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Short title: Stress and Marijuana

Mediating Processes Between Stress and Problematic Marijuana Use

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Abstract

Background: The literature widely reports that stress is associated with marijuana use, yet, to date, the path from stress to marijuana related problems has not been tested. In this study, we evaluated whether negative affect mediates the relationship between stress and marijuana use. **Methods:** To that end, we tested models to determine mediators between problems with marijuana use (via Marijuana Problem Scale), stress (via Early Life Stress Questionnaire, Perceived Stress Scale), and negative affect (via Beck Depression Inventory; Beck Anxiety Inventory) in 157 current heavy marijuana users. Mediation tests and bootstrap confidence intervals were carried out via the “Mediation” package in R. **Results:** Depression and Anxiety scores both significantly mediated the relationship between Perceived Stress and problematic marijuana use. Only depression significantly mediated the relationship between early life stress and problematic marijuana use. Early life stress, perceived stress and problematic marijuana use were significant only as independent variables and dependent variables. **Conclusions:** These findings demonstrate that (1) depression mediated both early life stress and perceived stress, and problematic marijuana use, and, (2) anxiety mediated perceived stress and problematic marijuana use. This mediation analysis represents a strong first step towards understanding the relationship between these variables, however, longitudinal studies are needed to determine causality between these variables. To conclude, addressing concomitant depression and anxiety in those who report either perceived stress or early life stress is important for the prevention of cannabis use disorders.

Keywords: early life stress, perceived stress, negative affect, depression, anxiety, cannabis

1. Introduction

In the last decade, while most adolescent drug and alcohol use patterns have had a steady or declining trend, marijuana use is on the rise (Brooks-Russel, et al. 2013; Johnston et al., 2014). An estimated 9% of people who try marijuana (MJ) become dependent on it (Anthony, 1994), which underlines the need to elucidate factors that lead to cannabis use disorders. Previous studies have established a significant co-occurrence of cannabis use disorders (CUDs) with increased life stress, both in terms of childhood trauma and the perception of life stress (Bonn-Miller, Vujanovic, & Zvolensky, 2008; Conway, Compton, Stinson, & Grant, 2006; De Bellis, 2002). Additionally, not only has childhood trauma been linked to marijuana use later in life (Chu, 2012), but it has also been linked to increased anxiety and depression (Hovens et al., 2012). Thus, stress also leads to greater negative affect (i.e., depression or anxiety), which overlaps substantially with drug dependence (Hovens et al., 2012; Kessler, 1997).

In general, an estimated 20% of individuals with negative affect also demonstrate substance use disorders, while 18-28% of those with substance use disorders also have an affective disorder (Grant et al., 2004). This comorbidity may partly be related to stress. For example, in terms of MJ, the association between stress and MJ use was found to be due to a mediating role of ability to regulate negative affect. Specifically, Bonn-Miller et al found that scores on the Difficulties in Emotional Regulation questionnaire (K.L. Gratz, 2004) mediated the relationship between stress and MJ use in individuals with post-traumatic stress disorder (Bonn-Miller et al., 2011). Similar associations were tested

by Johnson et al. (2009) where they reported that coping motives (i.e. “to forget my worries”) for MJ use mediated the relationship between anxious arousal and frequency of MJ use (Johnson, Bonn-Miller, Leyro, & Zvolensky, 2009). These studies suggest that aspects of negative affect play a role in the relationship between stress and MJ use. However, to our knowledge, a mediation model testing the path from stress to negative affect to indicators of marijuana dependence has not yet been examined.

The existing literature describes a link between stress, negative affect and subsequent problematic marijuana use. In this study, we examined the comorbidity between stress and marijuana use by testing mediation models that examined the relationship between marijuana problems, early life stress, perceived stress, depression, and anxiety. We hypothesized that both depression and anxiety mediate the relationship between stress and problems associated with marijuana use.

2. Methods

The Institutional Review Board of the Mind Research Network approved all of the study procedures.

2.1. Participants.

The participants for this study took part in a larger study of marijuana use focused on determining the neurobiological antecedents of substance use disorders (described in Filbey et al, 2009, 2010). The participants were recruited from the general community in the Albuquerque-metro area via media advertisements and were financially compensated

for their participation. Overall, 157 heavy marijuana users were recruited. Of those, five were excluded because of missing data (Table 1).

2.2. *Inclusion/Exclusion Criteria.*

All of the participants were required to provide written informed consent in order to participate in the study. The inclusion criteria were: (1) 18 - 55 years of age to minimize potential aging effects, and, (2) marijuana use of at least once per week. The presence of THC-COOH metabolites were verified by urinalysis and only those positive for THC-COOH were included in this study. The exclusion criteria were diagnosis of psychotic and neurological disorders including a history of traumatic brain injury. Because the larger study included an MRI scan, participants were also excluded if they had any MRI contraindications (i.e., left-handedness, pregnancy, metallic implants in the body, claustrophobia, etc.). The participants were also required to be free of other substance use besides marijuana, nicotine, and alcohol during the experiment (verified via urine toxicity screen).

