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Cortisol effects of D-amphetamine relate to traits of fearlessness and aggression but not anxiety in healthy humans

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Abstract

The current study utilized personality measures thought to relate to noradrenergic and catecholamine function (i.e., sensation seeking, anxiety and aggression) to investigate individual differences in amphetamine-induced increases in cortisol. The goal of the study was to better understand variations in responses to psychostimulants in healthy volunteers.

Method: A placebo-controlled within-subjects investigation of salivary cortisol responses to oral D-amphetamine (20 mg) was conducted in seventy ($N=70$) young adults. Personality traits were assessed using the Eysenck Personality Inventory (EPI), Sensation Seeking Scale Form V (SSS-V) and the Multidimensional Personality Questionnaire-Brief Form (MPQ-BF).

Results: A more rapid rise in salivary cortisol after D-amphetamine was associated with SSS-V Thrill Seeking ($r=-0.32$ with time to peak, $p<0.05$). A greater peak increase in cortisol and a greater recovery after amphetamine was positively associated with MPQ-BF Aggression ($r=+0.35$, $p<0.05$; $r=+0.38$, $p<0.05$). In contrast, cortisol responses were unrelated to a composite measure of trait anxiety (EPI/MPQ-BF Anxiety Index).

Conclusions: The findings suggest that the personality traits of aggression and thrill seeking are related to cortisol responses to D-amphetamine, raising the possibility that personality may predispose certain individuals to use drugs through a glucocorticoid pathway. The data also suggest a distinction between fear and anxiety, as amphetamine-induced cortisol responses were associated with measures of trait fear but not measures of trait anxiety in the current sample.

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1. Introduction

Individuals are known to vary in both their subjective responses to D-amphetamine and in the extent to which this drug increases levels of cortisol (Alessi et al., 2003; Nurnberger et al., 1982; Sachar et al., 1985, 1981, 1980). The sources of these individual differences are poorly understood, but some of the differences may be related to personality. Previous studies suggest that individual differences in the magnitude of mood responses to amphetamine are associated with personality traits such as psychoticism, novelty seeking, reward sensitivity and affective lability (Corr and Kumari, 2000; Hutchison et al., 1999; Kavoussi and Coccaro, 1993; White et al., 2006). To date, however, few studies have examined the association between personality and the effects of amphetamine on the hypothalamic–pituitary–adrenal (HPA) axis.

Preclinical data suggest that HPA responses to drugs, including D-amphetamine, may be related to risk for drug abuse. For instance, rats that show greater HPA reactivity to novelty are more likely subsequently to self-administer psychostimulants (Piazza et al., 1991, 1990; Dellu et al., 1996). Administration of corticosterone increases amphetamine self-administration in animals that are slow to acquire self-administration (Piazza et al., 1991). Glucocorticoids themselves may have direct reinforcing properties, as indicated by reports that they can maintain self-administration (Dellu et al., 1996). These preclinical data suggest that reactivity of the HPA axis could provide a marker for the vulnerability to psychostimulant drug use and dependence.

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Few studies have examined the relationship between HPA reactivity and responses to amphetamine in humans. Alessi et al. (2003) recently investigated the relationship between salivary cortisol response to D-amphetamine (5–20 mg) and novelty seeking, measured by wrist monitor activity during 2 h in a novel recreational environment. Individuals with high activity (HR; high novelty seeking) or low activity (LR; low novelty seeking) in the novel room did not differ in their cortisol responses to amphetamine, although HR subjects tended to have higher baseline levels of salivary cortisol. In other studies, neither a single dose of cortisol nor exposure to an acute stress procedure affected subjective responses to D-amphetamine (Wachtel et al., 2001; Soderpalm et al., 2003; Harris et al., 2003).

One alternative strategy to study individual differences in response to stimulant drugs is to examine the relationship between amphetamine-induced cortisol release and personality traits thought to be mediated by specific catecholamines. Amphetamine increases dopamine, serotonin and norepinephrine concentrations at the synapse by reversing catecholamine transporters, blocking the reuptake and increasing the release of these neurotransmitters (Kahlig et al., 2005; Pifl et al., 1995, 1999). Several lines of evidence suggest that amphetamine may release cortisol through a noradrenergic mechanism. Amphetamine is 5-fold to 200-fold more potent at the norepinephrine transporter (NET) than at dopamine and serotonin transporters (DAT; SERT; Han and Gu, 2006). Cortisol responses to amphetamine are blocked or reduced by drugs that antagonize noradrenergic alpha-1 receptors, but not by drugs such as pimozide or haloperidol which affect dopamine receptors (Saphier and Feldman, 1991; Feldman et al., 1995; Saphier and Feldman, 1989; Rees et al., 1970; Besser et al., 1970; Marantz et al., 1976; Nurnberger et al., 1982, 1984). Natural (i.e., non-drug-induced) cortisol release is also mediated by an alpha-1 mechanism (Feldman et al., 1995). Overall, cortisol release is controlled by the paraventricular nucleus (PVN) of the hypothalamus, which is innervated by noradrenergic fibers originating in the A2 and locus cerulear brainstem groups (Feldman et al., 1988, 1995; Reyes et al., 2005). These regions have reciprocal connections with limbic structures such as the central amygdala and are involved in fight/flight responses to stress (Van Bockstaele et al., 1998, 2001). Thus, responses to amphetamine that are related to noradrenergic function, such as release of cortisol, may also be related to personality measures that relate to noradrenergic function, such as traits related to fear, fight or flight.

