Emotional traits predict individual differences in amphetamine-induced positive mood in healthy volunteers

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Abstract

Background Previous research on emotional correlates of individual differences in subjective responses to D-amphetamine has focused on relatively broad personality traits. Yet, emotional functioning is best characterized by several narrow sub-components, each of which may contribute uniquely to amphetamine response. Here, we examine several specific subdomains of emotional functioning in relation to acute amphetamine response.

Method At a baseline session, healthy stimulant-naive volunteers (N=97) completed measures of several subdomains of baseline trait emotional functioning and then completed two counterbalanced experimental sessions during which they received a single oral dose of 20 mg D-amphetamine or placebo. Acute subjective drug response measures were completed at repeated intervals before and after drug administration. Data from subjective measures that were significantly modulated by amphetamine were reduced using principal component analysis (amphetamine or placebo) into three higher-order factors of “positive mood,” “arousal,” and “drug high.” Amphetamine did not significantly alter any “negative” subjective states. Separate multiple regression analyses were conducted regressing these three drug factors on baseline trait emotional functioning scales.

Results The combined set of trait emotional functioning indicators accounted for approximately 22 % of the variance in acute amphetamine-induced positive mood changes. Greater anticipatory pleasure and greater anxious distress each uniquely predicted greater amphetamine-induced positive mood. Trait emotional functioning did not significantly predict amphetamine-induced changes in arousal or drug high.

Discussion Emotional traits appear to moderate drug-induced positive mood but not other dimensions of amphetamine effects. Different facets of emotional functioning may differentially modulate amphetamine’s subjective effect profile.

Keywords Amphetamine · Emotion · Human · Subjective effects

Introduction

Laboratory studies consistently show significant inter-individual variability in the acute subjective effects of D-amphetamine (AMPH) on feelings of positive mood, euphoria, and drug-related arousal (Crabbe et al. 1983; Silberman et al. 1981; White et al. 2006; Kirkpatrick et al. 2013). Individual differences in AMPH’s subjective effects among young, drug-naive individuals are especially important because the initially “positive” subjective effects of a drug are thought to increase the likelihood of subsequent repeated use of the drug (see Comer et al. 2010; de Wit and Phillips 2012; Fischman and Foltin 1991; Jasinski 1991 for discussion). Thus, it is important to identify potential sources of variability in acute AMPH responses in young adults because individual differences in AMPH subjective response in this population may contribute to subsequent risk for abuse.
Depressive symptoms and other aspects of emotional disturbance have been linked to variability in both stimulant abuse risk and acute AMPH response. Data from clinical studies indicate that a relatively large proportion of individuals with a history of stimulant use disorders (including amphetamines and cocaine) have comorbid symptoms of depression and anxiety (Ross et al. 1988; Grant et al. 2004; Hall et al. 1996; Glasner-Edwards et al. 2010), and there is evidence that some of these symptoms predate the development of substance use disorders in general (Buckner et al. 2013; De Graaf et al. 2003). Furthermore, the severity of depression and anxiety symptoms has been positively associated with both the frequency of methamphetamine use and the severity of methamphetamine dependence (Darke et al. 2008, 2011). Additionally, severity of depression symptoms has been associated with intensity of amphetamine response in the laboratory among individuals with no history of drug use disorder. For example, Tremblay and colleagues (2002, 2005) found that non-drug-abusing individuals with severe major depressive disorder (vs. non-depressed controls) reported greater subjective reward following a single oral AMPH dose; among those with major depression, higher severity of depressive symptoms was associated with greater AMPH response. Overall, these results suggest that emotional functioning is an important factor in AMPH response and may be an indicator for abuse risk in general. However, it is unclear if enhanced AMPH sensitivity extends to a healthy population with variation in depression- and anxiety-related emotional symptoms below the clinical-diagnostic psychiatric threshold. This is an important omission, as experiencing just one or two (vs. no) symptoms of emotional disorder is associated with stimulant use frequency and likelihood of transitioning from initiation to dependence (Leventhal et al. 2010). Hence, individual differences in response to the rewarding effects of amphetamine may perhaps explain differences in propensity to transition from experimentation to regular use of stimulant drugs between those with subclinical mild/moderate (vs. minimal/no) emotional disturbance.

