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STRESS AND CUE-ELICITED CRAVING AND REACTIVITY IN MARIJUANA-DEPENDENT INDIVIDUALS

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Abstract

Rationale—Cue-elicited craving and stress responses have been identified as predictors of relapse in drug dependence, but little research exists on the contribution of these factors to marijuana use specifically.

Objectives—The aims of the present study were to evaluate (1) responses to a psychological stressor, (2) responses to marijuana-related cues, and (3) if an exposure to a psychological stressor augmented craving subsequently elicited by marijuana-related cue exposure in marijuana-dependent individuals.

Methods—Subjective (craving, stress), neuroendocrine (ACTH, cortisol), and physiologic responses to the presentation of neutral and marijuana cues were assessed after randomization to a stress (Trier Social Stress Task; TSST) or no-stress control condition in marijuana-dependent individuals. Outcome measures were assessed at baseline, post-stressor/pre-neutral cue, post-neutral cue, and post marijuana cue.

Results—87 participants completed procedures (stress group, n=45; non-stress group, n=42). The stress group had a significant increase over the non-stressed group in stress rating ($p<0.001$), craving ($p=0.028$), cortisol ($p<0.001$), and ACTH ($p<0.001$) after completion of the TSST. An increased craving response for all participants was seen following presentation of the marijuana cues ($p=0.005$). Following the TSST or no-stress condition, the non-stressed group had an increase in craving to marijuana cues as compared to neutral cues ($p=0.002$); an increase in craving was not observed in the stress group ($p=0.404$).

Conclusions—Marijuana cue exposure and a social stressor increased craving in marijuana-dependent individuals. Completion of the TSST did not increase craving response to subsequent marijuana-cue exposure.

Keywords

Marijuana; Cannabis; Stress; Craving; HPA axis

Introduction

Craving has been shown to play a central role in the maintenance of substance use disorders (Childress et al, 1988; Drummond et al, 1990; Weiss et al, 1995; Franken et al, 2000). The systematic investigation of craving has occurred chiefly through studies of cue reactivity. Compared to other substances, there has been limited research on marijuana-related craving and cue reactivity. Regular marijuana users have been shown to spend more time looking at and report higher craving to marijuana-related pictorial cues than neutral cues (Field et al. 2006; Wolfling et al. 2008). Active imagery scripts have also been shown to increase craving in marijuana users (Singleton et al. 2002). Recently, Gray and colleagues (2008) demonstrated the ability to elicit cue-induced craving in marijuana using adolescents and young adults. A cue exposure paradigm has also been used to evaluate genetic influences on marijuana withdrawal and craving (Haughey et al. 2008) and in imaging studies (Filbey et al. 2009; Filbey et al. 2010).

Among chronic users of marijuana, stress has also been shown to be a significant factor in maintenance of use (see Hyman and Sinha 2009 for review). For example, in a treatment seeking sample, Copeland and colleagues found stress relief to be the most commonly reported benefit from and reason for continuing marijuana use (Copeland et al. 2001). Studies have also shown that coping motives are associated with levels of marijuana use (Bonn-Miller et al. 2007) and marijuana-related problems (Simons et al. 2005; Lee et al. 2007), and that marijuana users expect relaxation and tension reduction from use (Galen and Henderson, 1999). Further, stress-related factors such as negative life events (Wills et al. 2001; Windle and Wiesner 2004) and traumatic stress (Lipschitz et al. 2003; Bremner et al. 1996; Vlahov et al. 2004; Schiff et al. 2007) have been demonstrated to be associated with marijuana use.

The interplay of stress and cues may have significant real-life importance, as individuals in stressful situations who are exposed to an opportunity to use may have an increased risk of relapse. An experimental paradigm to assess the impact of a psychological stressor on cue induced craving in alcohol dependent individuals has been recently developed (Thomas et al, 2011). Although they found that stress did not enhance the salience of alcohol cues, it does not preclude such an effect occurring in individuals who use marijuana given its frequent reported use for stress reduction. The specific aims of the present study were to evaluate responses to marijuana-related cues in marijuana-dependent subjects, to evaluate responses to a psychological stressor in marijuana-dependent subjects, and to assess the impact of a psychological stressor on response to marijuana-related cue exposure. It was hypothesized that marijuana-dependent subjects would exhibit marijuana cue reactivity to marijuana cues as compared to neutral, control cue and that subjects exposed to a psychological stressor would exhibit greater reactions as compared to subjects exposed to a non-stress control condition. It was also hypothesized that subjects exposed to a psychological stressor before exposure to marijuana cues would show greater reactivity to marijuana cues as compared to subjects exposed to a non-stress control condition before marijuana-cue exposure.