<Insert Table 1 Here>

2.3. *Outcome measures.*

Stress was operationalized as perceived stress and early life stress. Perceived stress was assessed using the Perceived Stress Scale (PSS) (Cohen, Kamarck, & Mermelstein, 1983), a 14-item self-report questionnaire assessing how debilitating symptoms of stress are for each participant (e.g. “In the last month, how often have you

felt that you were unable to control the important things in your life?”). Early Stress was measured with the Early Life Stress Questionnaire (ELSQ), a 20-item scale regarding potentially traumatic events that occurred before the age of 18 (e.g. “before the age of 18, were you physically abused?”) (McFarlane et al., 2005). Marijuana problems were measured using the Marijuana Problem Scale (MPS), a 19 item self-report scale identifying the manner and degree to which marijuana use may interfere with an individual’s day-to-day life (e.g. memory loss, legal problems, etc.) (Stephens, Roffman, & Curtin, 2000). Negative affect was operationalized as symptoms of anxiety and depression, which were assessed using the Beck Anxiety Inventory (BAI) (Creamer, Foran, & Bell, 1995) and the Beck Depression Inventory (BDI) (Steer, Beck, Riskind, & Brown, 1986), respectively. Each questionnaire comprised 21 questions regarding symptoms of depression in the past two weeks (e.g. “I feel the future is hopeless and that things cannot improve”) or anxiety in the past week (e.g. “fear of the worst happening”).

3. Calculation.

All analyses were performed in R, with basic correlation and linear regression functions, as well as the **mediation** package, when applicable (Hayes & Preacher, 2013; Imai, Keele, & Tingley, 2010). All variables of interest were included in a zero-order correlation analysis (Table 3). Potential confounding variables (age, sex, number of cigarettes per day, and number of alcoholic beverages per day) were examined, and those that were significantly correlated with variables of interest (PSS, ELSQ, MPS, BAI, BDI) were covaried in the mediation analyses. To determine the relationship between negative affect and marijuana use, we tested a single-mediation model according to procedures

outlined by Imai, Keele, and Tingley (Imai, Keele, & Tingley, 2010). The mediation analyses began with correlation analyses between all variables (MPS, PSS, ELSQ, BAI, BDI). We then performed linear regression analyses with and without the predicted mediator to determine the effect on the relationship between the dependent variable and the independent variables. MPS, PSS, ELSQ, BAI, and BDI were all analyzed as mediators, independent and dependent variables in the model. All analyses were co-varied for age and sex. The model was considered to be mediation if the relationship between the independent variable and dependent variable became insignificant when the mediator was included.

4. Results

4.1 Non-collinearity between variables.

A discriminant correspondence analysis (DCA) (TExPosition and TInPosition packages in R) was performed to rule out collinearity between variables (Abdi, Edelman, Valentin, Dowling, 2009; Beaton, D., Rieck, J., Abdi, H., 2013; Beaton, D., Rieck, J., Chin Fatt, C.R., Abdi, H., 2013). DCA revealed four significant components. Component 1 accounted for 50.36% of the variance, with an associated eigenvalue of 0.14, $p < 0.01$. Component 2 accounted for 22.14% of the variance, with an associated eigenvalue of 0.06, $p < 0.01$. Component 3 accounted for 17.98% of the variance, with an associated eigenvalue of 0.051, $p < 0.01$. Component 4 accounted for 9.52% of the variance, with an associated eigenvalue of 0.03, $p < 0.01$. Bootstrap confidence intervals were calculated, and all variables were distinct at the 95% confidence interval (Appendix, Figures 1 and

2). In sum, early life stress, perceived stress, depression, and anxiety scores are independent from each other and are therefore modeled separately in the mediation analyses.

4.2. Zero order correlations.

All behavioral variables of interest (scores for anxiety, depression, early life stress, perceived stress, and problematic marijuana use) were positively correlated. Because age and sex were correlated with some variables of interest, they were included as covariates in the mediation analyses. Number of tobacco and alcohol use per day was not correlated with any variables of interest, and were therefore left out of the mediation analyses. However, due to their frequent use and abuse in instances of marijuana use as well as stress, tobacco and alcohol use variables were included as covariates in a secondary analysis with no effect on the results (Table 3). Depression and anxiety scores were only significant as mediators. Early life stress, perceived stress, and problematic marijuana use were significant in the roles of the independent and dependent variable. Only significant mediation models are reported here.

<Insert Table 2 Here>

4.3. Anxiety.

Anxiety mediated the relationship between early life stress and problematic marijuana use. The average mediation effect estimate is 0.30, 95% CI = 0.11 – 0.51, $p < 0.01$. The average direct effect estimate is 0.09, 95% CI = -0.17 – 0.44, $p = 0.48$. The

total effect estimate is 0.39, 95% CI = 0.12 – 0.77, $p < 0.01$, and the estimated proportion mediated is 0.77, 95% CI = 0.32 – 2.17, $p < 0.01$.

<Insert Figure 1 Here>

Anxiety did not mediate the relationship between perceived stress and problematic marijuana use. The average mediation effect estimate is 0.10, 95% CI = 0.02 – 0.17, $p=0.02$. The average direct effect estimate is 0.18, 95% CI = 0.09 – 0.30, $p<0.01$. The total effect estimate is 0.28, 95% CI = 0.18 – 0.38, $p < 0.01$, and the estimated proportion mediated is 0.36, 95% CI = 0.07 – 0.63, $p = 0.02$.

4.4. Depression.

Depression mediated the relationship between early life stress and problematic marijuana use. The average mediation effect estimate is 0.28, 95% CI = 0.09 – 0.52, $p=0.01$. The average direct effect estimate is 0.10, 95% CI = -0.13 – 0.38, $p=0.40$. The total effect estimate is 0.39, 95% CI = 0.08 – 0.74, $p = 0.02$, and the estimated proportion mediated is 0.73, 95% CI = 0.32 – 2.02, $p = 0.02$.

<Insert Figure 2 Here>

Depression mediated the relationship between perceived stress and problematic marijuana use. The average mediation effect estimate is 0.21, 95% CI = 0.12 – 0.30, $p < 0.01$. The average direct effect estimate is 0.07, 95% CI = -0.02 – 0.18, $p=0.09$. The total

effect estimate is 0.28, 95% CI = 0.17 – 0.39, $p < 0.01$, and the estimated proportion mediated is 0.74, 95% CI = 0.45 – 1.06, $p < 0.01$.

