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Does stress reactivity or response to amphetamine predict smoking progression in young adults? A preliminary study

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Abstract

Recent studies with laboratory animals indicate that a constellation of behavioral factors predict progression to self-administer drugs. Relatively little is known about behavioral or biological factors that predict the progression in drug use from initial experimentation to regular use in human drug users. The present exploratory study examined reactivity to an acute stressor and reactivity to a single dose of a dopaminergic drug as predictors in progression to heavier smoking in young cigarette smokers over a 6-month period. Forty-four college students who were light to moderate smokers participated in three laboratory sessions, followed by a follow-up interview 6 months later to determine smoking level. On one of the laboratory sessions subjects underwent the Trier Social Stress Test, and on the others they ingested capsules containing placebo or 20 mg D-amphetamine. Outcome measures included subjective ratings of mood and measures of heart rate and salivary cortisol. We found modest positive relationships between stress reactivity and certain responses to amphetamine. Further, stress-induced increases in cortisol were positively related to increases in cigarette smoking in the 31 subjects who we were able to contact at 6 months. Although these results are highly preliminary, they resemble the relationships previously reported in laboratory animals, suggesting that some of the same factors that predict drug-self-administration in rodents predict progression in drug use among young adults.

Keywords: Acute stress; D-Amphetamine; Smoking; Progression; Individual differences; Human; Subjective effects; Cortisol

1. Introduction

In studies with laboratory animals, certain behaviors appear to predict greater susceptibility to self-administer drugs (Deroche et al., 1993; Marinelli and Piazza, 2002; Piazza and Le Moal, 1996). Rats that exhibit (i) more exploratory behavior in a novel environment, (ii) greater glucocorticoid reactivity to acute stress, (iii) a greater behavioral response and (iv) more dopamine release after a stimulant drug (referred to as 'High Responder' animals) learn more rapidly to self-administer drugs (Piazza et al., 1991). The neurobiological basis of these phenotypes has been studied extensively (Kabbaj, 2004; Marinelli, 2005), and similar findings have been reported using other drugs, including nicotine (Suto et al., 2001). Although a growing body of literature suggests that reactivity to stress, novel stimuli or stimulant drugs predict the susceptibility to initiation or escalation of drug use in animals, few studies have explored this phenomenon in humans. We attempted to extend the animal findings to humans by studying young, occasional smokers who were at risk for escalating their cigarette smoking.

To our knowledge, only one previous laboratory study used this approach to examine individual differences in responses to stimulant drugs in humans. Alessi et al. (2003) investigated the effects of oral D-amphetamine in healthy adults, to determine whether individual differences in spontaneous motor activity in a novel environment predicted either the reinforcing or behaviorally activating effects of the drug. These investigators grouped participants according to their level of motor activity before drug administration (high responders: HR and low responders: LR), and compared the groups' responses to amphetamine (physical activity and prepulse inhibition). Pre-drug activity was not related to amphetamine responses. Another source of information about individual differences in stimulant responses comes from studies measuring personality. At least two studies have reported positive relationships between responses to stimulants and personality traits such as sensation-seeking and extraversion (Kelly et al., in press; White et al., 2005). Personality traits in

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humans may parallel the individual differences in behavior in animals. Indeed, both locomotor activity in rats and the personality dimension of extraversion in humans have been linked to dopamine function (Depue et al., 1994; Depue and Collins, 1999). Thus, it may be that correlations between personality and acute drug responses in humans are related to the individual differences described by Piazza and colleagues in rats.

One quasi-naturalistic context in which behavioral predictors of drug use may be identified is in the progression from occasional to regular cigarette smoking among young adults. Most adolescents and young adults have tried cigarettes (e.g., 53% of 18 year olds in 2004; SAMSHA, 2005), but only a fraction of these individuals escalate their use to become daily smokers. The initiation and progression of smoking has been linked to many psychosocial factors such as delinquency, lack of religiosity, lack of involvement in sports, emotional distress, peer influence, friends' smoking and approval, parental smoking, family conflicts, and alcohol and marijuana use (Aaron et al., 1995; Escobedo et al., 1993; Flay et al., 1998; Orlando et al., 2001; Resnick et al., 1997; Webster et al., 1994). However, few studies have examined progression in cigarette use in relation to biological factors, including the risk factors that have been identified in rat self-administration, such as stress reactivity or acute responses to a dopaminergic drug. Thus, it is possible that either reactivity to an acute stressor or reactivity to an acute dose of a dopaminergic drug predicts escalation of cigarette use, just as these factors predict drug-taking in rats.

