Published in final edited form as:

Psychopharmacology (Berl). 2012 March ; 220(1): 143–153. doi:10.1007/s00213-011-2498-7.

Effects of amphetamine on reactivity to emotional stimuli

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Abstract

Rationale—Most studies of the reinforcing effects of stimulants have focused on the drugs' capacity to induce positive mood (i.e., euphoria). However, recent findings suggest drugs may also alter emotional reactivity to external stimuli, and that this may occur independently of direct effects on mood.

Objectives—We aimed to examine effects of D-amphetamine, a prototypic stimulant, on self-reported and psychophysiological reactivity to emotional stimuli as well as overall subjective mood. We predicted that amphetamine would enhance reactivity to pleasant stimuli, particularly, stimuli with social content and that these effects would be independent of the drug's direct effects on mood.

Methods—Over three sessions, 36 healthy normal adults received placebo, D-amphetamine 10 and 20 mg under counterbalanced double-blind conditions. At each session, emotional reactivity to standardized positive, neutral, and negative pictures with and without social content was measured in self-reports and facial muscles sensitive to emotional state. Drug effects on cardiovascular variables and subjective mood were also measured.

Results—Amphetamine produced euphoria, feelings of drug effect, and increased blood pressure. Most notably, amphetamine enhanced self-reported positive reactions to all pictures and psychophysiological reactions to positive pictures. These effects were not significantly related to drug-induced mood changes. Contrary to our hypothesis, effects of amphetamine on emotional reactivity were not moderated by social content.

Conclusions—This study demonstrates a previously unexamined and potentially reinforcing effect of stimulant drugs in humans, distinct from more typically measured euphorogenic effects, and suggests new areas of research in stimulant abuse risk and adaptations occurring during drug dependence.

Keywords

Amphetamine; Emotion; Reward; Electromyography; Psychophysiology

Introduction

Drug-induced changes in emotional state contribute to the reinforcing effects of drug of abuse (Kassel 2010). For example, stimulant drugs induce positive subjective mood (i.e., euphoria), and these positive mood effects appear to encourage repeat uses of the drug (de Wit et al. 1986). However, drugs may also subtly alter reactivity to external emotional stimuli, either by enhancing responses to naturally pleasant stimuli or dampening effects of

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Conflicts of Interest None

negative stimuli. Such alterations in emotional reactivity to environmental stimuli may also constitute a reinforcing effect. Indeed, drug users report that one of the main reasons they take drugs is to enhance social situations and positive events (e.g., at parties; Boys et al. 2001). Furthermore, there is evidence that the effects of drugs on responses to emotional stimuli may be independent of their direct, mood-altering effects (Harmer et al. 2008; Leyton et al. 2005, 2007). Thus, synergistic effects in which drugs alter reactivity to contextual emotional stimuli may be an important, overlooked process mediating the reinforcing effects of drugs. Here, we examine the acute effects of a prototypical stimulant, *D*-amphetamine, on self-reported and psychophysiological reactivity to standardized emotionally valenced stimuli.

Several previous studies have demonstrated that psychoactive drugs, both abused and therapeutic, modulate reactivity to emotional stimuli. For example, alcohol (Donohue et al. 2007) and diazepam (Patrick et al. 1996) dampen responses to negative stimuli, whereas the opioid remifentanyl increases ratings of the pleasantness of neutral pictures without affecting negative pictures (Gospic et al. 2008). Interestingly, some drugs may modulate emotional reactivity to external stimuli without producing direct, subjectively detectable changes in mood state. For example, selective serotonin reuptake inhibitors (SSRIs) increase reactions to positive emotional stimuli *without* measurably altering overall subjective mood in healthy volunteers (Harmer et al. 2003, 2008; Norbury et al. 2008). These findings support the idea that drugs affect reactivity to emotional stimuli, perhaps independently of their direct effects on subjective mood.

There is further preclinical and clinical evidence that dopaminergic drugs alter responses to salient/emotional stimuli, particularly, stimuli with social content, and that they may do so through different mechanisms than those involved in the induction of subjective euphoric mood. In laboratory animals, dopaminergic drugs, such as amphetamine, enhance the incentive value of conditioned and unconditioned reinforcers (Cador et al. 1991; Everitt and Robbins 2005; Taylor and Robbins 1984; Wise 1996), which may be an analog of affective responses to positive stimuli in humans. In humans, dopamine depletion reduces amphetamine-induced responding to rewarding cues without reducing amphetamine-induced euphoria, further suggesting that amphetamine's effects on reactivity to emotionally significant stimuli may be distinct from its effects on positive mood (Leyton et al. 2005, 2007). Evidence from animal and human studies also suggest that enhancement of positive stimuli may apply most strongly to social stimuli. First, there is substantial overlap between the neural networks activated by drugs of abuse and those activated by social stimuli, including the anterior cingulate, nucleus accumbens, orbitofrontal cortex, and amygdala (Britton et al. 2006a, b). Second, in rats, administration of a stimulant drug greatly potentiates the rewarding effect of social contact with another rat in a place preference procedure (Thiel et al. 2008, 2009). Last, in humans, amphetamine increases preference for the opportunity to socialize over a monetary reward (Heishman and Stitzer 1989; Higgins et al. 1989).

