Psychopharmacology
DOI 10.1007/s00213-017-4648-z

ORIGINAL INVESTIGATION

Blunted stress reactivity in chronic cannabis users

Carrie Cuttler[1,2] · **Alexander Spradlin**[1] · **Amy T. Nusbaum**[1] · **Paul Whitney**[1] · **John M. Hinson**[1] · **Ryan J. McLaughlin**[1,2,3]

Received: 28 March 2017 / Accepted: 7 May 2017

Abstract
Rationale One of the most commonly cited reasons for chronic cannabis use is to cope with stress. Consistent with this, cannabis users have shown reduced emotional arousal and dampened stress reactivity in response to negative imagery.
Objectives To our knowledge, the present study represents the first to examine the effects of an acute stress manipulation on subjective stress and salivary cortisol in chronic cannabis users compared to non-users.
Methods Forty cannabis users and 42 non-users were randomly assigned to complete either the stress or no stress conditions of the Maastricht Acute Stress Test (MAST). The stress condition of the MAST manipulates both physiological (placing hand in ice bath) and psychosocial stress (performing math under conditions of social evaluation). Participants gave baseline subjective stress ratings before, during, and after the stress manipulation. Cortisol was measured from saliva samples obtained before and after the stress manipulation. Further, cannabis cravings and symptoms of withdrawal were measured.
Results Subjective stress ratings and cortisol levels were significantly higher in non-users in the stress condition relative to non-users in the no stress condition. In contrast, cannabis users demonstrated blunted stress reactivity; specifically, they showed no increase in cortisol and a significantly smaller increase in subjective stress ratings. The stress manipulation had no impact on cannabis users' self-reported cravings or withdrawal symptoms.
Conclusion Chronic cannabis use is associated with blunted stress reactivity. Future research is needed to determine whether this helps to confer resiliency or vulnerability to stress-related psychopathology as well as the mechanisms underlying this effect.

Keywords Cannabis · Marijuana · Stress · Cortisol · Craving · Withdrawal

Introduction

Cannabis is the most widely used illicit substance worldwide (United Nations Office on Drugs and Crime 2012). In the USA, recent state legislative reform permitting the use of cannabis for medicinal and now recreational purposes has led to a reduction in social stigma and perceived harms of chronic cannabis use among both adolescents (Stolzenberg et al. 2016) and adults (Okaneku et al. 2015; Schuermeyer et al. 2014). This has coincided with a steady rise in the prevalence of daily cannabis use (SAMHSA 2014), which is only expected to increase in coming years.

Perhaps the most commonly cited reason for continued cannabis use in chronic users is to cope with elevated levels of perceived stress (see Hyman and Sinha 2009, for a comprehensive review of this literature). A recent meta-analysis of cross-sectional studies shows a high prevalence of cannabis use among individuals with stress and anxiety disorders, and vice versa (Kedzior and Laeber 2014). Although the direction of these relationships has yet to be established, evidence indicates that the second most common reason medical cannabis patients report using cannabis is to

✉ Carrie Cuttler
carrie.cuttler@wsu.edu

[1] Department of Psychology, Washington State University, PO Box 644820, Pullman, WA 99164-4820, USA

[2] Translational Addiction Research Center, Washington State University, Pullman, WA, USA

[3] Department of Integrative Physiology and Neuroscience, Washington State University, Pullman, WA 99164-7620, USA

Published online: 31 May 2017

treat anxiety (Sexton et al. 2016) and that cannabis consumption reduces feelings of stress/anxiety in medical cannabis patients (Webb and Webb 2014). Moreover, stress coping motives are largely unique to cannabis relative to other drugs of abuse and are specific to chronic experienced users (Copeland et al. 2001).

Double-blind, placebo-controlled studies have further corroborated these self-report data, as acute cannabis or Δ-9-tetrahydrocannabinol (THC) administration dampens amygdala responses to affective stimuli (Gruber et al. 2009). Research by Childs et al. (2017) suggests that dose may be important to consider, as a low dose of oral THC attenuated cannabis users' subjective stress ratings after an acute stressor, while a high dose increased subjective stress ratings, and neither dose influenced cortisol or heart rate. It has also been shown that THC administration reduces emotional arousal to threatening faces (Phan et al. 2008; Cornelius et al. 2010). Notably, these studies have further shown that acute cannabinoid administration reduces amygdala reactivity in response to social signals of threat (Phan et al. 2008) and enhances connectivity between the amygdala and prefrontocortical subregions (Gorka et al. 2015), which is critical for proper emotional regulation, stress coping, and cortisol secretion (Phan et al. 2005; Urry et al. 2006).

These data suggest a mechanism by which *acute* cannabis consumption may elicit stress-alleviating effects. However, comparatively fewer studies have examined the effects of *chronic* cannabis consumption on stress-related endpoints, and the results of these studies have been equivocal. For instance, while some have shown that chronic cannabis use is associated with higher baseline cortisol concentrations (King et al. 2011; Monteleone et al. 2014; Somaini et al. 2012), others have reported no significant differences (Block et al. 1991). Furthermore, D'Souza and colleagues have shown that THC-induced increase in cortisol is blunted in frequent users relative to naïve controls (Ranganathan et al. 2009). Chronic cannabis users also exhibit impaired adrenocorticotropic hormone and cortisol release as well as reduced emotional reactivity in response to unpleasant pictures compared to non-users (Somaini et al. 2012). Moreover, higher levels of cannabis use have been associated with lower levels of amygdala reactivity in response to images of threatening faces (Cornelius et al. 2010). These results may indicate that chronic cannabis use is associated with hypothalamic-pituitary-adrenal (HPA) axis dysfunction. Alternatively, they may indicate that chronic cannabis use could provide beneficial effects in individuals exhibiting abnormal emotional responses to threatening stimuli.

Although these data suggest a relationship between cannabis consumption and stress responsivity, surprisingly, no studies have examined the impact of an acute stressor on subjective or physiological indices of stress in chronic cannabis users compared to non-users. Thus, the objective of our study was to determine the effects of an acute stressor on subjective stress, as well as on basal and stress-induced salivary cortisol concentrations in chronic heavy cannabis users compared to non-users. Additionally, given that stress can precipitate symptoms of withdrawal and craving in drug users (Cleck and Blendy 2008), we further sought to examine whether acute stress increases subjective reports of cannabis craving and withdrawal in chronic cannabis users. Based on data described above indicating blunted emotional reactivity and amygdala activation in chronic users (Cornelius et al. 2010), we hypothesized that chronic cannabis users would exhibit dampened subjective and physiological stress responses compared to non-users but that acute stress would nevertheless exacerbate cravings and symptoms of withdrawal.

Methods

Design and procedure

A 2 × 2 factorial design was used, with stress condition (stress, no stress) as a manipulated between-subject factor and cannabis use status (cannabis users, non-users) as a non-manipulated between-subject factor. The Washington State University Institutional Review Board reviewed and approved the study; thus, all procedures were performed in accordance with the ethical standards described in the 1964 Declaration of Helsinki.