Toward this end, the goal of the current study was to investigate the association between D-amphetamine effects on cortisol release in healthy humans and personality measures thought to relate to catecholamine and noradrenergic system function. There were two main hypotheses. First, it was hypothesized that amphetamine-induced cortisol increases would be positively related to physical fearlessness such as SSS-V Thrill and Adventure Seeking. Similar measures of trait fearlessness have been associated with mood responses to D-amphetamine (White et al., 2006), ocular dilation to other alpha-1 noradrenergic agonists (phenylephrine; White and Depue, 1999) and cerebral spinal fluid (CSF) norepinephrine (Ballenger et al., 1983). The trait measure of fearlessness has also been hypothesized to relate to between-subject differences in dopamine function (Cloninger, 1986, 1987; Gerra et al., 2000; Corr and Kumari, 2000; Zuckerman and Kuhlman, 2000), which is also relevant to individual differences in amphetamine effects. Second, cortisol responses were expected to be unrelated to two aspects of trait negative affect: anxiety proneness and aggressiveness (measured here by the Eysenck Personality Inventory (EPI)/Multidimensional Personality Questionnaire-Brief Form (MPQ-BF) Anxiety Index and MPQ-BF Aggression scale). Negative affect is an aversive, psychometrically complex personality trait that may have less of a noradrenergic component than trait fear (see White and Depue, 1999), and which has failed to predict mood responses to D-amphetamine (White et al., 2006) and physiological responses to other catecholamine drugs (White and Depue, 1999; Depue et al., 1994). This drug challenge study may assist our understanding of catecholamine contributions to the traits of fear versus anxiety, and our understanding of temperamental differences in the potential vulnerability to drug abuse in healthy humans.

The current analysis consisted of a reexamination of data pooled from several previous published and unpublished studies conducted in this laboratory (N=30, Wachtel et al., 2001; de Wit and Wachtel, 2001; N=40, White et al., 2006).

2. Methods

2.1. Participants

Healthy volunteers (N=70), aged 18–35, were recruited from a university community. Potential participants were screened using a structured clinical interview and completed a psychiatric symptom checklist (SCL-90; Derogatis, 1983), the Michigan Alcoholism Screening Test (MAST; Selzer, 1971; Selzer et al., 1975). Psychiatric diagnoses were made according to DSM IV (APA, 1994). Participants also received an electrocardiogram and physical examination. Individuals taking prescription medications or smoking more than 2.5 cigarettes/day were excluded from the study due to potential interactions between D-amphetamine and noradrenergic compounds or medications on their cortisol response. Individuals with an Axis I psychiatric disorder (APA, 1994), a history of psychosis, or a history of drug or alcohol dependence were excluded to eliminate noise due to psychiatric disorder and treatment. Individuals with hypertension and women who were pregnant were excluded for safety reasons, and candidates with less than a high school education or not fluent in English were also excluded.

2.2. Procedure

Participants provided informed consent which, for blinding purposes, listed drugs other than those that would be administered (e.g., stimulant, sedative, antihistamine, hormone and placebo). Participants agreed not to take any drugs other than their usual amounts of caffeine and nicotine for 24 h before

and after each session. They were instructed to consume a standard breakfast (bagel, no vitamins, fruit juices or bananas) 1 h prior to arrival to the lab to standardize stomach contents. Urine and breath samples were obtained to verify drug and alcohol abstinence and to test for pregnancy before each session. Participants were adapted to the lab through a series of visits to the lab suites for psychiatric screening and medical clearance prior to study involvement. 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.