The specific subdomains of emotional functioning that predict AMPH response are also unclear. Symptoms of depression and other emotional disturbances, as well as emotional functioning in general, are highly heterogeneous, with features that often do not cluster together into a single category or empirically common dimension (Shafer 2006). Rather, emotional functioning in clinical and healthy populations is likely best characterized by a cluster of interrelated subdomains of emotional functioning that may manifest as symptoms or traits (Insel et al. 2010; Cuthbert and Insel 2013). Each of these subdomains may differentially predict acute AMPH subjective response.

Based on research of underlying dimensions of depression-related emotional functioning (Watson et al. 1988a; Clark and Watson 1991) and psychobiologically plausible moderators of AMPH response (Tremblay et al. 2002, 2005), important trait emotional functioning subdomains that may modulate AMPH response include pleasure capacity (i.e., motivation to engage in and response to pleasant activities), anhedonia (i.e., diminished enjoyment and pleasure in response to normally pleasant activities), general distress (i.e., symptoms of worry, irritability, tensions, sadness, concentration problems), and trait positive and negative affect. Interestingly, there is an accumulation of suggestive evidence that the same neurochemical systems that underlie the effects of AMPH—which is a potent releaser of dopamine (DA), norepinephrine (NE), and serotonin (5-HT) (Rothman et al. 2001)—partially mediate the above components of emotional functioning. For example, all three of these monoamine neurotransmitters are likely to be involved in variations in positive mood (Ruhé et al. 2007). Additionally, anhedonia and low positive affect have been linked with decreased DA function in particular (Wise 1982) and are putatively pathognomonically specific to depression and distinct from anxiety (Watson et al. 1988a; Clark and Watson 1991). Further, NE function has been implicated in anxiety and general distress responses (Bremner et al. 1996) and may reflect underlying dimensions of emotional functioning that are shared among depression and anxiety. Hence, these aspects of emotional functioning may collectively account for multiple pathways that modulate AMPH subjective response.

This study investigated several measures of trait emotional functioning as predictors of acute subjective response to a single oral dose of 20 mg AMPH (vs. placebo) administered double blind on separate counterbalanced days in healthy young adults. Our primary goal was to test the notion that by assessing multiple subdomains of emotional functioning, we could collectively account for variance in subjective AMPH response profiles. We therefore hypothesized that combined variance across multiple subdomains of emotional functioning (i.e., anhedonia, capacity for pleasure experience, depression- and anxiety-related general distress, and trait positive and negative affect) would collectively predict individual differences in AMPH response. Because of the paucity of research isolating distinct domains of emotional functioning and disparate dimensions of AMPH response, we did not make hypotheses regarding which subdomains of emotional functioning would uniquely predict particular AMPH response outcomes.

**Methods**

**Participants**

Healthy adult volunteers (N=97) were recruited from the Los Angeles area via Internet announcements, newspaper advertisements, community bulletin boards, and local human...
subject participated in a study on individual differences in psychoactive drug effects. Inclusion criteria were the following: age between 18 and 35 years, at least a high school education, fluency in English, and BMI of 19–30. Exclusion criteria included night shift work, any medical or psychiatric condition requiring medication, and any other conditions that increased risk for participation, such as lifetime history of bipolar or panic disorder or any other current DSM-IV Axis I disorder. Participants were also excluded if they reported any history of problems related to substance use, being treated for a substance use disorder, smoking more than 10 cigarettes per week, history of recreational or medical use of stimulants (D-amphetamine, methamphetamine (MDMA), methylphenidate), consuming more than three cups of coffee per day, or had positive urine toxicology screens for drugs of abuse. Women who were pregnant, breastfeeding, or planning to become pregnant during the study were not eligible.

The study was reviewed and approved by the Institutional Review Board at the University of Southern California in accordance with the Code of Federal Regulations (Title 45, Part 46) adopted by the National Institutes of Health and the Office for Protection from Research Risks of the US Federal Government. The study was conducted ethically in accordance with the Helsinki Declaration of 1964 (revised 1989) and the National Advisory Council on Drug Abuse Recommended Guidelines for the Administration of Drugs to Human Subjects.

