EXAMINING THE STRESS-CANNABIS LINK ACROSS THE STRESS SPECTRUM

By

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Abstract

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May 2017

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Previous research has established a link between stress and cannabis. The overall goal of my dissertation was to further elucidate the nature of this link. In Study 1, moderators and mediators of the relationship between stress and cannabis were tested. In a sample of 578 young adult cannabis users, both chronic stress and early life stress were significantly associated with increased cannabis problems. Early life stress was also significantly associated with increased frequency of cannabis use, but chronic stress was not. Moderation analyses revealed a significant role of sex such that chronic stress was only associated with increased cannabis problems in males, and early life stress was only associated with frequency of cannabis use in females. Mediation analyses revealed that chronic stress and early life stress may lead to increased use of cannabis to cope, which in turn may lead to increased problematic cannabis use. Further, results suggest that stress may also lead to negative affect, which in turn leads to problematic cannabis use.

In Study 2, chronic cannabis users ($n = 39$) and non-users ($n = 40$) from the community underwent an acute stress manipulation. Chronic cannabis users showed reduced subjective and

physiological stress (i.e., salivary cortisol) reactivity compared to non-users in response to the stress manipulation. Chronic cannabis users in the stress condition did not show elevated cannabis cravings or withdrawal symptoms relative to those in the no-stress condition.

In tandem, these findings suggest that chronic cannabis use may protect individuals from the effects of acute stress, and that stress does not appear to cause increases in cravings and withdrawal symptoms; however, under conditions of chronic stress, cannabis users may be more likely to experience symptoms of negative affect and to use cannabis to cope with stress, and doing so may lead to problematic cannabis use. Males may be especially vulnerable to these effects. Implications for understanding the long-term effects of cannabis use and stress are discussed.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Dedication

My dissertation is dedicated to my grandma Doris. You always answered when I needed someone to talk to, you always gave me the best advice you could without judgment, and you always made sure that I knew how much you believed in me. I wish you were still here so you could celebrate this accomplishment with me.

CHAPTER ONE

INTRODUCTION AND AIMS

Stress is the physical, mental, or emotional strain or tension that occurs in response to a

myriad of environmental factors interpreted as threats (e.g., problems at school, financial strains,

relationship difficulties; Sapolsky, 2004). A recent national survey found that only 37% of

Americans believe they can manage their stress adequately (American Psychological Association

[APA], 2013). The statistics are even grimmer for those living in the Pacific Northwest; whereas

approximately 33% of adults in the U.S. report feeling overwhelmed by stress, approximately

44% of Seattle residents have indicated that they feel overwhelmed (APA, 2013). Younger

people also report higher levels of stress and more stress-related symptoms (APA, 2015).

Consistent with these findings, a recent survey of students at Washington State University

(WSU) revealed that half of our students reported feeling "more than average" or "tremendous"

levels of stress at some point in the past 12 months, and 86% felt overwhelmed by all they had to

do (American College Health Association, 2015). This is particularly concerning because

unmanaged chronic stress can lead to a broad array of negative outcomes, including depressed

mood, feelings of anger, difficulty sleeping, digestive problems, and more frequent and persistent

viral infections (National Institute of Mental Health, 2015). Stress may also predispose

individuals to substance abuse and substance-related problems (e.g., Fishbein et al., 2007;

Labouvie, 1986; Sinha, 2001; Sinha, 2008; Windle & Wiesner, 2004).

Cannabis use is currently at an all-time high in the US, with a recent national survey

indicating that 44% of Americans have used cannabis at least once in their life – higher than at

any other time in Gallup's 46 years of surveying (Gallup, 2015). Further, approximately 8.4% of

Americans reported using cannabis within the past 30 days (Substance Abuse and Mental Health

Services Administration [SAMHSA], 2015), and its use is particularly common among Washington State residents between the ages of 18-25, with over 36% reporting use of cannabis in the past month compared to 16% of those ages 26 or older (SAMHSA, 2015). On the November, 2012 general ballot, recreational cannabis was legalized in Washington State, and to date more than 380 recreational cannabis dispensaries have opened across the state (502 Data, 2017), with many more recreational cannabis dispensary licenses allotted for future distribution (Rummel, 2014). The rapid growth of the recreational cannabis industry and the reduction in stigma surrounding cannabis use resulting from its legalization are expected to increase the already high proportion of our population using cannabis (Palamar, 2014).

One of the most commonly reported reasons for cannabis consumption is for relaxation and tension reduction (i.e., because it relieves stress; Copeland, Swift, & Rees, 2001; Green, Kavanaugh, & Young, 2003; Hathaway, 2003; Reilly, Didcott, Swift, & Hall, 1998). In fact, cannabis is cited as a coping tool for dealing with negative affect and problems in life more than any other drug (Green, Kavanaugh, & Young, 2003). What this means is that many individuals use cannabis as a form of self-medication, specifically to cope with stress in their lives. However, the effectiveness of using cannabis as a mechanism for coping with stress and the long-term consequences of using cannabis for this purpose are not well understood. The elevated rates of cannabis use and stress in Washington State make it particularly important to our residents that we acquire a better understanding of the nature of this link.

To date, there is evidence of a link between cannabis and stress. As previously indicated, many individuals report using cannabis to cope with problems in their lives. Further, childhood abuse (both physical and sexual) is correlated with increased cannabis use (Harrison, Fulkerson, & Beebe, 1997), and both early life stress and chronic stress predict increased levels of problems

2

caused by cannabis use (e.g., having memory problems, being unable to meet one's responsibilities; Ketcherside & Filbey, 2015). There has been, however, a paucity of research conducted to examine the dynamics of the cannabis-stress relationship. As such, there remain many unanswered questions about the nature of this link. For example, are there specific conditions under which the link between cannabis and stress is strengthened or weakened? What are the factors that drive the stress-cannabis link? Do cannabis users respond to stress differently? And does stress cause elevations in cannabis cravings and withdrawal? Given the lack of answers to these important questions, the overall goal of my dissertation research was to further elucidate the nature of the relationship between stress and cannabis.

To achieve this goal, I conducted two studies. In Study 1, I collected data using a large-scale anonymous online survey to examine potential mediators and moderators of the stress-cannabis link. In doing so, I measured both early life stress and chronic stress to examine the types of stress related to cannabis. This study also allowed me to gather novel information regarding whether, why, and when there is a relationship between cannabis use and stress. In Study 2, I conducted an experiment involving an acute stress manipulation to examine differences in the stress response of chronic cannabis users compared to non-users and to determine whether an acute stressor causes cannabis users to report increased cannabis withdrawal symptoms and cravings. This study allowed me to obtain novel insights into the differences in the stress response of cannabis users compared to non-users, as well as to directly examine how acute stress may contribute to continued cannabis consumption. Together, these two studies help to answer several important and pressing questions regarding the nature of the relationship between cannabis use and three different types of stress: early life stress, chronic stress, and acute stress.

CHAPTER TWO

STUDY 1: MODERATORS AND MEDIATORS OF THE STRESS-CANNABIS LINK

BACKGROUND

Stress and cannabis use have been linked in previous research (see Hyman & Sinha, 2009 and Scholssarek, Kempkensteffen, Reimer, & Verthein, 2016 for review); however, little is known about the conditions under which this link is strongest or the mechanisms underlying this link. Therefore, the two aims of Study 1 were to: i) examine potential moderators of the relationship between cannabis and stress and ii) examine potential mediators of the relationship between cannabis and stress. Based on the results of previous research, the following variables were identified as putative moderators and mediators of the stress-cannabis link: biological sex, negative affect, and coping motives (i.e., using cannabis to cope with negative affect and other problems). In examining the role that these variables play in the stress-cannabis relationship, I focused on two cannabis use variables (frequency of cannabis use and cannabis problems) and two types of stress (early life stress and chronic stress).

To date, the bulk of published research on the relationship between stress and cannabis has largely focused on adolescents and the different background experiences or factors that predict future cannabis consumption and problems, including cannabis dependence and abuse. Three large-scale literature reviews have identified some common risk factors. Specifically, Sinha (2001), Sinha (2008), and Hyman and Sinha (2009) identified maladaptive coping, early life stress, family problems, and affiliation with deviant peers as significant indicators of future cannabis dependence. These factors are largely inter-related. For example, family problems such as abuse or neglect may directly lead to stress during a period of time (i.e., childhood and adolescence) in which the brain pathways involved in emotional regulation are developing

(Hyman & Sinha, 2009). Prolonged exposure to stress in early life may result in changes to how the brain responds to stress (Bugental, 2004; DeBellis, 2002; Heim & Nemeroff, 2001; Heim et al., 2000), and it may lead to an exaggerated response to subsequent stressors (Glaser, Os, Portegijs, & Myin-Germeys, 2006; Harkness, Bruce, & Lumley, 2006). Also, a child who is subjected to turbulence in her/his family life may not have the guidance necessary to learn skills to effectively cope with her/his environment. He/she may, in turn, rely on friends and others around her/him for care. If those others happen to be deviant peers, this could further exacerbate the problems faced by the child, potentially leading to increased access to cannabis and increased acceptance of cannabis use. Together these stress-related factors from adolescence may contribute to increased cannabis use and, potentially, an increased likelihood of developing cannabis dependence. For this reason, the link between early life stress and cannabis (in addition to the link between cannabis and chronic stress) was tested in the present study.

As discussed in Chapter 1, individuals report using cannabis to cope with negative aspects of their lives more than any other drug (Green, Kavanaugh, & Young, 2003). As such, several studies on cannabis have highlighted the importance of considering one's level of cannabis coping motives (i.e., using cannabis to cope with negative affect and other problems). For example, there is evidence that symptoms of PTSD are associated with increased levels of cannabis coping motives (Bonn-Miller, Vujanovic, & Zvolensky, 2008). Moreover, Brodbeck and colleagues (2007) found significantly higher psychosocial distress (i.e., unpleasant feelings that occur in response to stress and impact functioning) in young adults who used cannabis primarily for coping motives, but not in those who used cannabis primarily for social reasons. Moreover, Johnson and colleagues (2009) found that coping motives mediated the relationship between cannabis use and anxious arousal (i.e., somatic tension and arousal). Similarly, Bujarski

and colleagues (2012) discovered that the relationship between distress intolerance and cannabis problems was mediated by coping motives and that this effect was significantly larger in women than in men. Finally, Spradlin, Mauzay, and Cuttler (2017) provided evidence that coping motives mediate the relationship between symptoms of obsessive-compulsive disorder and cannabis misuse. To my knowledge, coping motives have not been examined as a mediator of the link between stress and cannabis. Therefore, the second aim of the present study was to test the hypothesis that stress predicts increased cannabis use and cannabis problems through coping motives.

Another variable that appears to be important to the link between cannabis and stress is negative affect. Negative affect refers to a broad category of unpleasant feelings or emotions and includes specific feelings like those associated with depression and anxiety. Similar to stress, negative affect often co-occurs with drug dependence (e.g., Hovens et al., 2012; Kessler, 1997). Ketcherside and Filbey (2015) considered the roles of depression and anxiety in the relationship between chronic stress and cannabis problems, as well as early life stress and cannabis problems. First, they found that chronic stress and early life stress both predicted increases in cannabis problems. They then conducted separate mediation analyses and found that depression mediated the relationship between both chronic stress and cannabis-related problems and between early life stress and cannabis-related problems, and that anxiety mediated the relationship between chronic stress and cannabis-related problems. These results indicate that stress may lead to problematic cannabis use because of the negative affect that is produced by that stress. This study points to the importance of considering both a history of stress as well as recent levels of stress when predicting cannabis problems. Because of the cross-sectional nature of the study, however, it is impossible to determine the causal nature of the relationships detected. Moreover,

6

it is also important to note that there is great deal of overlap in symptoms of anxiety and symptoms of depression (e.g., Zbozinek et al., 2012), so it is possible that both served as mediators because of that overlap. Therefore, I aimed to test models in Study 1wherein symptoms of depression and anxiety were combined to create a negative affect variable that could be probed as a mediator of the stress-cannabis link.

Finally, there may be sex differences in the relationship between stress and cannabis. To date, sex has not been tested as a moderator of the stress-cannabis link; however, research on cannabis and anxiety and cannabis and depression has revealed numerous sex differences. For example, Patton and colleagues (2002) studied adolescent Australian school children into young adulthood to examine the relationship between cannabis use frequency and subsequent depression and anxiety. At the end of a seven-year follow-up, they found that female daily users of cannabis demonstrated a five times greater odds of reporting a state of depression and anxiety, relative to females who did not use cannabis. This effect was not detected in males. Interestingly, adolescent anxiety and depression were not associated with either weekly or daily cannabis use at follow-up. The results of this longitudinal study therefore imply that heavy use of cannabis during adolescence can increase females' risk of experiencing depression and anxiety in adulthood. Tu, Ratner, and Johnson (2008) also observed sex differences in the link between cannabis use and depression and anxiety, along with other aspects of mental health. They conducted a cross-sectional survey of adolescent Canadian school children from seventh through twelfth grade to evaluate cannabis use rates and mental health status. Their findings indicated that female heavy users reported significantly poorer mental health than non-users, while male heavy users did not show a difference in mental health compared to non-users. Finally, Crane, Langenecker, and Mermelstein (2015) surveyed American young adults over a six-year period to

examine the relationship between symptoms of depression and cannabis use. Contrary to the results of Patton et al. (2002) and Tu, Ratner, and Johnson (2008), Crane, Langenecker, and Mermelstein (2015) found a relationship between symptoms of depression and frequency of cannabis use in males only that did not vary across the six-year time period. Although the results of these studies are somewhat contradictory, they highlight the importance of considering sex as a potential moderator of the relationship between cannabis and stress.