These findings led us to the hypothesis that amphetamine would enhance emotional reactivity to positive stimuli and, particularly, social stimuli in humans. We were also interested in determining whether the direct, euphoric effects of amphetamine mediated its effects on reactivity to emotional stimuli. Healthy volunteers received *D*-amphetamine (0, 10, and 20 mg) under double-blind conditions, before viewing matched, standardized negative, neutral, and positive pictures with social and nonsocial content. Emotional reactivity to the pictures was assessed with self-report ratings of the pictures as well as highly sensitive psychophysiological measurements of emotional facial muscle responses (corrugator and zygomatic muscles). This allows us to examine both consciously accessible emotional reactions to the pictures as well as responses that may be more automatic, less conscious,

and thus less susceptible to self-presentation (Dimberg et al. 2000, 2002). We also assessed the direct effects of amphetamine on overall mood state using standard subjective measures.

Methods and materials

Study design

This within-subject design consisted of three sessions at which participants received placebo, 10 or 20 mg amphetamine in counterbalanced order under double-blind conditions. At each session, they viewed different but matched sets of positive, negative, and neutral pictures. Study sessions were separated by at least 72 h.

Participants

Healthy participants (20 female, 16 male) ages 18–35 were recruited through flyers and online advertisements. Participants completed a 2-h screening consisting of physical examination, electrocardiogram, modified Structured Clinical Interview for DSM-IV (SCID; First et al. 1996), and self-reported health and drug use history. Inclusion criteria were: body mass index between 18 and 35, no medical conditions/contraindications to amphetamine, not pregnant, nursing, or trying to become pregnant, no past year DSM-IV Axis I disorders or lifetime history of drug dependence, mania or psychosis, some previous recreational drug use, no previous adverse amphetamine reactions, smoking <10 cigarettes per week, and high school education level. Participants were primarily Caucasian ($n=26$, 72%), in their 20s ($M=24.3$, $SD=4.5$) with some college education ($M=15.4$, $SD=1.5$) and light to moderate recreational drug use (see Table 1).

Participants were instructed to refrain from recreational and over-the-counter drugs for 24 h before and 12 h after sessions, with compliance verified using breath alcohol (Alcosensor III, Intoximeters, St. Louis, MO) and urine tests (ToxCup, Branan Medical, Irvine, CA). Participants were asked to maintain normal caffeine and nicotine intake for 24 h before and 12 h after sessions, and fast for 9 h prior to sessions. Female participants provided urine samples for pregnancy tests before each session. Women not on hormonal birth control were scheduled only during the follicular phase (White et al. 2002). Participants were informed that they might receive a stimulant, tranquilizer, marijuana-like drug, or placebo. All participants provided informed consent. All procedures were approved by The University of Chicago Institutional Review Board and were carried out in accordance with the Declaration of Helsinki.

Procedure

Participants first attended an orientation during which they were familiarized with tasks and psychophysiological equipment. They then completed three 4-h individual study sessions. Participants arrived at 9:00 a.m., completed breath and urine tests, then consumed a standard snack and completed baseline measures of mood, subjective drug effects, blood pressure, and heart rate. At 9:30 a.m., they took two opaque size 00 gelatin capsules containing 10 or 20 mg of *D*-amphetamine with dextrose filler, or placebo (dextrose only). From 9:30 to 11:00 a.m., participants relaxed (watching a movie from a selection available or reading; participants were not allowed to do stressful work or studying), and measures of mood, subjective drug effects, blood pressure, and heart rate were obtained at 10:00 and 11:00 a.m. Then psychophysiological sensors were attached, and participants completed picture viewing, and two other tasks not presented here, in counterbalanced order. After the tasks (approximately 12:10 p.m.), sensors were removed, and mood, subjective drug effects, blood pressure, and heart rate were reassessed at 12:30 and 1 p.m. At 1:30 p.m., participants completed an end of session questionnaire and left the laboratory.