The present study had two goals. First, we examined the relationships between responses to an acute oral dose of D-amphetamine and stress reactivity in humans. We hypothesized that the magnitude, or quality, of subjective responses (e.g., feelings of well-being) after amphetamine would be related to hormonal or psychological reactivity to an acute social stressor. Subjective responses to amphetamine in humans are, like locomotor responses to stimulants in rodents, thought to be mediated by dopamine. As such, the acute amphetamine administration in smokers was considered to be a dopamingeric challenge, parallel to the drug-induced increases in locomotor activity in rodents. Second, we investigated whether acute responses to either stress or amphetamine predicted escalation of cigarette smoking over a 6-month period. Adolescents and young adults are at high risk for becoming regular daily smokers, but the factors that predict which individuals are at risk are poorly understood. We hypothesized that greater subjective response to amphetamine (e.g., euphorigenic effects) or greater responses to acute stress, or both, would be predictive of an increase in smoking over the next 6 months.

2. Materials and methods

2.1. Subjects

Male (N=24) and female (N=20) light, non-dependent cigarette smokers, aged 18–24, were recruited from the University of Chicago and the surrounding communities through posters and newspaper advertisements without regard to race or ethnicity. Participants completed an initial phone screening and then an in-person interview including a physical examination and electrocardiogram. Candidates were eligible if they smoked at least once a month but not more than 6 cigarettes per day. Only light smokers were recruited because the study was designed to identify predictors of escalation of cigarette use, early in the natural history of smoking. During screening subjects completed a questionnaire regarding their current and lifetime use of recreational drugs. Candidates were excluded if they had a Major Axis I DSM-IV disorder (APA, 1994) including drug abuse or dependence, high blood pressure or a history of cardiovascular problems, not completed high school, or a body mass index outside of 19–26 kg/m^2. Women were not allowed to participate if they were taking oral contraceptives or pregnant. All participants gave informed consent prior to participating in the study and the protocol was approved by the institutional review board.

2.2. Design

The study used a double blind, placebo-controlled design, in which each subject participated in two drug sessions and one stress session conducted in the laboratory, and then 6 months later subjects were interviewed to provide information about their cigarette and other drug use. The three laboratory sessions included two 4-h drug sessions and one 90-min stress session, in randomized order. During the drug sessions, participants received either placebo or D-amphetamine (20 mg). During the stress session, they completed the Trier Social Stress Test (TSST; Kirschbaum et al., 1993). Sessions were conducted from 8 am to noon. Six months after their last session subjects were contacted by telephone or email to complete a questionnaire on their current level of recreational drug use, with a focus on cigarette smoking. Laboratory sessions were conducted in comfortably furnished rooms with a television/VCR, magazines, and a computer for administering questionnaires.

2.3. Procedure: drug administration sessions

Upon arrival at the laboratory for the two drug sessions, volunteers provided a urine sample for drug and pregnancy (women) testing. Breath alcohol and carbon monoxide levels were measured to detect recent use of cigarettes or alcohol. Subjects were rescheduled if they had any detectable breath alcohol levels, or if their carbon monoxide levels were greater than 4 ppm. Participants then completed baseline subjective measures (see below) and physiological measures including heart rate, blood pressure and salivary cortisol, were obtained. Ten minutes later, they ingested a capsule containing either placebo or D-amphetamine (20 mg). Physiological and subjective measures were obtained 30, 60, 90, 120, 180 and 240 min after drug administration. At 120 min, volunteers also completed behavioral tasks that assessed impulsive behavior, which are not reported here.

2.4. Procedure: Trier Social Stress Test (TSST) session

As with the drug sessions, participants were first tested for drug use or pregnancy, and were rescheduled if necessary (see

above). An initial saliva sample was obtained and volunteers received a Polar S610 heart rate monitor to measure heart rate continuously throughout the stress session. Twenty minutes before the TSST began, another saliva sample was obtained, and subjects completed subjective effects questionnaires. Ten minutes before the TSST began, another saliva sample was obtained and a research assistant informed the participant that s/he would be required to present a 5-min speech and answer arithmetic questions in front of interviewers trained in monitoring non-verbal behavior. Subjects were told that the task would be videotaped for further behavioral analysis. After the instructions and 10 min preparation time, the subject provided a saliva sample and was taken to a separate "examination" room for the TSST. In the examination room, two interviewers sat behind a table. A video camera and monitor were in plain view to the participant, whose presentation appeared on the monitor. The participant was introduced to the interviewers and instructed to stand 1 m from the table and begin their speech. Interviewers provided no positive feedback during the speech or arithmetic tasks, but prompted the subject to continue speaking if they stopped. After the task, the participant returned to the individual testing room to complete further subjective questionnaires and provide saliva samples at 15, 20, 40, and 70 min after beginning the TSST.