Design

The study used a within-subjects design in which, following the baseline session, single doses of oral D-amphetamine (20 mg) and placebo were administered in two separate, double-blind, counterbalanced experimental sessions. At each 4-h experimental session, a battery of subjective and cardiovascular measures was administered before and at repeated intervals following drug (or placebo) administration to characterize drug response.

Procedure

After preliminary phone eligibility assessment, participants attended an in-person screening session that included written informed consent, a psychiatric interview, and a physical examination with an electrocardiogram. Eligible participants then completed a battery of measures of emotional functioning, which were study predictor variables (described below). Participants were told that the purpose of the study was to evaluate individual differences in drug response. They were told that they could possibly receive a stimulant, a sedative, an antidepressant, or a placebo.

Experimental sessions were conducted in the morning from 9:00 a.m. to 1:00 p.m. between 2 and 14 days apart. Subjects were tested individually and remained in a room with television and reading materials for the 4-h session. Volunteers could watch emotionally neutral movies and read during the visits when measurements were not being taken. Women were tested during the follicular phase of their menstrual cycle (as D-amphetamine effects are dampened during the luteal phase; White et al. 2002) unless they reported taking birth control medications. Participants were provided with a light breakfast after fasting from midnight the night before each session. Upon arriving, participants provided urine and breath samples to confirm drug and alcohol abstinence and women were tested for pregnancy; participants testing positive were excluded. Then, the baseline (pre-manipulation) subjective assessment was administered. At approximately 9:30 a.m., participants ingested a capsule containing placebo or 20 mg D-amphetamine and then administered with subjective measures at +30, +60, +90, +150, and +180 min after capsule administration. At 180 min (approximately 12:30 p.m.), participants completed end-of-session ratings and were discharged at approximately 1:00 p.m., provided that their heart rate and blood pressure had returned to baseline levels.

Baseline session measures

Participants provided demographic information, and psychiatric eligibility was assessed using Structured Clinical Interview for DSM-IV Non-patient Edition (First et al. 2002). Additionally, the following measures were utilized to assess several subdomains of trait emotional functioning:

- **Anhedonia** was measured with the Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al. 1995), a 14-item survey that measures the capacity to experience pleasure in the past few days. Each of the items is rated on a 4-point Likert scale (from strongly disagree to strongly agree). Mean scores ranged from 1 to 4. A lower mean score indicated higher levels of anhedonia.

- **Pleasure capacity** was measured using the 18-item Temporal Experience of Pleasure Scale (TEPS; Gard et al. 2006) that was designed to measure individual trait dispositions in both anticipatory (TEPS-ANT, 10-item subscale; example item=“I look forward to a lot of things in my life”) and consummatory (TEPS-CON, 8-item subscale; example item=“I really enjoy the feeling of a good yawn”) experiences of pleasure. Each of the items was rated on a 6-point Likert scale [from 1 (very false for me) to 6 (very true for me)], and each subscale was calculated as a mean score (range=1 to 6). A higher mean score indicated greater pleasure capacity for each subscale.

- **Depression-related general distress** and **anxiety-related general distress** were measured using the 62-item Mood...
and Anxiety Symptom Questionnaire-Short Form (MASQ; Watson et al. 1995). To assess general levels of current symptoms of depressed mood and anxiety, we used the 62-item MASQ. Participants indicated how much they have experienced each symptom on a 5-point Likert scale [from 1 (not at all) to 5 (extremely)]. We used the MASQ-GDD subscale for depression-related general distress and the MASQ-GDA subscale for anxiety-related general distress. Each subscale was calculated as a mean score (range=1 to 5).

- **Trait positive and negative affect** were measured using the 20-item Positive and Negative Affect Schedule (PANAS; Watson et al. 1988b). Participants were presented with a list of 20 mood-related adjectives and asked to rate the extent to which they felt that in general. Items were rated on a 5-point Likert scale [from 1 (not at all) to 5 (extremely)]. Each subscale (i.e., positive and negative) was calculated as a mean score (range=1 to 5).