Measures

Subjective and cardiovascular drug effects—The Profile of Mood States (POMS; Johanson and Uhlenhuth 1980) was used to measure subjective mood. It is a 72-adjective list rated on five-point Likert scales from 0 (“not at all”) to 4 (“extremely”), containing eight subscales. For this study, we used the Elation and Arousal subscales, which are sensitive to amphetamine (Gabbay 2003). Elation was our measure of positive mood, whereas Arousal, which contains both positive and negative mood items, was our measure of general emotional activation. The Addiction Research Center Inventory (ARCI; Chait et al. 1985; Martin et al. 1971) was used to measure prototypical subjective effects of several drug classes. It is a 52-item true/false scale with six subscales. We focused on the scale of amphetamine-like effects. The Drug Effects Questionnaire (DEQ; Fischman and Foltin 1991), provided further information about subjective drug effects. It consists of a set of visual analog scales on which participants mark from 1 to 100 how much they like the drug’s effects, dislike the drug’s effects, feel the drug’s effects, feel high, and want more of the drug. We focused on DEQ “Feel” scores of subjective drug effect. Lastly, we measured blood pressure and heart rate using portable monitors (Life Source, A&D, Tokyo, Japan), and used mean arterial pressure (MAP; [systolic BP+2diastolic BP]/3) as our measure of cardiovascular effects (heart rate results were redundant with blood pressure and are not discussed further). Participants completed the POMS, ARCI, and cardiovascular measures at baseline (–20), 30, 90, 180, and 210 min after capsule administration. Subjects completed the DEQ at 30, 90, 180, and 210 min after the capsule (as the drug cannot be rated prior to administration).

Emotional stimuli—We used pictures from the International Affective Picture System (IAPS; Lang et al. 1999) as emotional stimuli. IAPS pictures are normatively rated on valence (positivity vs. negativity) and arousal and have been previously used to study alcohol and nicotine (Cinciripini et al. 2006; Donohue et al. 2007; Robinson et al. 2007). Although the IAPS is not normatively rated for social relevance, based on previous research and unpublished ratings of a smaller picture set (Cacioppo et al. 2009; Gros et al. 2009 and unpublished data provided by L.W. Hawk), we defined “social” as depicting at least two people or parts of people (e.g., two people talking or a hand pointing a gun at another person), and “nonsocial” as depicting no people or parts of people (e.g., a car accident with no bodies visible or a slice of pizza). To avoid adaptation, we constructed three sets matched on normative arousal and valence. At each session, the participant saw a different set, counterbalanced to pair each set equally with each drug condition. Within each set were six subsets of nine pictures each (social/negative, nonsocial/negative, social/neutral, nonsocial/neutral, social/positive, and nonsocial/positive) matched on arousal and absolute valence. Within each negative and positive subset were three pictures from each valence tertile (mildly, moderately, and extremely negative/positive), allowing for enhancement while retaining separation of positive and negative sets.¹ Pictures were presented in fixed random order, with no more than two of the same valence in a row. Picture trials consisted of a 3 s prepicture fixation, a 6 s picture period, a 3 s postpicture fixation, then subjective ratings.

Participants rated pictures using the evaluative space grid (Larsen et al. 2009), a two-dimensional grid allowing independent 0 (not at all) to 4 (extreme) ratings of positivity and negativity, and a 0 (not at all) to 9 (extreme) rating of arousal. Psychophysiological reactions were assessed using electromyography (EMG) of corrugator and zygomatic facial muscles. Activity in the corrugator (“frown”) muscle is increased by negative and suppressed by positive stimuli, while activity in the zygomatic (“smile”) muscle is increased by highly positive stimuli (Larsen et al. 2003). EMG was measured over left brow and cheek using 4 mm Ag/AgCl electrodes. Sites were cleaned with alcohol and lightly abraded, and any site with impedance above 20 k Ω (measured with a Model 1089 MK III Checktrode; UFI, Morro

Bay, CA, USA) was reapplied. EMG signals were amplified 5,000×, submitted to a 10–500 Hz band pass filter, digitized at 1,000 Hz, submitted to a 60 Hz comb band stop filter, rectified, and integrated over 20 ms using EMG100C amplifiers, an MP150 Data Acquisition System and Acknowledge software from Biopac Systems (Goleta, CA USA). EMG data were square root transformed to correct positive skew typical of EMG data. Trials with excessive baseline activity or artifactual activations were identified and excluded. Mean EMG over a 1 s prepicture baseline was subtracted from mean EMG over the 6 s picture period to index reactivity.

Statistical analyses

Analyses were performed using a polynomial contrast regression approach to repeated measures analysis of variance (RMANOVA; Judd et al. 2009). Gender, dose order, and picture set/dose pairing were examined as covariates but did not affect primary results. The effects of amphetamine on POMS Elation and Arousal, ARCI-A and MAP were examined using a 3 (Dose) by 5 (Time) RMANOVA, with follow-up *t*-tests comparing each dose with placebo at each time point. DEQ Feel Drug scores were skewed, making individual time-point comparisons inappropriate, so area under the curve scores were compared in a one-way (Drug) RMANOVA. The effect of amphetamine on picture ratings, corrugator, and zygomatic EMG was examined using 3 (Drug) by 3 (Picture Valence) by 2 (Social Content) RMANOVA. For any significant interaction between Drug and Picture Valence or Drug, Picture Valence, and Social Content, planned comparisons of each drug dose with placebo for each picture type were conducted. We examined whether effects of amphetamine on emotional reactivity to the pictures were distinct from its effects on elation and arousal using procedures from Judd et al. (2001) for within-subject mediation. In a set of supplementary analyses, we also examined correlations between “typical” amphetamine effects and our measures of emotional reactivity and between our various measures of emotional reactivity (see Supplemental Information).