2.5. Follow-up data collection

Six months after the last completed session, subjects were contacted via phone or email and asked about their current drug and alcohol use, with an emphasis on their cigarette use.

2.6. Physiological measures

Physiological measures included heart rate, blood pressure and salivary cortisol. In the drug sessions heart rate and blood pressure were measured at regular intervals using a Critikon Dinamap 1846 SX/P Version 089 monitor. In the stress session heart rate was measured continuously using a Polar® S610i heart rate monitor (Polar Electro Inc., Lake Success, NY). Blood pressure was not measured during the stress sessions. Saliva samples were collected during all three sessions using Salivette® cotton wads (Sarstedt Inc., Newton, NC). During drug sessions, samples were collected 10 min before and 30, 60, 90, 120, 180 and 240 min after drug administration. During the stress session, saliva samples were collected 30, 20 10 min and immediately before the TSST began, and then at 15, 20, 40, and 70 min after the task began.

2.7. Subjective effects measures

During drug sessions, subjective effects were assessed using the Profile of Mood States questionnaire (POMS; McNair et al., 1971), and the Addiction Research Center Inventory (ARCI; Martin et al., 1971), before and at 30, 60, 90, 120, 180 and 240 min after capsule administration. During the stress session, participants completed the POMS 20 min before and at 15, 20, 40 and 70 min after the TSST began. The POMS is a 72-item questionnaire used to assess subjective effects of drugs (Johanson and Uhlenhuth, 1980). The ARCI is a true–false questionnaire that yields five subscales: a measure of euphoria, the MBG (Morphine–Benzedrine Group); two measures of stimulant-like effects: the A (Amphetamine) scale and the BG (Benzedrine Group) scale; a measure of sedation, the PCAG (Pentobarbital–Chlorpromazine Group) scale; and a measure of dysphoria, the LSD (Lysergic Diethylamide) scale.

2.8. Data analysis

Peak changes were calculated by subtracting the pre-capsule or pre-stress measure from the highest or lowest value during the session for each subject, for all measures. To derive a single value of response to amphetamine, the peak score for each time point on the placebo session was subtracted from the corresponding score for the drug session, and the largest (or smallest) difference value was taken as the peak score. Thus, for each measure each subject had a single value for response to amphetamine and for response to stress. Pearson Product Moment correlations were calculated to examine stress response in relation to drug response.

The number of cigarettes subjects reported smoking weekly at 6 months follow-up were examined in relation to demographic characteristics at intake, as well as in relation to

Table 1
Demographic characteristics and drug use summary for subjects (N=44) who participated in the laboratory phase of the study

Men (N)	24
Women (N)	20
Age, years (mean±S.E.M.)	20.2±0.3
Weight, kg (mean±S.E.M.)	65.7±3.0
Race/ethnicity[a]	
White	38
Black	2
Asian	4
Native American	1
Unknown	2
Education	
Partial college	34
College degree	9
Advanced degree	1
Current drug use (Mean±S.E.M.)	
Cigarettes at initial screening (cigarettes/week)	10.7±1.8
Cigarettes at 6-month follow-up (cigarettes/week)	9.0±1.6
Alcohol (drinks/week)	7.3±0.8
Lifetime marijuana use (N)	
Never	7
1–10 times	11
11–50 times	15
51–100 times	4
Over 100 times	8
Lifetime drug use (N; ever used)	
Stimulants	12
Tranquilizers	3
Hallucinogens	18
Opiates	19
Inhalants	9

[a] Three subjects endorsed multiple races.

Table 2
Mean values (+/− SEM) on measures on which there were significant effects of 20 mg D-amphetamine (AMPH) or placebo (N=44)