### Experimental session measures

**Acute subjective drug response** was measured using the Drug Effects Questionnaire (DEQ), the Profile of Mood States (POMS), and the Addiction Center Research Inventory (ARCI). The DEQ (Fischman and Foltin 1991) consists of four 100-mm visual analog scales in which participants rate how much they “feel the drug,” “like the drug,” “feel high,” and “want more,” with the left anchor labeled “no drug effect” and the right anchor labeled “strong effect.” The POMS (Johanson and Uhlenhuth 1980; McNair et al. 1971) is a 72-item adjective checklist of momentary mood states rated on a 5-point Likert scale from 0 (not at all) to 4 (extremely). It has several subscales, including anxiety, depression, vigor, fatigue, friendliness, anger, elation, arousal, confusion, and overall positive mood and negative mood composites. The ARCI (Martin et al. 1971) is a 49-item true-false questionnaire that has five empirically derived subscales validated to measure characteristic effects related to specific drug classes: amphetamine (A; stimulant effects), benzedrine group (BG; energy and intellectual efficiency), morphine-benzedrine group (MBG; euphoria), pentobarbital-chlorpromazine-alcohol group (PCAG; sedation), and lysergic acid diethylamide (dysphoria and somatic complaints).

### Drug

Tablets of d-amphetamine sulfate (AMPH; 4×5 mg; Amedra Pharmaceuticals) were encapsulated in 00 opaque capsules with dextrose filler. Placebo capsules looked identical but contained only dextrose. The 20-mg d-amphetamine dose was selected based on previous studies indicating differences in acute drug response as a function of trait personality measures (White et al. 2006; Kirkpatrick et al. 2013).

### Data analysis

#### Preliminary analyses

Descriptive statistics and intercorrelations of emotional functioning and demographic characteristics of the sample were first calculated. To characterize the acute effects of AMPH over the time course of the session, each subjective and cardiovascular outcome measure was calculated as area under the curve (AUC) as in prior work (Kirkpatrick et al. 2013). Placebo session AUC values were subtracted from AMPH session AUC values in order to generate “drug effect” difference scores. We also characterized acute effects of AMPH on the individual cardiovascular and subjective measures for the entire sample using one-sample *t* tests (test value=0) of the drug effect difference scores.

#### Primary analyses

**Data reduction** To reduce the subjective data into factors appropriate for analysis with emotional functioning predictors, the subjective effect outcome measures significantly altered by AMPH (i.e., difference scores were significantly different than 0) were entered into a principal component analysis (promax rotation, eigenvalue=1) following the procedures for data reduction reported previously (Kirkpatrick et al. 2013). Outcome measures that loaded greater than 0.4 on a single factor but did not cross-load on multiple factors were used to calculate factor scores (i.e., the unweighted average AUC difference score values for outcome measures which loaded on each factor). This process resulted in three distinct factors, which we named positive mood, arousal, and drug high (see below).

**Hypothesis testing** Emotional functioning measures were tested as predictors of AMPH-related subjective effect factor scores using multiple regression models. We tested separate regression models for each subjective effect factor score (positive mood, arousal, and drug high). Each model was constructed in a two-step process in which all seven emotional functioning predictors were added simultaneously to a baseline model including only gender, age, and ethnicity in order to examine the incremental predictive effects after controlling for demographics. For models in which the *R*² change for the incremental predictive effects of the set of emotional functioning predictors over and above demographics was significant (*p* <0.05), we reported standardized regression weights (*β*) as well as zero-order correlation and squared semipartial correlation coefficients, for each predictor.
Results

Sample characteristics and intercorrelations of trait emotional functioning measures

Ninety-seven participants (68 females and 29 males) with a mean±SD age of 23.3±4.1 completed this study. Overall, the sample was relatively ethnically diverse (36 Asian, 12 Black, 6 Hispanic, 2 Middle Eastern, 12 Multiracial, 29 White). Table 1 shows the descriptive statistics and intercorrelations among the seven emotional functioning scales. The intercorrelations of the emotional functioning measures ranged from minimal to strong \( r = 0.00 \) to \( 0.62 \), suggesting that the variables were tapping multiple constructs that were distinct in some cases and overlapping in other cases. For example, PANAS negative was correlated with both depression-related general distress (MASQ-GDD; \( r = 0.60 \)) and anxiety-related general distress (MASQ-GDD; \( r = 0.57 \)). Overall, correlational analyses revealed that no pair of baseline trait measures was empirically redundant (Table 1).