2.3. Amphetamine administration

The data presented here were obtained from studies in which healthy volunteers received placebo and a moderate dose of d-amphetamine (20 mg; Wachtel et al., 2001; de Wit and Wachtel, 2001; White et al., 2006). This dose of D-amphetamine reliably increases subjective psychostimulant mood measures (Foltin and Fischman, 1991a,b; Martin et al., 1971; Wachtel and de Wit, 1999) and modestly increases salivary cortisol (Alessi et al., 2003). The D-amphetamine tablets (Dexedrine®) were placed in opaque, colored gelatin capsules (size 00) with dextrose filler and placebo capsules contained only dextrose. Subjects ingested drug and placebo capsules under double blind conditions on separate sessions, conducted at least 72 h apart. Sessions began at 9 a.m. to control for circadian effects. Subjects completed questionnaires and physiological measures before capsule ingestion and every 30 min thereafter until 4.5 h after the capsules.

2.4. Salivary cortisol assessment

Saliva for cortisol analysis was collected every 30 min beginning at 9 a.m. using a Salivette® (Sarstedt, Inc., Newton, NC). Salivary cortisol levels (μg/dl) were assayed by the Core Laboratory of the Clinical Research Center at The University of Chicago using 98-well plate Enzyme ImmunoAssay (EIA) methodology (High Sensitivity Salivary Cortisol Enzyme Immunoassay Kit; Salimetrics LLC, State College, PA, USA).

2.5. Personality assessment

Personality measures included a measure of trait fearlessness (Thrill and Adventure Seeking; Sensation Seeking Scale Form V; Zuckerman et al., 1978) and two aspects of negative affect: anxiety proneness (Stress Reaction scale, Multidimensional Personality Questionnaire-Brief Form, Patrick et al., 2002; Neuroticism factor, Eysenck Personality Inventory, Eysenck and Eysenck, 1968) and aggressiveness (Aggression scale, Multidimensional Personality Questionnaire-Brief Form, Patrick et al., 2002). Because measures of trait fearlessness and anxiety are typically independent, separate measures of the traits were used to assess the potentially differential association between cortisol responses and the separate traits of fear versus anxiety in the current sample (for discussion, see Watson and Clark, 1984; White and Depue, 1999). The aggression scale was included to assess whether associations with trait negative affect were unique to the core features of negative affect. Measures of aggression load most highly on negative affect and anxiety, but these loadings are lower than those of other measures, such as the tendency to experience stress at high rates (stress reaction; Tellegen, 1982), which constitutes a more central feature of negative affect. As such the aggression scale was included as a potentially discriminative test of the association between amphetamine responses and the core (e.g., anxiety proneness) versus distal (e.g., aggression proneness) features of trait negative affect. Thus, the current personality assessment provides separate measures of core versus peripheral features of fear versus anxiety traits for use regarding the response to amphetamine.

In the current data, 64 participants had personality data available on EPI Neuroticism ($N=24$) or MPQ-BF Stress Reaction ($N=40$). These measures provide roughly equivalent measures of the tendency to experience anxiety, stress and negative emotion (Patrick et al., 2002; Tellegen, 1982). In order to maximize the analyzable sample size, scores on each scale were weighted by item length and combined into a general measure of trait anxiety (EPI/MPQ-BF Anxiety Index). Fifty-eight participants had personality data available on SSS Form V Thrill and Adventure Seeking (Zuckerman et al., 1978), which provided a measure of trait fearlessness. Forty participants had personality data available on MPQ-BF Aggression, which provided a measure of trait aggressiveness.

2.6. Data analysis

First, we conducted a drug (placebo, amphetamine) by time analysis of variance to characterize the effects of amphetamine on salivary cortisol. Data were pooled across samples ($N=30$, Wachtel et al., 2001; de Wit and Wachtel, 2001; $N=40$, White et al., 2006). Least significant difference (LSD) post hoc comparisons were conducted to determine which conditions differed (two-tailed, $p<0.05$) within and between sessions.

Second, we examined relationships between the personality measures, in order to determine whether traits of fear and anxiety were independent in the current sample. Pearson correlations were conducted between the measures of trait thrill seeking (SSS-V Thrill and Adventure Seeking), anxiety (EPI/MPQ-BF Anxiety Index) and aggression (MPQ-BF Aggression). Significance was set at $p<0.05$ (two-tailed).

Third, we examined relationships between personality and baseline (30 min pre-drug) salivary cortisol levels on the placebo and amphetamine sessions, in order to provide information about cortisol levels prior to capsule administration. Basal cortisol was assessed approximately 30 min prior to capsule administration on each session (9 a.m.). Pearson

correlations were conducted to determine the relationship between personality and the average of basal cortisol on the two sessions. Pearson correlations were also conducted between average basal cortisol and cortisol levels after amphetamine, in order to determine the relationship between the drug effect and baseline cortisol. Significance was set at $p<0.05$ (two-tailed).