Measure	Placebo		Amphetamine	
	Pre-capsule (−10 min)	Post-capsule (120 min)	Pre-capsule (−10 min)	Post-capsule (120 min)
Physiological				
Heart rate	71.5±1.5	63.7±1.3***	69.6±1.4	70.0±1.6
Cortisol	18.9±1.4	7.7±1.1***	18.1±2.1	14.6±1.6
ARCI [a]				
A	2.2±0.2	2.5±0.3	2.6±0.3	5.4±0.5***
BG	5.0±0.2	4.5±0.4	5.8±0.2	8.0±0.4***
LSD	3.3±0.2	3.9±0.3	3.4±0.2	4.0±0.2*
MBG	2.5±0.4	2.4±0.5	2.8±0.4	6.4±0.8***
PCAG	4.5±0.4	5.4±0.5	4.6±0.4	2.3±0.4***
POMS [b]				
Friendly	11.5±0.8	9.2±0.9***	10.8±0.9	11.9±1.1
Anxiety	3.2±0.4	2.8±0.4	4.4±0.5	4.1±0.4
Depression	2.0±0.5	1.6±0.5	2.8±0.6	0.7±0.2**
Fatigue	3.8±0.6	3.7±0.6	3.8±0.5	1.3±0.3***
Anger	1.7±0.4	1.5±0.4	2.2±0.5	0.6±0.2***
Elation	4.5±0.5	3.1±0.4**	4.2±0.4	6.5±0.7**
Confusion	4.5±0.4	4.2±0.4	4.9±0.4	3.1±0.2***
Vigor	7.8±0.9	6.3±0.7	8.2±0.8	12.4±1.1***
Arousal	2.8±1.3	1.2±1.3	3.9±1.2	12.2±1.5***
Positive mood	2.5±0.7	1.5±0.7	1.4±0.9	5.8±0.8***

Pre-capsule and post-capsule means were compared for the Placebo and Amphetamine sessions. p-values: * denotes $p \leq 0.05$, ** denotes $p \leq 0.01$, and *** denotes $p \leq 0.001$.
[a] Addiction Research Center Inventory.
[b] Profile of Mood States.

responses to stress and drug in the laboratory. In all analyses, differences were considered to be significant if $p<0.05$, with Bonferroni correction, unless otherwise noted.

3. Results

3.1. Demographic measures

Participant demographics and characteristics are listed in Table 1. Most subjects were Caucasian students, and all were light smokers about 20 years of age. They reported smoking on average about 10 cigarettes a week. The 13 subjects who could not be reached for follow-up did not differ from the 31 subjects who were reached on demographic characteristics including sex, age, race, and baseline levels of smoking cigarettes, using alcohol, and smoking marijuana.

3.2. Baseline physiological measures

There were no differences across the drug or stress sessions at baseline on measures of heart rate, blood pressure or cortisol levels.

3.3. Subjective and physiological effects of D-amphetamine

Table 2 shows the mean peak pre and post amphetamine and placebo scores for the outcome measures. Compared to placebo, D-amphetamine significantly increased self-reported stimulation on the A ($F(5,190)=20.1$, $p<0.001$) and BG scales of the ARCI ($F(5,190)=14.9$, $p<0.001$; Fig. 1), and euphoria on the MBG scale ($F(5,190)=22.9$, $p<0.001$). Amphetamine decreased feelings of sedation on the PCAG scale ($F(5,190)=7.3$, $p<0.001$). Participants also reported increased Friendliness (POMS; $F(5,215)=9.4$, $p<0.001$), Elation (POMS; $F(5,215)=11.0$, $p<0.001$), Vigor (POMS; $F(5,215)=11.8$, $p<0.001$),