Acute subjective drug effects in the overall sample

AMPH significantly increased heart rate, blood pressure, three ARCI scales [A (stimulant), BG (energy), MBG (euphoria)], five POMS scales (arousal, elation, friendliness, positive mood, and vigor), and DEQ ratings of feel the drug, feel high, like the drug, and want more. AMPH significantly decreased ARCI PCAG (sedation) and POMS (fatigue). The effect size for all significant drug effects ranged from medium to large \[ t(96) = 2.3\text{–}10.8; \text{Cohen’s } d = 0.23\text{–}1.10, \] for all analyses. AMPH did not significantly alter responses on acute “negative” mood measures: ARCI LSD and POMS anger, anxiety, confusion, depression, and negative mood. Thus, these measures were not included in the principal component analysis below.

Reduction of subjective effect outcome measures

Principal component analysis of the subjective effects (Table 2) indicated that there were three correlated factors that explained 72.1 % of the variance: Factor 1 was labeled “positive mood,” factor 2 was labeled “arousal,” and factor 3 was labeled “drug high.” The italicized factor loadings in Table 2 indicate the outcome measures that were used to calculate the factor scores used in subsequent analyses. The positive mood factor was significantly correlated with both arousal and drug high factors \( r = 0.56 \) and \( 0.38 \), respectively, and arousal and drug high were significantly correlated \( r = 0.21 \).

Relationship between trait emotional functioning measures and acute AMPH-related subjective effects

The set of trait emotional functioning measures explained a significant portion of variance in AMPH-related positive mood effects over and above demographics \( R^2 \text{ change} = 0.222, F \text{ change}(7,86) = 3.7, p = 0.002 \). In this model, greater anticipatory pleasure (TEPS-ANT) and anxiety-based general distress (MASQ-GDA) and lower negative affect (PANAS negative) independently predicted greater AMPH-induced increases in positive mood (see Table 3). Additionally, there was a non-significant trend indicating that higher anhedonia

<table>
<thead>
<tr>
<th>Variable</th>
<th>M (SD)</th>
<th>Intercorrelations (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1  2  3  4  5  6  7</td>
</tr>
<tr>
<td>1 SHAPS</td>
<td>3.5 (.3)</td>
<td>(0.78)</td>
</tr>
<tr>
<td>2 TEPS-ANT</td>
<td>4.7 (.6)</td>
<td>0.36** (0.70)</td>
</tr>
<tr>
<td>3 TEPS-CON</td>
<td>4.4 (.8)</td>
<td>0.33** 0.46** (0.71)</td>
</tr>
<tr>
<td>4 MASQ-GDA</td>
<td>1.3 (.3)</td>
<td>−0.04 0.04 0.21* (0.74)</td>
</tr>
<tr>
<td>5 MASQ-GDD</td>
<td>1.3 (.4)</td>
<td>−0.14 0.16 0.12 0.62** (0.85)</td>
</tr>
<tr>
<td>6 PANAS (positive)</td>
<td>3.5 (.6)</td>
<td>0.19 0.21* 0.17 0.00 −0.14 (0.86)</td>
</tr>
<tr>
<td>7 PANAS (negative)</td>
<td>1.5 (.5)</td>
<td>−0.29** 0.05 0.08 0.57** 0.60** 0.06 (0.91)</td>
</tr>
</tbody>
</table>

Internal consistency estimates (Cronbach’s \( \alpha \)) are shown in parentheses

SHAPS Snaith-Hamilton Pleasure Scale (measure of anhedonia); TEPS-ANT Temporal Experience of Pleasure Scale, anticipatory scale (measure of anticipatory pleasure capacity); TEPS-CON Temporal Experience of Pleasure Scale, consummatory scale (measure of consummatory pleasure capacity); MASQ-GDA Mood and Anxiety Symptom Questionnaire, general distress anxiety scale (measure of anxiety-related distress); MASQ-GDD Mood and Anxiety Symptom Questionnaire, general distress depression scale (measure of depression-related distress); PANAS Positive and Negative Affect Schedule (measures of trait positive and negative affect)

**p<0.01; *p<0.05
Drug Effects Questionnaire, by AMPH were not included in the PCA factor scores. Subjective effect scales that were not significantly altered italicized factor loadings indicate the items that were used to calculate POMS group), PHB-benzedrine group; PCAG=pentobarbital-chlorpromazine-alcohol inventory (A=amphetamine scale; BG=benzedrine group; MBG=mor-

spectively), indicating that these measures were not strongly associated with AMPH response in the absence of the entire set of trait emotional functioning predictors. Given the moderate to strong correlations found between some of the trait emotional functioning measures, we conducted tests for multicollinearity in the model. Overall, tolerances for predictors were between 0.47 and 0.76, indicating that the individual predictors were non-redundant.