<Insert Figure 3 Here>

5. Discussion

To date, the interplay between marijuana use, stress, and negative affect has not yet been directly examined via mediation models. As expected, we found that stress is associated with problematic marijuana use, and that this relationship is mediated by depression and anxiety. This is consistent with the literature, which demonstrates a connection between childhood trauma, affective disorders, and drug use (Bradley et al., 2011; Lupien, McEwen, Gunnar, & Heim, 2009). Our results also support reports by Bonn-Miller et al. (2011) and Johnson et al (2008) positing that dysregulated emotion plays a role in the relationship between stress and problematic marijuana use. Against our predictions, anxiety did not mediate the relationship between perceived stress and marijuana problems, which reflects inconsistencies in the literature regarding the relationship between anxiety and marijuana. Tavoracci et al. (2013) for example found that PSS scores did not differ between marijuana using and non-marijuana using university students. Unlike the mediating effects of depression, there may be additional mediators, such as family history (Watson et al., 2007) contributing to the mediating effects of anxiety between PSS and marijuana use, which may partly be related to the differential effects of stress on anxiety (i.e., hypocortisolemia vs. hypercortisolemia in

depression) (Boyer, 2000). While this is a strong first step in determining the relationship between these variables, longitudinal studies are needed in order to directly answer these questions.

Building upon previous work suggesting a potential role of dysregulated emotion in the association between stress and marijuana use, our findings suggest that when stress leads to negative affect, the individual becomes prone to problematic marijuana use. This report contributes to the literature in a number of ways. First, we focused on problems related to marijuana use as an independent variable rather than frequency of use as in previous studies. This approach, therefore, focuses on factors that lead to pathological use (vs. normative) that is more closely related to CUDs. Related to this point, our findings were in “heavy” marijuana users defined as using multiple times per week (vs. recreational use). Specifically, 72% of our participants use daily (vs. 18.62% as mentioned in Bonn-Miller et al. (2011)). Hence, relationship patterns between negative affect and marijuana use are more clinically relevant. Second, we operationalized stress comprehensively by evaluating both early life stress (as previously reported) and perceived stress. Stress during childhood is of particular significance due to its potential impact on important developing brain neural circuits related to mood and reward.

The relationship between these constructs is not surprising given their shared neurobiological underpinnings. Sinha and colleagues suggest that stress leads to drug use due to chronic dysregulation in the hypothalamic-pituitary-adrenal (HPA) axis (Sinha, 2008). Indeed, individuals who report early life stress demonstrate changes in HPA axis response to stress compared to healthy controls (Heim, Newport, Bonsall, Miller, & Nemeroff, 2001; Heim, Mletzko, Purselle, Musselman, & Nemeroff, 2008; C. Heim,

Newport, D.J., Mletzko, T., Miller, A.H., Nemeroff, C.B., 2008). Similarly abnormal HPA axis response has been noted in marijuana users (Somaini et al., 2012; van Leeuwen et al., 2011) which is posited to persist post-abstinence from marijuana, and in mood disordered populations (Wardenaar et al., 2011).

Interpretation of these findings must take some limitations into consideration. Although discriminant component analysis revealed that perceived stress, early life stress, depression and anxiety are theoretically distinct constructs, the cross-sectional design of this study precludes inferences regarding causality. To elucidate directionality between these constructs, a prospective, longitudinal design would be necessary. In addition, there are limitations to the reliability of retrospective self-report data. Finally, this sample is 72% male, and the results might, therefore, implicate sex biases; although, no variable was significantly different between sexes.

Future directions should address these limitations, with a sex-balanced, longitudinal study. Additionally, a direct measure of coping such as the Marijuana Motives Measure (Lee, Neighbors, Hendershot, & Grossbard, 2009) would provide greater insight into the self-reported factors that lead to marijuana use, and could give greater dimension to the potentially different underlying mechanisms associated with different types of use. Furthermore, study of the acute stress response in this population via neuroimaging would provide insight into how and where the stress response differs in pathologic marijuana users compared to healthy controls.

To conclude, approaches in the clinical treatment of CUDs could benefit from also considering the evaluation of depression and anxiety in a number of ways. First, the

presence of stress (either due to childhood trauma or perceived stress) with concurring symptoms of depression and anxiety can be used as a risk profile for the development of CUDs. This could facilitate prediction and early intervention, and suggests the importance of monitoring these 'high-risk' individuals. Second, treatment for those with concurrent CUDs and stress should equally address underlying symptoms of depression and anxiety. For example, studies have demonstrated that stress and negative affect increased subjective craving for alcohol and marijuana, which was found to be associated with increased risk for relapse (Hyman & Sinha, 2009). Thus, failure to address these mediating factors may dampen the efficacy of current treatment. In sum, prevention and intervention strategies should take a more comprehensive approach during all CUD stages.

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Appendix

Figure 1. Discriminant Component Analysis (DCA) results for components 1 and 2.
All variables are distinctly separated by their bootstrapped 95% confidence intervals.

