Published in final edited form as:

Am J Drug Alcohol Abuse. 2015 March ; 41(2): 146–152. doi:10.3109/00952990.2014.945590.

Impact of acute guanfacine administration on stress and cue reactivity in cocaine-dependent individuals

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Abstract

Background—Stress and drug-paired cues increase drug craving and noradrenergic activity in cocaine-dependent individuals, thus medications that attenuate noradrenergic activity may be effective therapeutic treatment options for cocaine-dependent individuals.

Objectives—To examine the impact of acute administration of the α -2 adrenergic receptor agonist guanfacine on responses to multiple risk factors for relapse in cocaine-dependent individuals.

Methods—In a double-blind, placebo-controlled study, cocaine-dependent individuals (N=84), were randomized to receive either 2 mg guanfacine (n=50) or placebo (n=34). Within each treatment arm, subjects were randomized to either a stress (guanfacine n=26; placebo n=15) or a no-stress (guanfacine n=24; placebo n=19) group. Participants in the stress group performed the Trier Social Stress Test. Subjects in each group were exposed to a neutral cue and then to cocaine-related cues. Plasma cortisol and subjective responses were compared between the four groups.

Results—The no-stress guanfacine group reported greater craving in response to cocaine-cues as compared to the neutral cue ($p<0.001$). The guanfacine stress group reported greater subjective stress at the neutral cue than at baseline ($p=0.032$). The cocaine-cue increased subjective stress in the guanfacine ($p<0.001$) no-stress group. There were no effects of guanfacine on cortisol levels in either the stress or no stress groups (all $p>0.70$).

Conclusion—This study found no effects of a single 2 mg dose of guanfacine on reactivity to stress and cues alone or on the interaction of stress and drug cues. In cocaine-dependent

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Declaration of Interest

Authors Moran-Santa Maria, Baker and Ramakrishnan declare no conflict of interest. Kathleen Brady lists: Consultant AstraZeneca Pharmaceuticals Aimee McRae lists: Forest Pharmaceuticals medication provided for separate NIH grant.

individuals an acute 2 mg dose of guanfacine may not be an effective therapeutic treatment strategy.

Introduction

Relapse to drug use following abstinence is a major impediment in the treatment of cocaine dependence. While several compounds are currently in various stages of clinical trials, there are no FDA-approved medications for cocaine dependence. One limitation in the development of effective treatments has been the lack of empirically controlled approaches to test the effects of putative medications on drug-seeking behavior precipitated by specific risk factors. One particularly salient feature that occurs during abstinence from compulsive drug use is the ability of stress and drug-associated environmental cues (e.g. locations where drug was consumed or drug paraphernalia) to elicit drug craving, and consequently reinstate drug-seeking and drug-taking. For example, rodents withdrawn from chronic cocaine will reinstate cocaine-seeking behavior in response to drug-paired cues (1, 2) and stress (3). Abstinent cocaine abusers report intense drug craving and physiological arousal when exposed to stimuli previously associated with cocaine use (4). In addition, stress and negative affect are frequently reported by cocaine-dependent individuals prior to a relapse episode and human laboratory studies demonstrate that both cues and stress increase cocaine craving (5–7), and data from preclinical models of relapse demonstrate that stress potentiates cue-induced cocaine-seeking behavior in rodents (8). Thus, these data suggest that stress may increase the vulnerability of cocaine-dependent individuals to cue-induced craving and relapse.

Of note, both cues and stress increase noradrenergic activity in cocaine-dependent individuals (9). Thus, noradrenergic activity may be a critical neurobiologic substrate involved in multiple risk factors for relapse. Converging evidence from preclinical and clinical studies suggests that dysregulation in the noradrenergic system contributes to cocaine craving and relapse during drug withdrawal (9–12). For example, preclinical studies have associated increased noradrenergic tone with the anxiogenic effects of drug withdrawal (10, 11). In rodent models of drug withdrawal and relapse, increasing noradrenergic transmission reinstates cocaine-seeking behavior while inhibition of noradrenergic transmission attenuates cocaine-seeking behavior (13–15). The α_2 adrenergic agonist clonidine has non-selective effects at the imidazoline I1 and α_2B receptors in the thalamus, which may account for clonidine's potent effects on blood pressure and sedation (16–18). While lofexidine has shown promise clinically in reducing stress induced craving in opioid addicts, the drug has not received FDA approval (19), and therefore has limited access for human research studies. Each of the α_2 adrenergic receptor subtypes are found ubiquitously throughout the brain, however the α_2A subtype has been localized to the prefrontal cortex (20, 21). Guanfacine (*Tenex*) is a highly selective α_2A agonist that and is ten times less effective at reducing blood pressure and producing sedation than other α_2 -adrenoreceptor agonists such as clonidine, and therefore less problematic in terms of side effects. In a recent study, Fox and colleagues demonstrated that 4-weeks of daily guanfacine administration (2–3 mg/day) attenuated cue induced cocaine craving, anxiety and arousal in a cohort of treatment seeking cocaine-dependent individuals (22).