In the models predicting AMPH-related increases in arousal or drug high factor, the set of emotional functioning measures did not significantly predict variance in AMPH effects over and above demographic variables ($R^2$ change=0.04–0.09, $F$ change $(7,86)=0.7–1.2$, $p=0.291–0.706$).

**Discussion**

In support of our hypothesis, assessing multiple subdomains of depression-related emotional functioning allowed us to characterize a broad spectrum of inter-individual variation in emotional functioning that collectively explained variance in AMPH-induced enhancement of acute positive mood. These results are consistent with earlier findings that individual differences in positive AMPH response are related to major depression status and severity on a composite measure that concatenates all depressive symptoms into a single syndrome index among clinically depressed individuals (Tremblay et al. 2002, 2005). Here, we extend previous findings by presenting evidence that subclinical variation in these subdomains of emotional functioning in non-depressed healthy volunteers also predicts AMPH response. Thus, the current results suggest that individual differences in sensitivity to amphetamine’s acute effects may be due in part to normal variation in trait emotional functioning and not to pathological emotional functioning per se. We also demonstrate that there is a

### Table 2: Principal component analysis (PCA) of acute AMPH-related subjective effect measures ($N=97$)

<table>
<thead>
<tr>
<th></th>
<th>Factor 1 Positive mood</th>
<th>Factor 2 Arousal</th>
<th>Factor 3 Drug high</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feel</td>
<td>−0.280</td>
<td>−0.025</td>
<td>0.905</td>
</tr>
<tr>
<td>Like</td>
<td>0.383</td>
<td>0.089</td>
<td>0.451</td>
</tr>
<tr>
<td>High</td>
<td>0.123</td>
<td>−0.040</td>
<td>0.808</td>
</tr>
<tr>
<td>More</td>
<td>0.382</td>
<td>−0.089</td>
<td>0.451</td>
</tr>
<tr>
<td>ARCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.092</td>
<td>0.592</td>
<td>0.325</td>
</tr>
<tr>
<td>BG</td>
<td>−0.034</td>
<td>0.862</td>
<td>0.119</td>
</tr>
<tr>
<td>MBG</td>
<td>0.464</td>
<td>0.327</td>
<td>0.249</td>
</tr>
<tr>
<td>PCAG</td>
<td>−0.098</td>
<td>−0.842</td>
<td>0.113</td>
</tr>
<tr>
<td>POMS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arousal</td>
<td>0.367</td>
<td>0.634</td>
<td>−0.094</td>
</tr>
<tr>
<td>Elation</td>
<td>0.983</td>
<td>−0.012</td>
<td>−0.066</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.127</td>
<td>−0.865</td>
<td>0.145</td>
</tr>
<tr>
<td>Friendliness</td>
<td>0.941</td>
<td>−0.104</td>
<td>−0.031</td>
</tr>
<tr>
<td>Positive mood</td>
<td>0.890</td>
<td>0.053</td>
<td>−0.004</td>
</tr>
<tr>
<td>Vigor</td>
<td>0.780</td>
<td>0.110</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Italicized factor loadings indicate the items that were used to calculate factor scores. Subjective effect scales that were not significantly altered by AMPH were not included in the PCA

*DEQ* Drug Effects Questionnaire, *ARCI* Addiction Research Center Inventory (A=amphetamine scale; BG=benedrine group; MBG=mor-

### Table 3: Regression parameter estimates for trait emotional functioning measures as predictors of AMPH-induced changes in positive mood (factor 1), controlling for demographic variables ($N=97$)