In summary, previous research has established a link between stress and cannabis and has helped to identify several variables that may play an important role in the relationship between stress and cannabis. Those additional variables include biological sex, negative affect, and coping motives. Therefore, the primary aim of Study 1 was to further elucidate the nature of the relationship between cannabis and stress by identifying moderators and mediators of the relationship. I hypothesized that sex would moderate the relationships between stress and cannabis, and that coping motives and negative affect would mediate the relationships.

METHODOLOGY

Participants

A total of 1,334 undergraduate students completed Study 1. This robust sample size provided sufficient power to conduct tests of indirect effects (i.e., mediation models) and to buffer the low levels of cannabis users and males who participate in the WSU Psychology Department's human subject pool. Data collection began during the Fall 2015 semester, and collection was completed after the Fall 2016 semester.

After data collection was completed, the data were filtered to ensure the sample met several criteria. First, 80 participants (approximately 6% of the total sample) were excluded because they failed a deviant response check. The 10 items of the deviant responding validity

8

subscale of the Psychopathic Personality Inventory (PPI; Lilienfeld & Andrews, 1996) were randomly interspersed throughout my survey to detect random responders, and participants who endorsed more than four PPI items in an aberrant manner were excluded from all analyses. Second, participants must have used cannabis within the past 30 days. This criterion was chosen to ensure that a wide range of cannabis use was available for analysis while also removing the influence of the large percentage of non-users who completed the study.

A final sample of 578 undergraduate students was included in the analyses conducted for Study 1. This sample comprised primarily females (65.6%) and individuals who identified as white (68.2%), followed by Hispanic or Latino (11.9%), black (6.9%), Asian (5%), Pacific Islander (2.8%), and Native American (1.4%). Approximately 3.6% of participants indicated their ethnicity was something other than the answer choices available. Among the participants, the average age was approximately 20 years old ($SD = 1.71$). Participants reported using cannabis, on average, approximately 10 days ($SD = 6.51$) of the past month, and approximately 19% of the participants reported using cannabis once a day or more. The average age of first cannabis use among participants was approximately 16 ($SD = 2.12$).

Materials

Demographic information: A short demographics questionnaire was included in the survey to assess age, sex, ethnicity, and other demographic characteristics.

Perceived Stress Scale (PSS): The PSS is a 10-item self-report inventory for measuring the severity of symptoms of stress in the last month (i.e., levels of chronic stress; Cohen, 1988). Participants rate how often they have experienced stress (e.g., "how often have you been upset because of something that happened unexpectedly") on a 5-point scale with anchors as follows: 0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, and 4 = very often. The psychometric

properties of the measure are sound among college students and include high internal

consistency ($\alpha \geq .70$) and high test-retest reliability ($r \geq .70$; see Lee, 2012 for review). Scores

for each participant were computed by taking an average of all 10 items. These summary scores

could range from 0 to 4, with higher scores indicating more chronic stress.

Beck Anxiety Inventory (BAI): The BAI is a self-report instrument for measuring severity

of anxiety with an emphasis on discrimination between symptoms of anxiety and depression

(Beck, Epstein, Brown, & Steer, 1988). The inventory is composed of 21 items measuring

common symptoms of anxiety, including cognitive (e.g., fear of the worst happening) and

somatic (e.g., sweating not due to heat) components. Participants respond according to how

bothersome each symptom has been over the past week using a 4-point scale with the following

anchors: 0 = not at all; 1 = mildly: it did not bother me much; 2 = moderately: it wasn't pleasant

at times, and 3 = severely: it bothered me a lot. Psychometric properties of the instrument include

high internal consistency ($\alpha = .92$), one-week test-retest reliability ($r = .75$), discriminant validity

(low correlation with a measure of symptoms of depression, $r = .25$), and concurrent validity

(moderate correlation with a measure of trait anxiety, $r = .51$; Beck, Epstein, Brown, & Steer,

1988). Participants' BAI scores were computed by taking the average of all of the items on the

measure. Possible scores could range from 0 to 3, with higher scores reflecting more severe

anxiety symptomology.

Beck Depression Inventory (BDI-II): The BDI-II is a self-report inventory for measuring

the severity of symptoms of depression (Beck, Steer, Ball, & Ranieri, 1996). The inventory

contains 21 groups of four statements describing symptoms of depression, such as changes in

mood, motivation, sleep, and diet. Participants are instructed to mark one answer choice for each

item corresponding to the one statement in each group that best describes how they have felt

during the past two weeks, including today (e.g., "I am sad all the time and can't snap out of it"), with higher numbers corresponding to more severe symptoms of depression. The inventory has demonstrated high internal consistency (α = .91; Beck, Steer, Ball, & Ranieri, 1996) and high one-week test-retest reliability (r = .93; Beck, Steer, & Brown 1996). It has also shown good concurrent validity (Beck, Steer, & Brown, 1996). Participants' BDI-II scores were computed by averaging all of the items they responded to in the inventory. Possible scores could range from 0 to 3, with higher scores reflecting more severe symptoms of depression.

Early Life Stress Questionnaire (ELSQ): The ELSQ is a self-report inventory used to measure exposure to potentially traumatic events before the age of 18 (Cohen et al., 2006). It is based on Sanders and Becker-Lausen's Child Abuse and Trauma Scale (1995). Participants use a yes/no scale to respond to 19 items to indicate whether they experienced each specific event during their childhood (e.g., sexual abuse, the death of a sibling, premature birth or other birth complications). The initial version of the questionnaire has shown high internal consistency (α = .90) and test-retest reliability at a six- to eight-week follow-up (r = .89; Sanders & Becker-Lausen, 1995). The ELSQ also has significant correlations with other measures, such as depression (r = .40) and stressful life events (r = .29; Sanders & Becker-Lausen, 1995). Total scores were computed by averaging the number of traumatic events each participant experienced. These scores had a possible range between 0 and 1, with higher scores indicating more exposure to potentially traumatic events during childhood and adolescence.

Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory (DFAQ-CU): The DFAQ-CU is a self-report inventory for measuring cannabis use across six factors: number of sessions of cannabis use per day, frequency of cannabis use, age of onset of cannabis use, quantity of loose-leaf cannabis typically consumed, quantity of cannabis

concentrates typically consumed, and quantity of cannabis-infused edibles typically consumed (Cuttler & Spradlin, 2015). It comprises 33 items using various rating scales to measure numerous aspects of cannabis consumption, including different methods of ingestion (e.g., smoking, vaporizing, eating) and potency of consumed cannabis. However, only the frequency subscale was considered in the present study. This subscale has excellent reliability ($\alpha = .87$), good predictive validity with measures of cannabis use disorders ($r = .59$), cannabis abuse ($r = .60$), cannabis dependence ($r = .21$), and problems associated with cannabis use ($r = .74$). The frequency subscale has also shown sound concurrent validity with other measures of cannabis consumption (e.g., $r = .81$ for the DFAQ-CU frequency subscale with the Marijuana Smoking History Questionnaire frequency subscale). Total scores were computed by averaging the items of the frequency subscale of the DFAQ-CU after standardizing those items and adjusting outliers to the highest non-outlying value. Higher scores on the frequency subscale indicate more frequent cannabis use.

Marijuana Problems Scale (MPS): The MPS is a self-report measure of the manner and degree to which marijuana use interferes with day-to-day functioning (e.g., by causing problems with one's partner, by causing one to procrastinate; Stephens, Roffman, & Curtin, 2000). Participants respond to 19 items based on whether the statement represents a problem they have experienced in the last month, with 0 = no problem, 1 = minor problem, and 2 = serious problem. Previous research has shown that the MPS has high internal consistency ($\alpha = .86$) and significant correlations with depression ($r = .26$) and distress tolerance ($r = -.18$; Buckner, Keough, & Schmidt, 2007). An average MPS score was computed for all participants that could range from 0 to 2, with higher scores indicative of more problems caused by marijuana use.

Marijuana Motives Measure (MMM): The MMM is a self-report measure designed to assess the reasons people use cannabis (Simons, Correia, Carey, & Borsari, 1998). It measures five distinct motives to use cannabis: coping motives (e.g., "to forget my worries"), enhancement motives (e.g., "because it's fun"), social motives (e.g., "because it helps me enjoy a party"), conformity motives (e.g., "because my friends pressure me to use marijuana"), and expansion motives (e.g., "to know myself better"). Participants respond to 25 items using a 5-point response scale with anchors as follows: 1 = almost never/never, 2 = some of the time, 3 = half of the time, 4 = most of the time, and 5 = almost always/always. The factor structure of the MMM has been evaluated and confirmed in both student (e.g., Chabrol, Ducongé, Casas, Roura, & Carey, 2005; Simons, Correia, Carey, & Borsari, 1998; Zvolensky et al., 2007) and broader young adult samples (Benschop et al., 2015). Only the coping motives factor was scored and analyzed in the present study. This factor has shown good internal consistency in previous research (e.g., α = .85; Benschop et al., 2015). Average scores for coping motives were computed using the coping motives items, with possible scores ranging between 1 and 5. Higher scores represent stronger endorsement of coping motives for cannabis use.

Procedure

Participants completed an anonymous online survey. The questionnaires contained within the survey are detailed in the Materials section, and they were administered in the same order as presented there. The survey required 40-50 minutes to complete, on average, and participants were compensated with one credit that they could apply to an eligible psychology course.

Prior to analysis, the data were screened per the inclusion/exclusion criteria described in the Participants section. A missing values analysis was computed on all items to create composite scale scores, as well as sex, with approximately 3.43% of all cases missing in the

13

dataset. As noted in the Materials section, in order to deal with these missing values, averaging was used to compute composite scale scores. All variables were then screened for outliers, defined as scores falling more than 3.29 standard deviations (SDs) from the sample mean. The small number detected ($< 1\%$) were converted to a score equivalent to 3.29 SDs from the mean (Tabachnick, Fidell, & Osterlind, 2001). All data screening and cleaning took place in IBM SPSS (version 24). The data were then transferred into Mplus (version 7.11) for all other analyses. Models were tested using full-information maximum likelihood estimation to deal with missing data at the variable level. A conservative alpha of .01 was used to determine statistical significance in all analyses. This more conservative level was selected to reduce inflation in Type I error as a result of the large number of analyses conducted and the robust sample size.

With regards to mediation analyses, 99% bias-corrected confidence intervals (CIs) were used to test for the significance of indirect effects. Because indirect effects are calculated by multiplying two regression coefficients together, they are extremely sensitive to non-normality in the relationships between predictors and mediators and between mediators and outcome variables. Confidence intervals for the significance of indirect effects were generated via bootstrapping with 10,000 iterations, which is the primary method for addressing this issue (see Hayes, 2013; Jose, 2013). Code for testing mediation and moderation models in Mplus was written using the templates provided by Stride and colleagues (2015). Finally, for analyses involving a latent variable (i.e., the negative affect mediation analyses), symptoms of anxiety were used to set the metric of the unobserved variable. The fit of all measurement models was evaluated using the following criteria: a non-significant χ^2 test, a comparative fit index (CFI) and a Tucker-Lewis index (TLI) greater than 0.80, and a root mean square error of approximation (RMSEA) less than 0.06 (see Hooper, Coughlan, & Mullen, 2008 for review). If the

14

measurement models met these criteria, the models were said to have good fit, and the structural component of the models was then evaluated. In instances where a large sample size is used (such as this one), there is a very high likelihood of a significant χ^2 test (Bentler & Bonett, 1980; Jöreskog & Sörbom, 1993), so many researchers recommend evaluating the structural model when all other fit statistics fall within the appropriate ranges (see Hooper, Coughlan, & Mullen, 2008 for review). As such, in cases where the measurement model did not meet these criteria but only because of a significant χ^2 test (i.e., when negative affect was tested as mediator of the relationship between early life stress and frequency of cannabis use), the structural model was still evaluated.

RESULTS

Bivariate Correlations

Bivariate correlations between all variables are provided in Table 1. Of particular interest, early life stress was significantly associated with both cannabis problems, $r(576) = .22, p < .001$, and frequency of cannabis use, $r(576) = .14, p = .001$. Chronic stress was significantly correlated with cannabis problems, $r(576) = .18, p < .001$, but not with frequency of cannabis use, $r(576) = -.09, p = .03$. Finally, sex (which was coded as follows: 0 for male, 1 for female) was significantly correlated with chronic stress, $r(576) = .18, p < .001$, as well as with cannabis problems, $r(576) = -.22, p < .001$, and frequency of cannabis use, $r(576) = -.22, p < .001$, such that females were higher than males in chronic stress, and males were higher than females in cannabis problems and frequency of cannabis use.

Table 1

Bivariate Correlations Between All Variables

Variable	1	2	3	4	5	6	7
1. Sex	--						
2. Chronic Stress	.18**	--					
3. Early Life Stress	.06	.18**	--				
4. Cannabis Problems	-.22**	.18**	.22**	--			
5. Frequency of Cannabis Use	-.22**	-.09	.14*	.31**	--		
6. Coping Motives	-.06	.27**	.20**	.37**	.42**	--	
7. Anxiety Symptoms	.13*	.54**	.32**	.28**	.04	.28**	--
8. Depressive Symptoms	.12*	.62**	.35**	.31**	.01	.33**	.63**

Note. $* p < .01, ** p < .001.$

Sex as a Moderator of the Relationship Between Stress and Cannabis

Sex was tested as a moderator of the relationships between chronic stress and cannabis problems (Model 1), chronic stress and frequency of cannabis use (Model 2), early life stress and cannabis problems (Model 3), and early life stress and frequency of cannabis use (Model 4). The results of these analyses are presented in Table 2.