Participants were recruited via ads posted in local recreational marijuana dispensaries, local retail locations, as well as on Facebook and Craigslist. Prior to scheduling an appointment, each participant was screened to ensure that he/she was eligible. To be eligible, participants had to report no current diagnosed or treated psychiatric conditions, no diagnosed chronic medical or neurological disorders, and no current use of medications containing steroids. Participants also could not be heavy users of alcohol (e.g., defined as use of alcohol four or more days of the week) and could not have used any illicit drugs in the past 6 months. Further, cannabis users were required to use cannabis on a daily or near daily basis (defined as using cannabis a minimum of 3–4 days per week) for at least 1 year and to abstain from cannabis on the day of testing. Non-users were required to have used cannabis fewer than 10 times in their lives and never in the past year.

Upon arrival, participants were asked to sit quietly and wait outside the lab room for 10 min to allow for any increases in cortisol due to traveling and attempting to locate the lab to diminish. After providing written informed consent, participants completed a brief survey, provided a baseline subjective stress rating, and gave their first saliva sample. Participants then completed either the stress or no stress condition of the Maastricht Acute Stress Test (MAST), providing another subjective stress rating half-way through the MAST. Immediately

after the MAST, participants once again gave a subjective stress rating and saliva sample. Participants then completed measures of cannabis withdrawal symptoms and cravings. Finally, participants provided a urine sample, were debriefed, and compensated with $25. Experimenters were blind to participants' cannabis use status until the urine sample was tested after participants left the laboratory.

Materials

Screening Participants were screened via brief open-ended questions to ensure that they met the study eligibility requirements. Specifically, participants were asked when they had last used cannabis, how frequently they use cannabis, for how long they had been using cannabis at that frequency, approximately how many times they had used cannabis in their lifetime, whether they had used any illicit drugs in the past 6 months, how often they drink alcohol, and how many drinks they consume when they drink alcohol. They were also asked whether they had a current diagnosed psychological disorder or were being treated for a psychological disorder; whether they had any diagnosed chronic medical or neurological disorders; whether they were currently taking prednisone, dexamethasone, or any other steroids; whether they had ever had a head injury involving a loss of consciousness for more than 2 min; and whether they had ever been diagnosed with a learning disability or intellectual disability.

Survey A brief survey was administered to assess demographic characteristics, chronic stress (the 10-item Perceived Stress Scale (PSS); Cohen and Williamson 1988), and cannabis use patterns (the Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory; Cuttler and Spradlin 2017). The measure of chronic stress was used to ensure that there were no baseline differences in chronic stress across the groups and to control for individual differences in chronic stress, as it is known that chronic stress can impact responses to acute stress (Herman 2013). The measure of cannabis use patterns was administered to assess lifetime and current cannabis use and to confirm that participants met the eligibility requirements of the study.

Subjective stress Subjective stress was measured by asking participants to rate how much stress they were currently experiencing using a scale ranging from 0 (indicating no stress) to 10 (indicating extreme stress). Similar single-item measures of subjective stress have demonstrated content, criterion, and construct validity (Elo et al. 2003).

Salivary cortisol Saliva samples were collected using salivettes (Sarstedt, Germany). Participants were required to refrain from ingesting anything other than water for 30 min prior to their testing session. To collect saliva samples, participants were instructed to rinse their mouth for 1 min and then to tip the swab into their mouth, chew on it for 1 min, and then place it carefully back in to the plastic tube without touching it. Saliva samples were taken before, during, and after exposure to the stressor and subsequently stored at −20 °C until analysis. Radioimmunoassays for salivary cortisol concentrations were performed according to methods previously described (Tu et al. 2006) using a cortisol enzyme immunoassay kit (Salimetrics, State College, PA). The assay's detection limit was 0.01 μg/dL, and the intra-assay coefficient of variance was 5.67%.

THC urine test THC pre-dosage urine tests from Kappa City Biotech (Saint Victor, France) were used to confirm the presence or absence of THC in urine. This test was used to ensure that cannabis users were indeed cannabis users (that they had detectable levels of THC in their urine) and that the non-users had no THC in their system.

Maastricht Acute Stress Test (Smeets et al. 2012) Stress was manipulated using the MAST, a multidimensional stress paradigm that combines elements of physical, psychosocial, and unpredictable stress. Participants in the stress condition were required to place their hand in cold water (36 °F) for trials of various lengths (45, 60, 90 s), which participants were told were randomly set by the computer. Between these trials, participants were required to count backwards from 2043 by 17 and were given negative feedback and required to start again each time they made an error. Participants were further monitored on a webcam, which they were told would be later evaluated and which was displayed directly in front of them so they could view themselves. Participants in the no stress control condition were required to place their hand in lukewarm water (92 °F) for trials of the same lengths as those used in the stress condition. Between trials, they were required to count from 1 to 25, but they received no feedback and were not video monitored. The entire MAST procedure lasted approximately 10 min. In previous studies, the MAST has produced similar subjective stress increases and increased salivary cortisol responses, compared to more traditional cold pressor tasks and the Trier Social Stress Test (Smeets et al. 2012). Further, the stress condition of the MAST has been shown to produce significantly higher salivary cortisol responses compared to the no stress condition of the MAST (Smeets et al. 2012).

Withdrawal symptoms and cravings The Marijuana Withdrawal Checklist (Budney et al. 2003) is a 15-item inventory that was used to measure withdrawal symptoms. Scores were averaged such that they could range from 0 (none) to 3 (severe). The MWC shows good internal consistency ($\alpha = 0.81$) and sensitivity to effects associated with abstinence (Budney et al. 1999, 2003). Cronbach's alpha in the present

sample was 0.77. The Cravings Questionnaire-Short Form (Heishman et al. 2001) is a 12-item inventory that was used to measure cannabis cravings. Scores were averaged such that they could range from 1 (strongly disagree to experiencing cravings) to 7 (strongly agree to experiencing cravings). Cronbach's alpha in the present sample was 0.86.

Participants

A total of 87 participants passed the initial screening and were tested. However, five participants were subsequently excluded because their self-reported cannabis use patterns on the day of testing were discrepant from their responses at the time of screening and no longer conformed to our eligibility requirements (e.g., they used cannabis on the day of testing, or in the case of non-users, had used cannabis more than 10 times in their life).

The remaining 82 participants ranged from 20 to 64 years of age with a mean of 25.84 (SE = 0.86) years. The majority of participants identified as white (70.7%), but the sample was well balanced with respect to sex (52.4% male). Complete demographic characteristics broken down by group are provided in Table 1.

Approximately half of the final sample ($n = 40$) comprised cannabis users. All of the cannabis users tested positive for THC in urine; almost all ($n = 38$; 95%) reported last using cannabis the day prior to testing; one participant (2.5%) reported last using cannabis this week, and one participant (2.5%) reported last using cannabis last week. Over half (55%) of the cannabis users reported using cannabis more than once a day, 32.5% reported using it once a day, 5% reported using cannabis five to six times per week, and 7.5% reported using it three to four times per week. All cannabis users reported using cannabis on a daily or near daily basis (a minimum of three to four times per week) for at least 1 year, with the majority (65%) reporting the use of cannabis on a near daily basis for 3+ years.

The remaining ($n = 42$) participants comprised non-users. The majority of the non-users (76.2%) reported never having used cannabis. The remaining 23.8% of non-users reported that they last used cannabis over a year ago and that they had used cannabis 10 or fewer times in their entire life. All non-users tested negative for THC in urine.