The aim of the present study was to examine the impact of acute guanfacine administration on stress and cue reactivity in cocaine-dependent individuals. Given the preclinical and clinical findings demonstrating that attenuation of noradrenergic activity decreases drug seeking behavior, we hypothesized that cocaine-dependent individuals receiving an acute dose of guanfacine would exhibit significantly lower reactivity to stress, cues and to cues that are preceded by a stressor than cocaine-dependent individuals receiving placebo.

Methods

Participants

This study was conducted as part of a larger human laboratory study examining medication effects on relapse factors for cocaine-dependence. A total of 84 non-treatment seeking cocaine-dependent individuals who responded to local media advertisements over a 48-month period completed the laboratory procedures and were included in the present analyses. Written informed consent was obtained before study assessments were administered. All procedures were conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki, and received Institutional Review Board (IRB) approval. The Mini-International Neuropsychiatric Interview (MINI) which permits accurate diagnosis of current psychiatric disorders using DSM-IV criteria (23) and the substance use module of the Structured Clinical Interview for DSM-IV (SCID-IV), were used for current and lifetime substance use disorder and psychiatric diagnosis (24). General exclusion criteria included (1) pregnancy, nursing, or ineffective means of birth control; (2) premenstrual dysphoric disorder; (3) history of or current significant hematological, endocrine, cardiovascular, pulmonary, renal, gastrointestinal, or neurological diseases; (4) history of or current psychotic, panic, eating, or bipolar affective disorders; (5) current major depressive and PTSD; (6) history of or current medical conditions that might affect HPA axis activity; (7) synthetic glucocorticoid or exogenous steroid therapy within one month of testing; (8) psychotropic medications, opiates or opiate antagonists, benzodiazepines, antipsychotics, beta-blockers and other medications that might interfere with HPA axis activity or physiologic measurements; (9) acute illness or fever; (10) body mass index ≥ 35 ; (11) Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for substance dependence except caffeine, nicotine or marijuana within the past 60 days or (12) unwillingness or inability to maintain abstinence from alcohol and other drugs of abuse (except nicotine) for three days prior to the cue-reactivity sessions.

Study Design

To minimize the impact of recent drug/alcohol use on cue/stress reactivity and to minimize the potential for an interaction between the study medications and cocaine or alcohol, the participants were asked to remain abstinent from cocaine and other drugs for a minimum of three days prior to the study procedures. Subjects were instructed to arrive at the Medical University of South Carolina (MUSC) Clinical and Translational Research Center (CTRC) at 10:00 a.m. on study day 1. Upon arrival, abstinence was assessed using self-reports, urine drug screens (Roche Diagnostics, Indianapolis, Indiana), and breathalyzer tests (AlcoSensor III, Intoximeters, Inc., St. Louis, Missouri). Female participants performed a urine pregnancy test. If the pregnancy and drug tests were negative (with the exception of THC),

study procedures continued. If an individual tested positive for cocaine, alcohol or any drug of abuse with the exception of THC the session was rescheduled. Due to the extended period of detection of THC in urine, THC positive urine drug screens were allowed if the participant denied use in the past three days.