Table 2

Sex Moderates the Relationship Between Stress and Cannabis

	β	SE
Model 1: Chronic Stress and Cannabis Problems		
$R^2 = .10$		
Intercept	.91**	0.16
Sex	-.54**	0.09
Chronic Stress	.68**	0.17
Chronic Stress x Sex	-.27*	0.09
Model 2: Chronic Stress and Frequency of Cannabis Use		
$R^2 = .05$		
Intercept	.72**	0.15
Sex	-.43**	0.09
Chronic Stress	-.04	0.16
Chronic Stress x Sex	-.01	0.09
Model 3: Early Life Stress and Cannabis Problems		
$R^2 = .10$		
Intercept	.78**	0.16
Sex	-.47**	0.09
Early Life Stress	.57*	0.17
Early Life Stress x Sex	-.19	0.10
Model 4: Early Life Stress and Frequency of Cannabis Use		
$R^2 = .08$		
Intercept	.76**	0.15
Sex	-.46**	0.09
Early Life Stress	-.23	0.15
Early Life Stress x Sex	.22*	0.09

Note. β = standardized regression coefficient; *SE* = standard error; R^2 = proportion of variance accounted for in the model; * $p < .01$, ** $p < .001$.

There was a significant interaction between sex and chronic stress in predicting cannabis problems. Further probing of this relationship indicated that the relationship between chronic stress and cannabis problems was significant in males, β = .40, $p < .001$, but not in females, β = .13, $p = .013$. This interaction is depicted in Figure 1.

Figure 1

Sex Moderates the Relationship Between Chronic Stress and Cannabis Problems
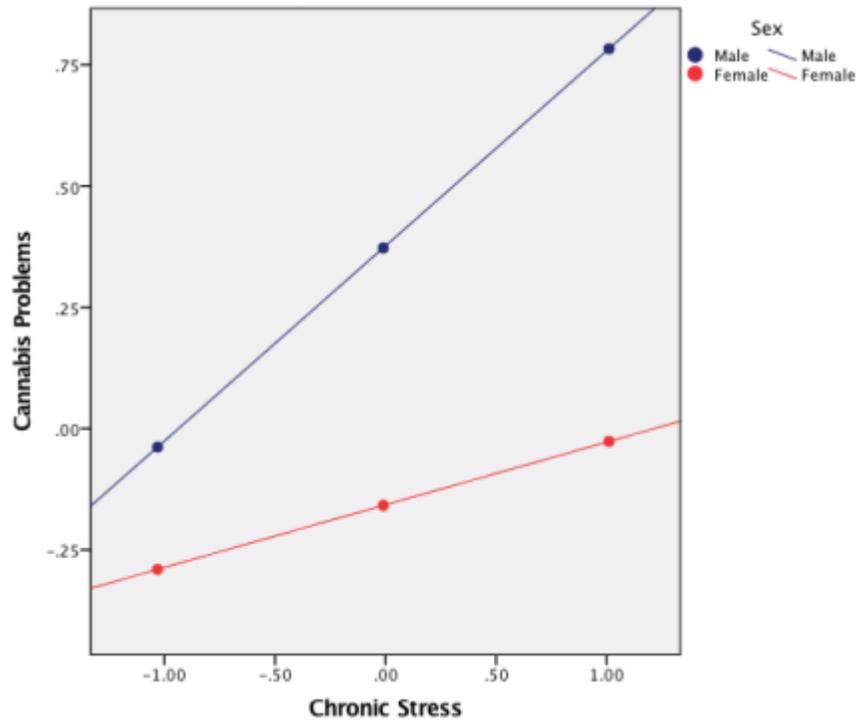
Sex did not moderate the nonsignificant relationship between chronic stress and frequency of cannabis use, nor did it moderate the relationship between early life stress and cannabis problems; however, the interaction between sex and early life stress did significantly predict frequency of cannabis use. Examination of the nature of this interaction revealed a significant relationship between early life stress and frequency of cannabis use in females, β = .22, p < .001, but not in males, β = -.004, p = .98 (see Figure 2).

Figure 2

Sex Moderates the Relationship Between Early Life Stress and Frequency of Cannabis Use
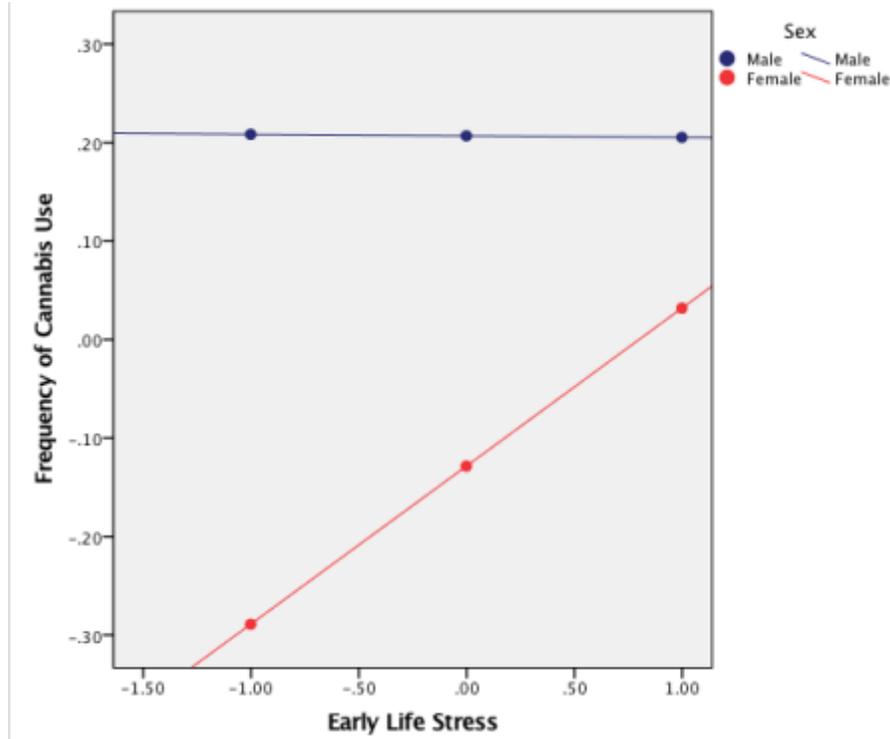
Coping Motives as a Mediator

Several mediation models were tested to determine whether coping motives accounted for the relationships between chronic stress and cannabis problems, early life stress and cannabis problems, and early life stress and frequency of cannabis use. Coping motives were not tested as a mediator of the relationship between chronic stress and frequency of cannabis use because those variables were not significantly correlated with each other, thus, there was no reason to parcel that relationship into its indirect and direct components. Because sex was found to moderate many of these relationships, sex was entered as a covariate in all models tested.

Results of these analyses demonstrated that coping motives functioned as a mediator of the relationship between chronic stress and cannabis problems (i.e., the confidence interval for the indirect effect did not cross 0; Figure 3). Further, the indirect pathway from chronic stress to

coping motives to cannabis problems accounted for approximately 45% of the total relationship

between chronic stress and cannabis problems. The direct path between chronic stress and

cannabis problems was no longer significant with the indirect pathway in the model, $\beta = .12$, $p =$

.01.

Figure 3
Coping Motives Mediate the Relationship Between Chronic Stress
and Cannabis Problems, Controlling for Sex

$R^2 = .08$
Total effect: $\beta = .22$ (0.05), $p < .001$
Indirect effect: $\beta = .10$ (0.03), $CI = .05 - .20$
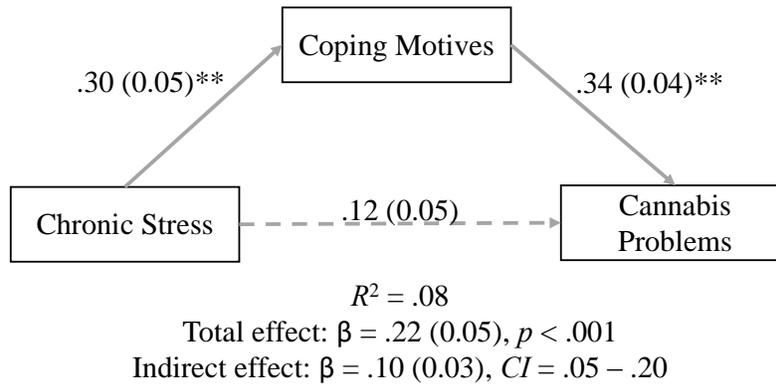
Note. All path coefficients are standardized regression coefficients
with standard errors in parentheses; β = standardized regression
coefficient; R^2 = proportion of variance accounted for in the model;
CI = bias corrected 99% confidence interval using bootstrapping with
10,000 iterations. * $p < .01$, ** $p < .001$.

In the second mediation analysis, the indirect effect of early life stress on cannabis

problems through coping motives was tested. Results revealed a significant indirect effect via

coping motives (Figure 4). Further, this indirect pathway accounted for approximately 35% of

the total relationship between early life stress and cannabis problems. The direct path between

early life stress and cannabis problems was reduced in magnitude with the indirect path in the

model, but it remained significant, $\beta = .15$, $p = .001$.

Figure 4

*Coping Motives Mediate the Relationship Between Early Life Stress and
Cannabis Problems, Controlling for Sex*

.24 (0.05)**   Coping Motives   .33 (0.04)**

Early Life Stress   .15 (0.05)*   Cannabis Problems

$R^2 = .09$
Total effect: $\beta = .23$ (0.05), $p < .001$
Indirect effect: $\beta = .08$ (0.03), $CI = .03 - .17$
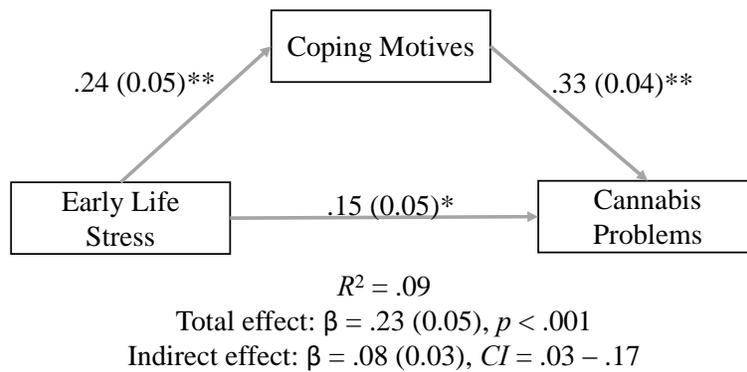
Note. All path coefficients are standardized regression coefficients
with standard errors in parentheses; β = standardized regression
coefficient; R^2 = proportion of variance accounted for in the model;
CI = bias corrected 99% confidence interval using bootstrapping with
10,000 iterations. * $p < .01$, ** $p < .001$.

Finally, a third mediation analysis was conducted wherein coping motives was tested as

the mediator of the relationship between early life stress and frequency of cannabis use. Results

revealed a significant indirect effect of early life stress on frequency of cannabis use via coping

motives (Figure 5). This indirect path through coping motives accounted for approximately 57%

of the relationship between early life stress and frequency of cannabis use. With the indirect path

in the model, the direct relationship between early life stress and frequency of cannabis use was

no longer significant, $\beta = .05$, $p = .17$.

Figure 5

Coping Motives Mediate the Relationship Between Early Life Stress and Frequency of Cannabis Use, Controlling for Sex

$R^2 = .07$
Total effect: $\beta = .14$ (0.04), $p = .001$
Indirect effect: $\beta = .08$ (0.02), $CI = .03 - .14$
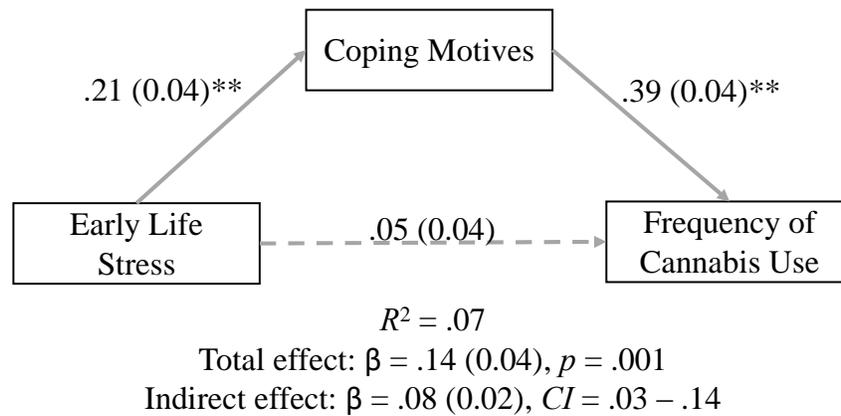
Note. All path coefficients are standardized regression coefficients with standard errors in parentheses; β = standardized regression coefficient; R^2 = proportion of variance accounted for in the model; CI = bias corrected 99% confidence interval using bootstrapping with 10,000 iterations. * $p < .01$, ** $p < .001$.

Negative Affect as a Mediator

Negative affect was also tested as a mediator of the significant associations between chronic stress and cannabis problems, early life stress and cannabis problems, and early life stress and frequency of cannabis use. As in the previous mediation analyses, the non-significant relationship between chronic stress and frequency of cannabis use was not tested in a mediation model. Before running the mediation analyses, negative affect was modeled as a latent variable comprising anxiety symptoms and depressive symptoms, with anxiety symptoms used to set the metric of the unobserved variable. Because these mediation analyses included a measurement model, fit statistics are provided for each model tested.