Fourth, to address our primary goal we examined individual differences in salivary cortisol responses to amphetamine in relation to personality. Peak increases in cortisol after amphetamine administration were determined for each subject (criteria: peak level achieved after drug consumption and prior to a plateau in the drug effect; interrater reliability = 0.99), and three measures of cortisol responses were calculated: (i) the time to peak drug effect on the AMP session (in minutes from capsule administration; $Time_p$), (ii) the magnitude of the increase in cortisol after amphetamine minus the placebo peak (Peak) and (iii) the magnitude of the decrease in cortisol from drug peak to the end of the session after amphetamine compared to placebo (Recovery). Participants with missing cortisol data (placebo session: $N=4$, AMP session: $N=4$) were dropped from analysis. Pearson correlations were conducted to determine the association between the magnitude of amphetamine-induced cortisol responses and personality. In order to determine whether associations were outlier driven, Cook's distance scores were calculated for each datapoint, and correlations were re-run with high influence points (≥2 S.E.M.) excluded from the analysis. Significance was set at $p<0.05$ (two-tailed) to minimize Type I error. Exploratory gender analyses and hierarchical multiple regression were conducted for findings significant at the 0.05 level. Analyses were conducted in SPSS version 11.5 (SPSS, 2002).

3. Results

3.1. Sample characteristics

Participants were mostly young Caucasian adults with post-secondary education, with low to moderate levels of current and lifetime drug use (Table 1).

Table 1
Sample characteristics

Measure	$N=70$
Age (years)	23.4±3.9
Gender (% male)	52.9
Weight (BMI = 19–27)	
Males (kg.)	75.1±8.3
Females (kg.)	60.9±6.9
Race (%)	
White	62.9
Black	22.9
Asian	11.4
Latino	2.9
Education (%)	
High school	4.3
Some college	41.4
College degree	44.3
Post-graduate	10
Current recreational substance use	
Alcohol (drinks/week)	3.5±3.6
Caffeine (cups/day)	6.7±6.6
Marijuana (% >0.5 cig/week)	12.5
Cigarettes (% >2.5 cig/day/>5 cig/week)	0
Lifetime rec. substance use (% ever used)	
Stimulant	12.9
Sedative	2.9
Opiate	8.6
Hallucinogen	21.4
Marijuana	63.9
Inhalant	12.9

3.2. Drug effects

Compared to placebo, amphetamine increased salivary cortisol levels (drug by time interaction, $F(6,360)=14.89$, $p<0.001$). As seen in Fig. 1, salivary cortisol levels in the placebo condition continued to decline throughout the session. On the amphetamine session, cortisol levels began to rise within 30 min of drug administration and peaked on average 90 to 210 min later (peak: $p<0.001$ vs. placebo). Cortisol levels after amphetamine began to decline toward the end of the session, but did not return to drug-free levels by the end of the session 4.5 h later (recovery: $p<0.01$ with timepoints +150, +210 post-capsule). By the end of the session cortisol levels returned to levels close to the pre-capsule baseline scores (p = n.s. with timepoints +30, +60 post-capsule, Fig. 1), but did not reach the levels for the placebo condition at the same time of day.

3.3. Personality

Scores on SSS-V Thrill Seeking and the EPI/MPQ-BF Anxiety Index were unrelated ($r=-0.03$, n.s., $N=58$), as expected, supporting the idea that the personality dimensions of the core of negative affect (anxiety) and fearlessness are independent (Watson and Clark, 1984). The aggression scale typically loads most highly on negative affect and anxiety factors, and scores on MPQ-BF Aggression and EPI/MPQ-BF Anxiety Index were positively associated in the current sample ($r=0.34$, $p<0.05$, $N=40$). These data suggest that the sample is appropriate for understanding the relationship between cortisol responses and traits of fear versus anxiety, and the relationship between cortisol responses and the core features (EPI/MPQ-BF Anxiety Index) versus distal features (MPQ-BF Aggression) of negative affect.