<Figure to be in color on the web, black and white on paper>

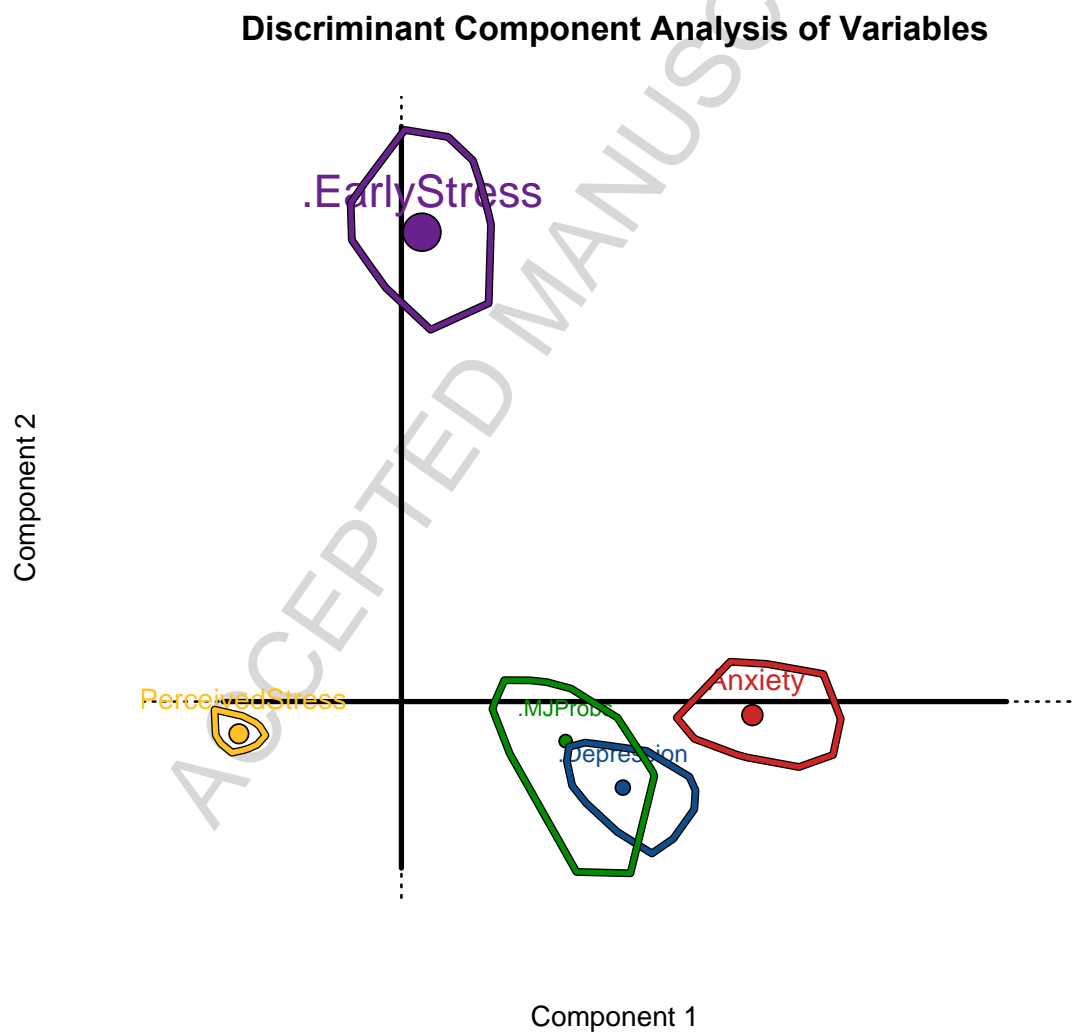
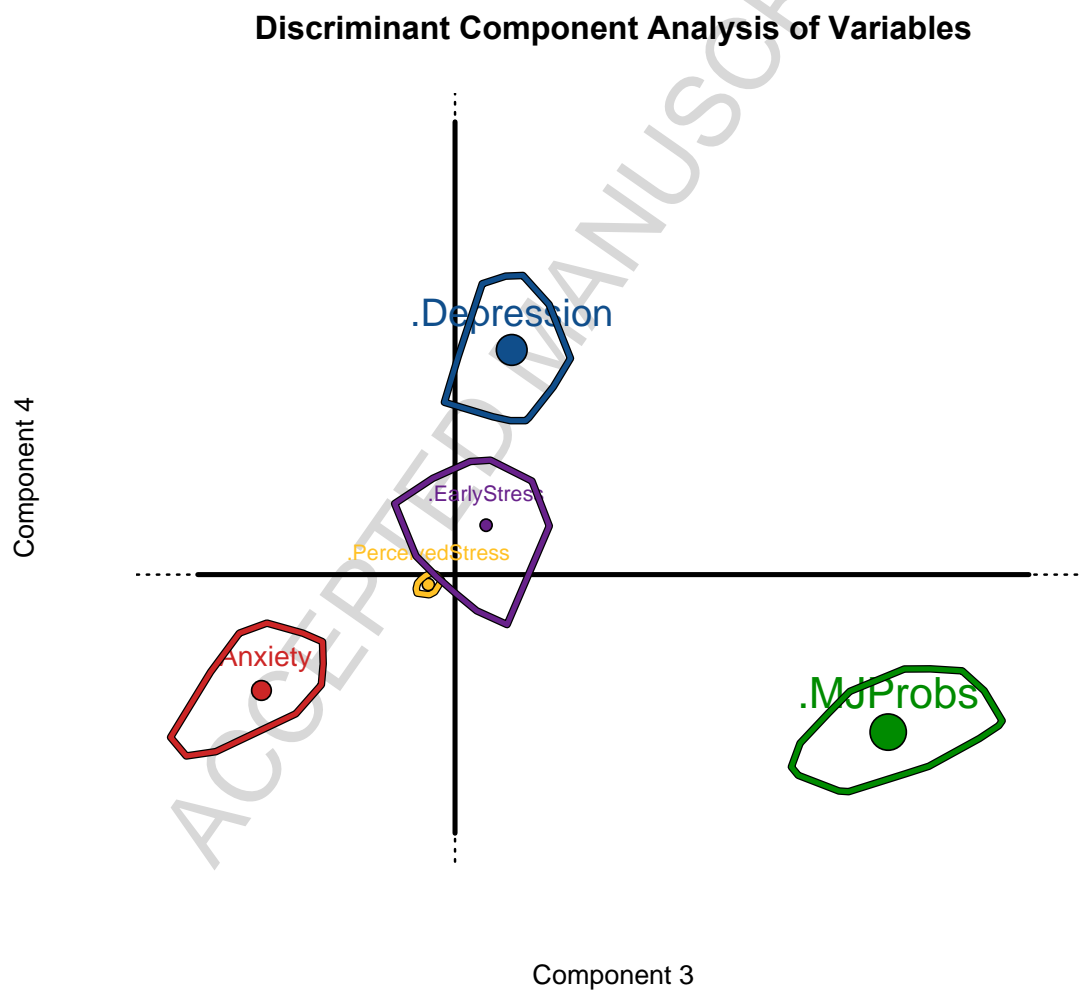