<table>
<thead>
<tr>
<th></th>
<th>$\beta$</th>
<th>$t$ (96)</th>
<th>$p$</th>
<th>Tolerance</th>
<th>Zero order</th>
<th>Semipartial $^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHAPS</td>
<td>−0.198</td>
<td>−1.699</td>
<td>0.09</td>
<td>0.638</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>TEPS-ANT</td>
<td>0.456</td>
<td>3.861</td>
<td>&lt;0.001</td>
<td>0.621</td>
<td>0.30</td>
<td>0.13</td>
</tr>
<tr>
<td>TEPS-CON</td>
<td>−0.078</td>
<td>−0.678</td>
<td>0.50</td>
<td>0.649</td>
<td>0.10</td>
<td>0.00</td>
</tr>
<tr>
<td>MASQ-GDA</td>
<td>0.422</td>
<td>3.224</td>
<td>0.002</td>
<td>0.505</td>
<td>0.22</td>
<td>0.09</td>
</tr>
<tr>
<td>MASQ-GDD</td>
<td>−0.098</td>
<td>−0.719</td>
<td>0.47</td>
<td>0.466</td>
<td>0.12</td>
<td>0.00</td>
</tr>
<tr>
<td>PANAS (positive)</td>
<td>−0.132</td>
<td>−1.247</td>
<td>0.22</td>
<td>0.755</td>
<td>−0.12</td>
<td>0.01</td>
</tr>
<tr>
<td>PANAS (negative)</td>
<td>−0.277</td>
<td>−2.088</td>
<td>0.04</td>
<td>0.491</td>
<td>−0.02</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*SHAPS* Snaith-Hamilton Pleasure Scale (measure of anhedonia); *TEPS-ANT* Temporal Experience of Pleasure Scale, anticipatory scale (measure of anticipatory pleasure capacity); *TEPS-CON* Temporal Experience of Pleasure Scale, consummatory scale (measure of consummatory pleasure capacity); *MASQ-GDA* Mood and Anxiety Symptom Questionnaire, general distress anxiety scale (measure of anxiety-related distress); *MASQ-GDD* Mood and Anxiety Symptom Questionnaire, general distress depression scale (measure of depression-related distress); *PANAS* Positive and Negative Affect Schedule (measures of trait positive and negative affect)
complex set of relationships between several subdomains of trait emotional functioning and acute AMPH subjective response, suggesting multiple psychobiological pathways linking emotional functioning and this indicator of stimulant abuse liability.

Among the set of emotional functioning subdomains examined, greater anticipatory pleasure predicted greater AMPH-induced positive mood incremental to the other emotion indicators. That is, people who reported tendencies toward more excitement and motivation to engage in pleasurable experiences experienced greater AMPH-related increases in positive mood, which is consistent with previous work showing a relationship between acute AMPH subjective effects (at similar doses) and individual differences in reward sensitivity (White et al. 2006; Kirkpatrick et al. 2013), a similar trait that reflects motivation to approach incentive stimuli. Reward sensitivity has been linked to DA function, with higher reward sensitivity scores predicting physiological response following administration of a D2 receptor agonist (Depue et al. 1994). Additionally, several lines of evidence link anticipation of reward with DA function in both animal and human studies (Schott et al. 2008; Schultz et al. 1992; Berridge and Robinson 1998). Hence, common underlying neurochemical mechanisms may explain why anticipatory pleasure and conceptually similar traits predict greater AMPH response.

Anxiety-related general distress (as measured by the MASQ-GDA) also incrementally predicted greater AMPH-related increases in positive mood. Anxiety-related general distress is implicated in forms of anxiety that are highly comorbid with depression, such as generalized anxiety and PTSD (Campbell et al. 2007; Rector et al. 2007). Several studies have found increases in basal levels of plasma NE in patients with PTSD and GAD (Charney et al. 1989; Sevy et al. 1989; Southwick et al. 1999; Geracioti et al. 2008), and both of these disorders are associated with increased likelihood of cocaine and amphetamine use disorders in the general population (Conway et al. 2006; Shaffer and Eber 2002). Thus, it is possible that individuals who have more anxiety-related general distress symptomatology may be more sensitive to AMPH’s acute effects because of the drug’s potent effects on the NE system. Of course, while it is important to note that the individuals in the current study were not clinically anxious (i.e., they had no axis I disorders and reported relatively low subclinical scores on the MASQ-GDA), these data suggest that even subclinical variability in anxious symptoms may be an important source of sensitivity to amphetamine’s acute effects. Nevertheless, future studies should examine whether the current findings generalize to a clinical population.