Methods

Screening

Participants were recruited primarily through community advertisements between January 2008 and June 2009. All procedures were conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki and received approval from the Medical University of South Carolina (MUSC) Institutional Review Board. All participants gave written, informed consent prior to study procedures.

To be eligible for participation, individuals had to be between 18 and 65 years of age and meet DSM-IV criteria for marijuana dependence. Exclusion criteria included current abuse of or dependence on any other substance (with the exception of caffeine or nicotine); presence of a current major Axis I disorder; use of any psychoactive medication; use of medication known to alter HPA axis function; having a body mass index greater than or equal to 39; and presence of a medical condition which may alter HPA axis or physiologic response.

All potential participants were evaluated for medical exclusions through routine physical exam, blood chemistries, and urine drug screen. The MINI International Neuropsychiatric Interview (Sheehan et al. 2006) was used to assess for psychiatric exclusions, and the substance use module of the Structured Clinical Interview for DSM-IV (First et al. 1994) was used for substance use disorder diagnosis. Current symptoms of anxiety and depression were assessed and quantified using the Hamilton Anxiety Scale (HAM-A; Hamilton 1959) and Hamilton Depression Scale (HAM-D; Hamilton 1960). Substance use in the three months prior to participation was assessed using the Time-Line Follow-Back (Sobell and Sobell 1978), and the Inventory of Drug Taking Situations (IDTS; Turner et al. 1997) was administered to assess precipitants of marijuana use. Following completion of the assessment instruments and procedures, eligible individuals were scheduled to complete the laboratory session.

Laboratory Procedures

The test session was conducted in the MUSC Clinical and Translation Research Center (CTRC). Prior to leaving the pre-test assessment interview, participants were instructed to arrive at 11:00am on test day, and to avoid caffeine on the day of the test session. Participants were also instructed to abstain from marijuana the day of testing and other drug (including alcohol) use for three days prior to testing. A urine sample was tested for the presence of drugs (marijuana, cocaine, opiates, barbiturates, benzodiazepines, and stimulants) on the day of testing and a breathalyzer sample obtained; if positive for alcohol or any drug with the exception of marijuana, the session was rescheduled. Nicotine patches were provided to participants who smoked cigarettes to avoid nicotine withdrawal.

Participants were served lunch and allowed to acclimate to the CTRC prior to testing. At 1:00pm, participants were assessed with the 12-item Marijuana Craving Questionnaire (MCQ; Heishman et al. 2009) to establish a baseline level of marijuana craving. An indwelling catheter was placed to facilitate blood draws. Two baseline measurements of stress (subjective rating on a 0–10 Likert scale, cortisol, ACTH) and craving (MCQ) were collected at 1:30pm and 1:55pm. Blood samples for ACTH and cortisol were collected in iced EDTA tubes. Plasma was separated from cells by centrifugation, and the serum sample was frozen at –70 degrees C until thawed for assay. ACTH was measured by the IMMULITE 2000 ACTH test (Siemens Healthcare Diagnostics, Flanders, NJ). Preparation, set-up, dilutions, adjustment, assay and quality control procedures were performed according to the operator's manual. At 28 pg/ml, the intra-assay coefficient of variation (cv) was 1.8%. The functional sensitivity (lowest reportable concentration) was 5.9 pg/ml. Cortisol was assayed using the ADVIA Centaur XP immunoassay system (Siemens Healthcare Diagnostics, Flanders, NJ). Functional sensitivity was 0.2 µg/dl and intra-assay cv was 2.15% at 44 ug/dl.

Stress Induction

At 2:00pm, the experimental stress challenge began. Urn randomization was used to assign participants to either the Trier Social Stress Test (TSST) or a no-stress control condition. Gender and level of marijuana use (<1 joint/day at baseline vs. more) were the urn factors.