Statistical analyses

An a priori power analysis indicated that a sample size of 82 would provide power of 0.80 to detect medium-sized effects ($\eta_p^2 = 0.09$) using factorial ANCOVA with four groups and an alpha of 0.05. To control for variability in cortisol levels due to individual differences, potential differences in burden of travel, and time of day, cortisol difference scores were created. Specifically, baseline cortisol levels were subtracted from post-stress manipulation cortisol levels. Similarly, to account for individual differences in subjective stress ratings, baseline subjective stress ratings were subtracted from subjective stress ratings at time points 1 (during the stressor) and 2 (immediately after the stressor). Table 2 shows the baseline levels of cortisol, subjective stress, and chronic stress across the four groups.

Results

Baseline differences

Approximately half of the cannabis users ($n = 19$) were randomly assigned to the stress condition, and the other half ($n = 21$) were randomly assigned to the no stress condition. These two groups did not differ significantly with respect to when they last used cannabis, $t(38) = 1.44$, $p = 0.16$, $d = 0.45$, the frequency they reported using cannabis, $t(38) = 0.94$, $p = 0.35$, $d = 0.30$, or the number of years they reported using cannabis, $t(35) = -0.64$, $p = 0.53$, $d = 0.21$.

Half of the non-users ($n = 21$) were randomly assigned to the stress condition, and half ($n = 21$) were randomly assigned to the no stress condition. These two groups were perfectly matched with respect to whether they had ever used cannabis, $\chi^2(1) = 0.00$, $p = 1$, $\varphi_c = 0.00$, and in ratings of the number of times they had used cannabis in their entire life, $\chi^2(2) = 0.00$, $p = 1$, $\varphi_c = 0.00$.

As shown in Table 1, comparisons of the four groups revealed significant differences in the percentage of white cannabis users in the no stress condition and white non-users in the no stress condition, as well as in the percentage of employed/student cannabis users in the stress condition and employed/student non-users in the stress condition. As such, these variables were entered in as covariates in the primary analyses (i.e., 2 × 2 ANCOVAs).

As shown in Table 2, comparisons of the baseline stress measures (cortisol, subjective stress ratings, chronic stress scores) across the four groups revealed only a significant difference in the mean baseline subjective stress ratings of the cannabis users in the stress condition and the mean baseline subjective stress ratings of the non-users in the stress condition. Once again, difference scores were computed by subtracting baseline subjective stress ratings from subjective stress ratings during the MAST and after the MAST to statistically control for this baseline difference.

Finally, there were no significant differences in the time of day (coded into hours) that cannabis users in the stress and no stress conditions were tested, $t(38) = 1.67$, $p = 0.10$, $d = 0.53$, in the time of day that non-users in the stress and no stress conditions were tested, $t(40) = 0.78$, $p = 0.44$, $d = 0.24$, in the time of day that cannabis users in the stress condition and non-users in the stress condition were tested, $t(38) = -0.21$,

Table 1 Demographic characteristics of cannabis users and non-users in the stress and no stress conditions

	Cannabis users		Non-users	
	Stress	No stress	Stress	No stress
Age	M = 26.05 (SE = 1.44)	M = 25.14 (SE = 1.86)	M = 26.95 (SE = 2.23)	M = 25.24 (SE = 1.19)
Gender (male)	63.2%	71.4%	33.3%	42.9%
Ethnicity (white)	84.2%	*81.00%*	66.7%	*52.4%*
Education (post-secondary degree)	47.6%	47.4%	71.4%	71.4%
Current employment (employed or student)	*68.4%*	80.9%	*95.2%*	95.2%
Income (<$20,000)	73.7%	85.7%	76.2%	80.0%
Relationship status (single)	73.7%	85.7%	85.7%	76.2%

For all seven variables, t tests and chi-squared tests were conducted to compare (i) cannabis users in the stress condition to cannabis users in the no stress condition, (ii) non-users in the stress condition to non-users in the no stress condition, (iii) cannabis users in the stress condition to non-users in the stress condition, and (iv) cannabis users in the no stress condition to non-users in the no stress condition. The only significant differences that were detected were in the comparison of the percentage of white cannabis users in the no stress condition and white non-users in the no stress condition, $\chi(1) = 3.86$, $p = 0.05$, $\varphi_c = 0.30$, and in the comparison of the percentage of employed/student cannabis users in the stress condition and employed/student non-users in the stress condition, $\chi(1) = 3.86$, $p = 0.05$, $\varphi_c = 0.35$. Ital values denote significant difference

M mean, SE standard error of the mean

$p = 0.83$, $d = 0.07$, or in the time of day that cannabis users in the no stress condition and non-users in the no stress condition were tested, $t(40) = -1.23$, $p = 0.22$, $d = 0.38$.

Stress response

Cortisol A 2 × 2 ANCOVA with cannabis use status (cannabis user, non-user) and stress condition (stress, no stress) as between-subject factors and sex, ethnicity, employment status, and chronic stress as covariates was conducted to examine putative effects of cannabis use and the stress manipulation on cortisol difference scores. The results revealed a significant main effect of stress, $F(1, 74) = 14.20$, $p < 0.001$, $\eta_p^2 = 0.16$, and a cannabis × stress interaction, $F(1, 74) = 8.28$ $p = 0.003$, $\eta_p^2 = 0.10$. As depicted in Fig. 1, follow-up one-way ANCOVAs revealed significantly higher cortisol difference scores in the non-users under conditions of stress relative to the non-users in the no stress condition, $F(1, 36) = 19.65$, $p < 0.001$, $\eta_p^2 = 0.35$. In contrast, the cortisol difference scores of the cannabis users in the stress condition were not significantly different than the cortisol difference scores of the cannabis users in the no stress condition, $F(1, 34) = 0.80$, $p = 0.38$, $\eta_p^2 = 0.02$. Thus, cannabis users show reduced cortisol mobilization in response to acute stress.

Subjective stress ratings A series of 2 × 2 ANCOVAs with cannabis use status (cannabis user, non-user) and stress condition (stress, no stress) as between-subject factors and sex, ethnicity, employment status, and chronic stress as covariates were conducted with subjective stress difference scores as the dependent variables. The results of the analysis on subjective stress difference scores at time point 1 (during the stressor) revealed a significant main effect of stress, $F(1, 60) = 41.56$, $p < 0.001$, $\eta_p^2 = 0.41$, and a cannabis × stress interaction, $F(1,$

Table 2 Baseline stress in cannabis users and non-users in the stress and no stress conditions

	Cannabis users		Non-users	
	Stress	No stress	Stress	No stress
Baseline cortisol	M = 0.22 (SE = 0.04)	M = 0.17 (SE = 0.03)	M = 0.16 (SE = 0.02)	M = 0.19 (SE = 0.04)
Baseline subjective stress rating	*M = 3.16 (SE = 0.47)*	M = 2.29 (SE = 0.50)	*M = 1.86 (SE = 0.40)*	M = 2.29 (SE = 0.46)
Baseline chronic stress	M = 18.89 (SE = 1.03)	M = 14.48 (SE = 1.20)	M = 16.00 (SE = 1.61)	M = 15.14 (SE = 1.17)