Regarding the remaining specific subdomains of trait emotional functioning and acute AMPH-induced positive mood, we found that negative affect was inversely related to drug response. This finding appears to contradict the positive relationship between AMPH effects and anxious distress, given conceptual similarity between negative affect and anxious distress and the relatively strong correlation between the measures used to assess these subdomains (i.e., PANAS negative and MASQ-GDA). It is important to note, however, that the zero-order correlation between PANAS negative and AMPH-induced positive mood (i.e., the association between the two variables in the absence of all other trait emotional functioning predictors) revealed that this trait emotional functioning measure was not significantly associated with acute AMPH-induced positive mood. Perhaps, this finding indicates that when variance in other domains of emotional functioning are partially out, the remaining variance in trait negative affect taps a construct in which lower affect intensity predicts greater AMPH effects. We also found suggestive evidence that individuals higher in anhedonia reported greater increases in positive mood. Although this is consistent with previous studies (Tremblay et al. 2002, 2005; Newton et al. 2005), the current finding should be treated with caution as the relationship merely reached trend-level significance and zero-order correlations between SHAPS and AMPH-induced positive mood were not significant. Depression-related general distress, consummatory pleasure experience, and trait positive affect did not incrementally predict variation in AMPH-induced changes in acute positive mood states. Given that this is the first study to explore these measures as predictors of AMPH response, it is difficult to relate these null findings to prior empirical work. On balance, the overall results suggest that some subdomains of emotional functioning are more pertinent to individual differences in AMPH subjective response than others and that these subdomains may be less pertinent.

We did not find evidence that measures of trait emotional functioning predicted variation in AMPH-induced changes in subjective arousal or drug high, of which the latter may have greater face validity as a measure of amphetamine reward. Patterns whereby individual difference in emotional traits predict some domains of subjective AMPH response, but not others, is common in the literature (White et al. 2006; Kirkpatrick et al. 2013). Prior work on depression and anhedonia also shows prediction of AMPH response on outcomes overlapping with our positive mood factor but not other AMPH outcomes (Tremblay et al. 2005). Given that recreational users of amphetamines often report using these stimulants specifically because of their effects on enhanced mood and sociability (Halkitis et al. 2005; Kelly et al. 2006; Rodgers et al. 2006), it is possible that the current subjective effect factor of positive mood may be an important indicator of amphetamine’s abuse potential. Of course, this is speculative; future longitudinal studies might examine the relationship between early amphetamine-induced social/emotional responses and risk from transitioning from experimentation to regular use.
In noting study limitations, we tested only one dose of AMPH. Hence, it would be of use to test dose-response effects in future work, given evidence that response to intermediate doses may have correlates that are distinct from the 20-mg dose used here (Hart et al. 2012). While we examined variability at the lower end of the emotional disturbance continuum, it is unclear whether these findings would generalize to individuals with current diagnosable psychopathology, which we excluded for human subject protection purposes. Additionally, while we excluded individuals with a past history of medical use of stimulants (e.g., amphetamine for ADHD treatment), we did not assess for ADHD. Considering that there is evidence suggesting neuroanatomic differences between individuals with ADHD and healthy controls (including differences in dopaminergic functioning in the striatum and noradrenergic functioning in the prefrontal cortex; Baroni and Castellanos 2015) and associations between ADHD and emotional disturbance (Kessler et al. 2006), it is possible that individuals with ADHD may have influenced the relationships between trait emotional functioning and AMPH subjective effects demonstrated here. Future studies should assess ADHD symptomatology and parse the relative roles of ADHD and emotional functioning in AMPH response. Finally, we utilized only self-report measures in this study and future research utilizing some objective indicators of AMPH reward (e.g., drug choice) would be useful to explore if these results extend to other abuse liability indices.

Limitations notwithstanding, these findings further our knowledge of the individual differences in acute AMPH response that may help to elucidate the mechanisms of the drug’s abuse potential in individuals with unique profiles of emotional functioning. These results suggest exploring how anticipatory pleasure and other related traits might modulate AMPH response and abuse liability could be of value. Further, they highlight the value of comprehensive characterization of multiple subdomains of emotional functioning to explain individual differences in AMPH response.

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References


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