Study participants were randomly assigned to guanfacine (n=50) or placebo (n=34) treatment. All medication was dispensed in a double-blind manner. The larger study also included a separate group of participants who received daily doses of modafinil (data not shown). To maintain the study blind, subjects who were randomized to guanfacine received placebo daily for two days and on the third day received a 2 mg dose of guanfacine. Cognitive dysregulation has been associated with the vulnerability to relapse in cocaine-dependent populations, the 2 mg dose guanfacine was chosen based on data from healthy controls that demonstrated that 1 mg had no effect, while 2 mg improved cognitive function (25, 26). (27–29). In addition, other studies utilizing an acute dose of guanfacine found that the prevalence of side effects increased at doses above 2 mg (17). Subjects randomized to the placebo group received placebo daily for three days. Guanfacine and placebo were administered in identical, opaque gelatin capsules. Medications were packaged and dispensed by the MUSC Investigational Drug Service, who also oversaw the randomization procedures for the study. Subjects were asked to remain in the CTRC for approximately one hour to monitor for potential side effects. Subjects returned to the CTRC at 10:00 a.m. on the next day (day 2). On day 2, subjects were breathalyzed and a drug test was performed. Female participants also performed a urine pregnancy test. Participants with clean drug tests and negative pregnancy tests were administered a second placebo capsule and were admitted to the MUSC hospital for an overnight stay. Admitting subjects to the CTRC for the last two days of study was done to ensure abstinence from cocaine and other substances and to standardize diet and activity. Smokers were provided with a nicotine patch. All subjects received a 2000 kcal standardized ADA diet.

At 10:00 a.m. on day 3, subjects were escorted to the CTRC and were placed in the procedure room. Craving was assessed with a multi-item cocaine craving questionnaire (to establish a baseline level of cocaine craving), and an indwelling catheter was inserted to facilitate blood draws. At 11:00 a.m. participants received either a guanfacine (2 mg) or a placebo capsule. The timing of guanfacine administration relative to the stress and cue tasks was selected based on data from the manufacturer (Watson Laboratories Inc., Corona, CA) demonstrating that the time to peak plasma concentrations of guanfacine occurs from 1 to 4 hours with an average of 2.6 hours after a single oral dose. A standardized lunch was served at 12:00. Two post-medication baseline assessments were collected at 1:40 and 1:55. Participants were randomized within each treatment group to stress or no-stress groups. Participants in the no-stress condition were asked to sit quietly and read travel magazines alone for 15 min. Participants randomized to the stress group performed the Trier Social Stress Task (TSST) (30) and were told that at 2:00 (s)he would soon perform to an audience a speech and arithmetic task. The topic of the speech was why (s)he should be hired for a particular job (the individual's "dream job"). The participant was asked to deliver the speech as though speaking to a group of hiring managers. The experimenter then gave the participant 5 min to prepare the speech. At 2:05, three individuals unfamiliar to the participant (the audience) entered the room and were seated; the individual was instructed by

one audience member (the spokesperson) to stand and begin his/her prepared speech (without notes) for five minutes. If the individual paused, (s)he was instructed by the spokesperson to continue. At the end of the speech task (2:10), the individual was instructed to serially subtract 13 from 1,022 as quickly and accurately as possible. The mental math recitation continued for 5 min, at the end of which time, the spokesperson instructed the individual to stop and to be seated, and the audience left the procedure room.

The cue reactivity session began immediately following the TSST or no-stress procedure. Standardized cue exposure instructions were provided to the participant, stating that two sets of items would be presented. At 2:20, the control (neutral) cue which consisted of a tray of pinewood chips was placed on a table directly in front of the participant. The subject was encouraged to inspect and handle the cue. Two minutes later, the experimenter re-entered the room and removed the control cue. A blood sample and subjective data were collected. At 2:27 participants were presented with a tray of cocaine cues. For crack cocaine users the cocaine cues consisted of a small bag of simulated crack cocaine, the subject's preferred style of crack pipe, a lighter, and money (\$20 bill). For powder or IV users, simulated cocaine, cocaine paraphernalia, and money were used. The participant was encouraged to inspect and handle the cues. Two minutes later, the experimenter re-entered the room, and removed the cocaine cues. A blood sample and subjective data were collected. The neutral cue was always presented prior to the cocaine cues. The cues employed in the present study were identical to the ones used in previous clinical studies of cue reactivity and are validated triggers of drug craving in cocaine-dependent populations (31, 32).