Figure 2. Discriminant Component Analysis (DCA) results for components 3 and 4.

All variables are distinctly separated by their bootstrapped 95% confidence intervals.

<Figure to be in color on the web, black and white on paper>



References

- Abdi, H., Edelman, B., Valentin, D., Dowling, W.J. (2009). *Experimental Design and Analysis for Psychology, Chapter 6, section 7.2*. New York: Oxford University Press.
- Akirav, I., & Fattore, L. (2011). Cannabinoid CB1 and Dopamine D1 Receptors Partnership in the Modulation of Emotional Neural Processing. *Frontiers in Behavioral Neuroscience*, 5, 67. doi: 10.3389/fnbeh.2011.00067
- Anthony, J.C., Warner, L.A., Kessler, R.C. (1994). Comparative Epidemiology of Dependence on Tobacco, Alcohol, Controlled Substances, and Inhalants: Basic Findings From the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology*, 2(3), 244-268.
- Beaton, D., Rieck, J., Abdi, H. (2013). TInPosition: Inference tests for TExPosition (Version R Package version 0.10.5).
- Beaton, D., Rieck, J., Chin Fatt, C.R., Abdi, H. . (2013). TExPosition: Two-table ExPosition (Version R package version 2.6.7).
- Beck, A. T. (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *Am J Psychiatry*, 165(8), 969-977. doi: 10.1176/appi.ajp.2008.08050721
- Bonn-Miller, M. O., Vujanovic, A. A., Boden, M. T., & Gross, J. J. (2011). Posttraumatic stress, difficulties in emotion regulation, and coping-oriented marijuana use. *Cognitive behaviour therapy*, 40(1), 34-44. doi: 10.1080/16506073.2010.525253

- Bonn-Miller, M. O., Vujanovic, A. A., & Zvolensky, M. J. (2008). Emotional dysregulation: association with coping-oriented marijuana use motives among current marijuana users. *Substance use & misuse*, 43(11), 1653-1665. doi: 10.1080/10826080802241292
- Boyer, P. (2000). Do anxiety and depression have a common pathophysiological mechanism? [Review]. *Acta psychiatrica Scandinavica. Supplementum*(406), 24-29.
- Bradley, B., DeFife, J. A., Guarnaccia, C., Phifer, J., Fani, N., Ressler, K. J., & Westen, D. (2011). Emotion dysregulation and negative affect: association with psychiatric symptoms. *Journal of Clinical Psychiatry*, 72(5), 685-691. doi: 10.4088/JCP.10m06409blu
- Bremner, J. D., Randall, P., Vermetten, E., Staib, L., Bronen, R. A., Mazure, C., Charney, D. S. (1997). Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse – a preliminary report. *Biol Psychiatry*, 41(1), 23-32.
- Brooks-Russel, A., Farhat, T., Haynie, D., Simons-Morton, B. (2013). Trends in Substance Use Among 6th- to 10th-Grade Students From 1998 to 2010: Findings From a National Probability Study. *The Journal of Early Adolescence*. doi: 10.1177/0272431613501409
- Budney, A. J., Roffman, R., Stephens, R. S., & Walker, D. (2007). Marijuana dependence and its treatment. *Addiction science & clinical practice*, 4(1), 4-16.

- Chabrol, H., Ducongé, E., Casas, C., Roura, C., Carey, K. (2005). Relations between cannabis use and dependence, motives for cannabis use and anxious, depressive and borderline symptomatology. *Addictive behaviors*, 30(4), 829-840.
- Choi, D. C., Furay, A. R., Evanson, N. K., Ostrander, M. M., Ulrich-Lai, Y. M., & Herman, J. P. (2007). Bed nucleus of the stria terminalis subregions differentially regulate hypothalamic-pituitary-adrenal axis activity: implications for the integration of limbic inputs. *J Neurosci*, 27(8), 2025-2034. doi: 10.1523/JNEUROSCI.4301-06.2007
- Chu, D. C. (2012). The links between religiosity, childhood sexual abuse, and subsequent marijuana use: an empirical inquiry of a sample of female college students. *International journal of offender therapy and comparative criminology*, 56(6), 937-954. doi: 10.1177/0306624X11413560
- Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of health and social behavior*, 24(4), 385-396.
- Conway, K. P., Compton, W., Stinson, F. S., & Grant, B. F. (2006). Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *The Journal of clinical psychiatry*, 67(2), 247-257.
- Creamer, M., Foran, J., & Bell, R. (1995). The Beck Anxiety Inventory in a non-clinical sample. *Behaviour Research and Therapy*, 33(4), 477-485.
- Critchley, H. D., Wiens, S., Rotshtein, P., Ohman, A., & Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience*, 7(2), 189-195. doi: 10.1038/nn1176