One participant was omitted from EMG analyses due to jaw grinding, one was omitted from ARCI-A, DEQ, and POMS and zygomatic EMG analyses due to missing data, and one was removed from zygomatic EMG analyses due to outlier values (>3 SD on several picture types).

Results

Subjective mood and cardiovascular drug effects

Baseline POMS ratings were typical for our laboratory and did not significantly differ by dose. Amphetamine dose-dependently increased both POMS Elation and POMS Arousal

¹IAPS numbers for each subset, followed by IAPS normative mean valence (V, 1=extremely unpleasant–9=extremely pleasant) and arousal (A, 1=extremely unarousing–9=extremely arousing) ratings: Set 1 social/negative=6,022, 9,421, 2,053, 9,424, 4,621, 9,584, 2,694, 9,045, 9,594, V=3.03, A=5.13; Set 1 nonsocial/negative=9,560, 9,911, 9,320, 9,180, 1,274, 9,373, 7,360, 1,280, 9,010, V=3.08, A=5.08; Set 1 social/neutral=2,272, 9,700, 2,704, 2,595, 2,397, 2,580, 7,620, V=5.15, A=3.86; Set 1 nonsocial/neutral=7,211, 1,935, 7,055, 7,233, 7,207, 5,920, 7,182, 7,830, 7,285, V=5.12, A=4.00; Set 1 social/positive=4,598, 8,467, 8,600, 8,116, 4,601, 2,391, 2,216, 7,502, 8,420, V=6.99, A=5.32; Set 1 nonsocial/positive=1,640, 7,352, 5,991, 7,410, 5,450, 7,508, 5,260, 5,700, 8,170, V=6.94, A=5.20; Set 2 social/negative=9,420, 9,903, 6,838, 2,700, 6,562, 3,216, 2,312, 3,280, 9,926, V=3.12, A=5.18; Set 2 nonsocial/negative=9,301, 7,380, 9,561, 9,630, 9,621, 1,111, 1,220, 9,440, 9,390, V=3.07, A=5.25; Set 2 social/neutral=8,010, 3,210, 8,475, 2,393, 4,605, 2,485, 2,593, 2,606, 7,496, V=5.28, A=4.40; Set 2 nonsocial/neutral=9,472, 7,054, 5,510, 1,616, 7,242, 7,500, 5,395, 7,283, 5,661, V=5.11, A=3.81; Set 2 social/positive=2,594, 4,625, 9,156, 8,371, 2,373, 4,599, 2,345, 8,210, 8,496, V=6.92, A=5.24; Set 2 nonsocial/positive=7,289, 7,450, 1,660, 5,849, 8,500, 1,540, 5,660, 7,270, 5,480, V=6.92, A=5.12; Set 3 social/negative=6,212, 2,141, 9,425, 2,455, 2,691, 6,561, 6,836, 2,718, 4,635, V=3.04, A=5.15; Set 3 nonsocial/negative=9,140, 9,300, 9,620, 9,290, 9,470, 9,471, 9,008, 9,480, 9,110, V=3.00, A=5.05; Set 3 social/neutral=2,695, 9,582, 9,913, 9,411, 4,000, 2,396, 2,850, 2,579, 2,435, V=4.84, A=4.18; Set 3 nonsocial/neutral=5,120, 7,590, 7,037, 7,100, 7,546, 7,190, 7,183, 1,313, 1,947, V=5.25, A=3.73; Set 3 social/positive=2,605, 4,606, 2,358, 2,344, 4,624, 4,650, 2,352, 4,626, 8,499, V=6.93, A=5.14; Set 3 nonsocial/positive=1,661, 7,284, 7,481, 8,162, 8,531, 7,480, 7,260, 8,502, 5,600, V=6.92, A=4.89.

over time relative to placebo (linear dose $\times$ quadratic time, $F[1, 34]=20.24$, $p<.001$, $\eta_p^2=.37$ and $F[1, 34]=11.71$, $p<.001$, $\eta_p^2=.26$, respectively). Effects were significant at both doses, and follow-up t -tests indicated they were present both before and after the IAPS task (Fig. 1). Amphetamine (10 and 20 mg) also increased ARCI-A scores over time relative to placebo (linear dose $\times$ quadratic time, $F[1, 34]=24.02$, $p<.001$, $\eta_p^2=.41$; Fig. 2, top panel), area under the curve for “Feel Drug” scores on the DEQ (linear dose, $F[1, 34]=31.94$, $p<.001$, $\eta_p^2=.48$; Fig. 2, middle panel), and MAP over time relative to placebo (linear dose $\times$ quadratic time, $F[1, 35]=12.49$, $p=.001$, $\eta_p^2=.26$; Fig. 2, bottom panel).