The TSST is a standardized psychological stress challenge which has shown utility for evoking an HPA axis stress response in a laboratory setting (Dickerson & Kemeny 2004). If randomized to the TSST condition, the participant was told at 2:00pm that (s)he would be asked to give a speech and perform a follow-up task. The topic of the speech was why (s)he should be hired for a particular job, and the participant was instructed that the speech would be delivered to a group of hiring managers and that the presentation would be recorded. The participant was allowed five minutes to prepare his/her speech, at which point three individuals unknown to the participant entered the room. The participant was instructed to stand and deliver his/her prepared speech without notes for five minutes; instructions were given by an audience member to continue if the participant paused prior to the end of the five minute time period. At the end of the speech task, the participant was instructed to serially subtract 13 from 1,022 as quickly and accurately as possible. The mental math recitation continued for five minutes, at the end of which time (2:15pm) the audience left the room. If randomized to the no-stress condition, participants sat quietly and read travel magazines for the 15 minute time period. At 2:15pm, blood was drawn for cortisol and ACTH assays and subjective stress and craving ratings were assessed.

Cue Exposure

Immediately following the TSST or no-stress procedure and data collection, standardized cue exposure instructions were provided to participants, stating that two sets of items would be presented and audio played through headphones. At 2:25pm, control cues (note pad, pencil, marker, metal cup, toothpicks, teabags, bowl, cotton swabs, and small bottle) were presented to the participants. Incense was burned as an olfactory cue, and an auditory script previously used by Singleton and colleagues (2002) was played in which participants are asked to imagine a day at the beach. Neuroendocrine response and subjective ratings were then assessed. At 2:33pm, participants were presented with the marijuana cues (blunt wrap, rolling papers, pipes, a pipe cleaner, small bag containing fake marijuana, ashtray, water bong, and rolled fake joints). A marijuana scent stick was burned as an olfactory cue, and participants listened to a script prompting recall of a recent pleasant experience with marijuana. Participants were asked to remember as vividly as possible their surroundings and feelings immediately prior to and after smoking. Neuroendocrine measurements were taken immediately (2:36pm), 15 minutes (2:51pm), 30 minutes (3:06pm), and one hour (3:36pm) following the marijuana cue presentation. Craving and stress measurements were collected immediately (2:36pm), 15 minutes (2:51pm), and one hour (3:36pm) following the cue. After the final assessment, subjects were debriefed and compensated (\$175). In the event that a participant's craving level was elevated at the time of discharge, he or she was asked to remain in the CTRC until their craving subsided.

Data Analysis

Three primary hypotheses were specified *a priori*. Hypothesis 1 was that participants exposed to a psychological stressor would exhibit greater reactivity during the TSST (as determined by increases in subjective craving and stress ratings and neuroendocrine levels) as compared to participants exposed to a non-stress control condition. Hypothesis 2 was that all participants would exhibit greater cue reactivity to marijuana cues relative to neutral, control cues. The final hypothesis was participants exposed to a psychological stressor before exposure to marijuana cues would show greater cue reactivity to marijuana cues as compared to participants exposed to a non-stress control condition before marijuana cue exposure.

To test the three primary hypotheses, a repeated measures ANOVA framework was used; however, instead of the traditional repeated measures analysis, a mixed model with discrete time was used. This approach was needed to allow for the inclusion of all available data

through restricted maximum likelihood (REML) estimation (Patterson and Thompson 1971). The three time points of primary interest were those immediately following the stressor and each cue set. Baseline was calculated as the mean of the measurements collected at 1:30pm and 1:55pm and used as a covariate in the regression model. The correlation structure of the repeated measures was modeled using the unstructured and compound symmetry structures. In addition, the robust (or empirical) variance estimator was used to assess the sensitivity of the normality assumption on the model-based standard errors. The unstructured covariance structure was found to fit the data best as measured by AIC (Burnham and Anderson 2002). Model estimation was constructed in *SAS Proc Mixed*. Model-based estimates were used to construct group-level tests over time and to test the planned hypotheses. Overall statistical significance for the effects of group and time, their interaction, and the baseline measure was assessed using a likelihood ratio test that compared final model to a model consisting of an intercept terms alone. This approach is a generalization of the omnibus F test used in a repeated measures ANOVA model. Additionally, Pearson product-moment correlation coefficients were used in all correlation analyses. Stress versus non stress group correlations are compared using Fisher's r to z transformation.

The primary analysis was complemented by general descriptive analyses. Summary of clinical characteristics are denoted as mean $\pm$ standard deviation (SD) for continuous variables and n (%) for categorical variables. Group differences for continuous variables were tested via t-tests and categorical variables were tested with Pearson's Chi Square Test statistic. All statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc. Cary, NC, USA). No correction for multiple testing has been applied to reported p-values.