First, chronic stress was modeled to predict cannabis problems through negative affect. The model showed good fit (Table 3). Results revealed that chronic stress predicted increased cannabis problems through higher levels of negative affect (Figure 6). This indirect effect accounted for 196% of the relationship between chronic stress and cannabis problems (this

statistical anomaly is described in the discussion section). Further, with the indirect path in the

model, the direct path between chronic stress and cannabis problems was significant, $\beta = -.27$, p

$< .001$.

Table 3

Negative Affect Mediates the Relationship Between Chronic Stress and Cannabis Problems, Controlling for Sex

	β	SE
Measurement Model		
Negative Affect → Anxiety Symptoms	.75	--
Negative Affect →Depressive Symptoms	.87**	0.05
Structural Model		
Chronic Stress →Negative Affect	.73**	0.06
Chronic Stress → Cannabis Problems	-.23**	0.04
Negative Affect → Cannabis Problems	.64**	0.04
Sex → Chronic Stress	.17**	0.51
Sex → Negative Affect	.01	0.56
Sex → Cannabis Problems	-.27**	0.31

Note. $\chi^2(2) = 0.55$, $p = .76$; CFI = 1.00; TLI = 1.00; RMSEA = .00; β = standardized regression coefficient; *SE* = standard error; * $p < .01$, ** $p < .001$.

Figure 6

Negative Affect Mediates the Relationship Between Chronic Stress and Cannabis Problems, Controlling for Sex

$R^2 = .06$
Total effect: $\beta = .24$ (0.04), $p < .001$
Indirect effect: $\beta = .47$ (0.06), $CI = .32 - .65$
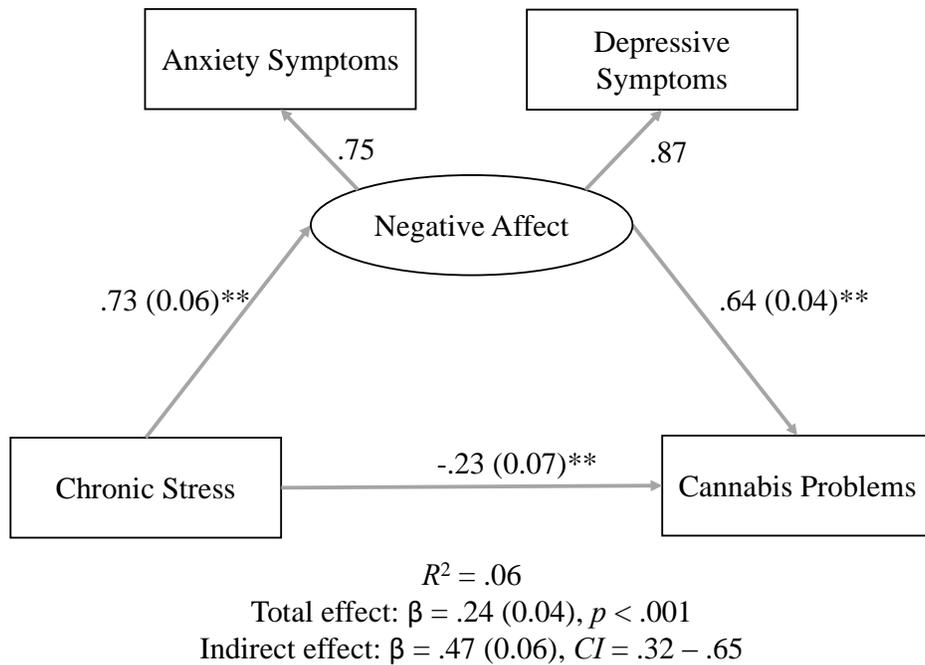
Note. All path coefficients are standardized regression coefficients with standard errors in parentheses; β = standardized regression coefficient; R^2 = proportion of variance accounted for in the model; CI = bias corrected 99% confidence interval using bootstrapping with 10,000 iterations. * $p < .01$, ** $p < .001$.

A second mediation model was tested wherein negative affect was tested as a mediator of the effect of early life stress on subsequent cannabis problems. The measurement model demonstrated sound fit (Table 4), so the structural model was evaluated. Results revealed a significant indirect effect of early life stress on cannabis problems via negative affect (Figure 7). This indirect effect accounted for approximately 63% of the total effect of early life stress on cannabis problems, and the direct effect of early life stress on cannabis problems was no longer significant with the indirect path in the model, $\beta = .10$, $p = .054$.

Table 4

Negative Affect as a Mediator of the Relationship Between Early Life Stress and Cannabis Problems, Controlling for Sex

	β	SE
Measurement Model		
Negative Affect → Anxiety Symptoms	.76	--
Negative Affect →Depressive Symptoms	.84**	0.06
Structural Model		
Early Life Stress →Negative Affect	.42**	0.14
Early Life Stress → Cannabis Problems	.10	0.06
Negative Affect → Cannabis Problems	.40**	0.03
Sex → Early Life Stress	.06	0.23
Sex → Negative Affect	.12*	0.71
Sex → Cannabis Problems	-.28**	0.31

Note. $\chi^2(2) = 0.29$, $p = .87$; CFI = 1.00; TLI = 1.00; RMSEA = .024; β = standardized regression coefficient; *SE* = standard error; * $p < .01$, ** $p < .001$.

Figure 7

Negative Affect Mediates the Relationship Between Early Life Stress and Cannabis Problems, Controlling for Sex

$R^2 = .07$
Total effect: β = .27 (0.04), *p* = .001
Indirect effect: β = .17 (0.03), *CI* = .10 – .25

Note. All path coefficients are standardized regression coefficients with standard errors in parentheses; β = standardized regression coefficient; R^2 = proportion of variance accounted for in the model; *CI* = bias corrected 99% confidence interval using bootstrapping with 10,000 iterations. * $p < .01$, ** $p < .001$.
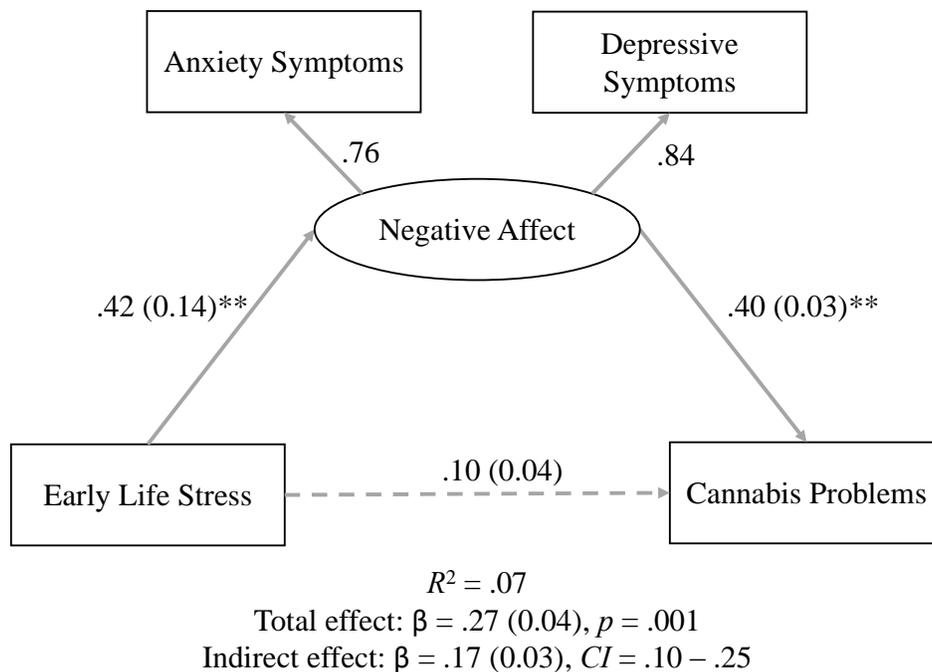
Finally, a third mediation model was tested wherein early life stress was modeled to predict frequency of cannabis use indirectly via negative affect. The measurement model had a significant χ^2 value, but CFI, TLI, and RMSEA all demonstrated sound model fit (Table 5). In contrast to the other models tested, early life stress was not found to have an indirect effect on frequency of cannabis use through negative affect (Figure 8).The direct effect remained significant, $\beta = .15$, $p = .002$.

Table 5
Negative Affect as a Mediator of the Relationship Between Early Life Stress and Frequency of Cannabis Use, Controlling for Sex

	β	*SE*
Measurement Model		
Negative Affect → Anxiety Symptoms	.75	--
Negative Affect →Depressive Symptoms	.84**	0.03
Structural Model		
Early Life Stress →Negative Affect	.41**	0.05
Early Life Stress → Frequency of Cannabis Use	.15**	0.00
Negative Affect → Frequency of Cannabis Use	.01	0.00
Sex → Early Life Stress	.06**	0.07
Sex → Negative Affect	.12**	0.23
Sex → Frequency of Cannabis Use	-.22**	0.02

Note. $\chi^2(2) = 14.94$, $p < .001$; CFI = .997; TLI = .99; RMSEA = .03; β = standardized regression coefficient; *SE* = standard error; * $p < .01$, ** $p < .001$.

Figure 8

Negative Affect Does Not Mediate the Relationship Between Early Life Stress and Frequency of Cannabis Use, Controlling for Sex

$R^2 = .07$
Total effect: $\beta = .15$ (0.04), $p = .001$
Indirect effect: $\beta = .01$ (0.02), $CI = -.05 - .06$

Note. All path coefficients are standardized regression coefficients with standard errors in parentheses; β = standardized regression coefficient; R^2 = proportion of variance accounted for in the model; CI = bias corrected 99% confidence interval using bootstrapping with 10,000 iterations. * $p < .01$, ** $p < .001$.
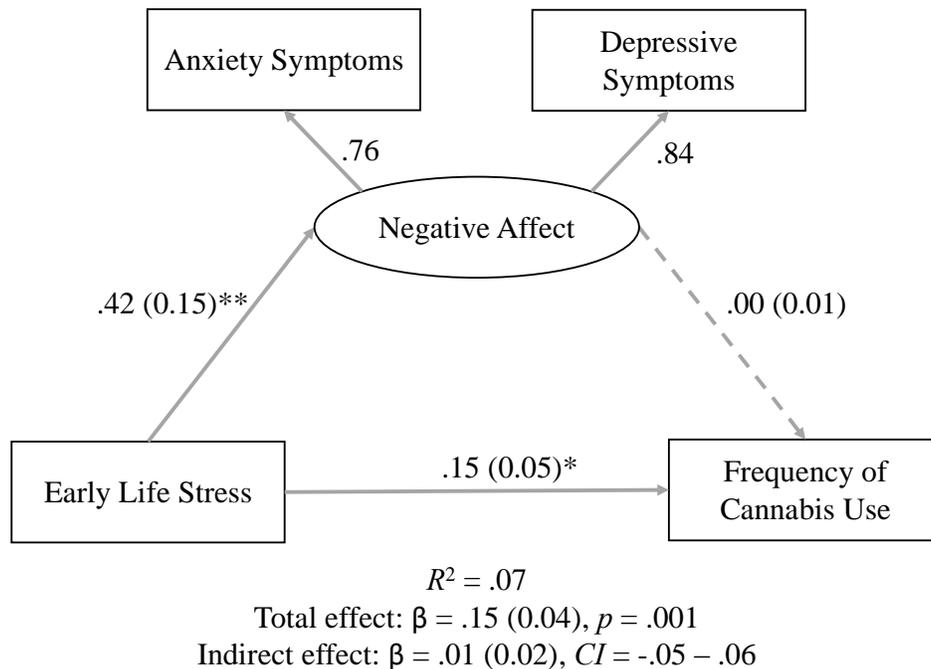
DISCUSSION

The goal of Study 1 was to further probe the relationship between cannabis and stress by examining multiple aspects of stress (i.e., chronic stress and early life stress) and cannabis use (i.e., frequency of cannabis use, cannabis problems) and by identifying potential moderators and mediators of the stress-cannabis link. Findings revealed significant associations between both types of stress and cannabis problems, as well as between early life stress and frequency of cannabis use. Sex played a moderating role in two of these relationships such that chronic stress was associated with increased cannabis problems in males only, and early life stress was associated with increased frequency of cannabis use in females only. Mediation analyses

revealed a consistent mediating role of coping motives and negative affect in the stress-cannabis link.

Findings from the present study build upon previous research in several ways. First, the present study examined stress in a comprehensive manner by evaluating both early life stress and chronic stress. The present study also assessed cannabis in two ways: how frequently cannabis was used (a measure of cannabis use), as well as level of cannabis problems (a measure of cannabis misuse). In other words, the present study evaluated normative use and use associated with negative outcomes. While the observed effects were small, they suggest that both types of stress are related to problematic cannabis use and that early life stress is related to increased frequency of cannabis use. These results are consistent with previous research describing a link between stress and cannabis more broadly (see Hyman & Sinha, 2009 and Scholssarek, Kempkensteffen, Reimer, & Verthein, 2016 for review), as well as between chronic stress, early life stress, and cannabis problems specifically (Ketcherside & Filbey, 2015). There are many factors that may contribute to problematic cannabis use (e.g., affect dysregulation [Simons & Carey, 2002]; social anxiety [Buckner, Heimberg, & Schmidt, 2011]), and the results of the present study provide evidence that chronic stress and early life stress may also contribute to problematic cannabis use. In other words, findings from Study 1 provide evidence that the more stress one has been experiencing or the more stressors one experienced as a child, the more one will experience negative consequences from cannabis consumption.

