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Personality and the Subjective Effects of Acute Amphetamine in Healthy Volunteers

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Individual differences in the positive mood and other subjective effects of *d*-amphetamine have been linked to personality traits related to sensation seeking. The current study extends these associations to separate personality traits of reward sensitivity, physical fearlessness, and impulsivity. A total of 128 healthy volunteers received oral doses of *d*-amphetamine (10 and 20 mg) or placebo in counterbalanced order. Their responses to the drug were measured using the Profile of Mood States, Addiction Research Center Inventory, and Drug Effects Questionnaire. Participants completed the Multidimensional Personality Questionnaire Brief Form to assess personality traits related to reward sensitivity (Agentic Positive Emotionality and Social Potency (SP)), physical fear (Harm Avoidance (HA)), and impulsivity (Control (CL)). Participants were rank ordered on each trait, and individuals with scores in the top and bottom thirds of scores on each trait were compared using ANCOVA. High trait physical fearlessness (low HA) was associated with greater positive activational effects of 10 mg *d*-amphetamine. High trait reward sensitivity (high SP) was marginally associated with greater positive activational effects of 20 mg *d*-amphetamine. High trait impulsivity (low CL) was unrelated to positive drug effects in response either dose. The two separate personality traits of physical fearlessness and reward sensitivity are associated with *d*-amphetamine effects on mood in healthy volunteers. Implications for the vulnerability to psychostimulant addiction in healthy nonaddicts are discussed.
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INTRODUCTION

The acute effects of *d*-amphetamine on measures such as elation, euphoria, and excitation vary across individuals (de Wit *et al*, 1986; Silberman *et al*, 1981; Nurnberger *et al*, 1982). Individual differences in the magnitude of the drug effect have been reported, on measures such as self-reports of control, friendliness, and arousal, and physician-rated elation (Crabbe *et al*, 1983; Silberman *et al*, 1981). Individual differences in the direction or quality of the effects of the drug have also been reported, including, for example, either increases or decreases in observer-rated excitation, self-rated tension, and fMRI measures of prefrontal cortex efficiency (Nurnberger *et al*, 1982; Crabbe *et al*, 1983; Mattay *et al*, 2003). Causes of such between-subjects differences are not well understood. However, commonalities exist between the neurochemical mechanisms of direct drug effects and the apparent neurobiological basis of personality traits, suggesting that individual differences in responses to stimulant drugs may relate systematically to individual differences in personality among other factors (for example, see Mattay *et al*, 2003; Reif and Lesch, 2003).

To date, most studies examining associations between personality and *d*-amphetamine effects have focused on the personality traits of Tridimensional Personality Questionnaire (TPQ) Novelty Seeking, SSS-V sensation seeking, and Eysenck Personality Questionnaire Psychoticism (EPQ-P), and have produced inconsistent results (Table 1). For instance, TPQ Novelty Seeking was positively associated with subjective stimulation in one study (Hutchison *et al*, 1999), and with elevated mood in another (Sax and Strakowski, 1998), but TPQ scores were unrelated to *d*-amphetamine effects in a third (Corr and Kumari, 2000). SSS-Form V sensation seeking was positively associated with subjective stimulation, elation, vigor, and positive mood effects of *d*-amphetamine in one study (eg Hutchison *et al*, 1999), but were unrelated in others (eg Alessi *et al*, 2003; Chait, 1993; de Wit *et al*, 1986). In another study, EPQ-P, a measure of fearless impulsivity associated with sensation seeking, was not associated with energetic arousal ratings in participants who received 5 or 10 mg *d*-amphetamine, but was positively associated with energetic

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Table 1 Personality Investigations of Positive Subjective Responses to *d*-Amphetamine

				Findings			
					EPQ/EPI	TPQ	
Authors	***N***	***d*-Amphetamine dose**	**Personality measures**	**SSS**	**P**	**NS**	**Details**
Alessi *et al* (2003)	24 (16)	0, 5, 10, 20 mg p.o.[a]	SSS Form V (Zuckerman *et al*, 1978)	n.s.			SSS scales unrelated to HR, LR groupings, mood/subjective effects on POMS, ARCI, VAS measures
Corr and Kumari (2000)	63 (31)	0, 5, 10 mg p.o.[b]	Eysenck Personality Questionnaire (EPQ; Eysenck and Eysenck, 1975); Tridimensional Personality Questionnaire (TPQ; Cloninger, 1989)		–, +	n.s.	High EPQ-Psychoticism Ss: Amphetamine group reported decreased energetic arousal, increased tense arousal, and decreased hedonic tone compared to placebo group on UWIST Mood Adjective Checklist (UMACL); TPQ Novelty Seeking, EPQ-Extraversion unrelated to amphetamine effects on UMACL
Hutchison *et al* (1999)	36 (18)	0, 20 mg p.o.[a]	SSS Form V (Zuckerman *et al*, 1978); TPQ Version 4 (Cloninger, 1987)	+		+	TPQ Novelty Seeking $r = 0.46$, $p < 0.05$ with subjective stimulation (BAES); SSS-V ES, Dis, BS r's = 0.42, 0.49, 0.46, $p < 0.05$ with BAES Stimulation; SSS-V Dis $r = 0.45$, 0.45, 0.41 with POMS Elation, Vigor, Positive Mood, $p < 0.05$
Sax and Strakowski (1998)	11 (6)	0, 0.25 mg/kg p.o.[a]	TPQ Version 4 (Cloninger, 1987)			+	TPQ Novelty Seeking $r = 0.73$, $p < 0.01$ with increase in behavioral ratings of elevated mood response to three doses
Chait (1993)	29 (13)	0, 7.5–20 mg[a,c]	SSS Form V (Zuckerman *et al*, 1978); Eysenck Personality Inventory (EPI; Eysenck and Eysenck, 1968); TPQ Version 4 (Cloninger, 1987); Drug Attitudes Scale (DAS; Goodstadt *et al*, 1978); 'morningness' questionnaire (Smith *et al*, 1989)	n.r.	n.r.	n.r.	Higher Speed scale scores (positive attitude toward amphetamines) on Drug Attitudes Scale in amphetamine choosers, $p < 0.05$; no associations reported between EPI, SSS-V, TPQ scores and POMS, ARCI, VAS ratings of drug effects
de Wit *et al* (1986)	31	0, 5 mg p.o.[a,c,d]	Sensation Seeking Scale (Total; Zuckerman, 1971); Rotter Internal/Extfernal Locus of Control (Rotter, 1966); TMAS (Taylor, 1953); Psychopathic State Inventory (Haertzen *et al*, 1980)	n.s.			Amphetamine choosers and non-choosers differed in mood responses to amphetamine, but did not differ on any personality trait, with the exception of greater PSI 'Search for High' scores in amphetamine choosers
Uhlenhuth *et al* (1981)	45 (16)	0, 5 mg p.o.[a,c]	EPI (Eysenck and Eysenck, 1968); Jackson Personality Research Form (Jackson, 1974); Bass Acquiescence Scale (Bass, 1956); Group Embedded-Figures Test (Witkin *et al*, 1971)		n.r.		No associations reported between personality and amphetamine effects on POMS mood ratings