Emotional reactivity to stimuli

Self-report reactions—To examine positivity ratings, positive pictures were rated more positively than neutral and negative pictures (linear valence, $F[1, 35]=505.14$, $p<.001$, $\eta_p^2=.94$). Social pictures were rated more positively than nonsocial pictures ($F[1, 35]=7.03$, $p=.01$, $\eta_p^2=.17$). Amphetamine (20 mg) significantly increased positivity ratings across all types of pictures (linear dose, $F[1, 35]=7.86$, $p=.008$, $\eta_p^2=.18$; Fig. 3). Social content did not moderate this effect. To examine negativity, negative pictures were rated more negatively than neutral and positive pictures (linear valence, $F[1, 35]=500.76$, $p<.001$, $\eta_p^2=.94$). Social negative pictures were rated less negatively than nonsocial ones, and social neutral pictures slightly more negatively than nonsocial neutral pictures (social $\times$ quadratic valence, $F[1, 35]=47.64$, $p<.001$, $\eta_p^2=.58$). Amphetamine did not affect negativity. In examining ratings of arousal, pictures with social content were more arousing ($F[1, 35]=4.46$, $p=.04$, $\eta_p^2=.11$), and negative pictures were more arousing than positive pictures (linear valence, $F[1, 35]=7.10$, $p=.01$, $\eta_p^2=.17$). Amphetamine (20 mg) significantly increased arousal ratings across all picture types (linear dose, $F[1, 35]=6.41$, $p=.02$, $\eta_p^2=.16$; Fig. 3).

Facial EMG—We first examined prepicture EMG activity. Amphetamine increased corrugator EMG during prepicture periods, perhaps due to increased arousal ($F[1, 34]=5.39$, $p=.03$, $\eta_p^2=.14$), and corrugator baselines were slightly (but significantly) higher before positive than negative pictures (linear valence, $F[1, 34]=5.19$, $p=.03$, $\eta_p^2=.13$), possibly indicating carry-over effects from fixed picture order. Prepictorial zygomatic activity did not differ by session or picture type. To ensure that prepicture differences were not responsible for effects observed in corrugator difference scores, we analyzed raw picture values for corrugator EMG and found substantively the same pattern of effects reported for difference scores.

In examining corrugator EMG, positive pictures elicited less activity, and negative pictures more activity, as compared to neutral pictures (linear valence, $F[1, 34]=26.43$, $p<.001$, $\eta_p^2=.44$). Social negative pictures elicited slightly more activation, and social positive pictures slightly less than nonsocial pictures (social $\times$ linear valence, $F[1, 34]=5.60$, $p=.02$, $\eta_p^2=.14$). Amphetamine (20 mg) significantly decreased corrugator activity to positive pictures relative to placebo ($t[34]=2.26$, $p=.03$; Fig. 4), without affecting activity for other types of pictures (linear dose $\times$ linear valence, $F[1, 34]=10.62$, $p=.003$, $\eta_p^2=.24$). Social content did not moderate this effect. In examining zygomatic activity, positive pictures elicited the highest activity, while negative pictures elicited slightly more than neutral pictures (quadratic valence, $F[1, 33]=10.96$, $p=.002$, $\eta_p^2=.26$). A quadratic effect is expected as the zygomatic is mildly active during disgust (Lang et al. 1993). Social pleasant pictures elicited more zygomatic activity than nonsocial ones (social $\times$ linear valence, $F[1, 33]=7.19$, $p=.01$, $\eta_p^2=.18$; Fig. 5). Furthermore, amphetamine had a significant effect on zygomatic reactivity specific to picture type (linear dose $\times$ linear valence, $F[1, 32]=6.87$, $p=.02$, $\eta_p^2=.17$). Amphetamine 10 mg significantly, and 20 mg marginally, increased reactivity to positive

pictures without affecting other picture types ($t[32]=-2.30$, $p=.02$, and $t[32]=-1.78$, $p=.08$, respectively). Social content did not moderate this effect.

Relationship between mood and emotional reactivity—We tested whether the effect of amphetamine on emotional reactivity to environmental stimuli was mediated by its overall effects on mood using procedures from Judd et al. (2001) for within-subject mediation. Mediation requires that (1) the outcome (emotional reactivity to pictures) is predicted by treatment (amphetamine), (2) the mediator (subjective mood) is also predicted by treatment, (3) the mediator predicts the outcome, and (4) controlling for the mediator diminishes the effect of treatment on the outcome. Criteria 1 and 2 were established by analyses outlined above. Criteria 3 and 4 were examined by regressing significant effects of amphetamine on picture reactivity onto a set of contrasts representing effects of amphetamine on elation and arousal.