The present study is also the first to provide evidence that the relationship between stress and cannabis is, in some instances, conditional upon sex. Specifically, chronic stress was related to increased cannabis problems only in males, and early life stress was related to frequency of cannabis problems in females only. Why is one effect observed in males only while the other is

28

observed in females only? At face value, these findings may seem contradictory; however, probing the interactions revealed that males use cannabis more frequently than females regardless of the amount of trauma they experienced while growing up. In other words, the increase in cannabis use associated with early life stress in females does not bridge the gap in overall cannabis usage rates between the sexes. Overall, males in the present study, as well as in previous research (see Cuttler, Mischely, & Sexton, 2016 for review), still use cannabis more frequently than females.

There are several implications of these sex effects. First, while researchers have long identified sex differences in substance use and abuse (see Becker & Hu, 2008 for review), these results suggest that males experiencing chronic stress may be especially prone to engaging in problematic cannabis use. Evidence from previous research indicates that males may be more vulnerable to the development of cannabis dependence (see Cuttler, Mischely, & Sexton, 2016 for review), and results from the present study provide evidence that this may be due to the influence of chronic stress. Second, results from Study 1 also provide evidence that females who experienced trauma early in life may use cannabis more frequently. Again, males still used cannabis more frequently than females in the present study, no matter how much childhood trauma they experienced. Nonetheless, females may be particularly susceptible to developmental changes because of early life stress that, down the line, lead to cannabis use. Third, early life stress predicted increased problematic cannabis use, regardless of sex. Thus, both sexes may be vulnerable to cannabis misuse because of trauma experienced during childhood and adolescence.

The results from Study 1 also provide evidence that cannabis coping motives mediate the link between stress and cannabis. For each significant relationship between stress and cannabis, there was a significant indirect effect through coping motives. In other words, chronic stress and

29

early life stress both predicted increased use of cannabis to cope with one's problems, and that predicted increased problematic cannabis use. Early life stress also predicted increased cannabis problems via coping motives. Further, coping motives explained between 23 to 57% percent of the total effect of stress on cannabis, which represents a large indirect effect. While the present study was the first to examine coping motives as a mediator of the stress-cannabis link, coping motives have been implicated as a mediating factor in the relationships between several different psychological constructs and cannabis-related outcomes (e.g., between distress intolerance and cannabis problems [Bujarski et al., 2012] as well as between obsessive-compulsive disorder symptoms and cannabis problems [Spradlin, Mauzay, & Cuttler, 2017]). As such it is not surprising that coping motives played an important role in the relationship between stress and cannabis.

Finally, findings from the present study also highlight the mediating role of negative affect in the relationship between stress and cannabis. Specifically, negative affect mediated the relationships between both types of stress (early life and chronic) and cannabis problems, but not between early life stress and frequency of cannabis use. Of note, negative affect accounted for approximately 63% of the relationship between early life stress and cannabis problems. Further, approximately 196% of the relationship between chronic stress and cannabis problems was accounted for by negative affect. The latter finding illustrates one of the issues with calculating effect sizes for indirect pathways in mediation models. In this case, it would appear that the strength of the relationships between chronic stress and negative affect, and between negative affect and cannabis problems, was much larger than the association between chronic stress and cannabis problems. This overlap between variables, particularly between negative affect and chronic stress, may be driving this statistical anomaly. Strange effects, such as this, happen

somewhat often with mediation analyses (Hayes, 2013). Unfortunately, alternative measures of effect size were not available for use in the present study due to the inclusion of covariates in the models, so ratios of the indirect effect to total effect were used. Regardless, the finding that negative affect mediated the relationship between stress and cannabis problems is consistent with results from previous research. For example, several studies have demonstrated a connection between early life trauma, affective disorders, and drug use (Bekh Bradley et al., 2011; Lupien, McEwen, Gunnar, & Heims, 2009). Further, in separate mediation models, Ketcherside and Filbey (2015) found that depression mediated both the relationship between chronic stress and cannabis problems and early life stress and cannabis problems. They also provided evidence that anxiety mediated the relationship between chronic stress and cannabis problems. The present study builds on these findings by testing the broader construct of negative affect, comprising both depressive symptoms and symptoms of anxiety. This is important because of the high level of overlap between symptoms of anxiety and depression (e.g., Zbozinek et al., 2012). My findings indicate that chronic stress and early life stress may lead to problematic cannabis use because they increase negative affect.

There are several limitations of the present study that should be considered when interpreting my findings. First, a cross-sectional design was used, meaning that inferences regarding the causal order of the variables in all models (i.e., their directionality) should be made with caution. While the temporal order of early life stress and cannabis problems supports the hypothesis that early life stress leads to cannabis problems, the direction of the relationship between chronic stress and cannabis problems is more difficult to ascertain. It is possible, for example, that chronic stress leads to increased coping motives, and then to more cannabis problems. Alternatively, cannabis-related problems may lead to increased coping motives and

31

then increased chronic stress. There may also be a feedback loop between the variables such that chronic stress leads to using cannabis to cope, which then leads to increased cannabis problems, which contributes to further increases in chronic stress.

A second limitation is that the sample comprised mostly white female college students who used cannabis occasionally. Though the entire sample endorsed using cannabis at least once within the past 3 months, it is important to investigate samples with different usage rates (e.g., strictly daily users, medical cannabis users) to establish whether the pattern of results from the present study generalizes to other populations. Nonetheless, college-aged individuals are particularly vulnerable to stress (APA, 2015), and they are also more likely to use cannabis than other age groups (Johnston, O'Malley, Bachman, & Schulenberga, 2013). As such, understanding the link between stress and cannabis in this population is of particular importance. A third limitation is that all measures were exclusively self-report instruments, which are subject to retrospective recall and other biases.

While the present study represents a big step forward in elucidating the nature of the relationship between stress and cannabis, longitudinal studies are needed to provide more insight into directionality of the observed effects. Further, by utilizing a sex-balanced sample, it would be possible to test more complicated models than those tested in Study 1. For example, instead of controlling for sex in the mediation models, as was done in the present study, a moderated mediation model wherein sex moderates at least one of the pathways between chronic stress, coping motives, and cannabis problems could be tested. This model could potentially provide additional information about whether coping motives mediate the relationships between stress and cannabis in one sex more than the other. Based on the results of bivariate correlations and mediation analyses, I suspect that coping motives would function as a more important mediator

for males, whereas negative affect would function as a more important mediator for females. Future research could also test models wherein both negative affect and coping motives were tested as mediators in serial. For example, this would permit for examinations into whether stress leads to negative affect, which in turn leads to increased cannabis coping motives, which ultimately contributes to more cannabis problems. These types of analyses would represent an important next step in understanding the relationships detected in the present study.

In conclusion, the results of the present study provide novel insights into the nature of the stress-cannabis link. Overall, the findings suggest that males may be particularly vulnerable to developing cannabis problems when experiencing chronic stress and that early life stress is also an important predictor of cannabis problems. Moreover, it appears that both the use of cannabis to cope and negative affect explain a substantial portion of the relationship between stress and cannabis. From a health standpoint, the findings from the present study have several important implications. Stress is a pervasive aspect of life, and in many cases stress is unpredictable and unavoidable. Therefore, targeting the stress component of the cannabis-stress link may be difficult. For example, quitting a stressful job may reduce stress in the short-term, but it may cause long-term issues (such as a shortage of funds to pay for food and housing or an inability to find alternative work). Further, there is no way to reverse the effects of early life stress on development. As such, other variables in the chain between stress and cannabis could be addressed instead. Based on the results of the present study, targeting the negative affect caused by stress and/or the use of cannabis to cope may be viable options for breaking the link between stress and cannabis. For example, the present study indicates that individuals experiencing chronic stress may have more problematic cannabis use because their stress leads to using cannabis to cope with that stress. By teaching people to use alternative coping mechanisms (e.g.,

meditation, exercise, problem-focused coping strategies), we may be able to prevent stress from

leading to cannabis problems. Individuals in treatment for cannabis-related problems with

concurrent chronic stress may also benefit from treatments such as Cognitive Behavioral

Therapy that focus on reducing symptoms of negative affect.

CHAPTER THREE

STUDY 2: CONSEQUENCES OF ACUTE STRESS FOR CHRONIC CANNABIS USERS

BACKGROUND

While Study 1 focused on two important types of stress (early life stress and chronic stress), there are also pressing questions concerning the relationship between *acute* stress and cannabis. Instances of acute stress comprise the broader 'chronic stress' considered in Study 1, so it is important to understand how cannabis users respond to stress in the short-term. While there is evidence that, at certain doses, acute cannabis intoxication reduces stress levels (Ware et al., 2010; Webb & Webb, 2014), as well as aspects of negative affect (Gorka, Fitzgerald & de Wit, 2015; Gruber, Rogowska, & Yurgelun-Todd, 2009), the effects of stress on chronic cannabis users who are not under the influence of cannabis are much less understood.

To date, four experiments have been conducted to examine chronic cannabis users' responses to an acute stressor (Buckner, Eckner, & Vinci, 2013; Buckner, Silgado, & Schmidt, 2011; Buckner, Zvolensky, Ecker, & Jeffries, 2016; McRae-Clark et al., 2011). McRae-Clark and colleagues (2011) subjected participants with cannabis dependence to the Trier Social Stress Test (TSST) or a neutral/control condition. The TSST is a commonly used method of inducing stress in humans, and it has been found to produce consistent elevations in both physiological levels of stress (e.g., increases in cortisol, increases in heart rate) and subjective levels of stress (McRae-Clark et al., 2011). Participants subjected to the stress condition of the TSST engage in a public speaking task that is evaluated by a panel of judges. Upon completion of the public speaking task, participants then complete a challenging mental arithmetic task. McRae-Clark et al. found that participants with cannabis dependence in the stress condition of the TSST showed significantly increased levels of stress (both physiological and subjective) and cravings

compared to the cannabis dependent participants in the control condition. Similarly, Buckner and colleagues (2013; 2016) found that heavy cannabis users reported greater cannabis cravings after a social interaction task (i.e., interacting with a confederate with the goal of making a good first impression) than after a reading task. Finally, in a separate study, Buckner, Silgado, and Schmidt (2011) found that female heavy cannabis users and heavy cannabis users with social anxiety disorder reported significantly higher cannabis cravings after a public speaking task than a reading task.

These experiments provide evidence that acute stress increases chronic cannabis users' cravings. Cravings are a strong predictor of future substance use and dependence (Childress, McLellan, Ehrman, & O'Brien, 1988; Drummond, Cooper, & Glautier, 1990; Franken, Kroon, Wiers, & Jansen, 2000; Weiss, Griffin, & Hufford, 1995), so understanding how cravings are initiated or exacerbated is important for understanding how to reduce cannabis use and treat cannabis dependence.

The studies conducted by McRae-Clark and colleagues (2011) and by Buckner and colleagues (2011; 2013; 2016) did not include measures of withdrawal symptoms, and they also did not include control groups of non-users. In other words, they were unable to compare the stress response of chronic cannabis users to the stress response of non-users. As such, many important questions about the nature of the relationship between acute stress and cannabis remain. For example, does frequent cannabis use alter the stress response such that chronic users show a heightened or dampened response to an acute stressor compared to non-users? Further, does stress increase chronic cannabis users' withdrawal symptoms? Some withdrawal symptoms (e.g., symptoms of anxiety) are an indicator of relapse in individuals with cannabis dependence

(Bonn-Miller & Moos, 2009), so withdrawal symptoms are an important variable to understand from a treatment perspective.

These pressing questions motivated the aims of the present study. Specifically, the first aim of Study 2 was to compare the impact of an acute stressor on chronic cannabis users' subjective and physiological stress response compared to non-users. I hypothesized that an acute stress manipulation would lead to a markedly different stress response (i.e., either heightened or blunted) in chronic cannabis users compared to controls. Evidence for the hypothesis that chronic cannabis users would exhibit an altered stress response, will help to advance our understanding of the direction of relationship between stress and cannabis use in humans. Moreover, such findings will help us to inform cannabis users about the potential consequences of chronic cannabis consumption and the effectiveness of using cannabis as a strategy for coping with acute stress.

The second aim of Study 2 was to determine whether an acute stressor causes increased cannabis withdrawal symptoms and cravings in cannabis users. Consistent with the findings of previous research, I hypothesized that chronic cannabis users would show increased cannabis cravings and increased withdrawal symptoms under conditions of stress relative to cannabis users in a no-stress condition. Evidence that an acute stressor increases cannabis cravings and withdrawal symptoms will advance our understanding of the factors involved in the maintenance of chronic cannabis use. These findings could potentially be used to help cannabis users develop healthier strategies to cope with stress (e.g., deep breathing and visualization exercises, mindful meditation, physical exercise, cognitive restructuring) to decrease reliance on cannabis.

METHODOLOGY

Participants

A total of 87 adults were recruited from the Pullman community. Participants were recruited using advertisements at local marijuana retailers (e.g., MJ's and We're Just Buds), local retail stores (e.g., Safeway, Café Moro), using advertisements on Facebook and Craigslist, and by contacting individuals who participated in prior research at the Health and Cognition Laboratory at WSU. Prior to scheduling an appointment, potential participants were screened for psychiatric illnesses, medical issues, neurological disorders, and learning and intellectual disabilities. They were also screened for medications that could impact their cortisol levels. Finally, participants were screened based on their cannabis use patterns. Chronic cannabis users had to have used cannabis daily or near daily for at least one year to be eligible, and they were also required to abstain from using cannabis on the day of testing (which was verified via self-report during testing). Non-users were required to have used cannabis fewer than 10 times in their life and never in the past year (which was also verified during via self-report during testing and through testing of tetrahydrocannabinol [THC] in urine). Eight participants were excluded from the final sample because of technical issues ($n = 6$), falling asleep during testing ($n = 1$), or violation of the cannabis use requirements (e.g., reporting use on the day of testing or, in the case of non-users, reporting use in the past year; $n = 1$).