For all three variables, t tests were conducted to compare (i) cannabis users in the stress condition to cannabis users in the no stress condition, (ii) non-users in the stress condition to non-users in the no stress condition, (iii) cannabis users in the stress condition to non-users in the stress condition, and (iv) cannabis users in the no stress condition to non-users in the no stress condition. The only significant difference that was detected was in the comparison of the mean baseline subjective stress ratings of the cannabis users in the stress condition and the non-users in the stress condition, $t(38) = -2.13$, $p = 0.04$, $d = 0.67$. Ital values denote significant difference

M mean, SE standard error of the mean

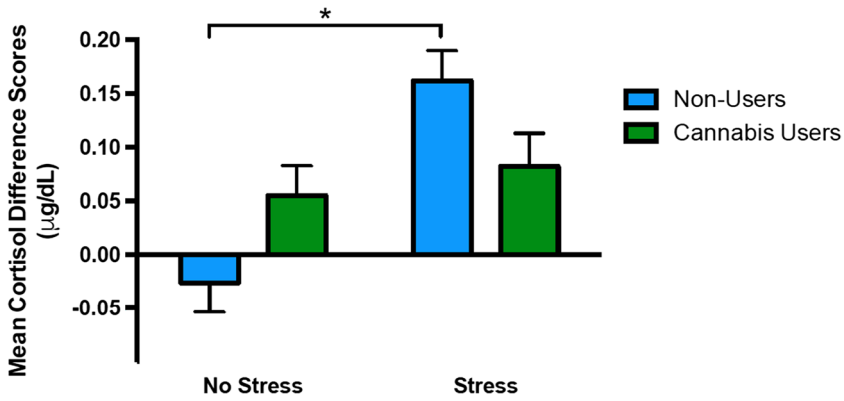

Fig. 1 Mean cortisol difference scores in non-users and cannabis users in the no stress and stress conditions of the MAST with standard error bars. *$p < 0.05$

60) = 4.79, $p = 0.03$, $\eta^2 = 0.07$. Follow-up tests revealed a significant effect of the stress manipulation on the subjective stress difference scores of non-users, $F(1, 28) = 30.03$, $p < 0.001$, $\eta_p^2 = 0.52$, as well as cannabis users, $F(1, 281) = 13.30$, $p = 0.001$, $\eta_p^2 = 0.32$. As depicted in Fig. 2, the interaction indicates that the effect of the stress manipulation on subjective stress ratings during the stressor was significantly smaller in the cannabis users than the non-users, once again providing evidence for a blunted stress response. At time point 2 (immediately after the stressor), there was only a significant main effect of stress, $F(1, 74) = 20.82$, $p < 0.001$, $\eta_p^2 = 0.22$, and no cannabis × stress interaction, $F(1, 77) = 2.07$, $p = 0.15$, $\eta_p^2 = 0.03$ (Fig. 3).

Relationships between cortisol and subjective stress ratings

Pearson bivariate correlation analyses indicated that overall cortisol difference scores were significantly positively correlated with subjective stress ratings at time point 1 (during the stressor), $r(66) = 0.42$, $p < 0.001$, as well as at time point 2 (immediately after the stressor), $r(80) = 0.27$, $p = 0.02$. Analyses broken down by group revealed that for non-users, cortisol difference scores were significantly positively correlated with subjective stress ratings at time point 1 (during the stressor), $r(32) = 0.59$, $p < 0.001$, as well as at time point 2 (immediately after the stressor), $r(40) = 0.45$, $p = 0.003$. In contrast, for the cannabis users, there were no significant correlations between cortisol difference scores and subjective stress ratings at time point 1 (during the stressor), $r(32) = 0.06$, $p = 0.75$, or at time point 2 (immediately after the stressor), $r(38) = -0.08$, $p = 0.61$. Tests of the difference between these two sets of correlations confirmed that the correlations detected in non-users are significant higher than those found in cannabis users ($p = 0.02$, $p = 0.01$, for time points 1 and 2, respectively).

Withdrawal symptoms and cravings Two separate 2 × 2 ANCOVAs were conducted with cannabis use status (cannabis user, non-user) and stress condition (stress, no stress) as between-subject factors; sex, ethnicity, employment, and chronic stress as covariates; and cannabis withdrawal symptoms and cravings as the dependent variables. The results of the analyses of withdrawal symptoms showed only a significant main effect of cannabis use status, $F(1, 74) = 6.92$, $p = 0.01$, $\eta_p^2 = 0.09$. The effect of the stress manipulation was not statistically significant, $F(1, 74) = 0.08$, $p = 0.78$, $\eta_p^2 = 0.001$, and the interaction between cannabis use and

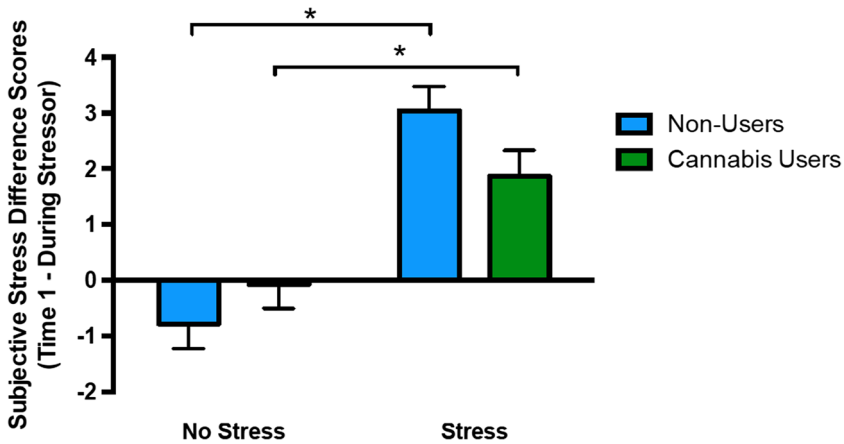

Fig. 2 Mean subjective stress difference scores in non-users and cannabis users during the no stress and stress conditions of the MAST with standard error bars. *$p < 0.05$

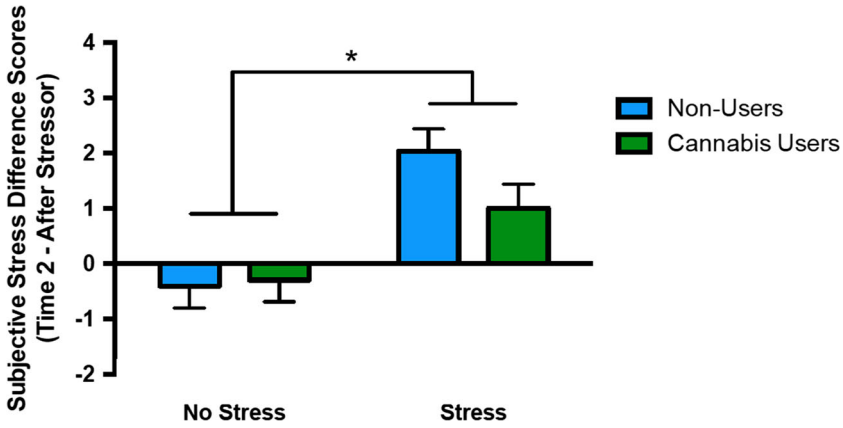

Fig. 3 Mean subjective stress difference scores in non-users and cannabis users immediately following the no stress and stress conditions of the MAST with standard error bars. *$p < 0.05$

stress was not statistically significant, $F(1, 74) = 0.09$, $p = 0.77$, $\eta_p^2 = 0.001$ (see Fig. 4). Planned comparisons of the cannabis users in the stress condition with cannabis users in the no stress condition also revealed no significant effect of the stress manipulation on cannabis users' self-reported withdrawal symptoms, $F(1, 34) = 1.81$, $p = 0.19$, $\eta_p^2 = 0.05$.