- Dannlowski, U., Stuhrmann, A., Beutelmann, V., Zwanzger, P., Lenzen, T., Grotegerd, D., . . . Kugel, H. (2012). Limbic Scars: Long-Term Consequences of Childhood Maltreatment Revealed by Functional and Structural Magnetic Resonance Imaging. *Biological psychiatry*, 71(4), 286-293. doi: DOI 10.1016/j.biopsych.2011.10.021
- De Bellis, M.D. (2002). Developmental traumatology: a contributory mechanism for alcohol and substances use disorders. *Psychoneuroendocrinology*, 27, 155-170.
- Demirakca, T., Sartorius, A., Ende, G., Meyer, N., Welzel, H., Skopp, G., . . . Hermann, D. (2011). Diminished gray matter in the hippocampus of cannabis users: possible protective effects of cannabidiol. *Drug and Alcohol Dependence*, 114(2-3), 242-245. doi: 10.1016/j.drugalcdep.2010.09.020
- Dennis, M., Funk, R., Godley, S., Godley, M., & Waldron, H. (2004). Cross-validation of the alcohol and cannabis use measures in the Global Appraisal of Individual Needs (GAIN) and Timeline Followback (TLFB; Form 90) among adolescents in substance abuse treatment. *Addiction*, 99 Suppl 2, 120-128. doi: 10.1111/j.1360-0443.2004.00859.x
- Di, S., Malcher-Lopes, R., Halmos, K., & Tasker, J. (2003). Nongenomic glucocorticoid inhibition via endocannabinoid release in the hypothalamus: a fast feedback mechanism. *J Neurosci*, 23(12), 4850-4857.
- Doll, B., Hutchison, K., Frank, M. (2011). Dopaminergic Genes Predict Individual Differences in Susceptibility to Confirmation Bias. *The Journal of Neuroscience*, 31(16), 6188-6198.

- Fernandez-Ruiz, J., Sagredo, O., Pazos, M. R., Garcia, C., Pertwee, R., Mechoulam, R., & Martinez-Orgado, J. (2013). Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid? *Br J Clin Pharmacol*, 75(2), 323-333. doi: 10.1111/j.1365-2125.2012.04341.x
- Filbey, F. M., Schacht, J. P., Myers, U. S., Chavez, R. S., & Hutchison, K. E. (2009). Marijuana craving in the brain. *Proceedings of the National Academy of Sciences of the United States of America*, 106(31), 13016-13021. doi: 10.1073/pnas.0903863106
- First, Michael B., Spitzer, Robert L, Gibbon Miriam, and Williams, Janet B.W. (2002). Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P). New York State Psychiatric Institute: New York: Biometrics Research.
- Fischl, B., Salat, D. H., van der Kouwe, A. J., Makris, N., Segonne, F., Quinn, B. T., & Dale, A. M. (2004). Sequence-independent segmentation of magnetic resonance images. *NeuroImage*, 23 Suppl 1, S69-84. doi: 10.1016/j.neuroimage.2004.07.016
- Gordon, H. W. (2002). Early environmental stress and biological vulnerability to drug abuse. *Psychoneuroendocrinology*, 27(1-2), 115-126.
- Grant, M. M., Cannistraci, C., Hollon, S. D., Gore, J., & Shelton, R. (2011). Childhood trauma history differentiates amygdala response to sad faces within MDD. *J Psychiatr Res*, 45(7), 886-895. doi: 10.1016/j.jpsychires.2010.12.004
- Grant, B. F., Stinson, F. S., Dawson, D. A., Chou, S. P., Dufour, M. C., Compton, W., . . . Kaplan, K. (2004). Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic

- Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry*, 61(8), 807-816.
doi: 10.1001/archpsyc.61.8.807
- Gratz, K.L., Roemer, L. (2004). Multidimensional Assessment of Emotion Regulation and Dysregulation: Development, Factor Structure, and Initial Validation of the Difficulties in Emotion Regulation Scale. *Journal of Psychopathology and Behavioral Assessment*, 26, 41-54.
- Gray, M. A., & Critchley, H. D. (2007). Interoceptive basis to craving. *Neuron*, 54(2), 183-186. doi: 10.1016/j.neuron.2007.03.024
- Hawkins, J. D., Catalano, R. F., & Miller, J. Y. (1992). Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: implications for substance abuse prevention. *Psychol Bull*, 112(1), 64-105.
- Hayes, A., Preacher, K. (2013). Statistical mediation analysis with a multicategorical independent variable. *British Journal of Mathematical and Statistical Psychology*, 67(3), 451-470. doi: 10.1111/bmsp.12028
- Heim, C., & Binder, E. B. (2012). Current research trends in early life stress and depression: review of human studies on sensitive periods, gene-environment interactions, and epigenetics. *Exp Neurol*, 233(1), 102-111. doi: 10.1016/j.expneurol.2011.10.032
- Heim, C., Mletzko, T., Purselle, D., Musselman, D. L., & Nemeroff, C. B. (2008). The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma. *Biol Psychiatry*, 63(4), 398-405. doi: 10.1016/j.biopsych.2007.07.002