N: total number of participants (number of female participants in parentheses); n.s.: not significant; n.r.: not reported.
[a]Within-subjects design.
[b]Between-subjects design.
[c]Choice procedure.
[d]*d,l*-Amphetamine.

arousal in another group of participants administered placebo. The data also suggested that EPQ-P may be associated with aversive, rather than pleasurable, responses to amphetamine (tense arousal; Corr and Kumari, 2000). Thus, while the personality measures of sensation seeking, novelty seeking, and psychoticism appear to be linked to individual differences in responses to *d*-amphetamine, the precise relationship between these personality traits and *d*-amphetamine responses remains unclear.

One factor that may contribute to these inconsistencies is the fact that sensation seeking is a complex personality dimension, which appears to involve several conceptually distinct emotional tendencies. Sensation seeking may include the tendency to respond strongly to external rewards, the tendency to fearlessly approach potentially harmful situations, and the tendency to act impulsively (Campbell and Heller, 1987; Zuckerman, 1989, 1993; Glicksohn and Abulafia, 1998). These specific tendencies can be measured separately by other personality scales. For example, the TPQ Reward Dependence (Cloninger, 1986), Extraversion (Lucas *et al*, 2000), and Multidimensional Personality Questionnaire (MPQ) and the MPQ Brief Form (MPQ-BF) Positive Emotionality scales (Tellegen, 1982; Patrick *et al*, 2002; Depue and Collins, 1999) are particularly well suited to assess sensitivity to reward. The MPQ and MPQ-BF Harm Avoidance scales are sensitive to the tendency to engage in potentially harmful behaviors (Tellegen, 1982; Patrick *et al*, 2002), and the TPQ Novelty Seeking (Cloninger, 1986), EPI Impulsivity, EPQ-P (Acton, 2003), MPQ Constraint, MPQ Control (Tellegen, 1982; Patrick *et al*, 2002), and P-ImpUSS scales (Zuckerman, 1989) can provide specific measures of impulsivity. Measures of each of these three dimensions correlate with self-reported sensation seeking (Zuckerman, 1989; Depue and Collins, 1999; Patrick *et al*, 2002; Campbell and Heller, 1987).

Tellegen's MPQ (and the shortened version MPQ-BF) has been empirically derived to provide orthogonal, relatively uncorrelated scales for the three traits in question (Tellegen, 1982; Patrick *et al*, 2002). This feature suggests that this questionnaire may be useful to examine the relations between the specific traits and responses to drugs. Several previous studies have examined MPQ scores in relation to acute drug responses, including bromocriptine (Depue *et al*, 1994), methylphenidate (Morrone-Strupinsky, 2002), and phenylephrine (White and Depue, 1999), and in relation to long-term drug use (methamphetamine; Goldstein *et al*, 2002). High scores on the MPQ factor of Positive Emotionality, which measures the personality dimension of reward sensitivity (Depue and Collins, 1999; Lucas *et al*, 2000), have been linked to greater eyeblink and prolactin responses to the dopamine D2 agonist bromocriptine (Depue *et al*, 1994) and greater growth hormone and contextual cue responses to methylphenidate (Morrone-Strupinsky, 2002). Low scores on the MPQ scale of Harm Avoidance, which measures the personality dimension of physical fear, have been associated with greater ocular dilator muscle response to the noradrenergic agonist phenylephrine (White and Depue, 1999) and with lowered orbitofrontal gyrus metabolism in recently abstinent, methamphetamine-dependent individuals (Goldstein *et al*, 2002). Other measures of impulsive behavior, which are likely associated with the MPQ-BF Control scale, have been shown to be associated with low cortisol and prolactin responses to the serotonergic agents paroxetine and fenfluramine (Reist *et al*, 1996; Coccaro *et al*, 1997).