Similarly, as shown in Fig. 5, the results of the analyses of cravings showed only a significant main effect of cannabis use status, $F(1, 74) = 136.67$, $p < 0.001$, $\eta_p^2 = 0.65$. The effect of the stress manipulation was not significant, $F(1, 74) = 1.33$, $p = 0.25$, $\eta_p^2 = 0.02$, and the interaction between cannabis use and stress was not significant, $F(1, 74) = 0.17$, $p = 0.68$, $\eta_p^2 = 0.002$. Planned comparisons of the cannabis users in the stress condition with cannabis users in the no stress condition also revealed no significant effect of the stress manipulation on cannabis users' self-reported withdrawal symptoms, $F(1, 34) = 1.42$, $p = 0.24$, $\eta_p^2 = 0.04$.

Discussion

The present study was conducted to examine the extent to which basal and stress-induced cortisol concentrations and subjective stress ratings differed between chronic cannabis users and non-users in response to a multidimensional acute stress manipulation. Despite abstaining from cannabis use on the day of testing, cannabis users exhibited no increase in salivary cortisol concentration in response to the stress manipulation compared to non-users. Moreover, cannabis users showed a diminished increase in subjective stress ratings during the acute stressor relative to non-users. These dampened responses to stress occurred in the absence of increased self-reported cravings and symptoms of withdrawal. Together, these data indicate that chronic cannabis users display blunted psychological and adrenal stress reactivity compared to non-users.

This study is unique in that it is the first to compare indices of subjective and physiological stress in chronic cannabis users and non-users following an acute stress manipulation with distinct psychological and physiological components. The main findings of this study are consistent with a growing body of literature indicating that chronic cannabis use is associated with blunted amygdala activation and emotional reactivity to images of threatening faces (Cornelius et al. 2010) and dampened hormonal responses to unpleasant images (Somaini et al. 2012). Thus, converging evidence indicates that chronic cannabis consumption may render users less reactive to stressful and negatively valent images, both at a psychological and physiological level. However, it is also possible that residual low levels of active cannabinoids and

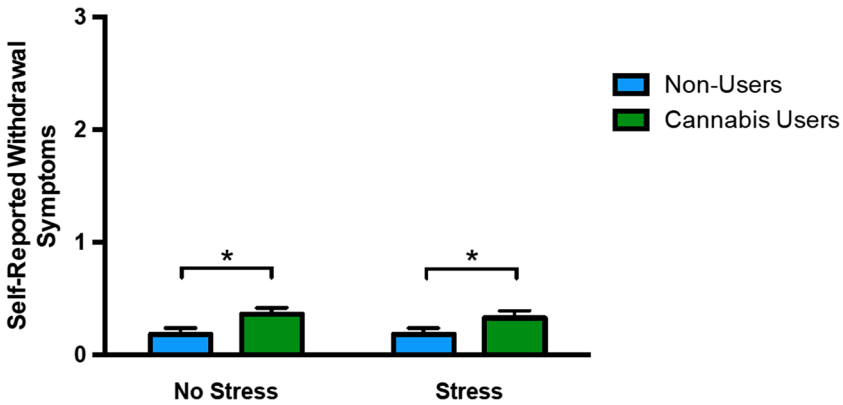

Fig. 4 Mean self-reported withdrawal symptoms in cannabis users and non-users following the no stress and stress conditions of the MAST with standard error bars. *$p < 0.05$

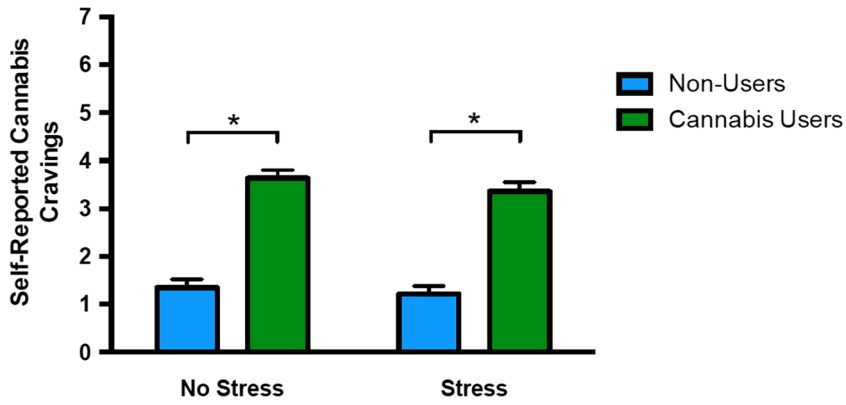

Fig. 5 Mean self-reported cravings in cannabis users and non-users following the no stress and stress conditions of the MAST with standard error bars. *$p < 0.05$

associated metabolites impacted stress reactivity, and it will be important for future research to examine stress reactivity in cannabis users after a longer period of abstinence.

These cannabis-related alterations in the stress response could be particularly beneficial in conferring enhanced resilience to stress, particularly in individuals exhibiting sensitized HPA axis responses and heightened emotional reactivity to stress. At the neurobiological level, excessive glucocorticoid activity can lead to atrophy in brain areas responsible for HPA axis negative feedback, such as the hippocampus, prefrontal cortex, and amygdala, which can contribute to the emergence of stress-related neuropsychiatric disorders involving hyperarousal as a symptom, such as melancholic depression (see McEwen 1998; McEwen et al. 2016 for reviews). Thus, chronic cannabis use may protect against exaggerated glucocorticoid secretion in individuals at risk for developing melancholic depression or other disorders characterized by persistent hyperarousal. In this respect, it is not particularly surprising that the most commonly cited reasons for medical cannabis use are to manage stress and alleviate symptoms of anxiety (Sexton et al. 2016; Webb and Webb 2014).

While a dampened emotional and hormonal response to stress can certainly be beneficial under certain circumstances, it is important to note that acute cortisol release typically serves an adaptive purpose, allowing individuals to mobilize energy stores and respond appropriately to threats in the environment (McEwen 1998). Thus, an inability to mount a proper hormonal response to stress could also have detrimental effects that could subsequently increase vulnerability for developing other pathological states. For instance, an inability to mount an effective cortisol response during a traumatic event has been identified as a key determinant of post-traumatic stress disorder susceptibility (see Yehuda 2009 for review). Additionally, the atypical subtype of major depression has been associated with reduced cortisol concentrations compared to healthy controls (Gold and Chrousos 2002; Lamers et al. 2013). Furthermore, in mice, high anxiety-like behavior is associated with significantly reduced corticosterone secretion to an acute stressor and a blunted response in the dexamethasone suppression test compared to normal and low anxiety mice (Sotnikov et al. 2014). These data indicate that blunted HPA axis reactivity may actually perpetuate the development of the very symptoms that individuals are using cannabis to alleviate. Therefore, chronic cannabis use may have either beneficial or detrimental consequences, which are likely dependent on individual differences in the sensitivity of HPA axis activation prior to initiating chronic cannabis use.