Blood samples and subjective ratings were assessed at 5- and 20-minutes prior to the stress/no-stress procedures, immediately following and 23 and 40 minutes after the neutral cue or cocaine cues. Blood samples were collected in EDTA-prepared tubes and immediately placed on ice. Plasma was obtained by centrifugation under refrigeration and the samples were frozen at -70°C until assayed in duplicate. Cortisol was assayed using the Roche Diagnostic Elecsys 2010 immunoassay analyzer and kits based on an electrochemiluminescence competitive immunoassay having a functional sensitivity of 0.29 $\mu\text{g/dL}$ and intra-assay reproducibility of less than 2%. Blood samples were processed and analyzed at the CTRC laboratory.

Data Analysis

An intent-to-treat approach that includes all randomized participants was used for all statistical analysis. Prior to the analysis, standard demographic and clinical characteristics were tabulated for all participants and compared between treatment assignments. Group differences in continuous characteristics were assessed using Wilcoxon Rank-Sum test, while differences in categorical characteristics were assessed using normal (Pearson's) Chi-Square tests or Fisher's Exact Test where appropriate. Demographic, clinical, and use characteristics were examined for univariate predictive relationships with the subjective and physiological outcomes.

Initial design adjusted models were fit using medication group assignment, stress assignment, time, baseline measures of the outcome and relevant interactions of interest. Additional models were also explored using an expanded range of possible covariates based

on baseline imbalances between treatment groups and covariates showing evidence as prognostic factors of the outcomes ($p < 0.10$). To test the primary hypotheses, linear mixed effects models were used to model the craving, stress and cortisol responses during the course of the laboratory procedures. Model estimation was constructed in SAS Proc Mixed. Model based estimates were used to construct group level tests over time and to test the pre-planned hypothesis. All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Significance for all planned comparisons was set at a 2-sided p -value of 0.05 and no correction for multiple testing has been applied to reported p values.

Results

Descriptive and Clinical Characteristics

Baseline demographic and clinical characteristics by condition (stress vs. no-stress) and treatment (guanfacine vs. placebo) are presented in Table 1. The study groups included mostly men; guanfacine no-stress ($n=20$ men, $n=4$ women), guanfacine stress ($n=25$ men, $n=1$ woman), placebo no-stress ($n=14$ men, $n=5$ women) and placebo stress ($n=12$ men, $n=3$ women). There were no differences between the two treatments or stress conditions in age, race, gender, marital status, smoking status or in total years of cocaine use. In addition, there were no differences between the four groups in the number of alcohol-dependent individuals, marijuana-dependent individuals or in the number of individuals currently in treatment. Participants in the guanfacine treatment group were more likely to have undergone treatment for any drug of abuse in the past. There were no differences between the groups in baseline craving, stress or plasma cortisol levels. Univariate predictive analysis showed that none of the measured baseline demographics or clinical characteristics were significantly predictive nor did they act as confounding factors when individually added to the design adjusted model, including the effect of past drug treatment (all $p > 0.30$). Covariates were additionally checked for moderation of the main effects (treatment and condition) and were found to have no impact on study outcomes (all $p > 0.10$).

Craving

Neutral cue—There were no differences between the stress and no-stress groups ($p=0.238$) in craving ratings assessed following exposure to the neutral cue (Figure 1).

Cocaine Cue—Participants in the no-stress group reported significantly greater craving in response to the cocaine-cue as compared to the neutral cue ($p < 0.001$), in both the no-stress guanfacine ($p < 0.001$) and no-stress placebo ($p=0.023$) groups. In the stress group, participants in both the guanfacine and placebo groups reported similar craving ratings in response to the cocaine and the neutral cue ($p=0.480$).

Stress

Neutral Cue—Participants in the stress group reported significantly greater subjective stress following the neutral cue than participants in the no-stress group ($p < 0.001$) (Figure 2). Participants in both the guanfacine-stress ($p=0.032$) and the placebo-stress group ($p < 0.001$) reported significantly greater subjective stress following the neutral cue than at baseline.

There were no significant differences between the guanfacine and placebo stress groups in the magnitude of the stress response.

Cocaine Cue—Participants in the no-stress group reported significantly greater subjective stress in response to the cocaine cue as compared to the neutral cue ($p<0.001$). The cocaine-cue increased subjective stress in both the guanfacine ($p<0.001$) and placebo ($p=0.018$) no-stress groups. Participants in the stress group reported similar subjective stress responses to the cocaine-cue as they did to the neutral cue ($p=0.461$).