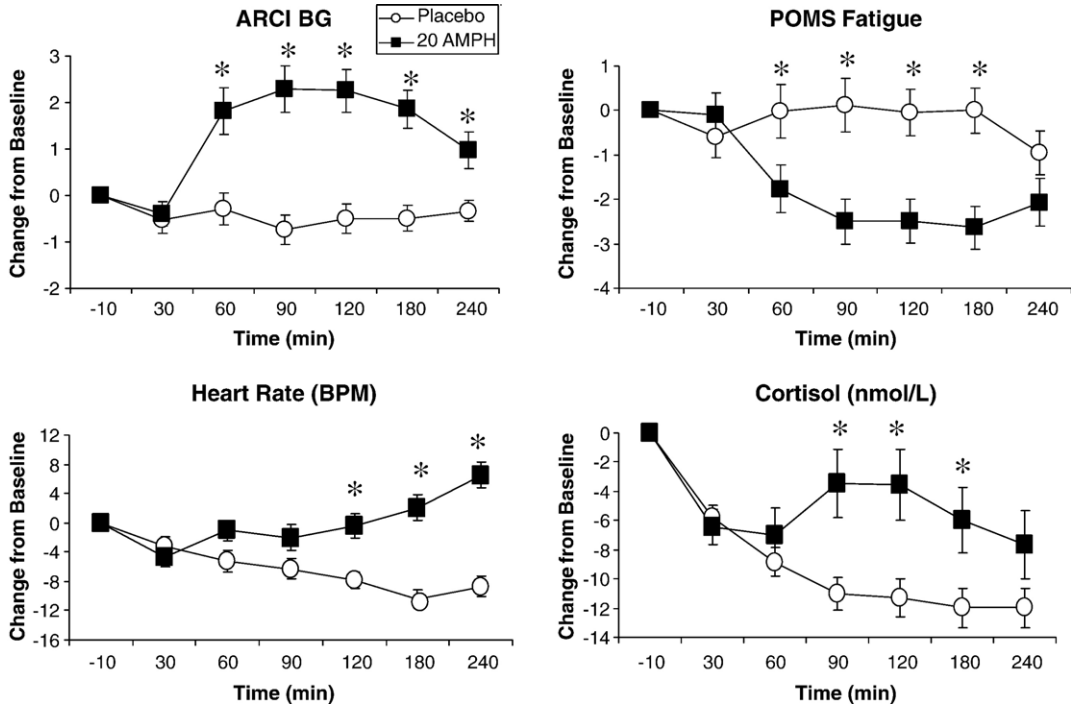

Fig. 1. Mean (and S.E.M.) values on selected measures after D-amphetamine (20 mg; filled symbols) and placebo (open symbols) at varying times after ingestion of the capsules (N=44). Asterisks indicate significant differences between drug and placebo sessions. ARCI BG scale shows that D-amphetamine increased feelings of stimulation, and POMS Fatigue shows that the drug decreased ratings of fatigue. Amphetamine also increased salivary cortisol levels, and increased heart rate toward the later portion of the sessions.

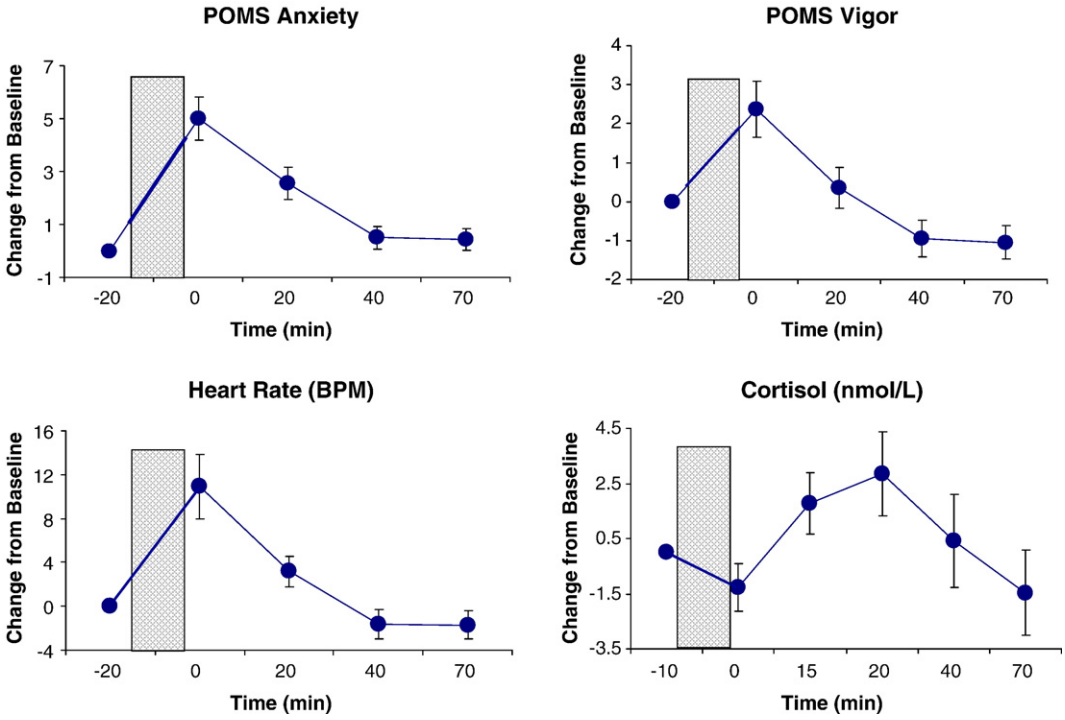

Fig. 2. Mean (and S.E.M.) values on Anxiety and Vigor (POMS) and heart rate and salivary cortisol levels on the stress session ($N=44$). Shaded bar indicates the time of the TSST stress procedure.

Arousal (POMS; $F(5,215)=14.9$, $p<0.001$), and Positive Mood (POMS; $F(5,215)=9.4$, $p<0.001$), and decreased Fatigue (POMS; $F(5,215)=6.4$, $p<0.001$; Fig. 1) and Confusion (POMS; $F(5,215)=3.9$, $p<0.01$). Amphetamine also increased heart rate ($F(5,215)=5.5$; $p<0.001$) and cortisol levels ($F(5,215)=2.8$; $p<0.05$; Fig. 1) relative to placebo.