As expected, there was a strong positive correlation between levels of perceived stress and salivary cortisol concentration in non-users. However, this correlation was conspicuously absent in chronic cannabis users. Thus, despite reporting increased subjective stress (albeit not to the extent of non-users), chronic cannabis users did not show a corresponding recruitment of cortisol during the stressor. This suggests that there may be a discordance between subjective and physiological stress measures in chronic cannabis users, which further supports the idea that these individuals have general impairments in cortisol mobilization.

The fact that we failed to observe a significant increase in cortisol in chronic cannabis users following the stress condition is especially interesting because the MAST includes a physiologically stressful component (holding hand in ice-cold water) along with a psychosocial component (performing difficult math under conditions of social evaluation). Based on previous findings that the hormonal response to emotionally valent stimuli is blunted in chronic cannabis users (Somaini et al. 2012), and that psychosocial and physiological stressors each activate the HPA axis via distinct pathways (Herman et al. 2016), one might predict that the stress dampening effects of chronic cannabis use would be specific to psychosocial stress, with the physiological stress response remaining intact. That cannabis users similarly failed to mount a proper cortisol response to the physiological component of the stressor further underscores the notion that the blunted stress response observed herein may be more detrimental than beneficial. Nevertheless, there is evidence that the normal hormonal response can recover following an extended period of

abstinence, even though the perceived unpleasantness of negative emotional images remains blunted (Somaini et al. 2012). Future research should therefore examine whether a period of abstinence would similarly lead to a recovery of the normal response to an acute stressor such as the MAST.

There are multiple mechanisms by which chronic cannabis use may be dampening physiological stress responsivity. For instance, acute stress exposure is well known to recruit catecholamines (i.e., noradrenaline and dopamine) to activate the HPA axis (McEwen and Sapolsky 1995), while chronic cannabis use has been associated with impairments in dopamine synthesis and release (see Sami et al. 2015 for review). Thus, the blunted endocrine stress response observed herein could be due to compromised recruitment of catecholamines in heavy cannabis users. In support of this, Volkow et al. (2014) have demonstrated that chronic cannabis users display attenuated behavioral, cardiovascular, and brain dopamine responses to methylphenidate, which increases catecholamine concentrations by blocking the dopamine and norepinephrine transporters. However, a recent PET study has shown that the striatal dopamine response to acute psychosocial stress is not significantly altered in chronic cannabis users (Mizrahi et al. 2013), which argues against this being a central mechanism underlying the observed effects.

Alternately, a more parsimonious explanation could be that chronic cannabis use is dampening stress reactivity by interfering with the normal actions of the endocannabinoid system, the primary target for cannabis in the brain. Indeed, mounting evidence has indicated a fundamental role for the endocannabinoid system in constraining HPA axis activation, promoting stress recovery, and dictating proper behavioral and emotional responses to stressful stimuli (Hill and Tasker 2012; McLaughlin et al. 2014). Endocannabinoid-mediated activation of the type 1 cannabinoid receptor is required for many glucocorticoid effects, particularly negative feedback inhibition of HPA axis activation (Di et al. 2003; Malcher-Lopes et al. 2006; Hill et al. 2011), while chronic cannabinoid administration causes alterations in endocannabinoid content in both humans (Morgan et al. 2013) and rodents (Di Marzo et al. 2000; González et al. 2004). Thus, cannabis-induced alterations in endocannabinoid signaling could contribute to the attenuated hormonal response observed herein. Clearly, future studies will be required to fully understand the precise mechanisms by which heavy cannabis use blunts stress reactivity.

Exposure to psychological and physiological stress is well known to augment craving in regular drug users (see Cleck and Blendy 2008 for review). Given the literature showing that stress coping motives often underlie cannabis-seeking behaviors in habitual users (Hyman and Sinha 2009), it is surprising that our group of heavy cannabis users did not report increased cravings in response to stress. Although this could be due to several factors, our data indicating that cannabis users also reported a diminished increase in subjective stress suggests that this acute manipulation in a controlled laboratory setting may not have been sufficient to augment cannabis craving. Alternatively, it could be that stress-induced cannabis craving only occurs in distinct subpopulations, such as those with social anxiety disorder. For instance, individuals with social anxiety disorder have been found to report greater cannabis craving during a public speaking task, an effect that was absent in cannabis users without social anxiety (Buckner et al. 2011). Similarly, cannabis users assigned to a social anxiety induction task (but not a reading task) reported increased cannabis craving, an effect that was exacerbated in individuals with social anxiety disorder (Buckner et al. 2013, 2016). Thus, the lack of effect on cannabis craving in the current study may be because the cannabis users were not sufficiently impacted by the stressor or because this phenomenon is unique to individuals experiencing pathological anxiety.

Less is known about the effects of acute stress on cannabis users' withdrawal symptoms, and to our knowledge, the present study represents the first attempt to examine this potential impact. Consistent with the findings on cannabis cravings, the results indicate that acute stress does not trigger cannabis withdrawal symptoms. However, the lack of significant effect may once again be a function of cannabis users' dampened stress response. Moreover, given that most participants had abstained from cannabis for less than 24 h and that cannabis withdrawal symptoms peak after approximately 1 week of abstinence (Hesse and Thylstrup 2013), it is possible that introducing an acute stressor after a more prolonged period of abstinence would exacerbate withdrawal symptoms, cannabis cravings, and possibly stress reactivity.

There are several noteworthy limitations to acknowledge. First, we did not obtain baseline measures of cannabis cravings and withdrawal symptoms because we did not want to illicit cravings or trigger withdrawal symptoms prior to the stress manipulation due to concerns that this would impact cannabis users' stress response. Nevertheless, future research should obtain these baseline measures in order to examine changes in cravings and withdrawal symptoms as a function of acute stress. Second, given the short period of abstinence, it is possible that residual levels of THC in the cannabis users may have influenced their responses. Once again, future research should attempt to replicate these findings after a more prolonged period of abstinence. Third, while all participants were screened for any illicit drug use in the past month, we did not measure or statistically control for illicit drug use beyond this period of time or for use of tobacco. Cigarette smokers also elicit lower salivary cortisol levels in response to stress (Ginty et al. 2014), and therefore, it will be important for future research to replicate these results in non-cigarette smokers or groups of cannabis users and non-users matched on tobacco use. Future research should also seek to balance the distribution of males and females across groups and

measure menstrual cycle phase in order to examine potential sex differences and/or menstrual cycle phase effects on the cannabis × stress interactions found in the present study.