To summarize effects of amphetamine on subjective mood, we calculated relative area under the curve scores for Elation and Arousal at each session by subtracting baseline scores from all subsequent scores in the same session and by calculating the area under those difference scores. Following Judd and colleagues (Judd et al. 2001; Muller et al. 2005), we constructed polynomial contrast variables representing linear (uniform dose-dependent effects) and quadratic (unique nonlinear effects of the 10 mg session) effects of drug on Elation and Arousal, and the interactions of those effects with gender. Contrast variables representing amphetamine's effects on emotional reactivity to the pictures (positivity ratings, arousal ratings, corrugator, and zygomatic EMG) were then regressed onto contrast variables representing amphetamine's effects on mood. Results are presented in Table 2. Gender did not significantly moderate any relationships and is omitted for simplicity of reporting.

Table 2 showed the beta weights and accompanying t -statistics test unique relationships between each predictor (mood effect) and each outcome (picture reactivity effect), controlling for other predictor variables. No beta weights were significant, indicating none of the mood effects of amphetamine uniquely predicted its picture reactivity effects. We also examined total variance explained by the full set of mood effects, represented by R^2 and accompanying F statistics in Table 2. These statistics showed effects of amphetamine on mood explained a small and nonsignificant proportion of its effects on picture reactivity (4–8% of the variance). Thus, Criterion 3 for mediation was not met. However, effects of amphetamine on emotional reactivity to the pictures were also no longer significant after controlling for mood effects (the regression intercept is equivalent to results of an analysis of covariance on picture reactivity with the mood effects as covariates). This could result either from explanatory power of the covariates (supporting Criterion 4) or from loss of power due to addition of predictor variables. Additional examination of correlations between all effects of amphetamine at both doses can be found in Supplemental Information.

Discussion

Congruent with our hypothesis, D -amphetamine decreased corrugator reactivity and increased zygomatic reactivity to positive pictures, both of which indicate increased positive reactions to naturally pleasant stimuli. Indeed, consistent with prior reports that zygomatic is only active to highly pleasant pictures (Larsen et al. 2003), there was comparatively little zygomatic activation to our “weak” set of positive pictures (two thirds mildly or moderately pleasant) under placebo. This suggests amphetamine pushed mildly/moderately positive pictures over the “threshold” for zygomatic activation. In a similar effect, but one that was not specific to picture type, amphetamine enhanced arousal and positivity ratings for all types of emotional stimuli. Contrary to our second hypothesis, amphetamine did not preferentially enhance reactivity to stimuli with social content. This is surprising, as

amphetamine preferentially increases the value of social rewards in both animals and humans. However, the stimuli we used were only nominally “social,” not actual social interaction, but rather pictures of others interacting. Furthermore, it is not known whether either ratings or psychophysiological activation index “value” in the same way as a choice procedure.

Interestingly, although amphetamine produced its expected effects of euphoria and arousal, these mood changes were not highly related to the drug’s effects on emotional reactivity to the pictures (accounting for only 4–8% of the variance). This suggests the effects of the drug on reactivity to emotional stimuli may represent a different underlying process not related to the effects of the drug on self-reported mood. This is consistent with the findings of Harmer et al. (2008) and Leyton et al. (2005, 2007). However, amphetamine-induced changes in picture reactivity were also no longer significant after covarying for mood effects. Although this may simply represent loss of power due to the addition of more explanatory variables, these findings do leave open questions about the independence of these phenomena. Future studies using experimental manipulations that may affect one outcome but not the other, such as tyrosine depletion or threshold doses of amphetamine that do not produce subjective effects, will be necessary to definitively disentangle the mechanisms underlying these various effects of amphetamine.

These findings have implications for drug abuse etiology and also for risk-taking under the influence of stimulants. The ability of drugs to enhance responses to emotional stimuli may contribute to drug use and abuse by making positive unconditioned or conditioned stimuli more attractive. Several recent studies reported that addicts exhibit diminished responses to naturally positive stimuli (Heinz et al. 2007; Lubman et al. 2008, 2009). Thus, the stimulus-enhancing effects of drugs may be particularly appealing to individuals with preexisting deficits in positive reactions. Alternatively, observed deficits in reward processing in addicts may *result* from drug use, perhaps from adaptation and lowered set points in neural systems after repeated drug-induced “boosts” of positive responses. Another possible implication is that enhancement of hedonically pleasant stimuli might increase the likelihood of engaging risky reward-related (e.g., sexual) behaviors (Frohman et al. 2009).