Table 3
Measures on which there were significant effects of stress ($N=44$)

Measure	Pre-stress [a]	Post-stress (15 min)
Physiological		
Heart rate	75.6±1.9	89.2±2.4***
Cortisol	7.8±1.2	8.9±1.3
VAS [b]		
Stimulated	23.4±2.9	52.8±4.2***
Calm	64.8±2.8	30.6±2.7***
Jittery	21.0±3.0	47.2±3.9***
Anxious	28.5±3.4	46.5±3.9***
Uneasy	18.5±2.9	46.6±4.4***
POMS [c]		
Friendly	10.7±1.0	7.8±0.9***
Anxiety	4.0±0.6	9.0±0.8***
Depression	2.2±0.8	3.8±1.1
Fatigue	3.8±0.7	2.8±0.6**
Anger	1.6±0.5	3.6±0.7***
Elation	3.9±0.5	3.2±0.5
Confusion	4.8±0.4	5.8±0.5
Vigor	7.3±0.8	9.6±1.0**
Arousal	2.9±1.5	9.3±1.7***
Positive mood	1.6±1.0	−0.6±1.4

Means were compared for the values pre- to 15 min post-stress. p-values: * denotes $p\leq0.05$, ** denotes $p\leq0.01$, and *** denotes $p\leq0.001$.

[a] Pre-stress measures were taken at −10 min for physiological measures (heart rate and blood pressure) and −20 min for subjective effects (VAS and POMS).

[b] Visual Analogue Scales.

[c] Profile of Mood States.

3.3.1. Time course of D-amphetamine effects

Most of the subjective effects of D-amphetamine began 60 min after administration of the capsule, and remained elevated throughout the session. Exceptions were the effects of amphetamine on Arousal (POMS), which lasted until 180 min after administration, Confusion (POMS), which was elevated compared to placebo from 90 to 120 min, and Friendliness (POMS) from 120 to 180 min after capsule administration. The time course of the increased heart rate followed a different

Table 4
Positive and negative correlations (r value) between peak changes in subjective and physiological responses to stress and 20 mg D-amphetamine ($N=44$)

Responses to stress	Responses to amphetamine	Correlation
Cortisol [a]	Cortisol	0.42 [b]
Confused (POMS)	Positive mood (POMS)	0.39 [b]
Fatigue (POMS)	Fatigue (POMS)	0.33 [c]
Cortisol	Depression (POMS)	0.32 [c]
Anxiety (POMS)	Friendliness (POMS)	0.31 [c]
Anxiety (POMS)	Confusion (POMS)	−0.41 [b]
Confusion (POMS)	Confusion (POMS)	−0.41 [b]
Vigor (POMS)	Fatigue (POMS)	−0.39 [b]
Arousal (POMS)	Fatigue (POMS)	−0.38 [c]
Fatigue (POMS)	Stimulation (ARCI BG)	−0.37 [c]
Elated (POMS)	Fatigue (POMS)	−0.36 [c]
Fatigue (POMS)	Stimulation (ARCI A)	−0.34 [c]
Elated (POMS)	Dysphoria (ARCI LSD)	−0.33 [c]

[a] Stress cortisol response was controlled for smoking.

[b] Correlations listed in the table are significant ($p<0.01$).

[c] Correlations listed in the table are significant ($p<0.05$).

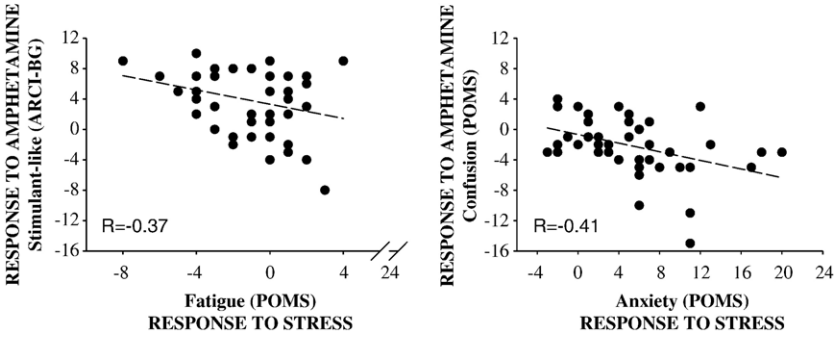

Fig. 3. Scatterplots for individual subjects' responses to D-amphetamine and their responses to stress ($N=44$). The left panel "Responses to amphetamine" shows peak change in scores after amphetamine minus change after placebo on ARCI BG (stimulation), and pre–post stress change on ratings of Fatigue (POMS) on the stress session. In the group as a whole, D-amphetamine increased ARCI BG scores, and stress decreased Fatigue. Thus, greater responses to stress were correlated with greater responses to D-amphetamine. The right panel shows the correlation between decreased Confusion ratings after D-amphetamine and increased Anxiety after stress. In the group as a whole, D-amphetamine decreased Confusion and stress increased Anxiety, so that again greater response to amphetamine was related to greater response to stress.