In conclusion, the results of the current study indicate that the subjective and physiological responses to an acute stressor are significantly blunted in heavy cannabis users compared to non-users. Additionally, a discordance between subjective and physiological stress was observed in cannabis users that may suggest general impairments in the recruitment of cortisol in response to stress. Notably, these aberrations occurred in the absence of increased self-reported craving and symptoms of withdrawal. Future studies will be needed to identify both the positive and negative implications of blunted stress reactivity in chronic cannabis users, the mechanisms by which chronic cannabis use impairs cortisol mobilization, and whether these effects are reversible following a period of abstinence.

Acknowledgements Washington State University's Dedicated Marijuana Account funded this study. We thank Anthony Berger for running the cortisol assays.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Block RI, Farinpour R, Schlechte JA (1991) Effects of chronic marijuana use on testosterone, luteinizing hormone, follicle stimulating hormone, prolactin and cortisol in men and women. Drug Alcohol Depend 28(2):121–128

Buckner JD, Silgado J, Schmidt NB (2011) Marijuana craving during a public speaking challenge: understanding marijuana use vulnerability among women and those with social anxiety disorder. J Behav Ther Exp Psychiatry 42(1):104–110. doi:10.1016/j.jbtep.2010.07.005

Buckner JD, Ecker AH, Vinci C (2013) Cannabis use vulnerability among socially anxious users: cannabis craving during a social interaction. Psychol Addict Behav 27(1):236–242. doi:10.1037/a0029763

Buckner JD, Zvolensky MJ, Ecker AH, Jeffries ER (2016) Cannabis craving in response to laboratory-induced social stress among racially diverse cannabis users: the impact of social anxiety disorder. J Psychopharmacol 30(4):363–369. doi:10.1177/0269881116629115

Budney AJ, Novy PL, Hughes JR (1999) Marijuana withdrawal among adults seeking treatment of marijuana dependence. Addiction 94:1311–1322. doi:10.1046/j.13600443.1999.94913114.x

Budney AJ, Moore BA, Vandrey RG, Hughes JR (2003) The time course and significance of cannabis withdrawal. J Abnorm Psychol 112:393–402. doi:10.1037/0021-843X.112.3.393

Childs E, Lutz JA, de Wit H (2017) Dose-related effects of delta-9-THC on emotional responses to acute psychosocial stress. Drug Alcohol Depend (in press)

Cleck JN, Blendy JA (2008) Making a bad thing worse: adverse effects of stress on drug addiction. J Clin Invest 118(2):454–461. doi:10.1172/JCI33946

Cohen S, Williamson G (1988) Perceived stress in a probability sample of the United States. In: Spacapan S, Oskamp S (eds) The social psychology of health: Claremont symposium on applied social psychology. Newbury Park, California

Copeland J, Swift W, Rees V (2001) Clinical profile of participants in a brief intervention program for cannabis use disorder. J Subst Abus Treat 20(1):45–52

Cornelius JR, Aizenstein HJ, Hariri AR (2010) Amygdala reactivity is inversely related to level of cannabis use in individuals with comorbid cannabis dependence and major depression. Addict Behav 35(6):644–646. doi:10.1016/j.addbeh.2010.02.004

Cuttler C, Spradlin A (2017) Measuring cannabis consumption. Psychometric properties of the Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory (DFAQ-CU). PLOS ONE (in press)

Di Marzo V, Berrendero F, Bisogno T, González S, Cavaliere P, Romero J, Cebeira M, Ramos JA, Fernández-Ruiz JJ (2000) Enhancement of anandamide formation in the limbic forebrain and reduction of endocannabinoid contents in the striatum of delta9-tetrahydrocannabinol-tolerant rats. J Neurochem 74(4):1627–1635

Di S, Malcher-Lopes R, Halmos KC, Tasker JG (2003) Nongenomic glucocorticoid inhibition via endocannabinoid release in the hypothalamus: a fast feedback mechanism. J Neurosci 23(12):4850–4857

Elo AL, Leppänen A, Jahkola A (2003) Validity of a single-item measure of stress symptoms. Scand J Work Environ Health 29:444–451

Ginty AT, Jones A, Carroll D, Roseboom TJ, Phillips AC, Painter R, de Rooij SR (2014) Neuroendocrine and cardiovascular reactions to acute psychological stress are attenuated in smokers. Psychoneuroendocrinology 48:87–97. doi:10.1016/j.psyneuen.2014.05.023

Gold PW, Chrousos GP (2002) Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. Mol Psychiatry 7(3):254–275. doi:10.1038/sj.mp.4001032

González S, Fernández-Ruiz J, Di Marzo V, Hernández M, Arévalo C, Nicanor C, Cascio MG, Ambrosio E, Ramos JA (2004) Behavioral and molecular changes elicited by acute administration of SR141716 to Delta9-tetrahydrocannabinol-tolerant rats: an experimental model of cannabinoid abstinence. Drug Alcohol Depend 74(2):159–170. doi:10.1016/j.drugalcdep.2003.12.011

Gorka SM, Fitzgerald DA, de Wit H, Phan KL (2015) Cannabinoid modulation of amygdala subregion functional connectivity to social signals of threat. Int J Neuropsychopharmacol 18(3):pyu104. doi:10.1093/ijnp/pyu104

Gruber SA, Rogowska J, Yurgelun-Todd DA (2009) Altered affective response in marijuana smokers: an FMRI study. Drug Alcohol Depend 105(1–2):139–153. doi:10.1016/j.drugalcdep.2009.06.019

Heishman SJ, Singleton EG, Liguori A (2001) Marijuana Craving Questionnaire: development and initial validation of a self-report instrument. Addiction 97(7):1023–1034. doi:10.1080/096552140120053084

Herman JP (2013) Neural control of chronic stress adaptation. Front Behav Neurosci 7:61. doi:10.3389/fnbeh.2013.00061

Herman JP, McKlveen JM, Ghosal S, Kopp B, Wulsin A, Makinson R, Scheimann J, Myers B (2016) Regulation of the hypothalamic-pituitary-adrenocortical stress response. Compr Physiol 6(2):603–621. doi:10.1002/cphy.c150015

Hesse M, Thylstrup B (2013) Time-course of the DSM-5 cannabis withdrawal symptoms in poly-substance abusers. BMC Psychiatry 13:258. doi:10.1186/1471-244X-13-258

Hill MN, Tasker JG (2012) Endocannabinoid signaling, glucocorticoid-mediated negative feedback, and regulation of the hypothalamic-pituitary-adrenal axis. Neuroscience 204:5–16. doi:10.1016/j.neuroscience.2011.12.030

Hill MN, McLaughlin RJ, Pan B, Fitzgerald ML, Roberts CJ, Lee TT, Karatsoreos IN, Mackie K, Viau V, Pickel VM, McEwen BS, Liu QS, Gorzalka BB, Hillard CJ (2011) Recruitment of prefrontal cortical endocannabinoid signaling by glucocorticoids contributes to

termination of the stress response. J Neurosci 31(29):10506–10515. doi:10.1523/JNEUROSCI.0496-11.2011

Hyman SM, Sinha R (2009) Stress-related factors in cannabis use and misuse: implications for prevention and treatment. J Subst Abus Treat 36(4):400–413. doi:10.1016/j.jsat.2008.08.005

Kedzior KK, Laeber LT (2014) A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population—a meta-analysis of 31 studies. BMC Psychiatry 14:136. doi:10.1186/1471-244X-14-136