The current study illustrates the value of psychophysiological indices of emotion in drug research. Relatively low correlations between the drug’s effects on psychophysiological and self-report ratings of emotional reactivity (see Supplemental Information) suggest that the effects of amphetamine on emotional reactivity may manifest differently in different individuals. Thus, some individuals’ responses to amphetamine might be “missed” using a single mode of measurement. Moreover, psychophysiological reactivity was affected for positive pictures only, while ratings of all types of pictures were altered by amphetamine. While the reasons for these different effects are not clear, there are a number of differences between psychophysiological and self-report measures that might partially account for them. Whereas self-ratings may be influenced by factors such as self-awareness or self-presentation, physiological indicators are less susceptible to these variables. Facial EMG reactions can be observed even when participants are explicitly directed to suppress their reactions and when stimuli are presented outside conscious awareness (Dimberg et al. 2000, 2002). Finally, although the current study focused on magnitude of emotional responses, “chronometric” parameters, such as duration and rise time, may be promising measures for future studies, as these reportedly distinguish pathological from normal emotion (Davidson 1998). Psychophysiological measures provide continuous, unobtrusive, and sensitive measurement of emotional responses, suited to capturing the full time course of responses.

The present findings should also be considered in the context of other drugs of abuse. Different drugs may vary in the degree to which they alter responses to emotional stimuli.

For example, high doses of alcohol suppress responses to negative stimuli (Donohue et al. 2007), while we found amphetamine enhances positive responses to stimuli. Animal studies of nicotine, another stimulant drug, have established that nicotine enhances the value of co-occurring positive stimuli (Caggiula et al. 2009), leading to a distinction between nicotine's relatively weak primary reinforcing effects and its "reinforcement-enhancing effect" on co-occurring stimuli, termed the "dual-reinforcement model." In humans, nicotine also appears to enhance the value of rewards (Barr et al. 2008; Dawkins et al. 2006), while having only weak effects on subjective mood (Rose et al. 2000). The findings of the current study suggest that this dual-reinforcement model might be profitably extended to other drugs of abuse, as amphetamine may also have reinforcement-enhancing effects in humans.

Limitations of this study include a relatively small participant sample with light drug use. A larger sample might enable the study of individual differences in the relationships between mood and picture responses (e.g., these relationships might vary based on high vs. low introspection or other individual characteristics). Participants did self-select by volunteering to participate in a drug study and thus may not represent the general population. The comparatively light level of drug use in our population also did not allow examination of the effects of the drug on emotional reactivity in heavy or dependent stimulant users. These effects might be different in heavier users, either due to preexisting differences or neural adaptations taking place over the course of dependence. Another limitation is the restricted range of stimuli, i.e., only pictures from the IAPS picture set, and the comparatively small number of pictures in each subset, which might decrease the accuracy of measurement. It is unknown how stimulants would impact the pleasantness of other types of stimuli (gustatory, monetary, etc.). Despite these limitations, these findings suggest a novel, potentially reinforcing effect of stimulants that may influence initiation and maintenance of stimulant use, and risk taking during stimulant use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Dr. John Cacioppo and his staff at the University of Chicago Center for Cognitive and Social Neuroscience for assistance with design and technical issues, and Cassandra Esposito, Celina Joos, and Megan Leino for their work on this study. The National Institute on Drug Abuse supported this work through grant R01 DA02812 to Dr. Harriet de Wit. Dr. Margaret Wardle is supported by a National Institute on Drug Abuse Training grant, T32 DA007255.

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Fig. 1.

Drug effects on mean ($\pm$ SEM) ratings of Profile of Mood States (*POMS*) on Arousal (*top panel*) and Elation (*bottom panel*) after placebo, 10 and 20 mg *D*-amphetamine ($N=35$). Amphetamine (10 and 20 mg) increased self-reported Arousal and Elation. * $p < .05$ Follow-up t -test between 20 mg and placebo, + $p < .05$ follow-up t -test between 10 mg and placebo

Fig. 2.

Drug effects on mean ($\pm$ SEM) ratings of Addictions Research Center Inventory (ARC) amphetamine scale (*top panel*), Drug Effects Questionnaire "Feel Drug" Visual Analog Scale (VAS, *middle panel*) and mean arterial pressure (*bottom panel*) after placebo, 10 and 20 mg amphetamine. Amphetamine (10 and 20 mg) produced typical increases in subjective ratings of drug effects and blood pressure. * $p < .05$ Follow-up t -test between 20 mg and placebo, + $p < .05$ follow-up t -test between 10 mg and placebo. Individual time-point tests of significance are omitted for "Feel Drug" ratings due to skew; areas under the curve for these ratings were compared instead

Fig. 3.