The final sample comprised 39 chronic cannabis users and 40 non-users. Among these participants, the average age was approximately 26 years old ($SD = 7.88$). Approximately 54% of the sample was male, and participants primarily identified as white (70.9%), followed by Asian (15.2%), Hispanic or Latino (2.5%), black (2.5%), Pacific Islander (1.3%), Native American (1.3%), and other (5.4%). Among the chronic cannabis users, approximately 89%

reported using cannabis once a day or more, approximately 5% reported using cannabis 5-6 times per week, and approximately 8% reported using cannabis 3-4 times per week. Most of the chronic cannabis users (77.8%) reported using cannabis for at least 5 years, and approximately 95% reported last using cannabis the day before testing, with the remaining 5% reported using within the last week. Among the non-users, approximately 78% reported that they had never tried cannabis. The remaining non-users had all not used within the past year and had used cannabis fewer than 10 times in their life.

Materials

Demographic information: A short demographics questionnaire was included to assess age, sex, ethnicity, and other demographic characteristics.

Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory (DFAQ-CU): The DFAQ-CU is a self-report inventory for measuring cannabis use across six factors: number of sessions of cannabis use per day, frequency of cannabis use, age of onset of cannabis use, quantity of loose-leaf cannabis typically consumed, quantity of cannabis concentrates typically consumed, and quantity of cannabis-infused edibles typically consumed (Cuttler & Spradlin, 2015). It comprises 33 items using various rating scales to measure numerous aspects of cannabis consumption, including different methods of ingestion (e.g., smoking, vaporizing, eating) and potency of consumed cannabis. Its subscales have shown good reliability (α ranges from .73 to .87), and the frequency and daily sessions subscales have shown good predictive validity with measures of cannabis use disorders ($r = .59$ and .57, respectively), cannabis abuse ($r = .60$ and .59, respectively), cannabis dependence ($r = .21$ and .24, respectively), and problems associated with cannabis use ($r = .74$ and .70, respectively). The DFAQ-CU also has shown sound concurrent validity with other measures of cannabis

consumption (e.g., $r = .81$ for the DFAQ-CU frequency subscale with the Marijuana Smoking History Questionnaire frequency subscale). In Study 2, the items of the DFAQ-CU were used to verify study eligibility and to assess cannabis usage patterns.

Maastricht Acute Stress Test (MAST): The MAST is an experimental protocol used to induce an acute stress reaction (Smeets et al., 2012). It is composed of several threatening aspects combined from previous stress protocols. This includes degrees of uncontrollability, unpredictability, psychosocial evaluation threats, and physiological stress. During a brief initial period of instruction, participants in the stress condition are informed that their facial expressions will be recorded by webcam and monitored by the experimenter for the duration of the task. They are further informed that a computer will randomly select the order and duration of the trials they are about to undergo. After this period of instruction, the acute stress phase begins. The acute stress phase lasts approximately 10 minutes. During this phase, participants perform a series of mental arithmetic challenges that require them to count backward by 17 from 2043; this task is interspersed between five cold pressor trials that require them to submerge their dominant hand in ice cold water (34 degrees F). Participants who make arithmetic errors are given negative feedback and are instructed to start anew. Participants submerge their hand for 90 seconds, engage in the arithmetic task for 45 seconds, submerge their hand again for 60 seconds, engage in the arithmetic task for 60 seconds, submerge their hand again for 60 seconds, engage in the arithmetic task for 90 seconds, submerge their hand for 90 seconds, engage in the arithmetic task for 45 seconds, and submerge their hand one last time for 60 seconds.

The MAST also includes a no-stress control condition wherein participants submerge their hand in lukewarm water (90 degrees F) and count from 1-25 repeatedly, with no social evaluation or negative feedback. The timing of the hand submersion and counting task match

those of the stress condition. In previous research, the stress condition of the MAST has been shown to elicit similar subjective stress responses as cold pressor trials alone, while also providing superior (i.e., heightened) salivary cortisol responses. The stress condition of the MAST also elicits similar subjective and salivary cortisol stress responses in comparison to the more complicated Trier Social Stress Test (Kirschbaum, Pirke, & Hellhammer, 1993).

Marijuana Craving Questionnaire–Short Form (MCQ-SF): The MCQ-SF is a 12-item version of the 42-item Marijuana Cravings Questionnaire (Heishman, Singleton, & Liguori, 2001). It measures four dimensions of marijuana craving: compulsivity (e.g., "I could not easily limit how much marijuana I smoked right now"), emotionality (e.g., "if I smoked marijuana right now, I would feel less tense"), expectancy (e.g., "smoking marijuana would make me content"), and purposefulness (e.g., "it would be great to smoke marijuana right now"). Participants respond to each item on a 7-point scale, from strongly disagree to strongly agree. Psychometric assessment of the MSQ-SF indicates that the 4-factor model has good fit and internal consistency (α ranged from .61 to .84 for the four dimensions; Heishman et al., 2009). Scores were computed by taking an average of all 12 items. Potential summary scores could therefore range from 1 to 7, with higher scores indicative of more symptoms of marijuana craving.

Marijuana Withdrawal Checklist (MWC): The MWC is used to measure symptoms of marijuana withdrawal (Budney, Moore, Vandrey, & Hughes, 2003). This is a 16-item self-report inventory for assessing various symptoms of marijuana withdrawal (e.g., irritability, sweating, depressed mood, nausea). Participants respond to each item on a 4-point scale to indicate their experience of each symptom, with 0 = none, 1 = mild, 2 = moderate, and 3 = severe. The MWC shows good internal consistency (α = .81) and sensitivity to effects associated with abstinence (Budney, Moore, Vandrey, & Hughes, 2003; Budney, Novy, & Hughes, 1999). Each

participant's responses on all 16 items were averaged, with possible scores ranging between 0 and 3. Higher scores are indicative of more severe symptoms of marijuana withdrawal.

Perceived Stress Scale (PSS): The PSS is a 10-item self-report inventory for measuring the severity of symptoms of stress in the last month (i.e., chronic stress; Cohen, 1988). Participants rate how often they have experienced stress (e.g., "how often have you been upset because of something that happened unexpectedly") on a 5-point scale with anchors as follows: 0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, and 4 = very often. The psychometric properties of the measure are sound among college students and include high internal consistency ($\alpha \geq .70$) and high test-retest reliability ($r \geq .70$; Lee, 2012). Scores for each participant were computed by summing the scale's items. These summary scores could range from 0 to 40, with higher scores indicating more chronic stress.

Salivary cortisol: Saliva samples were collected before and after the MAST to measure levels of the hormone cortisol, a physiological indicator of stress. For each sample, participants were given a synthetic cotton swab (Salviette, Sarstedt, Germany) and instructed to roll it around in their mouth and chew on it for 1 minute. The Salviette was then returned to its plastic container and stored at -20 degrees C. Samples were centrifuged at 4 degrees C, and cortisol concentrations were measured using a sensitive enzyme immunoassay kit (Salimetrics, State College, PA).

Subjective stress: Subjective stress was measured using an 11-point Likert-scale, with 0 = no stress and 10 = extremely stressed. Subjective stress ratings were collected immediately before each cortisol sample was obtained, as well as in the middle of the MAST paradigm.

Tetrahydrocannabinol (THC) urine test: Each participant took a THC urine test (NarcoCheck, Kappa City Biotech SAS, Saint Victor, France) to detect the presence of THC in

their urine. This test is taken in a similar manner as a urine pregnancy test and provides results based on six detection levels: no detectable THC, 25 ng/ml, 50 ng/ml, 150 ng/ml, 300 ng/ml, and 600 ng/ml.

Procedure

As previously described, to ensure participants met the eligibility requirements, participants were screened for age, cannabis use history, medications, medical conditions, and psychiatric conditions prior to scheduling a testing session. Once the appointment was scheduled, participants were pseudo-randomly assigned to a stress or no-stress condition. Of primary importance during assignment was achieving an equal number of chronic cannabis users and non-users in each condition. Assignment was done by a third party so that the experimenters would remain blind to the participants' cannabis use status during testing.

To prevent contamination of the saliva samples, participants were also instructed during scheduling to refrain from brushing their teeth, chewing gum, or ingesting anything other than water 30 minutes prior to their session. In addition, to ensure that there were no acute effects of previous cannabis intoxication, participants were told not to use cannabis on the day of the experiment. This was verified via self-report during the testing session.

Participants were tested individually in the Department of Psychology at WSU. When participants arrived, they were seated in a waiting area and told to relax for approximately 10 minutes to diminish any residual stress from traveling to the lab. They were also asked if they had anything to eat or drink prior to arriving. One participant violated these instructions and was required to spend an additional 20 minutes waiting outside the testing room before the session began. After this period passed, participants were brought into the laboratory, where they first provided informed consent. Participants were also asked not to inform the researcher of their

status as a chronic cannabis user or non-user until the end of the study when a urine sample would be provided and tested. Once consent was obtained, participants completed a brief survey that assessed their demographic information, their cannabis use patterns (DFAQ-CU), and their level of chronic stress (PSS). All participants were then required to rinse their mouth vigorously with water immediately prior to giving their first saliva sample. The first subjective stress rating and first saliva sample were then collected.

After the baseline stress measures were taken, participants were given instructions for the MAST, as well as the opportunity to ask questions of the experimenter. They then completed either the stress or no-stress condition of the MAST. At the mid-point of the MAST, participants were asked to provide a second subjective stress rating. After completion of the MAST, a third subjective stress rating and second saliva sample were collected. Participants then completed the MWC and MCQ. Finally, participants provided a urine sample, which was used to objectively verify THC levels, and then they were then debriefed. After they left the laboratory, the experimenter tested the urine sample using the THC urine test.

The data for the present study were analyzed using IBM SPSS (version 24). All variables were screened for univariate outliers, defined as scores falling more than 3.29 standard deviations from the mean. Outlying values were only detected in salivary cortisol ratings for four participants, and all outlying values were replaced with a score one unit higher than the nearest non-outlying value (Tabachnick, Fidell, & Osterlind, 2001).

To adjust for individual differences in baseline stress and salivary cortisol levels, difference scores were created for the analyses. Specifically, baseline cortisol levels were subtracted from cortisol levels immediately after the stressor, and baseline subjective stress

44

ratings were subtracted from subjective stress ratings during the acute stress manipulation, as well as from subjective stress ratings provided immediately after the stress manipulation.

RESULTS

Baseline Group Differences

Age was examined using a 2 x 2 ANOVA (cannabis use group x stress condition), with results revealing no effect of cannabis use group, $F(1, 75) = 0.09$, $p = .76$, or stress condition, $F(1, 75) = 0.56$, $p = .46$. Chi-square analyses were conducted to examine the balance of sex within the conditions. Results revealed that there were significantly more males in the chronic cannabis user group (approximately 69%) than in the non-user group (40%), $\chi^2(1) = 6.80$, $p = .01$, but there were no sex differences between the stress groups, $\chi^2(1) = 1.01$, $p = .31$. A 2 x 2 ANOVA (cannabis use group x stress condition) was used to examine differences in chronic stress levels. There was no effect of cannabis use group, $F(1, 75) = 0.42$, $p = .52$, but there was a significant main effect of stress condition, $F(1, 75) = 5.15$, $p = .03$, such that those randomly assigned to the stress condition were significantly higher in chronic stress than those in the no-stress condition. In addition, 2 x 2 ANOVAs (cannabis use group x stress condition) were used to test for differences in baseline subjective stress and salivary cortisol levels. There was no main effect of cannabis use group, $F(1, 75) = 1.79$, $p = .19$, or stress condition, $F(1, 75) = 0.49$, $p = .49$, on baseline subjective stress. There was also no main effect of cannabis use group, $F(1, 75) = 0.26$, $p = .61$, or stress condition, $F(1, 75) = 0.05$, $p = .83$, on baseline salivary cortisol levels. Because of the observed sex and chronic stress differences, sex and chronic stress levels were included as covariates in all subsequent analyses. Finally, several ANCOVAS were conducted (controlling for sex and chronic stress) to examine differences in amount of subtraction errors and average pain ratings in cannabis users vs. non-users in the stress condition. There was no

difference in number of subtraction errors, $F(1, 27) = 0.61$, $p = .44$, nor in average pain rating, $F(1, 27) = 0.34$, $p = .56$.

*Differences in Subjective Stress and Salivary Cortisol Between Cannabis Users and Non-Users*

Several 2 x 2 between-groups ANCOVAs were conducted to analyze changes in subjective stress and salivary cortisol levels, controlling for sex and chronic stress. The between-subjects factors were cannabis use group (cannabis user, non-user) and stress condition (stress, no stress). Results of analyses of subjective stress ratings revealed a significant cannabis x stress interaction on subjective stress changes from baseline to mid-MAST, $F(1, 61) = 6.33$, $p = .01$. This interaction was probed using a post-hoc analysis with the Bonferroni correction. Results revealed that both chronic cannabis users and non-users showed significant increases in subjective stress mid-MAST, but the increase in subjective stress for cannabis users was significantly smaller than the increase in non-users, $p < .001$ (Figure 9).