Results

Descriptive and Clinical Characteristics

A total of 157 individuals were evaluated for study participation, 107 individuals met initial eligibility requirements, and 87 completed laboratory procedures with valid data (stress group, $n=45$; non-stress group, $n=42$). Reasons for not completing the study included not returning for the laboratory visit ($n=16$), allergic reaction to the nicotine patch provided during the laboratory session ($n=2$), and having an elevated blood pressure upon presentation at the laboratory session ($n=1$). Data from one participant was excluded from all analyses due to the concerns of data integrity as the individual was participating in multiple research studies for other dependencies. The mean $\pm$ SD age of the study participants was 25.8 ($\pm$ 8.6) years and 67% were male. The stress group had a moderately lower self-rated Pleasant Emotions IDTS factor score than the non-stress group at the baseline measurement (57.1 ($\pm$ 19.5) vs. 66.5 ($\pm$ 19.4); $t_{85}=2.25$, $p=0.027$). There were no other differences between the groups in any of the clinical characteristics or demographic variables (Table 1).

Model Significance

The model likelihood ratio test revealed highly significant chi square test statistics for the subjective stress rating, cortisol levels, ACTH levels, the MCQ total score as well as all MCQ subscale scores ($X^2_4 > 94.9$, $p < 0.001$ in all cases). During the model fitting, interactions between the main effects of stress group and time were examined. Significant interactions were discovered between cortisol levels ($F_{2,80}=21.3$, $p < 0.001$), stress rating ($F_{2,73}=12.9$, $p < 0.001$), and MCQ total score ($F_{2,66}=5.9$, $p < 0.001$). ACTH levels showed a trend toward a possible stress group by time interaction ($F_{2,80}=2.8$, $p=0.062$). Overall group by time interactions were also seen in the compulsivity, emotionality, and expectancy subscales of the MCQ score ($p < 0.015$ in all cases), while the purposefulness subscale failed to achieve statistical significance ($p=0.101$).

Response to TSST (Hypothesis 1)

The stress group demonstrated an increased stress response compared to the non-stress group as measured by subjective stress rating, cortisol levels, and ACTH levels ($p < 0.001$ in all cases; Table 2). Following presentation of the neutral cue, the subjective stress rating in the stress group decreased and was no longer statistically greater than the measure at baseline; cortisol and ACTH remained elevated ($p < 0.001$ in both cases). The stress group also had a greater increase in craving as compared to the non-stress group following the TSST as measured by the total MCQ score ($p = 0.029$). The mean MCQ subscale scores in the stress group were numerically higher than the non-stress group, but only the emotionality subscale reached statistical significance ($p = 0.027$).

Overall Response to Marijuana Cues (Hypothesis 2)

There was a significant increase in MCQ total score ($p = 0.005$) in response to the marijuana cues over the neutral, control cues in all subjects (i.e., both stressed and non-stressed participants) (Table 3). Within the MCQ, statistically significant response increases were seen in the compulsivity and purposefulness subscales ($p = 0.006$ and $p = 0.005$, respectively). There was also a trend towards statistical significance for an increase in the emotionality subscale ($p = 0.071$).

Stress Group Differential in Response to Marijuana Cues (Hypothesis 3)

An inspection of these changes by treatment group revealed important differences in response profile, although not as hypothesized (Table 4). The non-stress group showed significant increases in craving (MCQ total score and all subscales) following the marijuana cue as compared to the neutral cue, whereas the stress group had no significant differences in craving scores between the two cue presentations.

Examination of the differential response to the marijuana cues by stress condition (i.e., MCQ total score effect modification) revealed a trend toward a larger increase in the non-stress group ($t = 1.74$, $p = 0.086$), but only changes in the expectancy domain of the MCQ ($p = 0.017$) and cortisol response ($p = 0.013$) were statistically different between groups.