Cortisol

Neutral Cue—Following exposure to the neutral cue, participants in the stress group exhibited significantly greater cortisol levels than participants in the no-stress group ($p<0.001$) (Figure 3). Participants in the guanfacine-stress group exhibited significantly greater cortisol levels following the neutral cue than at baseline ($p<0.001$). Participants in the placebo-stress group exhibited significantly greater cortisol levels following the neutral cue than at baseline ($p=0.001$).

Cocaine Cue—Cortisol levels in the stress group remained elevated throughout the cue session (neutral and cocaine) (12.9 ± 0.5 to 12.5 ± 0.5 ; $p=0.197$) while the cortisol levels in the no-stress group were similar to baseline levels throughout the cue session (9.3 ± 0.5 to 9.3 ± 0.5 ; $p=0.933$). No significant effects of guanfacine as compared to placebo on cortisol were noted within either condition (all $p>0.70$).

Discussion

In this preliminary study we examined the effects of an acute dose of guanfacine on responses to stress, cues and to cues that were preceded by a psychosocial stressor in a group of cocaine-dependent individuals. There were no significant differences between the guanfacine and placebo treated groups in cortisol, subjective craving or stress. Thus, taken together these data suggest that a single 2 mg dose of guanfacine may not be effective for attenuating reactivity to multiple risk factors for relapse in cocaine-dependent individuals.

In the present study, guanfacine had no effect on craving responses to the drug cue with or without previous stress exposure. Fox and colleagues recently examined the impact of repeated (3 weeks) of guanfacine (2 and 3 mg) on subjective responses to stress, drug-paired cues and to both stress and drug cues in a cohort of cocaine-dependent individuals. Guanfacine attenuated nicotine craving to all three imagery paradigms and, in contrast to the findings in our study, attenuated cue-elicited cocaine craving. Fox and colleagues found a significant effect of dose, suggesting that the 3 mg. dose was more effective at reducing cocaine craving than the 2 mg. dose. Although we used an acute 2 mg. dose of guanfacine, the present findings support Fox's work demonstrating greater efficacy at the 3 mg. dose in attenuating cue related craving in cocaine-dependent individuals. Of interest, Fox and colleagues found no effect of chronic guanfacine administration on stress-related craving, which is consistent with the present findings (22). However, guanfacine appeared to be effective at attenuating craving responses to all three relapse factors in cocaine-dependent women but not in cocaine-dependent men (33). The data in our study were collected

primarily (84%) from cocaine-dependent men. Thus, it is possible that there may be sex differences in subjective responses to multiple risk factors for relapse following an acute dose of guanfacine. In addition, the Fox study used daily dosing over three weeks as opposed to the acute, one dose paradigm of our study, so chronic dosing may be essential to the stress and drug-cue dampening effects of guanfacine. Studies exploring the effects of an acute dose of guanfacine on responses to stress and drug-cues cocaine-dependent women may be warranted.

Perhaps the most intriguing finding was that the craving response to the drug cue was greater in the no-stress group regardless of treatment. Data from preclinical studies have found that stress enhances cue-elicited drug seeking behavior in rodents withdrawn from chronic drug administration (8, 34). Of note, the preclinical findings were specific to either pharmacological stressors or physical stressors. In contrast, the TSST employs both cognitive (mental arithmetic) and social evaluative (audience) stress, and thus required “evaluation” of the task as either stressful or not stressful. In addition, data from preclinical studies suggests that female rodents are more susceptible to stress potentiated cue-reactivity than male rodents (35). The present findings were collected primarily from cocaine-dependent men. In addition, data from clinical studies suggests that cocaine-dependent women may be more vulnerable stress related craving than cocaine-dependent men (36–38), thus the TSST may serve as more effective primer of cue-elicited craving in women than men. It is also important to note that the data were collected after the participants were exposed to the neutral cue and not immediately after the TSST. Similar findings have been reported in alcohol and marijuana-dependent populations that were exposed to a similar laboratory stress/cue paradigm (39, 40). It is possible that presenting the cocaine cue immediately after the TSST would have enhanced craving responses to the cocaine cue.