- Heim, C., Newport, D. J., Bonsall, R., Miller, A. H., & Nemeroff, C. B. (2001). Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. *Am J Psychiatry*, 158(4), 575-581.
- Heim, C., Newport, D.J., Mletzko, T., Miller, A.H., Nemeroff, C.B. (2008). The link between childhood trauma and depression: insights from HPA axis studies in humans. . *Psychoneuroendocrinology*, 33, 693–710.
- Hovens, J. G., Giltay, E. J., Wiersma, J. E., Spinhoven, P., Penninx, B. W., & Zitman, F. G. (2012). Impact of childhood life events and trauma on the course of depressive and anxiety disorders. *Acta Psychiatrica Scandinavica*, 126(3), 198-207. doi: 10.1111/j.1600-0447.2011.01828.x
- Hyman, S. M., & Sinha, R. (2009). Stress-related factors in cannabis use and misuse: implications for prevention and treatment. *J Subst Abuse Treat*, 36(4), 400-413. doi: 10.1016/j.jsat.2008.08.005
- Imai, K., Keele, L., & Tingley, D. (2010). A general approach to causal mediation analysis. *Psychol Methods*, 15(4), 309-334. doi: 10.1037/a0020761
- Johnson, K. A., Bonn-Miller, M. O., Leyro, T. M., & Zvolensky, M. J. (2009). Anxious arousal and anhedonic depression symptoms and the frequency of current marijuana use: testing the mediating role of marijuana-use coping motives among active users. *J Stud Alcohol Drugs*, 70(4), 543-550.
- Johnston, L. D., O'Malley, P. M., Miech, R. A., Bachman, J. G., & Schulenberg, J. E. (2014). *Monitoring the Future national results on drug use: 1975-2013: Overview, Key Findings on Adolescent Drug Use*. Ann Arbor: Institute for Social Research, The University of Michigan.

- Kessler, R. C. (1997). The effects of stressful life events on depression. *Annual review of psychology*, 48, 191-214. doi: 10.1146/annurev.psych.48.1.191
- Kim, M. J., Loucks, R. A., Palmer, A. L., Brown, A. C., Solomon, K. M., Marchante, A. N., & Whalen, P. J. (2011). The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety. *Behavioural brain research*, 223(2), 403-410. doi: 10.1016/j.bbr.2011.04.025
- Koenen, K. C., Aiello, A. E., Bakshis, E., Amstadter, A. B., Ruggiero, K. J., Acierno, R., . . . Galea, S. (2009). Modification of the association between serotonin transporter genotype and risk of posttraumatic stress disorder in adults by county-level social environment. *Am J Epidemiol*, 169(6), 704-711. doi: 10.1093/aje/kwn397
- Koob, G. F., & Le Moal, M. (2008). Addiction and the brain antireward system. *Annual review of psychology*, 59, 29-53. doi: 10.1146/annurev.psych.59.103006.093548
- Lawston, J., Borella, A., Robinson, J.K., Whitaker-Azmitia P.M. (2000). Changes in hippocampal morphology following chronic treatment with the synthetic cannabinoid WIN 55,212-2. *Brain Research*, 877(2), 407-410.
- Lechner, W. V., Shadur, J. M., Banducci, A. N., Grant, D. M., Morse, M., & Lejuez, C. W. (2014). The mediating role of depression in the relationship between anxiety sensitivity and alcohol dependence. *Addict Behav*, 39(8), 1243-1248. doi: 10.1016/j.addbeh.2014.04.002
- Lee, C. M., Neighbors, C., Hendershot, C. S., & Grossbard, J. R. (2009). Development and preliminary validation of a comprehensive marijuana motives questionnaire. *Journal of Studies on Alcohol and Drugs*, 70(2), 279-287.

- Lorenzetti, V., Lubman, D. I., Whittle, S., Solowij, N., & Yucel, M. (2010). Structural MRI findings in long-term cannabis users: what do we know? *Subst Use Misuse*, 45(11), 1787-1808. doi: 10.3109/10826084.2010.482443
- Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, 10(6), 434-445. doi: 10.1038/nrn2639
- Magarinos, A. M., & McEwen, B. S. (1995). Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: involvement of glucocorticoid secretion and excitatory amino acid receptors. *Neuroscience*, 69(1), 89-98.
- McEwen, B. S. (2005). Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. *Metabolism*, 54(5 Suppl 1), 20-23. doi: 10.1016/j.metabol.2005.01.008
- McFarlane, A., Clark, C. R., Bryant, R. A., Williams, L. M., Niaura, R., Paul, R. H., . . . Gordon, E. (2005). The impact of early life stress on psychophysiological, personality and behavioral measures in 740 non-clinical subjects. *Journal of integrative neuroscience*, 4(1), 27-40.
- McGowan, P. O., Sasaki, A., D'Alessio, A. C., Dymov, S., Labonte, B., Szyf, M., . . . Meaney, M. J. (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci*, 12(3), 342-348. doi: 10.1038/nn.2270
- Meaney, M. J., Brake, W., & Gratton, A. (2002). Environmental regulation of the development of mesolimbic dopamine systems: a neurobiological mechanism for vulnerability to drug abuse? *Psychoneuroendocrinology*, 27(1-2), 127-138.

- Mier, D., Kirsch, P., & Meyer-Lindenberg, A. (2010). Neural substrates of pleiotropic action of genetic variation in COMT: a meta-analysis. *Molecular Psychiatry*, 15(9), 918-927. doi: 10.1038/mp.2009.36
- Naqvi, N. H., & Bechara, A. (2010). The insula and drug addiction: an interoceptive view of pleasure, urges, and decision-making. *Brain structure & function*, 214(5-6), 435-450. doi: 10.1007/s00429-010-0268-7
- NIDA, National Institute on Drug Abuse. (2012). Marijuana Abuse.
- NIDA, National Institute on Drug Abuse. (2013). Monitoring the Future.
- Piazza, P. V., & Le Moal, M. L. (1996). Pathophysiological basis of vulnerability to drug abuse: role of an interaction between stress, glucocorticoids, and dopaminergic neurons. *Annu Rev Pharmacol Toxicol*, 36, 359-378. doi: 10.1146/annurev.pa.36.040196.002043
- Raabe, F. J., & Spengler, D. (2013). Epigenetic Risk Factors in PTSD and Depression. *Front Psychiatry*, 4, 80. doi: 10.3389/fpsyt.2013.00080
- Russo, S. J., & Nestler, E. J. (2013). The brain reward circuitry in mood disorders. *Nature reviews. Neuroscience*, 14(9), 609-625. doi: 10.1038/nrn3381
- SAMHSA, Substance Abuse and Mental Health Services Administration. (2012). Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings *NSDUH Series H-44*. Rockville, MD: Substance Abuse and Mental Health Services Administration.
- Schacht, Joseph P, Hutchison, Kent E, Filbey, Francesca M. (2012). Associations between Cannabinoid Receptor-1 (CNR1) Variation and Hippocampus and

