* 223: 199–210.

White T, Justice AJH and de Wit H (2002) Differential subjective effects of d-amphetamine by gender, hormone levels and menstrual cycle phase. *Pharmacol Biochem Behav* 73: 729–741.

White TL, Lejuez CW and de Wit H (2007) Personality and gender differences in effects of d-amphetamine on risk taking. *Exp Clin Psychopharmacol* 15: 599–609.

Wiegmann DA, Stanny RR, McKay DC, et al. (1996) Methamphetamine effects on cognitive processing during extended wakefulness. *Int J Aviat Psychol* 6: 379–397.