3.4. Pre-drug differences

Average basal cortisol (pre-capsule) was not related to personality (r's ≤ |0.2|, n.s.). Average basal cortisol was also not related to peak cortisol responses to amphetamine (Peak, $Time_p$, r's ≤ 0.2, n.s.), but was associated with the magnitude of the recovery in cortisol after amphetamine compared to placebo (Recovery, $r=0.3$, $p<0.05$). This latter finding could reflect an association between high cortisol levels at initial presentation to the lab (basal cortisol) and the speed or magnitude of the decline in cortisol after challenge with amphetamine during the initial period of the descending limb of the cortisol response. This

Table 2
Personality and amphetamine-induced cortisol response (μg/dl), Pearson correlations

Personality constructs/ factor scales	Amphetamine-induced cortisol rise		
	$Time_p$	Peak	Recovery
Trait fearlessness			
SSS-V Thrill Seeking [a]	−0.32*	0.15	0.15
Trait negative affect			
EPI/MPQ-BF Anxiety Index [b]	0.05	0.13	0.08
MPQ-BF Aggression [c]	−0.24	0.35*	0.38*
Mean (S.E.M.)	150 m (5.8)	0.32 μg/dl (0.03)	0.16 μg/dl (0.03)

[a] Time: $N=55$; Peak, Recovery: $N=52$.
[b] Time: $N=60$; Peak, Recovery: $N=57$.
[c] Time: $N=37$; Peak, Recovery: $N=34$.
* $p \leq 0.05$ (two-tailed).

association suggests that individuals with relatively labile cortisol systems could show faster recovery of cortisol levels after challenge with D-amphetamine, at least during the initial period of cortisol descent measured during the current study.

3.5. Drug effects related to personality

SSS-V Thrill and Adventure Seeking was negatively associated with time to peak increase in cortisol after amphetamine effects on cortisol (Table 2). Participants who scored high on Thrill and Adventure Seeking had an earlier onset of peak cortisol responses to amphetamine ($Time_p$), as seen in Fig. 2. This effect remained significant after two datapoints with potential high influence (Cook's $d \geq 0.06$) were identified and excluded from analysis ($r=-0.35$, two-tailed $p<0.01$). Personality measures of trait anxiety (EPI/MPQ-BF Anxiety Index) and trait aggression (MPQ-BF Aggression) were unrelated to the time of the cortisol peak.

MPQ-BF Aggression was positively associated with the magnitude of the amphetamine-induced cortisol rise response

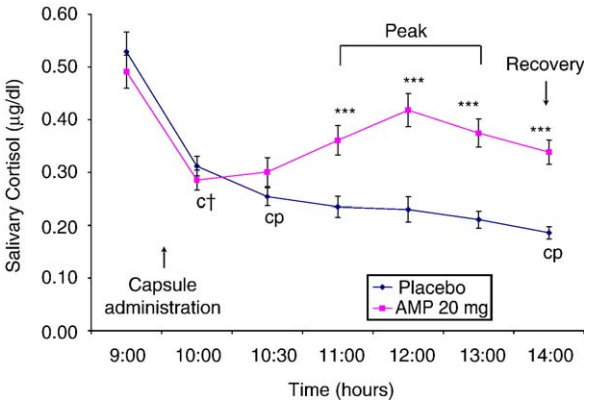

Fig. 1. Legend: Salivary cortisol levels, $N=70$. *Between session:* ***$=p<0.001$, amphetamine vs. placebo timepoints. *Within session*: peak$=p<0.01$ vs. adjacent timepoints, AMP session; recovery$=p<0.01$ vs. prior two timepoints, AMP session; c†$=$circadian decline vs. preceding timepoint, $p<0.01$, placebo and AMP session; cp$=$circadian decline vs. preceding timepoint, $p<0.05$, placebo session.

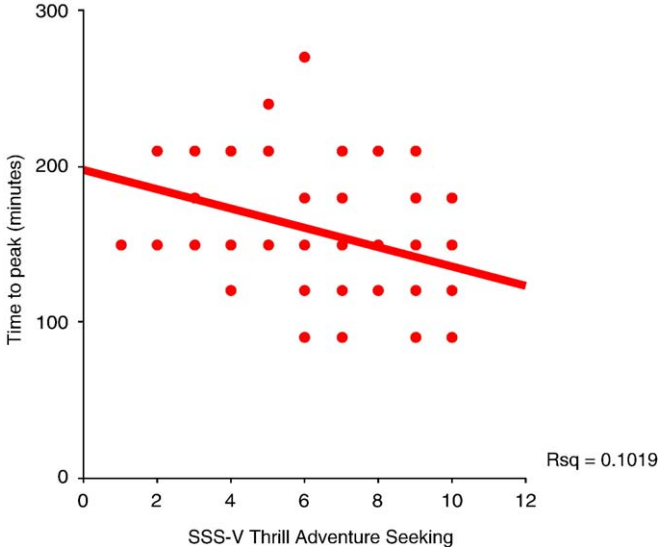

Fig. 2. Thrill seeking and time to peak amphetamine effects on cortisol.