The current study used the Brief Form of the MPQ to investigate the association between these three traits of reward sensitivity, physical fearlessness, and impulsivity in relation to responses to *d*-amphetamine (10 and 20 mg) in healthy volunteers. This study extends the previous studies by examining four specific personality–drug response relationships. First, MPQ-BF measures of reward sensitivity (ie Agentic Positive Emotionality, Social Potency scales) were expected to be positively associated with the positive activational effects of amphetamine. Second, MPQ-BF measures of physical fear (ie Harm Avoidance scale) were expected to be negatively associated with the positive activational effects of amphetamine. Third, MPQ-BF measures of low impulsivity (ie Control scale) were expected to be negatively associated with the positive subjective and mood effects of amphetamine. Amphetamine responses were expected to be unrelated to scores on other personality measures (eg Social Closeness, Stress Reaction, Absorption scales), which are orthogonal to these three traits.

The overarching goal of the current study was to use the MPQ-BF to clarify the specific personality correlates of *d*-amphetamine effects previously associated with sensation seeking, using orthogonal measures of the personality traits related to reward sensitivity, physical fearlessness, and impulsivity and several potentially discriminant traits in healthy volunteers. The doses of 10 and 20 mg were selected because they are safe and have been well characterized in healthy volunteers. The relatively low, 10-mg dose in particular was expected to provide a good measure of sensitivity to the drug's effects.

MATERIALS AND METHODS

Participants

Healthy volunteers ($N = 128$), aged 18–35 years, were recruited through notices placed in community and university newspapers and bulletin boards. Potential participants underwent a telephone screening interview and a structured clinical interview, and completed a psychiatric symptom checklist (SCL-90; Derogatis, 1983), the Michigan Alcoholism Screening Test (Selzer, 1971). All participants received a screening electrocardiogram and physical examination. Exclusion criteria were any current medical condition requiring medication, use of prescription drugs (including birth control pill) in the previous 6 months, medical conditions for which amphetamine is contraindicated (eg diabetes, asthma, glaucoma, hypertension, epilepsy, migraine), any Axis I disorder other than nicotine dependence (APA, 1994), drug allergies (except antibiotics), endocrine disorders, a history of psychosis, total abstention from all drugs including alcohol, and, in women, a history of menstrual irregularities or current or intended pregnancy or lactation. Individuals with less than a high school education, lack of fluency in English, or night shift work were also excluded.

Before the first session, subjects provided their informed consent. Subjects were told that the purpose of the study

was to study the effects of drugs on behavior. For blinding purposes, the consent form listed drugs other than those that would be administered (eg stimulant, sedative, antihistamine, hormone, and placebo). In the consent form, participants agreed not to take any drugs other than their usual amounts of caffeine and nicotine for 24 h before and 24 h following each session. The study was approved by the Institutional Review Board at The University of Chicago in accordance with the Code of Federal Regulations (Title 45, Part 46) 'Protection of Human Subjects' adopted by the National Institutes of Health and the Office for Protection from Research Risks. 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.

Procedure

Participants took part in a three-session, within-subjects, placebo-controlled crossover study investigating the mood-altering effects of two doses of *d*-amphetamine (10 and 20 mg) and placebo. Sessions were separated by at least 48 h, and women were tested only during the follicular phase of the menstrual cycle (days 2–14; White *et al*, 2002). Subjects were instructed to consume a light breakfast (bagel, no dairy, no acidic juices) 1 h prior to their test session, to standardize drug absorption.

Sessions were conducted from 0900 to 1345. Upon arrival at the laboratory, subjects provided urine and breath samples to confirm abstinence from alcohol and drugs, and women were tested for pregnancy. Urine samples were tested for *d*-amphetamine, cocaine, PCP, opiate, and marijuana use with Ontrak TesTstik™ test kits (Roche Diagnostic Systems Inc., Somerville, NJ). Breath alcohol level was assessed using an Alco-Sensor III hand-held Breathalyzer (Intoximeters Inc., St Louis, MO). No participant tested positive for drug use or pregnancy.

At 0915, baseline (pre-capsule) measures of heart rate and systolic and diastolic blood pressure were obtained, and subjects completed self-report mood and drug effects questionnaires (see below). At 0930, participants ingested opaque capsules containing either *d*-amphetamine (10 or 20 mg) or placebo with 100 ml of water. The drugs were administered in randomized order, under double-blind conditions. At 1000 and every 30 min until 1330, subjects completed self-report questionnaires and physiological measures were obtained. Subjects were permitted to leave the laboratory at 1345. After all three sessions were completed, a debriefing interview was conducted to explain the study and pay the subjects.

Prior to study participation, subjects completed personality measures (see below), selected to assess traits of reward sensitivity, fearlessness, and impulsivity.

Drugs

d-Amphetamine tablets (5 mg; Dexedrine®) were placed in opaque, colored gelatin capsules (size 00) with dextrose filler. Placebo capsules contained only dextrose. The doses of *d*-amphetamine (10 and 20 mg) were selected because they reliably increase subjective measures of stimulant effects (Martin *et al*, 1971; Foltin and Fischman, 1991).