Correlational Analyses

Baseline anxiety levels were significantly correlated with baseline stress ratings and MCQ score ($r = 0.59$ $p < 0.01$ and $r = 0.71$ $p < 0.01$, respectively). Peak anxiety ratings were correlated with peak stress and MCQ ratings ($r = 0.44$ $p < 0.01$ and $r = 0.54$ $p < 0.01$, respectively; Figure 2) in the non-stress group and the stress group ($r = 0.53$ $p < 0.01$ and $r = 0.38$ $p < 0.01$, respectively; Figure 2). Additionally, baseline stress was correlated with baseline MCQ score ($r = 0.59$ $p < 0.01$). There was no significant correlation between peak cortisol with either peak stress ($p = 0.91$) or peak MCQ responses ($p = 0.12$). Additionally, peak stress and peak MCQ were not significantly correlated in either the stress or no stress group ($\rho = 0.11$ $p = 0.46$ and $\rho = 0.24$ $p = 0.13$, respectively). The correlation coefficient between the anxiety response and the stress response for the stress group and the no stress group were not found to be significantly different ($z = 0.57$, $p = 0.57$). Similarly, the correlation coefficient between the anxiety response and the craving response (MCQ) for the stress group and the no stress group were not significantly different ($z = 0.91$, $p = 0.36$).

Discussion

This study was conducted to examine stress- and cue-elicited reactivity in marijuana-dependent individuals. The findings supported the primary hypotheses that the TSST and marijuana cue exposure would elicit reactivity. Previous work has shown the ability of marijuana-related cues to increase craving in dependent individuals (Gray et al, 2008;

Haughey et al, 2008; Filbey et al, 2009; Filbey et al, 2010); however, this is the first report to our knowledge demonstrating an increase in craving in response to a laboratory stressor in a marijuana-dependent population.

The finding of increase in craving following a stressor is in line with several reports (Coffey et al, 2006; Fox et al, 2007; Sinha et al, 2009; Childs & de Wit, 2010; Buchmann et al 2010; Perkins and Grobe, 1992) in other dependencies, though not all (Brady et al, 2006; Jansma et al, 2000; Rubonis et al, 1994, Thomas et al, 2011). It has been hypothesized that craving following a stressor may be due to the negative subjective effects of stress (Conklin & Perkins, 2005; Niaura et al, 2002). Measures of anxiety were examined to investigate their relationship to craving following the TSST. Peak anxiety ratings were significantly correlated with peak craving measures in both the stress and non-stress groups, suggesting that anxiety may play a role in both stress- and cue-induced marijuana craving.

A recent evaluation of cigarette craving in daily smokers found that craving following the TSST was related to the magnitude of cortisol response in daily smokers but not occasional smokers (Buchmann et al, 2010). The authors hypothesized that the cortisol secretion associated with smoking cigarettes may become sufficiently linked after prolonged regular smoking such that a cortisol surge in response to a stressful situation results in craving. Ad hoc analyses of the present data did not find a correlation between peak cortisol and MCQ score. As marijuana is generally smoked less frequently by individuals than cigarettes, it is possible that such a conditioned association, if it exists in heavy cigarette smokers, may not develop in marijuana users.

Reactivity to the marijuana cues was most pronounced in the non-stress group. Craving ratings in the stress group did not return to baseline levels following completion of the stress task (see Figure 1). However, following presentation of the neutral cue, there was no significant difference in craving between the stress and non-stress groups. Although there was not a statistically significant increase in craving following the marijuana cue presentation in the stress group, MCQ scores did not continue to diminish (i.e., did not show a continued return to baseline) but rather increased slightly, suggesting that even in stressed participants, the internal validity of the cue exposure was evident. The fact that this change was less pronounced in the stressed vs. non-stressed group suggests that stress did not have either an additive or multiplicative effect on cue reactivity.

The finding of increased craving in the non-stress condition is consistent with some clinical observations. For example, DeMarce and colleagues (2005) examined confidence ratings in ability to resist marijuana in high-risk situations among adult marijuana users, and found that participants had lower self-efficacy ratings for non-psychologically distressing situations as compared to psychologically distressing situations. Although not formally investigated in this study, data on drug use situations were collected at baseline. The IDTS factor scores indicated that participants showed greater interest in marijuana use during positive emotional periods than those associated with unpleasant emotions ($p < 0.01$; data not shown), further suggesting that individuals may choose to use marijuana in less stressful situations rather than in stressful ones.