(Peak $r=+0.35$, $p<0.05$; Fig. 3a), although this association became marginally significant ($r=+0.31$, two-tailed $p=0.09$, $N=30$) after exclusion of high-influence points. MPQ-BF Aggression was positively associated with the magnitude of the recovery in cortisol by the end of the session (Recovery $r=+0.38$, $p<0.05$, Fig. 3b), an association which remained significant after exclusion of high-influence data points ($r=+0.64$, two-tailed $p<0.001$, $N=28$). These data indicate that MPQ-BF Aggression was significantly associated with the magnitude of cortisol recovery after challenge with D-amphetamine and showed a trend toward a larger peak cortisol response. Findings for recovery should be interpreted with caution, as the current study investigated only an early portion of the descending limb, which limits conclusions to the initial cortisol recovery period.

3.6. Exploratory gender effects

Exploratory analyses indicated that the direction of effects appeared similar in males and females (e.g., Thrill Seeking and $Time_p$: males: $r=-0.38$, $N=26$; females: $r=-0.24$, $N=29$; Aggression and Peak: females: $r=+0.47$, $N=15$; males: $r=+0.26$, $N=19$; Aggression and Recovery: females: $r=+0.54$, $p<0.05$, $N=15$; males: $r=+0.35$, $N=19$). Interpretation of gender differences should be viewed with caution due to the small N.

3.7. Exploratory multiple regression

As fearlessness and aggression were each found to contribute to different aspects of cortisol variation, hierarchical multiple regressions were conducted in order to determine if the combined effects of fearlessness and aggression would account for significantly more variance in cortisol functioning than either alone. To assess this, hierarchical multiple regression was conducted for each cortisol outcome (i.e., $Time_p$, Peak, Recovery), with the stronger (significant) predictor from

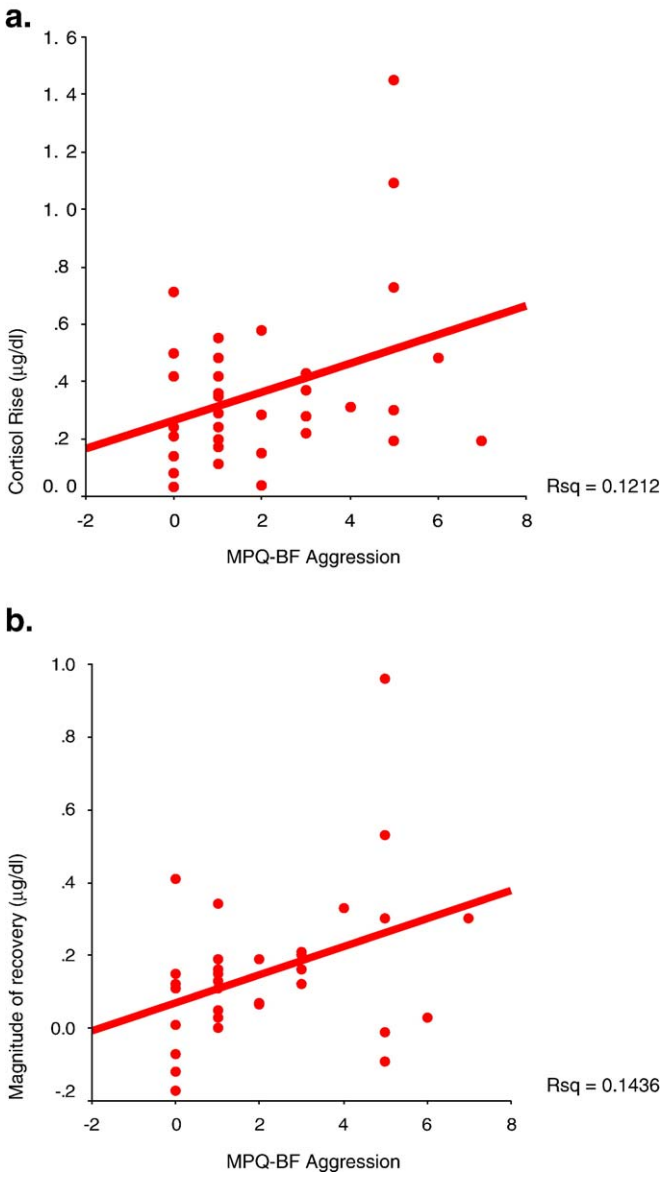

Fig. 3. Aggression and amphetamine-induced cortisol rise responses (µg/dl): a. Peak Drug Effect. b. Magnitude of Recovery.

Table 2 entered first in step 1 and the alternate trait (trait aggression/thrill seeking) added to the regression equation in step 2. The $R^2\Delta$ for step 2 is the increased variance accounted for by including both trait aggression and thrill seeking.