Dependent Measures

Subjective states assessment. Subjective and mood-altering effects of *d*-amphetamine were determined using the Addiction Research Center Inventory (ARCI; Martin *et al*, 1971), a visual analogue Drug Effects Questionnaire (DEQ), and a visual analogue adjective checklist (VAS), and an experimental version of the Profile of Mood States (POMS; McNair *et al*, 1971). The 49-item ARCI is a true–false questionnaire with five empirically derived scales sensitive to certain drugs or groups of drugs: A (AMPH-like, stimulant effects), BG (Benzedrine Group, energy and intellectual efficiency), MBG (Morphine-Benzedrine Group, euphoric effects), LSD (Lysergic Acid Diethylamide, dysphoric effects, somatic complaints), and PCAG (Pentobarbital–Chlorpromazine–Alcohol Group, sedative effects) (Martin *et al*, 1971; Fischman and Foltin, 1991). The DEQ is a locally developed visual analogue questionnaire that assesses the extent to which participants experience four subjective states: 'Feel Drug', 'Feel High', 'Like Drug', and 'Want More'. It is sensitive to several psychoactive drugs, including stimulants (Fischman and Foltin, 1991; Justice and de Wit, 2000a, b). The POMS consists of 72 adjectives commonly used to describe momentary mood states. Participants indicate how they feel at that moment in relation to each of the adjectives on a 5-point scale ranging from 'not at all' (0) to 'extremely' (4). The ARCI, DEQ, and POMS measures were chosen for analysis below as multiple measures of self-reported drug effects and subjective mood.

Independent Measures

Personality. Personality traits were assessed through MPQ-BF (Patrick *et al*, 2002). The MPQ consists of three superfactors, labeled Constraint, Positive Emotionality, and Negative Emotionality. Each superfactor consists primarily of three or four lower-order scales: Constraint consists primarily of Harm Avoidance, Control, and Traditionalism; Positive Emotionality consists primarily of Social Potency, Achievement, Social Closeness, and Well-Being; and Negative Emotionality consists primarily of Stress Reaction, Alienation, and Aggression (Patrick *et al*, 2002; Tellegen, 1982; Tellegen and Waller, in press). The brief form used in this study is strongly correlated with the long form of this questionnaire (Tellegen, 1982; Patrick *et al*, 2002). Four MPQ-BF scales were chosen *a priori* as measures of interest for the current study: the Agentic Positive Emotionality factor and the Social Potency scale, which measure reward sensitivity; the Harm Avoidance scale, which measures physical fear *vs* fearlessness; and the Control scale, which measures planfulness *vs* behavioral spontaneity. Three additional scales were included to test the discriminant validity of the above personality measures: Social Closeness, which measures affiliation rather than reward sensitivity; Stress Reaction, which measures anxiety proneness rather than physical fear; and Absorption, which measures the tendency to experience mental states vividly and quickly, providing an index of the spontaneity of mental state rather than behavior.

Data Analysis

First, we conducted a preliminary analysis of variance using all the participants to characterize the effects of amphetamine. A summary, area under the curve (AVC) measure was derived to characterize each subject's response to the drug, using the post post-capsule measures, and subtracting the pre-drug baseline score. Separate one-way ANOVAs (drug: placebo, 10 mg, 20 mg amphetamine) were conducted for each of the 19 dependent measures (Table 2). Least significant difference *post hoc* comparisons were conducted to determine which conditions differed. To reduce the data into a smaller number of higher-order drug effect factors more appropriate for analysis with personality, outcomes showing significant drug effects (Table 2) were entered into a principal components analysis (promax rotation; $N = 128$). Factor analyses were conducted separately for the two doses in order to determine whether the factor structure would replicate across doses. Based on examination of the scree plots, factors with eigenvalues greater than 2.0 were extracted and explained 50–60% of the variance in drug effects at each dose. Scores for each extracted factor were calculated as follows. *Z*-scores were calculated for area under the curve summary values for each drug outcome item, and Drug Effect factor scores were then calculated as the average *Z*-score of those scales uniquely loading (>0.5) on each factor, with no cross-loadings greater than 0.5 on the alternate factor (see Table 4 for details). The factors resulting from this principal components analysis formed the basis of the subsequent analyses examining relations between drug responses and personality.

Second, we examined relationships between the different personality measures, in order to determine whether the measures were independent in the current sample ($N = 128$). Pearson's product-moment correlations (two-tailed) were conducted between MPQ-BF measures of reward sensitivity (Agentic Positive Emotionality, Social Potency), physical fearlessness (Harm Avoidance), impulsivity (Control), and the three discriminant validity measures (Social Closeness, Stress Reaction, Absorption).

Third, we examined relationships between baseline (pre-drug) mood ratings on the study days and personality to determine whether the groups based on personality differed in mood states in the absence of drug. The pre-capsule mood ratings from the three experimental sessions were averaged for each subject. To be consistent with planned amphetamine analyses (see above), these means were transformed into standard scores (*Z*-scores) and data were reduced to an average of the POMS scales loading >0.5 on drug factor 1 (Positive Activation) (see Table 4). For each MPQ-BF trait, subjects were rank-ordered based on their scores on the specific personality scale indexing that trait (see Table 4), and individuals with scores in the lowest and highest third of the sample distribution on each trait

Table 2 F Values (ANOVA) for Drug Effects, Area Under the Curve (10 mg Amphetamine, 20 mg Amphetamine, or Placebo; $N = 128$)

	Amphetamine F(2,125)	Direction, amphetamine effect	Dose effects
DEQ			
Feel Drug	36.99****	↑	20>pl, 10>pl, 20>10****
Like Drug	23.70****	↑	20>pl, 10>pl, 20>10****
Feel High	22.51****	↑	20>pl, 20>10****, 10>pl**
Want More	14.78****	↑	20>pl, 20>10****, 10>pl^{+}
ARCI			
Amphetamine	37.66****	↑	20>pl, 10>pl, 20>10****
MBG	30.55****	↑	20>pl, 10>pl, 20>10****
Benzedrine	23.27****	↑	20>pl, 10>pl****, 20>10*
LSD	7.85****	↑	20>pl****, 20>10**
PCAG	13.68****	↓	20>pl, 10>pl****
POMS			
Vigor	34.03****	↑	20>pl, 10>pl, 20>10****
Arousal	26.52****	↑	20>pl, 10>pl, 20>10****
Elation	22.05****	↑	20>pl, 10>pl, 20>10****
Friendliness	17.11****	↑	20>pl, 10>pl****, 20>10^{+}
Positive Mood	11.39****	↑	20>pl****, 10>pl, 20>10**
Anxiety	6.22**	↑	20>pl****, 10>pl, 20>10^{+}
Fatigue	4.63**	↓	20>pl**, 20>10*
Confusion	1.64		
Anger	0.31		
Depression	1.11		