Consistent with previous studies of substance-dependent populations, the TSST increased subjective stress and plasma cortisol levels in a cohort of cocaine-dependent individuals (37, 39). The increase in cue-induced stress parallels findings from similar studies of cue-reactivity in cocaine-dependent populations (9, 22). Although stress and cues increase hypothalamic pituitary adrenal (HPA) axis activity and there is significant overlap between the HPA axis and the noradrenergic system, we found no effect of guanfacine on cortisol levels in response to stressor and the drug-cue. Clinical findings suggest that α_2 agonists may be effective at attenuating subjective measures of stress and negative affect (19, 22, 41); however, to our knowledge this is the first study to assess the impact of an α_2 agonist on HPA axis activity in a cocaine-dependent population. It is important to note that the dose of guanfacine was relatively low (2 mg), and a higher dose of guanfacine administered daily may yield different findings.

Interpretation of the present findings may be limited by the small sample size and thus should be viewed as preliminary data. In addition, the lack of assessment immediately after the TSST may have precluded us from finding group differences in stress responses. As noted earlier, the neutral cue may also have prevented us from observing an interaction between the stressor and the drug-paired cue. However, inclusion of a neutral cue was necessary to determine whether stress enhanced cocaine cue reactivity rather than simply induced urge to use (regardless of presence of cues). We recognize that counterbalancing is

often used to control for possible order effects in cue-reactivity research. However, presenting the cocaine-cue prior to the neutral could have potential carryover effects (42). Importantly, a growing literature suggests that there are important sex differences in the relapse experience of substance-dependent individuals (36, 43, 44). Only 16% of the subjects in the present study were females and thus we lack the power to systematically investigate sex differences in study outcomes. Despite these limitations and negative findings withstanding, this is the first study to our knowledge to assess the effects of an acute dose of guanfacine on reactivity to multiple risk factors for relapse.

Acknowledgments

This work was supported by National Institutes of Health; National Institute on Drug Abuse (R01DA021690), National Institute of Child Health and Human Development K12HD055885, National Center for Advancing Translational Sciences (UL1TR000062).

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Figure 1.

Effect of acute guanfacine on stress and cue induced subjective craving

Comparison of mean craving response to a cue preceded by stress (S) or no-stress (NS) between cocaine-dependent individuals pretreated with guanfacine and cocaine-dependent individuals pretreated with placebo. *Denotes a significant difference between the S and NS groups.

Figure 2.

Effect of acute guanfacine on stress and cue induced subjective stress

Comparison of mean stress response to a cue preceded by stress (S) or no-stress (NS) between cocaine-dependent individuals pretreated with guanfacine and cocaine-dependent individuals pretreated with placebo. *Denotes a significant difference between the S and NS groups. #Denotes a significant increase from the neutral cue in the NS group.

Figure 3.

Effect of acute guanfacine on cortisol response to stress and cues

Comparison of mean plasma cortisol levels in response to a cue preceded by stress (S) or no-stress (NS) between cocaine-dependent individuals pretreated with guanfacine and cocaine-dependent individuals pretreated with placebo. *Denotes a significant difference between the S and NS groups.

Table 1

Demographics and baseline characteristics

Characteristic	Overall N=84	Guanfacine		Placebo		Between Group P-Value
		No Stress (n=24)	Stress (n=26)	No Stress (n=19)	Stress (n=15)	
Age	41.5 (9.4)	40.9(9.5)	41.0(10.0)	44.0(8.6)	40.2 (9.1)	0.614
Male % (n)	84.5 (71)	83.3 (20)	96.2 (25)	73.7 (14)	80.0 (12)	0.126
Caucasian % (n)	31.0 (26)	37.5 (9)	19.2 (5)	42.1 (8)	26.7 (4)	0.478
Smoker % (n)	79.8 (28)	75.0 (18)	80.8 (21)	68.4 (13)	100.0 (15)	0.626
Cigarettes per day	9.8 (8.6)	9.0 (8.8)	8.2 (6.5)	10.5(9.4)	13.2(10.2)	0.189
Craving	1.6 (2.3)	2.0 (2.0)	1.2 (2.1)	1.6 (2.3)	1.8 (2.9)	0.751
Stress	1.3 (2.1)	1.9 (2.3)	1.1 (2.4)	1.3 (2.2)	0.5 (0.8)	0.472
Cortisol	10.1 (2.9)	9.6 (2.5)	10.6 (3.2)	9.9 (3.0)	10.3 (3.3)	0.850