Contrary to our final hypothesis, in the paradigm used in this study, exposure to a laboratory stressor did not enhance craving response to marijuana cues. As stated earlier, a similar finding has been reported in alcoholics by Thomas and colleagues (2011), whose procedures were adapted for the present study. Previous work assessing effect of negative mood on alcohol cue reactivity also failed to find augmentation of cue-induced craving (Cooney et al, 1997; Mason et al, 2008; Nesic and Duka, 2006). Together, these findings suggest that although stress may induce craving for substances, it may not be due to increasing the

salience of drug-related cues. Fishbein and colleagues (2006) found that the effect of stressors on past year marijuana use was mediated by social competencies, implying an indirect, rather than direct, impact of stress on increased marijuana use. The stressor used in this investigation, the TSST, was chosen because it has been shown to consistently induce a marked stress response (Kudielka et al. 2007) and incorporates both a social evaluative (public speaking) and performance (mental arithmetic) component (Dickerson and Kemeny 2004). As demonstrated by both the subjective and neuroendocrine responses of the participants completing the TSST, the task was effective in inducing stress in our sample. However, it is possible that chronic stress as opposed to the acute stress elicited by the TSST may have a greater impact on marijuana cue-induced craving and subsequent use.

The findings of the current study should be considered in the light of some limitations. As noted previously, the timeline of study procedures with the stress manipulation preceding cue presentation confounds interpretation of the neuroendocrine response to cue exposure. It is also noted that subjective response to stress was of short duration, as ratings of stress in the TSST-exposed group did not differ from baseline levels after exposure to the neutral cue. As such, it could be argued that presenting the marijuana cues immediately following the TSST would have been ideal for measuring reactivity during the period of greatest stress response. However, inclusion of a neutral cue was necessary to determine whether stress enhanced marijuana cue reactivity rather than simply induced urge to smoke (regardless of presence of cues). Further, it has been suggested that it is more naturalistic to have some temporal separation from stress (such as a work environment) and cues (such as paraphernalia at home) (Nesic and Duka, 2006). To note, cortisol and ACTH levels did remain elevated in the stress group throughout the cue exposure procedure. Our study design utilized a fixed order of cue presentation, with neutral cues preceding the marijuana cues. Although counterbalancing is commonly used in cue reactivity research to control for possible order effects, it has also been suggested that cue type by order of cue interactions may limit the utility of counterbalancing, in particular when carryover effects are likely as could occur with craving if the marijuana cue were to precede the neutral cue (Sayette et al, 2010). It is noted, however, that the lack of counterbalancing may limit the ability to fully assess the stress-cue interaction. Finally, although participants were instructed to not use marijuana on the day of testing, it was not possible to objectively confirm time of last use.

In summary, the results of this investigation demonstrated that exposure to marijuana-related cues increased craving in marijuana-dependent individuals. Further, an acute social stressor elicited robust stress responses (subjective and neuroendocrine) and increased craving for marijuana. However, in the paradigm used in this study, after the stressor condition, reactivity to subsequent marijuana-cue exposure was not increased. More research is needed to further elucidate the relationship between stress and marijuana craving.

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Figure 1.
MCQ total score over time by stress condition

Figure 2.

Correlation between anxiety response with stress and craving (MCQ) responses by stress group.

Data are shown as change from baseline measured values with best fit line and associated Pearson product-moment correlation coefficient. The correlation coefficient between the anxiety response and the stress response for the stress group ($r=0.533$, $n=45$) and the no stress group ($r=0.436$, $n=42$) were not found to be significantly different ($z=0.57$, $p=0.57$). Similarly, the correlation coefficient between the anxiety response and the craving response (MCQ) for the stress group ($r=0.383$) and the no stress group ($r=0.541$) were not significantly different ($z=0.91$, $p=0.36$).

Table 1

Demographics and clinical characteristics

Characteristic	Stress group n=45	No Stress Group n=42	P-Value
Age	25.5 (9.2)	26.2 (8.0)	0.71
Male n (%)	29 (64)	29 (69)	0.65
White n (%)	26 (58)	25 (60)	0.86
College Graduate n (%)	29 (64)	30 (71)	0.48
MCQ Total Score	45.6 (15.2)	48.1 (16.3)	0.46
Craving	5.0 (3.4)	5.5 (3.0)	0.44
Stress	2.3 (2.6)	3.3(3.1)	0.10
Cortisol (µg/dl)	9.7 (2.9)	10.3 (2.7)	0.31
ACTH (pg/ml)	27.8 (16.7)	24.3(16.8)	0.34
≥ 1 ounce/week n (%)	12 (27)	13(31)	0.66
Ounces per Wk	0.44 (0.4)	0.52 (0.4)	0.34
HAM A Total Score	3.24 (2.5)	3.36 (2.8)	0.84
HAM D Total Score	1.44(1.7)	1.76(2.3)	0.46
IDTS Factors			
Unpleasant Emotions	42.3 (20.0)	50.1 (23.5)	0.10
Physical Discomfort	33.3 (19.6)	36.0(21.6)	0.54
Pleasant Emotions	57.1 (19.5)	66.5(19.4)	0.03
Testing Personal Control	21.5(17.9)	21.1 (22.5)	0.93
Urges / Temptations	48.0 (19.2)	52.6 (25.6)	0.32
Conflict with Others	23.1 (20.4)	31.4(22.3)	0.07
Social Pressure to Use	42.6 (22.0)	47.9 (27.5)	0.31
Pleasant Time with Others	63.7 (18.8)	68.2(21.1)	0.30