Subjective responses were assessed through the empirically derived ARCI scales, the POMS scales, and DEQ items. $^{+}p \leqslant 0.10$; $*p \leqslant 0.05$; $**p \leqslant 0.01$; $****p \leqslant 0.001$.

measure ($N=43$ in each group; total $N=86$) were compared using one-way, between-subjects ANOVA.

Fourth, to address our primary goal, we examined subjective responses to amphetamine in relation to scores on the MPQ-BF. The drug effect factor scores (calculated above; ie Positive Activation; Feel/Somatic Effects) were assessed for personality effects using a series of ANCOVA models. Findings were corrected for multiple comparisons via Bonferroni correction. As described above, an extreme groups approach, rather than the full sample, was chosen to identify potentially vulnerable subsamples of healthy populations, and the lowest and highest third of the participants on each personality trait ($N=43$ in each group; total $N=86$) were compared. Responses on the placebo session were entered as covariates to control for expectancy effects. Potential interactions between personality traits were assessed *post hoc*, using multivariate linear models for drug effect outcomes related to more than one personality measure. The significance level for all statistical tests was set at $p<0.05$ (two-tailed).

Finally, several manipulation checks were conducted to assess order effects and beliefs regarding the drug classes received on each day of the study. Order effects were assessed by coding the order of amphetamine administration for each participant (placebo-first, 10 mg-first, 20 mg-first), and were included in drug effects ANCOVA models for outcomes with significant personality effects. To assess the effectiveness of the blinding, subjects indicated whether they believed they had received a stimulant, a sedative/tranquilizer, alcohol, or a placebo after each session. These results were compared across the drug conditions using χ^2 tests.

RESULTS

Sample Characteristics

Participants in the full sample ($N=128$; 64 women) were ethnically diverse (54% Caucasian, 22% African American, 13% Asian, 9% Latino, 1% Native American), in their early 20s (age 23.6 ± 4.1 years), well educated (15.1 ± 1.6 years education), and had BMIs in the normal range (BMI = 22.6 ± 2.3 kg/m^2; men: 73.9 ± 10.1 kg; women: 62.2 ± 8.5 kg). Participants reported a range of current recreational substance use (alcohol: 4.2 ± 3.6 drinks/week; caffeine: 1.2 ± 1.3 cups/day; marijuana: 0.9 ± 2.7 times/month; cigarettes: 0.8 ± 2.2 cigarettes/week) and lifetime recreational substance use (% ever used: stimulants 14.8%; sedatives 5.5%; opiates 12.5%; hallucinogens 32%; marijuana 57%; inhalants 10.9%).

Personality

All participants ($N=128$) had valid scores on the MPQ-BF. Mean scores on the scales (Social Potency, Absorption, Harm Avoidance, and Stress Reaction) were within the range of previously published scores (Patrick *et al*, 2002). Pearson correlations and descriptive statistics for the seven MPQ-BF scales are presented in Table 3.

We examined the relationships between different personality subscales in the full sample of 128 subjects. Table 3 indicates that the reward sensitivity scales (Agentic Positive Emotionality, Social Potency) were highly inter-related ($r=0.65$) and were independent of the physical fearlessness scale (Harm Avoidance) and the impulsivity scale (Control). Thus, the ability to measure reward sensitivity as separate from fearlessness or impulsivity appears to be good in the current sample. Harm Avoidance and Control were moderately correlated ($r=0.4$). The discriminant scales appeared to be independent of the larger traits: Social Closeness was not related to Agentic Positive Emotionality ($r=0.09$); Stress Reaction was not related to Harm Avoidance ($r=-0.05$); and Absorption was weakly associated with Control ($r=-0.22$).

Drug Effects and Drug Effect Factors

Amphetamine produced its expected effects on the DEQ, ARCI, and POMS measures, and most effects were dose dependent (see Table 2). Individual outcome scales showing significant drug effects (Table 2) were entered into a principal components analysis (promax rotation) for each dose. Factor loadings for each drug outcome scale appear in Table 4. As seen in Table 4, factor structure of drug responses at the 10 and 20 mg doses was similar, with the exception of DEQ Like Drug and DEQ Want More Drug, which loaded on the positive rather than the somatic factor in response to the 20 mg dose. Based on the common pattern of factor loadings across doses, Factors 1 and 2 have been labeled as Positive Activation and Feel/Somatic drug effects, respectively (see Table 4).

Table 3 MPQ-BF Personality Scores Intercorrelation Matrix and Descriptive Statistics (Pearson Correlations, Raw MPQ-BF Scores, $N=128$)

	1	2	3	4	5	6	7	M	SD
1 Agentic Positive Emotionality	1.00							64.9	12.5
2 Social Potency	0.65****	1.00						7.2	3.2
3 Harm Avoidance	−0.08	−0.23**	1.00					6.9	2.8
4 Control	0.12	−0.13	0.40****	1.00				8.1	3.0
5 Social Closeness	0.09 n.s.	0.23**	0.05	−0.07	1.00			7.8	3.1
6 Stress Reaction	−0.04	−0.15$^+$	−0.05 n.s.	0.01	−0.27***	1.00		3.9	3.3
7 Absorption	0.35****	0.24**	−0.26***	−0.22**	−0.15$^+$	0.25***	1.00	7.2	3.0

$^+p\leqslant0.10$; $^*p\leqslant0.05$; $^{**}p\leqslant0.01$; $^{***}p\leqslant0.005$; $^{****}p\leqslant0.001$.