Mean ($\pm$ SEM) ratings of positivity (*left panel*) and arousal (*right panel*), collapsed across slide type at placebo, 10 and 20 mg amphetamine. Amphetamine (20 mg) significantly increased positivity and arousal ratings across all types of pictures. * $p < .05$ Follow-up t -test between 20 mg and placebo

Fig. 4. Mean ($\pm$ SEM) corrugator reactivity (square root transformed) to negative, neutral, and positive slides at placebo, 10 and 20 mg amphetamine. Amphetamine (20 mg) significantly decreased corrugator reactions to positive pictures without affecting reactivity to neutral or negative pictures. * $p < .05$ Follow-up t -test between 20 mg and placebo

Fig. 5. Mean ($\pm$ SEM) zygomatic reactivity (square root transformed) to negative, neutral, and positive slides at placebo, 10 and 20 mg amphetamine. Amphetamine (10 mg) significantly enhanced of zygomatic reactions to positive pictures. * $p < .05$ Follow-up t -test between 10 mg and placebo

Table 1

Demographic and substance use characteristics

	<i>n</i> (%) or <i>M</i> (<i>SD</i>), Total <i>N</i> =36
<i>Demographic variables</i>	
Sex (male/female)	16/20 (44%/46%)
Ethnicity	35 (97%) Non-Hispanic
Race	26 (72%) Caucasian
	5 (13%) African-American
	2 (6%) Asian
	3 (8%) Other/mixed race
Age	24.3 (4.5)
Education in years	15.4 (1.5)
<i>Current substance use</i>	
Typical alcoholic drinks/week	7.5 (6.0)
Smoking at all in past month	3 (8.3%)
<i>Lifetime occasions recreational use</i>	
Cannabis	4 (11%) Never
	18 (50%) 1–10×
	12 (33%) 11–50×
	2 (6%) >100×
Tranquilizers	35 (97%) Never
	1 (3%) 1–10×
Stimulants	28 (78%) Never
	7 (19%) 1–10×
	1 (3%) 11–50×
Opiates	34 (94%) Never
	2 (6%) 1–10×
Hallucinogens	29 (81%) Never
	7 (19%) 1–10×
Entactogens	31 (86%) Never
	5 (14%) 1–10×
Other drugs	34 (94%) Never
	2 (6%) 1–10×
Any illicit drug	18 (50%) 1–10×
	10 (28%) 11–50×
	2 (5.6%) 51–100×
	2 (5.6%) >100×

Table 2

Within-subject mediational analyses amphetamine effect of interest

Potential mediator	Beta	F-test/t-test	F statistics, P and R ² values
Effect on positivity ratings_(linear dose)		$t(34)=2.73$, $p=.01$	
Linear effect on POMS Elation	-.06	$t(30)=0.02$, $p=.82$	
Quadratic effect on POMS Elation	.07	$t(30)=0.28$, $p=.78$	
Linear effect on POMS Arousal	.31	$t(30)=1.24$, $p=.23$	
Quadratic effect on POMS Arousal	-.15	$t(30)=0.54$, $p=.60$	
Effect after controlling for mediators (intercept)		$t(30)=0.92$, $p=.36$	
Total variance explained by mediators			$F(4, 30)=.62$, $p=.65$, $R^2=8\%$
Effect on arousal ratings (linear dose)		$t(34)=2.03$, $p=.01$	
Linear effect on POMS Elation	-.20	$t(30)=0.74$, $p=.46$	
Quadratic effect on POMS Elation	-.06	$t(30)=0.23$, $p=.82$	
Linear effect on POMS Arousal	.32	$t(30)=1.24$, $p=.22$	
Quadratic effect on POMS Arousal	.13	$t(30)=0.48$, $p=.64$	
Effect after controlling for mediators (intercept)		$t(30)=1.39$, $p=.17$	
Total variance explained by mediators			$F(4, 30)=.47$, $p=.76$, $R^2=6\%$
Effect on corrugator reactivity (linear dose×linear valence)		$t(33)=-3.35$, $p=.002$	
Linear effect on POMS Elation	-.30	$t(29)=1.13$, $p=.27$	
Quadratic effect on POMS Elation	-.20	$t(29)=0.77$, $p=.44$	
Linear effect on POMS Arousal	.05	$t(29)=0.22$, $p=.83$	
Quadratic effect on POMS Arousal	.20	$t(29)=0.71$, $p=.48$	
Effect after controlling for mediators (intercept)		$t(29)=1.22$, $p=.23$	
Total variance explained by mediators			$F(4, 29)=.62$, $p=.65$, $R^2=8\%$
Effect on zygomatic reactivity (linear dose×linear valence)		$t(32)=2.62$, $p=.01$	

Potential mediator	Beta	F-test/t-test	F statistics, P and R ² values
Linear effect on POMS Elation	.12	$t(28)=0.44$, $p=.66$	
Quadratic effect on POMS Elation	.23	$t(28)=0.83$, $p=.42$	
Linear effect on POMS Arousal	-.06	$t(28)=0.26$, $p=.80$	
Quadratic effect on POMS Arousal	-.09	$t(28)=0.32$, $p=.75$	
Effect after controlling for mediators (intercept)		$t(28)=1.24$, $p=.23$	
Total variance explained by mediators			$F(4, 28)=.31$, $p=.87$, $R^2=4\%$

POMS Elation Profile of Mood States Elation scale, *POMS Arousal* Profile of Mood States Arousal scale