Data are presented as Mean (Standard Deviation) unless otherwise noted.

Table 2

Stress and Craving Responses to TSST

End Points	Post TSST		T Statistic	P Value
	Stressed	Non Stressed		
MCQ Total Score	53.5 ± 1.7	48.1 ± 1.8	2.21	0.029
<i>MCQ Components</i>				
Compulsivity	9.4 ± 0.5	8.0 ± 0.5	1.92	0.059
Emotionality	13.0 ± 0.6	11.0 ± 0.6	2.25	0.027
Expectancy	14.8 ± 0.5	13.6 ± 0.5	1.7	0.089
Purposeful ness	16.4 ± 0.5	15.7 ± 0.6	0.95	0.358
Stress	5.4 ± 0.4	2.4 ± 0.5	4.74	<0.001
Cortisol (µg/dl)	12.8 ± 0.4	8.8 ± 0.4	7.26	<0.001
ACTH (pg/ml)	44.7 ± 2.8	28.8 ± 2.9	3.92	<0.001

Estimates for the stress/non-stress groups are listed as the least square means with associated standard errors for the response to the TSST after baseline adjustment.

Table 3

Stress and Craving Responses to Marijuana Cues

End Points	All Subjects (n=87)		
	Response	T Statistic	P Value
MCQ Total Score	2.32 ± 0.80	2.9	0.005
<i>MCQ Components</i>			
Compulsivity	0.79 ± 0.28	2.82	0.006
Emotionality	0.44 ± 0.24	1.83	0.071
Expectancy	0.27 ± 0.18	1.46	0.148
Purposefulness	0.83 ± 0.29	2.86	0.005
Stress	0.11 ± 0.18	0.6	0.551
Cortisol (µg/dl)	−0.68 ± 0.09	−7.28	<0.001
ACTH (pg/ml)	−1.12 ± 1.46	−0.77	0.444

Estimates are listed as the least square mean difference between the neutral and active marijuana cue responses for all subjects with associated standard errors (n=87).

Table 4

Effect of Stress Condition on Reactivity to Marijuana Cues

End Points	TSST Group			Non Stressed Group		
	Neutral Cue	Marijuana Cue	P value	Neutral Cue	Marijuana Cue	P value
MCQ Total Score	49.5 ± 1.2	50.5 ± 1.6	0.404	48.6 ± 1.2	52.3 ± 1.6	0.002
<i>MCQ Components</i>						
Compulsivity	8.3 ± 0.5	8.9 ± 0.5	0.088	8.1 ± 0.5	9.0 ± 0.6	0.026
Emotionality	11.6 ± 0.4	11.6 ± 0.5	0.947	11.4 ± 0.4	12.3 ± 0.5	0.011
Expectancy	13.7 ± 0.3	13.5 ± 0.4	0.488	13.3 ± 0.3	14.0 ± 0.4	0.008
Purposefulness	15.8 ± 0.5	16.3 ± 0.6	0.25	15.9 ± 0.3	17.1 ± 0.5	0.005
Stress	3.0 ± 0.3	2.8 ± 0.3	0.383	2.6 ± 0.3	3.1 ± 0.3	0.098
Cortisol (µg/dl)	14.6 ± 0.4	13.7 ± 0.4	<0.001	8.6 ± 0.4	8.1 ± 0.5	0.001
ACTH (pg/ml)	36.1 ± 2.5	34.8 ± 2.5	0.531	26.4 ± 2.5	25.5 ± 2.5	0.648

All estimates for neutral cue and active marijuana cue responses are least square means with standard errors. Delta values represent estimated change in response attributable to the marijuana cue presentation. The estimated difference in delta values is a contrast testing for a differential response by treatment group in response to the marijuana cue (i.e., effect modification).