Table 4 Principal Components Analysis, AUC Drug Effects ($N = 128$)

	10 mg		20 mg	
	Factor 1	Factor 2	Factor 1	Factor 2
Drug effect scales	Positive	Feel/Somatic	Positive	Feel/ Somatic
DEQ Feel	0.17	***0.77***	0.37	***0.85***
DEQ Like Drug	0.47	***0.51***	***0.72***	0.37
DEQ High	0.36	***0.76***	0.54	0.82
DEQ More	0.22	***0.54***	***0.62***	0.35
ARCI LSD	−0.21	***0.61***	−0.13	***0.65***
ARCI A	0.49	***0.51***	0.66	0.52
ARCI BG	***0.67***	0.34	***0.8***	0.25
ARCI MBG	***0.62***	0.37	***0.69***	0.48
ARCI PCAG[a]	−***0.64***	−0.22	−***0.68***	0.19
POMS Vigor	***0.84***	0.29	***0.88***	0.17
POMS Arousal	***0.81***	0.32	***0.82***	0.16
POMS Elation	***0.82***	0.08	***0.86***	0.17
POMS Friendly	***0.66***	−0.12	***0.76***	0.07
POMS Positive Mood	***0.84***	0.02	***0.85***	0.06
POMS Fatigue[a]	−***0.59***	−0.05	−***0.57***	0.08
POMS Anxiety	−0.04	0.41	−0.2	0.45

[a]Outcome inversely related to amphetamine; see Table 3.
Items loading >0.5 that were not cross-loaded on the alternate factor and that were entered into calculation of drug effect factor scores used in the personality analysis are in bold italics.

Table 5 Personality, Basal Mood and Higher-Order Drug Effects: Differences between Outer Thirds Personality Groups ($N = 86$)

	Basal mood		Drug effects	
	Positive	Direction	Positive	Direction/dose
Reward sensitivity				
1. Agentic Positive Emotionality	5.46*	H		
2. Social Potency			2.89^{+}	H/20 mg
Fearlessness				
3. Harm Avoidance			8.35***	L/10 mg
Impulsivity				
4. Control	8.8***	H		
Discriminant validity				
5. Social Closeness	3.66^{+}	H		
6. Stress Reaction	5.56*	L		
7. Absorption			3.07^{+}	H/20 mg
			3.95*	H/10 mg

$^{+}p \leqslant 0.10$; $^{*}p \leqslant 0.05$; $^{**}p \leqslant 0.01$; $^{***}p \leqslant 0.005$; $^{****}p \leqslant 0.001$. Direction: Significant elevation in outcome factors observed in: L = lowest personality score group ($N = 43$); H = highest personality score group ($N = 43$) on indicated personality scale. Basal mood: ANOVA ($N = 86$) between outer thirds of ranked MPQ-BF personality scores, F(1,84). Drug effects: ANCOVA on AUC drug effects ($N = 86$) between outer thirds of ranked personality scores, controlling for factor scores on placebo session, F(1,83). Somatic drug effects were not significantly related to MPQ-BF personality (n.s.), data not shown.

Pre-Drug Differences

Several MPQ scales were associated with basal mood states (ie prior to the ingestion of the capsules; Table 5). Participants who scored high on personality measures of Agentic Positive Emotionality, Control, and Social Closeness and who scored low on Stress Reaction had higher basal scores on POMS measures from the Positive Activation factor (POMS Vigor, Arousal, Elation, Friendliness, and Positive Mood and low Fatigue) compared to those with opposite scores on these traits. The results with Control remained significant after Bonferroni correction ($p < 0.005$). The directions of these baseline associations are consistent with those previously reported (Tellegen, 1985; Watson and Clark, 1984; Watson *et al*, 1992). However, it is notable that most of the significant associations between personality and the pre-drug mood states were with personality traits that were not related to self-reported mood effects after consumption of the capsules (see below).

Drug Effect Factors Related to Personality

Several MPQ scales were associated with the effects of amphetamine on the Positive Activational drug effects factor (Table 5). Associations between personality and positive drug factor are described below.

Associations with trait reward sensitivity. Participants who scored high on the MPQ-BF measure of Social Potency reported marginally greater levels of positive drug effects in response to the 20 mg *d*-amphetamine dose than did participants with low scores on this scale ($p \leqslant 0.10$). These data suggest a weak association between trait reward sensitivity and the positive activational effects of the 20 mg dose.

Associations with trait physical fearlessness. Participants who scored low on Harm Avoidance reported greater levels of positive drug effects after 10 mg *d*-amphetamine than those with high scores. The association remained significant after Bonferroni correction ($p \leqslant 0.005$). This drug effect is presented in Figure 1 and indicates a significant association between trait physical fearlessness and the positive activation induced by low-dose *d*-amphetamine.

Associations with trait impulsivity. There were no significant associations with MPQ Control. These data indicate that trait impulsivity was not associated with *d*-amphetamine effects in the current sample.