For time to peak ($Time_p$), thrill seeking was entered in the first step of the regression equation and accounted for 13% of the variance ($R^2=0.13$, $p<0.05$). When trait aggression was then entered in the second step of the equation, it accounted for an additional 7% of the variance in $Time_p$, a marginally significant increase ($R^2\Delta=0.07$, $F[1,34]=2.95$, $p<0.10$). In contrast, after trait aggression was entered in the first step of the regression equation for cortisol peak ($R^2=0.12$, $p<0.05$) and recovery ($R^2=0.14$, $p<0.05$), the inclusion of thrill seeking in step 2 failed to account for additional variance of either cortisol peak ($R^2\Delta=0.01$, $F[1,31]<1$) or recovery ($R^2\Delta=0.02$, $F[1,31]<1$). These data indicate that cortisol time-to-peak was marginally associated with trait aggression in addition to trait thrill seeking when the traits were treated as multiple predictors, while cortisol peak and recovery were related only to trait aggression in the current sample.

4. Discussion

This study indicates that the personality traits of thrill seeking and aggression, but not anxiety, were associated with cortisol responses to d-amphetamine. SSS-V Thrill Seeking was associated with an earlier onset of peak cortisol responses. MPQ-BF Aggression was associated with a greater magnitude of amphetamine effects at drug peak and the magnitude of cortisol recovery after drug peak. In contrast, a composite measure of anxiety proneness (EPI/ MPQ-BF Anxiety Index) was unrelated to either the timing or the magnitude of cortisol responses to amphetamine. These findings are discussed in turn.

The first finding was that subjects with high SSS-V Thrill Seeking scores displayed an earlier timing of the peak cortisol response to amphetamine, displaying a temporally faster onset of HPA axis response to the drug. The association was modest ($r=|0.32|$) and survived exclusion of high-influence datapoints. This finding, of a more rapid peak cortisol response in thrill seekers, suggests that salience of drug-related stimuli could be increased in thrill seeking individuals via a coordination of timing between the neuroendocrine response, glucocorticoid-mediated reinforcement and the stimuli surrounding the individual at the time of drug consumption and the peak drug effect. An earlier onset of peak responses could constitute one mechanism through which sensation seekers achieve increased rates of drug consumption and drug abuse. This possibility requires further test as an etiological risk factor for drug abuse.

The second finding was that subjects with high scores on MPQ-BF Aggression displayed a greater cortisol response at drug peak, followed by a greater recovery of cortisol levels by the end of the study sessions. Significance of the effects was stronger for recovery than peak, which appeared to be partially outlier-driven (see Results). As cortisol levels at recovery did not differ from those assessed earlier in the session ($t=1.25$, n.s.; see Fig. 1), this pattern suggests that aggression could be associated with a robust and temporally dynamic HPA axis response to amphetamine (i.e., elevated peak cortisol rise response, followed by a rapid recovery to pre-drug cortisol levels), at least during the initial period of the descending limb of the cortisol response curve assessed in the current study. The data suggest that these differences are not related to anxiety-negative affect (i.e., an angry hostility generated by a chronic state of anxiety), but rather appear more related to primary trait aggression. The results of the hierarchical multiple regression underscored the importance of trait aggression to cortisol responses, as trait aggression was strongly associated with peak and recovery responses to amphetamine, and marginally improved prediction of time to peak responses. These associations extend findings from several animal studies of temperamental differences in drug abuse vulnerability. For instance, rats that are highly responsive to novelty have greater amphetamine self-administration and greater cortisol responses to novelty than do low responders. In animals not prone to self-

administration, pretreatment with cortisol increases the acquisition of amphetamine self-administration to levels similar to those of high responders (Piazza et al., 1991). Thus, the current data are consistent with animal findings suggesting a glucocorticoid mechanism in temperamental differences in psychostimulant drug effects. The current data are also consistent with human studies that use an emotional challenge approach to cortisol reactivity. For instance, individuals with low levels of recent life stress have larger cortisol responses to laboratory stress (Roy, 2004), while individuals with high depression scores have lower but more sustained cortisol responses to similar stressors (Ellenbogen et al., 2002). These data suggest that low levels of internalized or experienced life stress could contribute to the rapid cortisol recovery after amphetamine here observed in high trait aggression individuals.