King GR, Ernst T, Deng W, Stenger A, Gonzales RM, Nakama H, Chang L (2011) Altered brain activation during visuomotor integration in chronic active cannabis users: relationship to cortisol levels. J Neurosci 31(49):17923–17931. doi:10.1523/JNEUROSCI.4148-11.2011

Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman AT, Penninx BW (2013) Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. Mol Psychiatry 18(6):692–699. doi:10.1038/mp.2012.144

Malcher-Lopes R, Di S, Marcheselli VS, Weng FJ, Stuart CT, Bazan NG, Tasker JG (2006) Opposing crosstalk between leptin and glucocorticoids rapidly modulates synaptic excitation via endocannabinoid release. J Neurosci 26(24):6643–6650. doi:10.1523/JNEUROSCI.5126-05.2006

McEwen BS (1998) Stress, adaptation, and disease. Allostasis and allostatic load. Ann N Y Acad Sci 840:33–44

McEwen BS, Sapolsky RM (1995) Stress and cognitive function. Curr Opin Neurobiol 5(2):205–216

McEwen BS, Nasca C, Gray JD (2016) Stress effects on neuronal structure: hippocampus, amygdala, and prefrontal cortex. Neuropsychopharmacology 41(1):3–23. doi:10.1038/npp.2015.171

McLaughlin RJ, Hill MN, Gorzalka BB (2014) A critical role for prefrontocortical endocannabinoid signaling in the regulation of stress and emotional behavior. Neurosci Biobehav Rev 42:116–131. doi:10.1016/j.neubiorev.2014.02.006

Mizrahi R, Suridjan I, Kenk M, George TP, Wilson A, Houle S, Rusjan P (2013) Dopamine response to psychosocial stress in chronic cannabis users: a PET study with [11C]-+-PHNO. Neuropsychopharmacology 38(4):673–682. doi:10.1038/npp.2012.232

Monteleone P, Di Filippo C, Fabrazzo M, Milano W, Martiadis V, Corrivetti G, Monteleone AM, Maj M (2014) Flattened cortisol awakening response in chronic patients with schizophrenia onset after cannabis exposure. Psychiatry Res 215(2):263–267. doi:10.1016/j.psychres.2013.12.016

Morgan CJ, Page E, Schaefer C, Chatten K, Manocha A, Gulati S, Curran HV, Brandner B, Leweke FM (2013) Cerebrospinal fluid anandamide levels, cannabis use and psychotic-like symptoms. Br J Psychiatry 202(5):381–382. doi:10.1192/bjp.bp.112.121178

Okaneku J, Vearrier D, McKeever RG, LaSala GS, Greenberg MI (2015) Change in perceived risk associated with marijuana use in the United States from 2002 to 2012. Clin Toxicol (Phila) 53(3):151–155. doi:10.3109/15563650.2015.1004581

Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, Tancer ME (2005) Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. Biol Psychiatry 57(3):210–219. doi:10.1016/j.biopsych.2004.10.030

Phan KL, Angstadt M, Golden J, Onyewuenyi I, Popovska A, de Wit H (2008) Cannabinoid modulation of amygdala reactivity to social signals of threat in humans. J Neurosci 28(10):2313–2319

Ranganathan M, Braley G, Pittman B, Cooper T, Perry E, Krystal J, D'Souza DC (2009) The effects of cannabinoids on serum cortisol and prolactin in humans. Psychopharmacology 203(4):737–744. doi:10.1007/s00213-008-1422-2

Sami MB, Rabiner EA, Bhattacharyya S (2015) Does cannabis affect dopaminergic signaling in the human brain? A systematic review of evidence to date. Eur Neuropsychopharmacol 25(8):1201–1224. doi:10.1016/j.euroneuro.2015.03.011

Schuermeyer J, Salomonsen-Sautel S, Price RK, Balan S, Thurstone C, Min SJ, Sakai JT (2014) Temporal trends in marijuana attitudes, availability and use in Colorado compared to non-medical marijuana states: 2003-11. Drug Alcohol Depend 140:145–155. doi:10.1016/j.drugalcdep.2014.04.016

Sexton M, Cuttler C, Finnell J, Mischley L (2016) A cross-sectional survey of medical cannabis users: patterns of use and perceived efficacy. Cannabis Cannabinoid Res 1:131–138. doi:10.1089/can.2016.0007

Smeets T, Cornelisse S, Quaedflieg CW, Meyer T, Jelicic M, Merckelbach H (2012) Introducing the Masstricht Acute Stress Test (MAST): a quick and non-invasive approach to elicit robust autonomic and glucocorticoid stress responses. Psychneuroendocrinology 37:1998–2008. doi:10.1016/j.psyneuen.2012.04.012

Somaini L, Manfredini M, Amore M, Zaimovic A, Raggi MA, Leonardi C, Gerra ML, Donnini C, Gerra G (2012) Psychobiological responses to unpleasant emotions in cannabis users. Eur Arch Psychiatry Clin Neurosci 262(1):47–57. doi:10.1007/s00406-011-0223-5

Sotnikov S, Wittmann A, Bunck M, Bauer S, Deussing J, Schmidt M, Touma C, Landgraf R, Czibere L (2014) Blunted HPA axis reactivity reveals glucocorticoid system dysbalance in a mouse model of high anxiety-related behavior. Psychoneuroendocrinology 48:41–51. doi:10.1016/j.psyneuen.2014.06.006

Stolzenberg L, D'Alessio SJ, Dariano D (2016) The effect of medical cannabis laws on juvenile cannabis use. Int J Drug Policy 27:82–88. doi:10.1016/j.drugpo.2015.05.018

Substance Abuse and Mental Health Services Administration (SAMHSA) (2014). Behavioral health trends in the United States: results from the 2014 National Survey on Drug Use and Health. Retrieved March 15th, from http://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf

Tu MT, Lupien SJ, Walker CD (2006) Diurnal salivary cortisol levels in postpartum others as a function of infant feeding choice and parity. Psychneuroendocrinology 31(7):812–824. doi:10.1016/j.psyneuen.2006.03.006

United Nations Office on Drugs and Crime (2012) World drug report. United Nations, New York

Urry HL, van Reekum CM, Johnstone T, Kalin NH, Thurow ME, Schaefer HS, Jackson CA, Frye CJ, Greischar LL, Alexander AL, Davidson RJ (2006) Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. J Neurosci 26(16):4415–4425. doi:10.1523/JNEUROSCI.3215-05.2006

Volkow ND, Wang GJ, Telang F, Fowler JS, Alexoff D, Logan J, Jayne M, Wong C, Tomasi D (2014) Decreased dopamine brain reactivity in marijuana abusers is associated with negative emotionality and addiction severity. Proc Natl Acad Sci U S A 111(30):E3149–E3156. doi:10.1073/pnas.1411228111

Webb CW, Webb SM (2014) Therapeutic benefits of cannabis: a patient survey. Hawaii J Med Public Health 73(4):109–111

Yehuda R (2009) Status of glucocorticoid alterations in post-traumatic stress disorder. Ann N Y Acad Sci 1179:56–69. doi:10.1111/j.1749-6632.2009.04979.x