Specificity of results. Three additional personality measures were included as potential discriminant tests of the specificity of relationships between amphetamine and the personality constructs of reward sensitivity, physical fearlessness, and behavioral impulsivity, as distinct from other personality constructs. These discriminant measures were Social Closeness (which measures affiliation rather than reward sensitivity), Stress Reaction (which measures

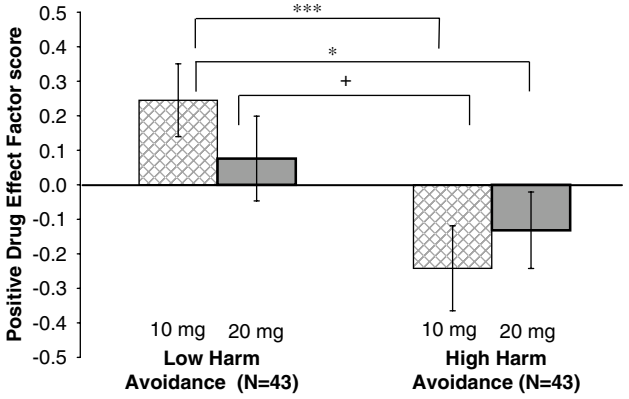

Figure 1 Trait physical fearlessness and positive activational responses to *d*-amphetamine. Higher-order positive drug effect (factor score) responses in participants with low and high scores on MPQ-BF Harm Avoidance; 10 and 20 mg effects. $^{*}p \leqslant 0.05$; $^{***}p \leqslant 0.005$; $^{+}p \leqslant 0.10$.

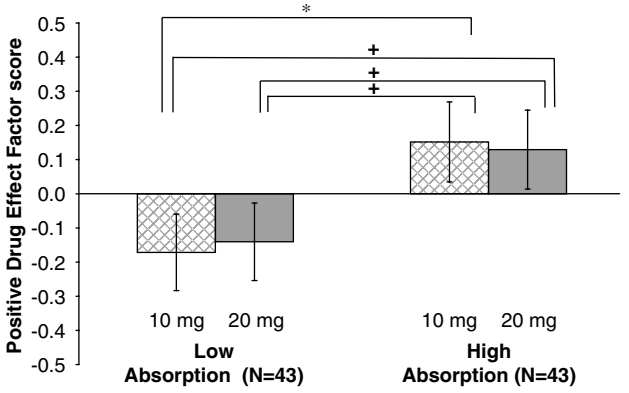

Figure 2 Trait Absorption and positive activational responses to *d*-amphetamine. Higher-order positive drug effect (factor score) responses in participants with low and high scores on MPQ-BF Absorption; 10 and 20 mg effects. $^{*}p \leqslant 0.05$; $^{+}p \leqslant 0.10$.

anxiety rather than physical fear proneness), and Absorption (which measures the predisposition toward mental imagery and flexibility of emotional/cognitive set rather than behavioral impulsivity). Discriminant findings are separated below by *a priori* contrasts of interest. *Reward sensitivity vs affiliation:* Scores on Social Closeness were not related to *d*-amphetamine effects, in contrast with marginal findings with Social Potency (Table 5). This suggests that *d*-amphetamine effects could be specifically associated with individual differences in the trait of reward sensitivity, as distinct from the associated trait of affiliative extraversion. *Physical fearlessness vs anxiety proneness:* Scores on Stress Reaction were not related to *d*-amphetamine outcomes (Table 5). This suggests that associations with trait physical fearlessness are specific to this trait, and are not associated with the separate trait of anxiety proneness. *Behavioral impulsivity vs mental imagery:* Scores on Absorption were related to positive drug effects in response to both doses (see Figure 2). In contrast, scores on the Control scale, which measures behavioral impulsivity, were not related to *d*-amphetamine effects (Table 5). These data suggest that *d*-amphetamine effects on positive activation are more likely to relate to individual differences in the flexibility of mental/emotional imagery (absorption) than to individual differences in behavioral impulsivity (low control).

Interactions. To assess whether individuals with extreme scores on two or more traits were at elevated risk for positive responses to *d*-amphetamine, personality interactions were assessed using multivariate linear models. A total of 56 participants had extreme scores on Absorption and one or more relevant traits (Harm Avoidance, Social Potency). The multivariate analysis indicated that interactions between personality traits were not significant ($p > 0.50$), and associations with Absorption remained marginally significant after controlling for scores on other traits (Positive factor effects: 10 mg: $F(1,52) = 2.6$, $p = 0.11$; 20 mg: $F(1,52) = 3.5$, $p < 0.10$). Thus, in individuals with extreme scores on more than one relevant personality trait, having high scores on multiple traits (eg fearlessness and absorption) did not appear to increase self-reports of positive drug effects beyond that associated with a single trait. This finding could reflect a true absence of interaction effects, or a ceiling effect on the psychometric self-report outcomes under study.

Validity Checks

Order effects. There were no significant effects of order or order by personality interactions for any outcome (n.s.).

Participant blindness. After 10 mg *d*-amphetamine, participants were equally likely to believe they received a stimulant ($N = 38$), sedative ($N = 32$), or placebo ($N = 47$; $\chi^2 = 2.9$, n.s.), and after placebo, they were equally likely to believe they received either placebo ($N = 53$) or an active substance (sedative or stimulant; $N = 64$; $\chi^2 = 1.03$, n.s.). After 20 mg *d*-amphetamine, they were more likely to report they had received a stimulant ($N = 73$) than a sedative or placebo ($N = 49$; $\chi^2 = 4.7$, $p < 0.05$). These data indicate that participants were relatively blind to the study drug administered on the 10 mg and placebo sessions.