pattern: Heart rate only exceeded placebo at 120 min after capsule ingestion, and continued to increase through the last time point (240 min; Fig. 1). The effects of amphetamine on cortisol began 90 min after capsule administration and continued until 180 min (Fig. 1). There were modest sex differences in certain responses to amphetamine. Amphetamine produced a greater increase in cortisol in men than women ($r=-0.36$; $p<0.05$), and it produced smaller increases in ratings of Friendliness (POMS) in men ($r=0.31$; $p<0.05$).

3.4. Subjective and physiological effects of stress

Relative to pre-stress baseline assessments, the TSST significantly increased ratings of Anxiety (POMS; $F(3129)=30.6$; $p<0.05$), Vigor (POMS; $F(3129)=16.6$; $p<0.05$), heart rate ($F(3114)=11.5$; $p<0.05$), and cortisol levels ($F(3132)=4.9$; $p<0.05$; Fig. 2; Table 3). Compared to men, women reported higher ratings of Friendliness ($r=-0.42$; $p<0.01$), lower ratings of Confusion ($r=0.33$; $p<0.05$), higher ratings of Elation ($R=-0.44$; $p<0.01$), and higher ratings of Positive Mood ($R=-0.44$; $p<0.01$) after stress. Peak change in cortisol after stress was negatively correlated with baseline cortisol measures ($R=-0.37$, $p<0.05$). Time to return to baseline following stress for heart rate and cortisol levels were calculated but these will not be discussed further because they were not related to response to amphetamine or progression to smoking.

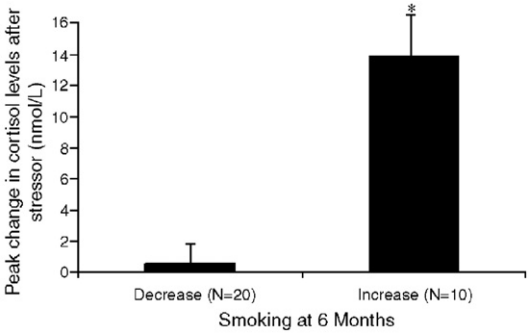

Fig. 4. Mean (and S.E.M.) increase in cortisol level after stress in subjects who did or did not increase in the amount they smoked between the time of screening and laboratory sessions to 6-month follow-up ($N=31$).

3.5. Relationships between stress reactivity and responses to D-amphetamine

After controlling for sex, stress reactivity was modestly correlated with responses to D-amphetamine on several measures (Table 4). Peak increases in cortisol levels after stress and amphetamine were positively correlated. Also, decreases in Fatigue (POMS) scores after stress and amphetamine were also correlated, and subjects whose Anxiety (POMS) increased after stress also reported greater increases in Friendliness (POMS) after amphetamine. Negative relationships were noted between several responses to stress and amphetamine. Many of these correlations reflected the patterns observed in the positive correlations, except that they used scales with inverse scoring (e.g., measures of stimulation such as Vigor, Arousal or ARCI A or BG scales vs. Fatigue). Individuals who reported greater Anxiety (POMS) after stress reported greater decreases in Confusion after amphetamine. Fig. 3 illustrates two of the negative correlations, between the decrease in Fatigue after stress, and the increase in stimulant-like effects (ARCI BG) after amphetamine, and the increase in Anxiety after stress and the decrease in Confusion after amphetamine.

3.6. Predictors of escalation in cigarette smoking

Follow-up data were obtained for 31 of the 44 participants. On average, levels of smoking did not change substantially over the 6-month period. At screening subjects smoked an average of 10.7 cigarettes per week, and at follow-up the mean was 9.0. The subjects who were lost to follow-up did not differ systematically from the subjects who responded at 6 months (i.e., in number of cigarettes smoked at screening, duration of smoking, gender or age), and the stress–drug correlations in the lost subjects did not differ substantively from the 31 who were followed. Responses to D-amphetamine during the laboratory phase of the study were not related to progression to smoking. However, peak increases in cortisol levels after acute stress were significantly positively related to progression to smoking ($F(1,30)=7.5$, $p<0.01$; Fig. 4). That is, subjects who exhibited a greater peak increase in cortisol after stress in the laboratory session increased their smoking more in the 6 months following the laboratory procedures.