Figure 9

*Chronic Cannabis Users Show Blunted Subjective Stress Reactivity, Mid-MAST*
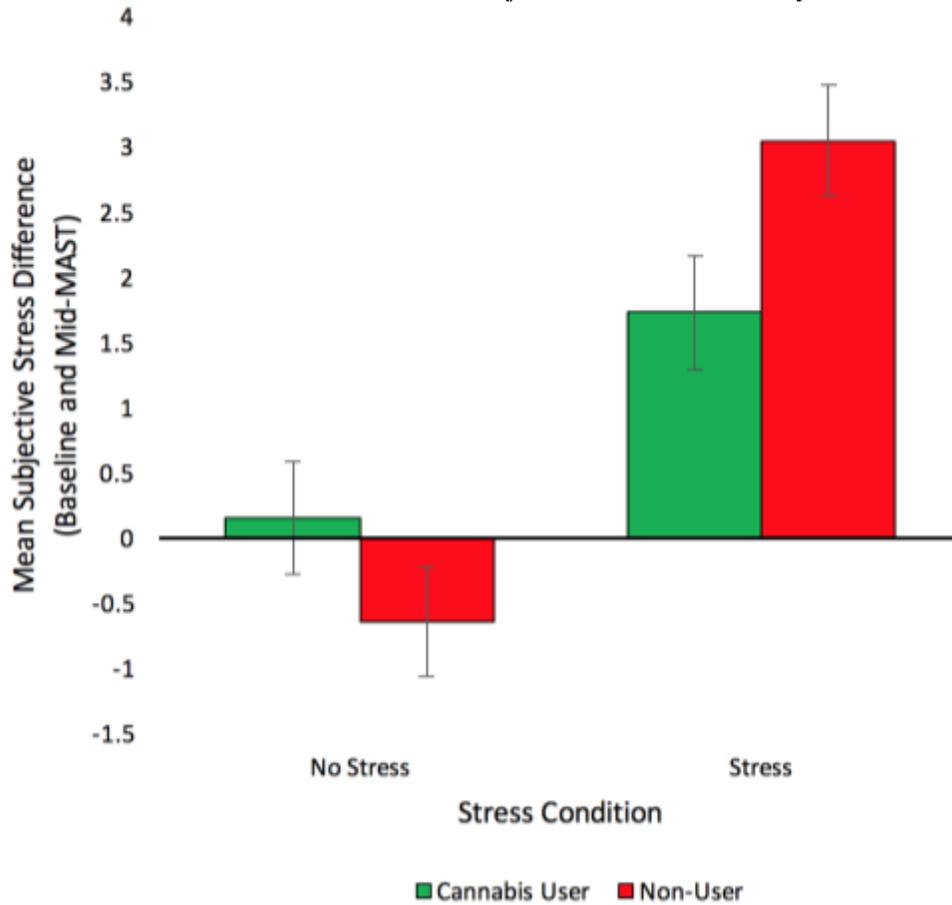
There was only a main effect of stress condition on subjective stress changes from baseline to post-MAST, $F(1, 73) = 20.62$, $p < .001$, such that those in the stress condition had a significantly larger change in subjective stress than those in the no-stress condition (Figure 10).

Figure 10

Chronic Cannabis Users and Non-Users Do Not Differ in Subjective Stress Reactivity, Post-MAST
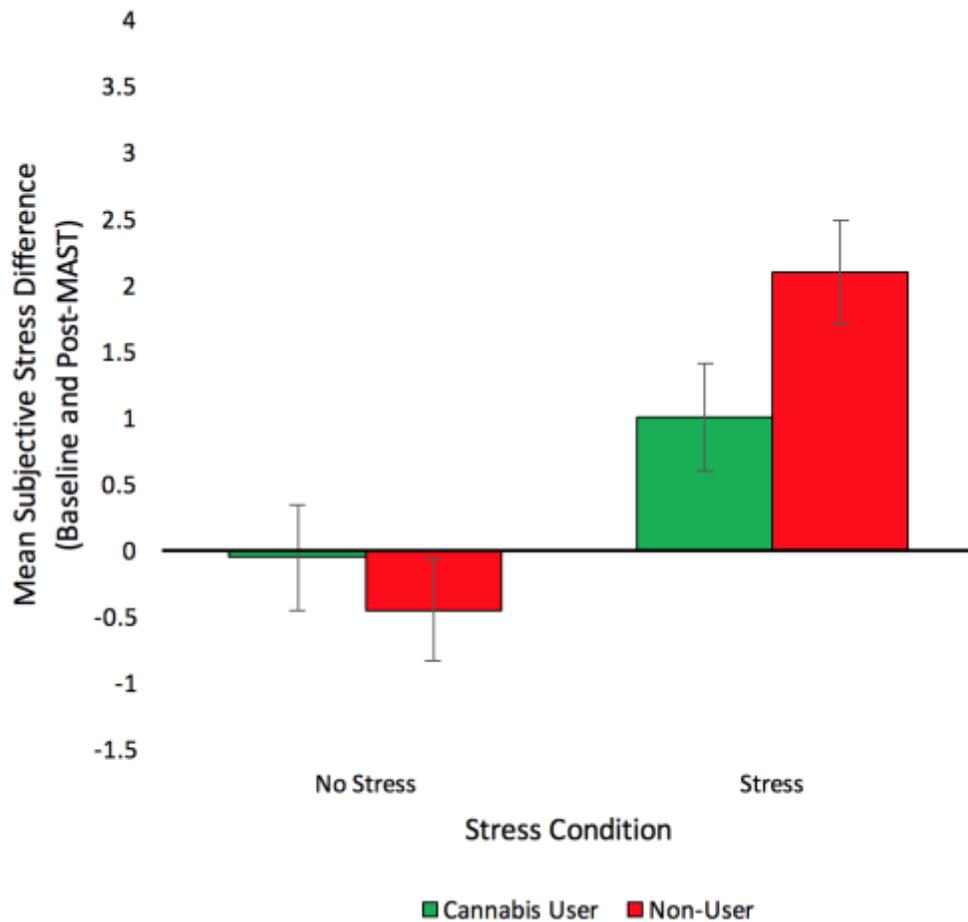
Finally, there was a significant cannabis x stress interaction on salivary cortisol level changes from baseline to post-MAST, $F(1,73) = 7.54$, $p = .01$. Further probing of the interaction using a post-hoc analysis with the Bonferroni correction revealed that the non-users demonstrated a significant difference in salivary cortisol levels across the stress and no-stress conditions, $p = .001$; cannabis users showed no differences in salivary cortisol levels across the stress and no-stress conditions, $p = .67$. (Figure 11).

Figure 11

Chronic Cannabis Users Show Blunted Physiological Stress Reactivity, Post-MAST
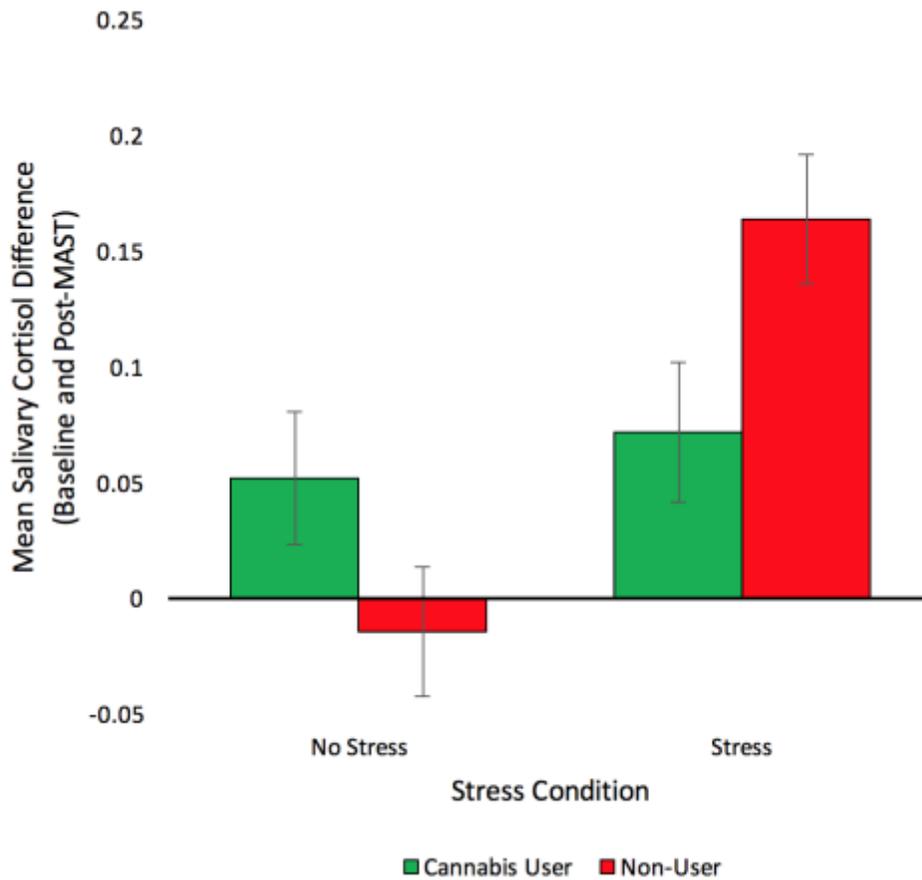
Differences in Withdrawal Symptoms and Cannabis Cravings Due to the Stress Manipulation

A multivariate one-way ANCOVA (i.e., MANCOVA) was used to compare chronic cannabis users' withdrawal symptoms and cannabis cravings across the stress and no-stress conditions, controlling for sex and chronic stress. Findings revealed no significant effect of stress on withdrawal symptoms, $F(1, 35) = 2.84$, $p = .10$ (Figure 12), and no significant effect of stress on cannabis cravings, $F(1, 35) = 0.62$, $p = .44$ (Figure 13).

Figure 12

Chronic Cannabis Users Show No Difference in Cannabis Withdrawal Symptoms Due to Stress
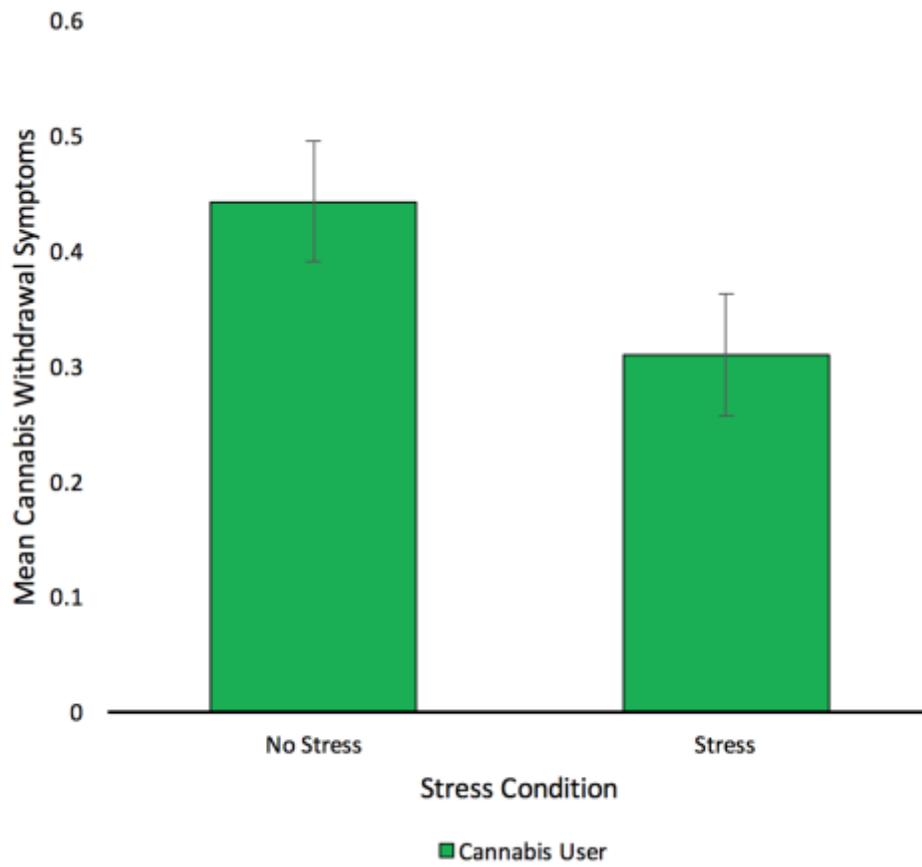
Figure 13

Chronic Cannabis Users Show No Difference in Cannabis Cravings Due to Stress
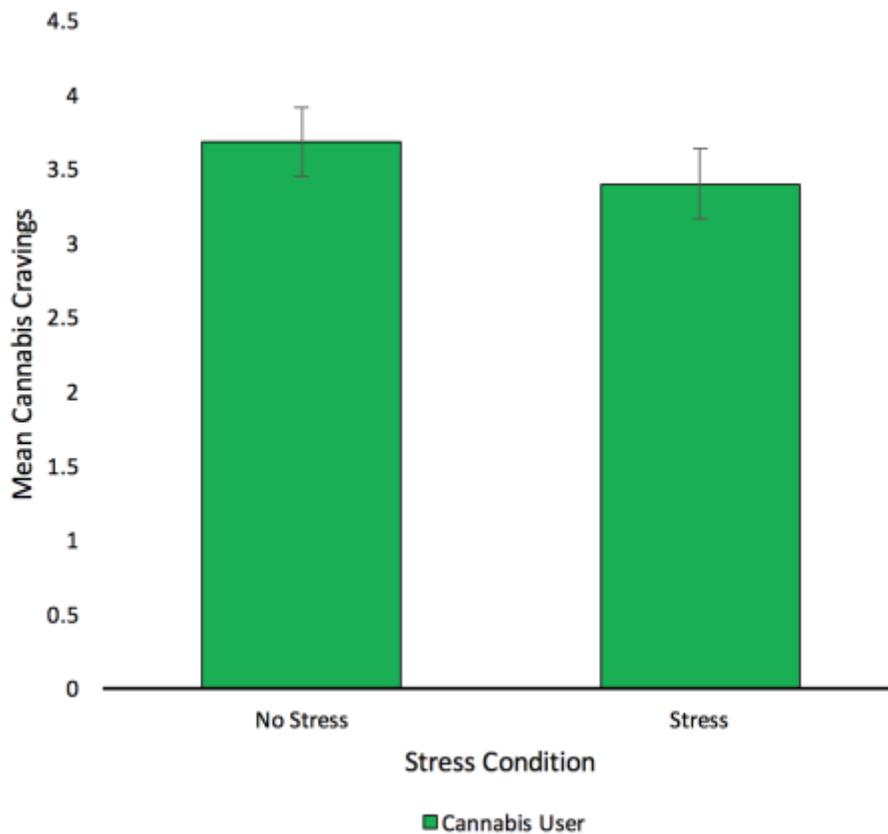
DISCUSSION

The goal of Study 2 was to expand our understanding of the relationship between cannabis use and stress by comparing chronic cannabis users' and non-users' response to an acute stressor and by examining whether an acute stress manipulation increased cannabis users' symptoms of cannabis cravings and withdrawal. Findings from the present study regarding the stress response were consistent with my expectations. They revealed that chronic cannabis users showed a reduced subjective stress and salivary cortisol response as a function of the acute stress manipulation compared to non-users. Contrary to my expectations, chronic cannabis users did not show elevated withdrawal symptoms and cravings due to the acute stress manipulation.