DISCUSSION

The personality traits of reward sensitivity, physical fearlessness, and the tendency to experience mental states vividly and quickly were associated with a number of specific subjective responses to *d*-amphetamine in the current sample. There were three main findings. First, compared to individuals with high trait physical fear, individuals with low trait physical fear reported greater positive activational responses to low-dose *d*-amphetamine, showing greater energy, intellectual activation, euphoria, vigor, arousal, elation, friendliness, positive mood, and less fatigue and sedation (drug effects factor 1, Positive Activation) after the 10 mg dose. These findings were the strongest of the study, and remained significant after correction for multiple comparisons. Second, individuals with high trait reward sensitivity had marginally greater positive responses as well as drug liking and drug wanting after the 20 mg dose. Third, individuals with high mental imagery/flexibility had greater positive drug responses to

both doses, and these effects were more significant at the lower (10 mg) dose. These findings are discussed in turn.

The first finding was that in healthy individuals with *low scores* on the trait measure of *fear of physical danger* (MPQ-BF Harm Avoidance), 10 mg *d*-amphetamine produced greater positive activational responses, that is, greater activation, euphoria, vigor, arousal, elation, friendliness, and positive mood, and less sedation and fatigue. Responses to amphetamine were unrelated to another negative emotional trait, Stress Reaction (Table 5), which measures anxiety proneness rather than trait fear (Tellegen, 1982; White and Depue, 1999). These findings indicate that individuals who are less fearful may be particularly vulnerable to the positive subjective effects of low doses of psychostimulants. In contrast, individuals who are high on Harm Avoidance may be protected from these activational effects.

The second finding was that 20 mg *d*-amphetamine produced greater activational drug effects, that is, greater energy, intellectual efficiency, euphoria, vigor, arousal, elation, friendliness, positive mood, lessened sedation and fatigue, and greater drug liking and drug wanting among individuals with *high scores* on a trait measure of *reward sensitivity* (MPQ-BF Social Potency). The effects of 20 mg *d*-amphetamine were not related to other personality measures, such as affiliative sociability (ie Social Closeness; see Table 5). The relationship between reward sensitivity and positive responses to *d*-amphetamine is consistent with the idea that a common neural mechanism, such as dopamine neurotransmission, mediates both trait reward sensitivity and subjective responses to a stimulant drug (Depue and Collins, 1999; Drevets *et al*, 2001). Although several previous studies failed to find an association between other measures of extraversion and amphetamine responses (eg Corr and Kumari, 2000; Chait, 1993; Uhlenhuth *et al*, 1981), the lack of effects in the previous studies could have been due to sample sizes or insensitivity of the extraversion measures used (see Depue and Collins, 1999; Lucas *et al*, 2000 for review).

The third finding was that subjects who scored high on trait mental imagery/flexibility (Absorption on the MPQ-BF) reported greater positive activational effects of *d*-amphetamine (10 and 20 mg). This relationship was significant at the 10 mg dose and showed a trend toward greater positive drug effects as well as greater drug liking and drug wanting at the 20 mg dose. In contrast, scores on the MPQ-BF measure of behavioral impulsivity (ie low Control) were unrelated to amphetamine effects. Our finding suggests that at both low and high doses, the personality trait of mental imagery and flexibility, but not behavioral impulsivity, may increase the vulnerability to positive, stimulant-like drug effects.

Overall, the present study had both strengths and weaknesses. Strengths included the use of an empirically derived personality instrument (MPQ-BF) with an orthogonal factor structure to assess temperament, multiple doses (10 and 20 mg p.o.) of *d*-amphetamine, a placebo control, assessment of basal mood on study sessions, a double-blind administration of drugs, a manipulation check for participant blindness, and a large ($N = 128$) sample of men and women. Previous studies are less than half this size (within-subjects studies: eg $N = 24$, Alessi *et al*, 2003; $N = 36$, Hutchison *et al*, 1999; $N = 11$, Sax and Strakowski, 1998; $N = 29$, Chait, 1993; $N = 45$, Uhlenhuth *et al*, 1981; between-subjects studies: $N = 20$–22 per group; see Corr and Kumari, 2000). Most significant associations between personality and the pre-drug, basal mood states were as expected for different personality groups, and were for outcomes that were not related to personality after consumption of the capsules (see Table 5). A limitation of the present study was that the sample consisted of a relatively homogeneous subject population, who were in a narrow age range (18–35 years), educated (all had completed high school and many had higher degrees), and who were physically and psychiatrically healthy. The relationships between personality and drug effects might be different in a more heterogeneous population sample including, for example, older individuals, drug users, and individuals with psychiatric disorders.

In toto, the current data indicate that the subjective effects of amphetamine vary as a function of specific personality traits in healthy volunteers. Lack of fear of physical danger, sensitivity to reward, and the tendency to experience internal emotional states vividly and quickly were associated with differences in the magnitude of amphetamine-induced energy, intellectual efficiency, euphoria, vigor, arousal, elation, friendliness, positive mood, lessened sedation and fatigue and, in response to the higher dose, greater drug liking and drug wanting. Notably, the effect of personality was most significant for the 10 mg dose, suggesting that individual differences in reactivity to the drug may be more readily detected at low doses. At the 10 mg dose, a substantial number of subjects were unable to guess the drug class they had received, whereas at the 20 mg dose, the pharmacological drug effects may override subtle individual differences. The results support the idea that certain personality traits relate to endogenous, between-subjects variations in the modulation of monoamine systems in humans, which can impact responses to stimulant drugs such as *d*-amphetamine that act on these systems. The results form the basis for future studies of the *specific* neurobiological mechanisms that may be involved in the vulnerability to psychostimulants in otherwise healthy individuals.

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