4. Discussion

We addressed two questions in this study: (i) whether responses to acute stress were correlated with responses to a single moderate dose of D-amphetamine in healthy light cigarette smokers, and (ii) whether responses to either stress or amphetamine were related to escalation of smoking over a 6-month follow-up period. The hypotheses were derived from studies with laboratory animals indicating that corticosterone responses to stress are correlated with behavioral and dopaminergic response to a stimulant drug, and that both are related to subsequent stimulant self-administration (Marinelli and Piazza, 2002; Piazza et al., 1989). Our results provided partial support for both of these relations in human participants. On certain measures, subjects' responses to acute stress were correlated with their responses to a single dose of D-amphetamine, and on one measure, response to stress was related to an increase in smoking 6 months later. Notably, our findings in humans were in the same direction as the findings reported with laboratory animals, suggesting that the same physiological processes may contribute to susceptibility to drug use in humans and non-humans.

The correlations between stress reactivity and responses to amphetamine fell into two main categories. First, there was a correlation on hormonal responses to stress and drug. Subjects who exhibited the largest peak increase in cortisol after stress also showed increased cortisol levels after amphetamine administration. Second, subjects who had more negative mood responses to the stress procedure (i.e., greater increases in ratings of Confusion, Fatigue or Anxiety) reported more positive subjective responses to D-amphetamine (i.e., increased Friendliness, decreased Confusion). These findings must be considered highly preliminary, especially because the correlations were not corrected for multiple comparisons. Nevertheless, it is notable that a similar trend was evident across a variety of measures: both physiological and subjective reactivity to the stress procedure was correlated with subjective responses to D-amphetamine. The correlations are especially notable when we consider the high degree of variability inherent in subjective self-report measures. Unlike objective measures of physiological or behavioral variables in humans or nonhumans, subjective reports are sensitive to many extraneous factors including expectations, reporting biases, other sources of individual differences, and aspects of the current context and state of the individual. Thus, the finding that the subjective responses in this study were correlated suggests that the relationships are fairly robust.

In this study, the only laboratory measure that was predictive of progression to smoking was the peak increase in cortisol after stress. Stress reactivity has been linked to relapse and difficulty quitting smoking (Al'absi, 2006), but to our knowledge it has not been linked to the progression in level of smoking. How stress reactivity might be related to escalation in smoking is not known. It is known that stress reactivity varies across individuals, due in part to genetic factors (Cohen and Hamrick, 2003; Rohleder et al., 2003). It is also known that stress reactivity differs in smokers and nonsmokers, although this may be a result of circulating levels of nicotine (Kirschbaum et al., 1994). Thus, it is possible that some as yet unidentified variable, which may have a genetic basis, influences both stress reactivity and smoking progression. Another possibility is that individuals who are more reactive to acute stress may smoke to relieve this stress. This seems unlikely, however, since there is little evidence that smoking, or nicotine, reduces the effects of acute stress (Perkins et al., 1992). It may also be that stress reactivity is associated with more positive mood effects of nicotine. This idea derives some support from our laboratory findings with amphetamine in the present study. That is, just as stress reactivity was correlated with response to acute amphetamine in this study, stress reactivity may also be related to the mood-altering or reinforcing effects of acute nicotine because it is also a stimulant/dopaminergic drug. These ideas could form the basis of future investigations in this area.

This study had a number of important limitations. First, the number of subjects was relatively small, given the variability in escalation of smoking among young adults, and the number of variables that can influence the decision of whether or not to smoke. Second, the study was conducted in a homogeneous sample of undergraduate students, whose responses may not be generalizable to the larger population. Third, the length of time of the follow-up period, 6 months, was short in relation to the natural history of cigarette smoking. Despite these limitations, the results suggest that both stress reactivity and responses to a dopaminergic drug may be related to smoking progression.

The mechanisms underlying the relationships between stress, drug response, and drug-seeking behavior are poorly understood. Studies with rats suggest that the correlations may be related to the shared role of the dopamine system (Piazza et al., 1991). Dopamine reactivity may also play a role in the relationship observed in the present study, but this idea is difficult to test in humans. Marinelli (2005) discusses a number of factors that may account for the association between locomotor response to novelty and self-administration in animals, including differences in drug sampling, in responding for rewards in general, and in learning ability. Although there is some support for individual differences in learning ability (Mitchell et al., 2005), this process is unlikely to account for our results in humans. It is unlikely that differences in learning mediate differences in progression from occasional smoking to regular daily smoking.

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