These findings suggest that, following a short period of abstinence, chronic cannabis users may have a blunted stress response in response to acute stress. In other words, chronic cannabis users may be less reactive to environmental threats, even while not under the influence of cannabis.

There is evidence that acute cannabis intoxication reduces stress reactivity and negative affect more generally (Gorka, Fitzgerald & de Wit, 2015; Gruber, Rogowska, & Yurgelen-Todd, 2009; Ware et al., 2010; Webb & Webb, 2014), but the present study is the first to show this reduced stress reactivity in cannabis users who are not under the influence of cannabis. Further, the present study is the first to provide evidence that these differences can be observed in terms of the personal experience of stress (i.e., subjective stress), as well as in biological indicators of stress (i.e., salivary cortisol). Thus, the present study provides robust evidence that sober chronic cannabis users show less stress reactivity in response to an acute stressor than non-users. While there are no previous studies that have examined this specific effect, our findings are consistent with results from several different lines of research investigating chronic cannabis users' responses to different types of negative stimuli. For example, when presented with threatening faces, chronic cannabis users with comorbid depression have shown reduced emotional reactivity and amygdala activation the more cannabis they reported regularly consuming (Cornelius, Aizenstein, & Hariri, 2010). Chronic cannabis users have also exhibited a dampened hormonal response to unpleasant images compared to healthy controls (Somaini et al., 2012). Therefore, the present study provides further evidence that chronic cannabis users are less reactive to negative stimuli more generally.

The implications of the findings from Study 2 are complex. On one hand, a dampening of the stress response may be beneficial in that long-term activation of the stress response is associated with structural changes in the brain that are linked to psychological dysfunction (see

McEwen, 1998; McEwan, Nasca, & Grew, 2016 for review). Chronic levels of cortisol elevation in humans are associated with memory deficits and hippocampal atrophy (Lupien et al., 1998), burnout syndrome (Melamed et al., 1999), and impaired selective attention (Lupien et al., 1994), for example, and there is some evidence that chronic cannabis users may have increased basal cortisol levels compared to non-users (King et al., 2011; Monteleone et al., 2014; Somaini et al., 2012). It is important to note, however, that many of these studies were conducted with individuals with comorbid diagnoses, and not all previous research has found elevated basal cortisol in cannabis users (e.g., Block et al., 1991). On the other hand, the release of cortisol during times of stress serves a functional purpose: it activates individuals so that they can respond to the demands of their environment (McEwen, 1998). There is evidence of reduced basal cortisol levels in individuals with certain types of major depression (Gold & Chrouso, 2002; Lamers et al., 2012). Similar evidence of perturbed cortisol release has been found in individuals with post-traumatic stress disorder (PTSD) and paranoid schizophrenia (Mason et al., 1986). Individuals with an underactive physiological response to stress may also be more susceptible to the development of PTSD (Yehuda, 2009). Therefore, the consequences of these differences in stress reactivity are presently difficult to discern. It is possible that, overall, chronic cannabis users are more protected from stress-induced illness than non-users due to their reduced stress reactivity. It is also possible, however, that chronic cannabis users may not be able to mount an appropriate response to cope with environmental threats and that this may put them at risk for other problems. Future research is required to ascertain the consequences of cannabis users' blunted stress response.

It is also worthwhile to note that there was a consistent trend in the results of Study 2 concerning the stress response of chronic cannabis users and non-users in the no-stress condition.

Though their responses were not significantly different, there was a pattern of chronic cannabis users showing increases in both subjective and physiological stress while subjected to the no-stress variant of the MAST paradigm, whereas non-users showed consistent decreases in subjective and physiological stress in the no-stress condition. It is easy to understand why, to date, no research has been published comparing the stress reactivity of chronic cannabis users and non-users in conditions of no stress; however, understanding this phenomenon may represent an important piece of the puzzle in terms of understanding stress in chronic cannabis users. In line with the null results of this comparison, it is entirely possible that the pattern observed was due to random chance. Chronic cannabis users and non-users did not significantly differ on baseline subjective stress, salivary cortisol, or chronic stress; however, it is also possible that chronic cannabis users may respond more strongly to non-threatening stimuli compared to non-users. Again, to my knowledge, no published study has investigated such an effect, and the observed effect in Study 2 was not statistically significant. Nonetheless, this would have important implications for understanding the long-term consequences of chronic cannabis use on cortisol levels.

Surprisingly, chronic cannabis users in the stress condition did not show higher levels of cannabis cravings compared to chronic cannabis users in the no-stress condition. These results diverge from the findings of previous research. As previously discussed, several studies have found increased cravings in chronic cannabis users subjected to a stress manipulation compared to chronic cannabis users in a no-stress condition (Buckner, Eckner, & Vinci, 2013; Buckner, Silgado, & Schmidt, 2011; Buckner, Zvolensky, Ecker, & Jeffries, 2016; McRae-Clark et al., 2011). Nonetheless, there are several potential reasons why this effect was not observed in Study 2. First, chronic cannabis users showed a blunted stress response compared to non-users when

subjected to the stress manipulation, so it is not surprising that their level of cravings did not increase. Second, there is evidence that social anxiety may moderate this relationship. For example, one study found that chronic cannabis users with social anxiety disorder reported greater craving in a public speaking task vs. a neutral task, whereas cannabis users without social anxiety disorder did not exhibit this effect (Buckner, Silgado, & Schmidt, 2011). Third, while previous research has relied exclusively on social stress manipulations (using the TSST), the present study utilized a multidimensional stress paradigm that manipulated physiological and social stress. While unlikely, it is possible that the differences between paradigms could explain these divergent findings concerning cannabis cravings.

Finally, the present study represents the first to examine whether an acute stressor causes symptoms of cannabis withdrawal. While cravings are one element of cannabis withdrawal, cannabis withdrawal is a larger syndrome involving a greater variety of components. Several previous studies have examined the nature of cannabis withdrawal symptoms in various populations (Allsop, Norberg, Copeland, & Budney, 2011; Budney, Moore, Vandrey, & Hughes, 2003; Hesse & Thylstrup, 2013; Milin, Manion, Dare, & Walker, 2008). These studies all concluded that some symptoms of cannabis withdrawal begin immediately after cessation of use; however, there is also evidence that some withdrawal symptoms build over several days before peaking and then declining. Hesse and Thylstrup (2013) most recently examined the time course of cannabis withdrawal syndrome. They evaluated all symptoms of cannabis withdrawal syndrome using the DSM-5 criteria for the disorder. Results revealed that several symptoms of withdrawal exhibited a significant curvilinear relationship such that the symptoms steadily increased across time of abstinence first before declining. The symptoms exhibiting this pattern included nervousness, depressed mood, and irritability. According to Hesse and Thylstrup

(2013), nervousness peaked four days after abstinence was initiated, depression peaked five days later, and irritability peaked two weeks after abstinence was initiated. These results suggest that chronic cannabis users may be more likely to show withdrawal symptoms in response to stress after several days of abstinence. Therefore, it is possible that the lack of an effect of stress on withdrawal symptoms was due to the short duration of abstinence and that stress effects on withdrawal symptoms could be detectable given a longer period of abstinence (e.g., after one week of abstinence). Because the primary aim of Study 2 was to compare the stress response of chronic cannabis users and non-users, we had to minimize the chances that withdrawal symptoms could impact the stress response of chronic cannabis users. Therefore, members of the chronic cannabis use group were instructed to abstain from cannabis use only on the day of testing. Future research examining the interplay between stress, cannabis use, and withdrawal symptoms should evaluate chronic cannabis users after longer periods of abstinence to examine whether cannabis users would continue to show a blunted response to stress and to examine whether acute stress would exacerbate withdrawal symptoms under these conditions.

Several limitations of Study 2 are noteworthy. When considering the broader implications of the present study, it is important to note that cannabis use was not manipulated, thus, it cannot be concluded that chronic cannabis use caused the differences observed in the stress response of chronic cannabis users. In other words, there could be additional variables that explain the differences between chronic cannabis users and non-users. For example, higher levels of the personality trait sensation seeking are associated with a reduced stress response to environmental threats, as well as increased substance use (see Roberti, 2004 for review). While several important factors (i.e., sex and chronic stress) were controlled for in the present study, it was not practical to control for all potential differences between cannabis users and non-users.

Nonetheless, future research should be conducted to rule out the possibility that preexisting differences between the groups are driving the effects. More generally, future research should investigate whether variables such as sex, chronic stress, and sensation seeking moderate the effect of chronic cannabis use on the stress response.

In summary, the results of the present study indicate that chronic cannabis users have reduced stress reactivity under a period of acute stress compared to non-users. Moreover, the stress manipulation had no impact on chronic cannabis users' withdrawal symptoms and cravings. Future research should seek to understand the long-term consequences of this blunted stress response, as well as the biological mechanisms that mediate the observed pattern of results. Future research should also examine stress reactivity and changes in cravings and withdrawal symptoms after differing durations of abstinence to determine whether duration of abstinence moderates any of the observed effects and to determine whether the differences observed in chronic cannabis users' stress response is altered by longer periods of abstinence.

CHAPTER FOUR

SUMMARY AND CONCLUSIONS

Cannabis intoxication produces feelings of tension reduction and relaxation (Copeland et al., 2001; Green et al., 2003; Hathaway, 2003; Reilly et al., 1998). As such, many individuals report using the drug to cope with stress and other problems in their life (Green et al., 2003). The aims of this dissertation were to address several pertinent questions regarding the cannabis-stress link. Namely, under what conditions does the link between cannabis and stress become strengthened or weakened? What are the factors that drive the stress-cannabis link? Do chronic cannabis users experience stress differently than non-users? And does acute stress contribute to cannabis cravings and withdrawal? These questions were investigated in two separate studies. A summary of the results from these studies and their broader implications are discussed below.

In Study 1, a significant relationship was detected between chronic stress and cannabis problems, early life stress and cannabis problems, and early life stress and frequency of cannabis use. In contrast, chronic stress was not related to frequency of cannabis use. Further, the relationship between chronic stress and cannabis problems was moderated such that chronic stress predicted increased cannabis problems in males only, and early life stress predicted increased frequency of cannabis use in females only. In other words, the relationship between stress and cannabis is partially conditional upon sex. Negative affect and cannabis coping motives were also identified as factors driving the relationship between stress and cannabis problems such that the effects of early life stress and chronic stress on cannabis problems was due to stress leading to increased negative affect and coping motives which in turn contribute to cannabis problems. In Study 2, chronic cannabis users showed less reactivity to an acute stressor compared to non-users. Further, the acute stressor did not cause increased cannabis cravings and

58

withdrawal symptoms in the chronic cannabis users, meaning that acute stress alone may not contribute to the factors that drive cannabis misuse.

The findings from Study 1 and Study 2 suggest several broader insights into the stress-cannabis link that have important implications. At a micro level, the findings suggest that chronic cannabis use may buffer individuals from the effects of acute stress, even when those individuals are not intoxicated. This may make chronic cannabis users more resilient when faced with stressful life events. It is also possible, however, that reduced stress reactivity in chronic cannabis users could exacerbate the effects of subsequent stressful life events, leading to long-term negative health consequences. Mounting an appropriate stress response is paramount to effectively dealing with stress (see Sapolsky, 2004 for review), and if chronic cannabis users are unable to respond adaptively to stressors, they may not be able to mitigate the impact of those stressors. Further, there was a nonsignificant trend toward increased stress reactivity in chronic cannabis users in the neutral/no-stress condition, whereas non-users showed reductions in stress in the same conditions. In other words, while chronic cannabis users may show blunted stress reactivity during periods of acute stress, they may also show elevated stress reactivity to non-threatening stimuli.

At a macro level, continued exposure to stressors may lead to an increase in problematic cannabis use. Further, when subjected to chronic stress, males may be more prone to the development of cannabis problems, and early life stress may lead to problematic cannabis use regardless of sex. This may be because these forms of stress cause elevations in negative affect and/or the use of cannabis to cope with problems, which in turn leads to problematic cannabis use. This also means that it may be possible to break the link between stress and problematic

cannabis use by targeting symptoms of negative affect for treatment and/or training individuals who use cannabis to cope by employing alternative coping strategies.

The overall goal of my dissertation research was to further elucidate the nature of the link between cannabis and stress. Taken together, the results of my studies suggest that, while chronic cannabis use may attenuate the effects of acute stressors in the short-term, use of cannabis to cope with chronic stress in the long-term may lead to cannabis problems.

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