The above associations between thrill seeking, aggression and cortisol responses could be mediated by several neural mechanisms, including amphetamine-induced effects on dopamine, serotonin and norepinephrine, each of which has implications for our understanding of fear versus anxiety traits. Amphetamine increases dopamine, serotonin and norepinephrine (NE) via reversal of catecholamine transporters (Goldstein et al., 1983; Ritz and Kuhar, 1989). Amphetamine effects on NE may have special relevance for the distinction between fear and anxiety. NE fibers originate in the A2 and locus ceruleus groups of the brainstem and project to the paraventricular nucleus (PVN) of the hypothalamus and amygdala, where they mediate cortisol responses to stress and behavioral responses to threat (Van Bockstaele et al., 1998). These responses are coordinated in their timing and are elicited by similar stimuli, and appear to constitute a coordinated neuroendocrine and physical response to stimuli of potential harm (Reyes et al., 2005; Van Bockstaele et al., 2001). The current amphetamine challenge was conducted in order to provide a test of individual differences in the sensitivity to a bolus release of norepinephrine and other catecholamines in the PVN in healthy individuals. Individuals who were relatively sensitive to threat (i.e., low in trait fearlessness) were expected to display blunted cortisol responses to amphetamine, due to a downregulation of catecholamine and NE receptors in the PVN as a result of chronic stress in these individuals (see Sitaram et al., 1984). In contrast, individuals who were relatively insensitive to threat (i.e., those who are high in trait fearlessness) were expected to display larger cortisol responses to amphetamine, because PVN receptors would be less subject to downregulation. The study included a separate measure of anxiety proneness and rumination about negative events (EPI/MPQ-BF Anxiety Index) in order to assess trait anxiety and the sensitivity to other types of negative stimuli (e.g., negative social evaluation). This measure was not expected to explain additional variance in cortisol responses beyond that explained by fear trait, because in other studies, trait fear but not trait anxiety has been associated with circulating NE (Ballenger et al., 1983), mood responses to amphetamine (White et al., 2006) and responses to other catecholamine agonists (White and Depue, 1999; Depue et al., 1994). As such, the current study provides preliminary data relevant to potential catecholamine contributions to a fear-anxiety distinction in humans and suggests a role of glucocorticoids in personality differences in amphetamine responses.

The growing literature on noradrenergic involvement in aggression and hostility (for review, see Haller et al., 1998) suggests a role for NE in the current results. Aggression has been found to associate with increased NE release (e.g., Korzan et al., 2001; van der Vegt et al., 2003), and elimination of NE has been found to eliminate aggression but not anxiety (Marino et al., 2005). Trait aggression/hostility has been found to relate to increased noradrenergic receptor sensitivity (Coccaro et al., 1991; see also Coccaro et al., 2003), and alpha-1 receptors have been found to mediate aggressive responses to certain NE drugs (e.g., high dose clonidine; Rogoz et al., 2001; Maj et al., 1982). These data suggest that increased noradrenergic receptor sensitivity, including but not limited to the alpha-1 subtype, could contribute to the robust cortisol peak and recovery observed here with trait aggression.

Strengths of the current study included the use of relatively independent measures of the personality traits of fearlessness and negative affect, placebo controls, a moderately high dose (20 mg p.o.) of D-amphetamine, double-blind administration of drugs and investigation of effects using a moderate to large sample. Limitations of the study included the use of participants who were relatively young (age 18 to 35), educated (completed high school), and pre-screened for medical and psychiatric disorders. Other limitations included the use of self-report to verify consumption of the standard pre-protocol breakfast, which standardized the timing and extent of drug absorption in the study participants, and measurement of recovery during the early period of the descending limb. Conclusions about the association between personality and cortisol responses are limited to the initial period of the descending limb of the cortisol response. The current findings may not generalize to a more heterogeneous population, including individuals who are older, under socioeconomic stress or who have a history of substance abuse or other psychiatric disturbance.

To sum up, the current data indicate that two personality traits may be associated with between-subject differences in the magnitude of cortisol responses to psychostimulants: trait fearlessness and trait aggression, each of which contributed approximately 10% to 15% of the total variance in cortisol time to peak, peak and recovery after amphetamine. The predisposition toward fearless thrill seeking and aggression could pose a special neuropsychosocial risk factor for glucocorticoid-mediated reinforcement and addiction in humans. In contrast, the core aspect of negative affect (e.g., anxiety and negative rumination; EPI/MPQ-BF Anxiety Index) was unpredictive of these effects. This dissociation suggests that anxiety proneness is less likely to be involved in glucocorticoid pathways to addiction. The current data further suggest a catecholamine contribution to a fear-anxiety distinction, as amphetamine-induced cortisol responses were associated with measures of trait fear but not trait anxiety in the current sample. Directions for future work include investigation of the specific mechanisms involved with regard to the traits of fearlessness and aggression, whether the timing or the magnitude of cortisol responses is more associated with elevations in the euphoric

effects of psychostimulants, and the ways in which these two traits may modulate the strength of these associations.

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