- Amygdala Volumes in Heavy Cannabis Users. *Neuropsychopharmacology*, 37(11), 2368-2376. doi: 10.1038/npp.2012.92
- Schellekens, A. F., Franke, B., Ellenbroek, B., Cools, A., de Jong, C. A., Buitelaar, J. K., & Verkes, R. J. (2012). Reduced dopamine receptor sensitivity as an intermediate phenotype in alcohol dependence and the role of the COMT Val158Met and DRD2 Taq1A genotypes. *Archives of General Psychiatry*, 69(4), 339-348. doi: 10.1001/archgenpsychiatry.2011.1335
- Sherry ST, Ward MH, Kholodov M, Baker J, Phan L, Smigielski EM, Sirotkin K. . (2001). dbSNP: the NCBI database of genetic variation.
- Sinha, R. (2008). Chronic stress, drug use, and vulnerability to addiction. *Ann N Y Acad Sci*, 1141, 105-130. doi: 10.1196/annals.1441.030
- Snyder, J. S., Soumier, A., Brewer, M., Pickel, J., & Cameron, H. A. (2011). Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. *Nature*, 476(7361), 458-461. doi: 10.1038/nature10287
- Sobel, Michael E. (1982). Asymptotic Confidence Intervals for Indirect Effects in Structural Equation Models. *Sociological Methodology*, 13 290–312. doi: 10.2307/270723
- Somaini, L., Manfredini, M., Amore, M., Zaimovic, A., Raggi, M. A., Leonardi, C., . . . Gerra, G. (2012). Psychobiological responses to unpleasant emotions in cannabis users. *European archives of psychiatry and clinical neuroscience*, 262(1), 47-57. doi: 10.1007/s00406-011-0223-5

- Steer, R. A., Beck, A. T., Riskind, J. H., & Brown, G. (1986). Differentiation of depressive disorders from generalized anxiety by the Beck Depression Inventory. *Journal of clinical psychology*, 42(3), 475-478.
- Stephens, R. S., Roffman, R. A., & Curtin, L. (2000). Comparison of extended versus brief treatments for marijuana use. *Journal of consulting and clinical psychology*, 68(5), 898-908.
- Tasker, J. (2004). Endogenous cannabinoids take the edge off neuroendocrine responses to stress. *Endocrinology*, 145(12), 5429-5430. doi: 10.1210/en.2004-1218
- Tavolacci, M. P., Ladner, J., Grigioni, S., Richard, L., Villet, H., & Dechelotte, P. (2013). Prevalence and association of perceived stress, substance use and behavioral addictions: a cross-sectional study among university students in France, 2009-2011. *BMC Public Health*, 13, 724. doi: 10.1186/1471-2458-13-724
- Thierry, A. M., Tassin, J. P., Blanc, G., & Glowinski, J. (1976). Selective activation of mesocortical DA system by stress. *Nature*, 263(5574), 242-244.
- Tye, K. M., Prakash, R., Kim, S. Y., Fenno, L. E., Grosenick, L., Zarabi, H., . . . Deisseroth, K. (2011). Amygdala circuitry mediating reversible and bidirectional control of anxiety. *Nature*, 471(7338), 358-362. doi: 10.1038/nature09820
- van Leeuwen, A. P., Creemers, H. E., Greaves-Lord, K., Verhulst, F. C., Ormel, J., & Huizink, A. C. (2011). Hypothalamic-pituitary-adrenal axis reactivity to social stress and adolescent cannabis use: the TRAILS study. [Research Support, Non-U.S. Gov't]. *Addiction*, 106(8), 1484-1492. doi: 10.1111/j.1360-0443.2011.03448.x

- van Wingen, G. A., Geuze, E., Vermetten, E., & Fernandez, G. (2011). Perceived threat predicts the neural sequelae of combat stress. *Molecular psychiatry*, 16(6), 664-671. doi: 10.1038/mp.2010.132
- Vyas, A., Mitra, R., Shankaranarayana Rao, B. S., & Chattarji, S. (2002). Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *J Neurosci*, 22(15), 6810-6818. doi: 20026655
- Wang, Y., Li, J., Chen, C., Chen, C., Zhu, B., Moysis, R. K., . . . Dong, Q. (2013). COMT rs4680 Met is not always the 'smart allele': Val allele is associated with better working memory and larger hippocampal volume in healthy Chinese. *Genes, Brain, and Behavior*, 12(3), 323-329. doi: 10.1111/gbb.12022
- Wardenaar, K. J., Vreeburg, S. A., van Veen, T., Giltay, E. J., Veen, G., Penninx, B. W., & Zitman, F. G. (2011). Dimensions of depression and anxiety and the hypothalamo-pituitary-adrenal axis. [Research Support, Non-U.S. Gov't]. *Biological psychiatry*, 69(4), 366-373. doi: 10.1016/j.biopsych.2010.09.005
- Watson, S., Owen, B. M., Gallagher, P., Hearn, A. J., Young, A. H., & Ferrier, I. N. (2007). Family history, early adversity and the hypothalamic-pituitary-adrenal (HPA) axis: Mediation of the vulnerability to mood disorders. *Neuropsychiatric disease and treatment*, 3(5), 647-653.
- Yang, R. J., Mozhui, K., Karlsson, R. M., Cameron, H. A., Williams, R. W., & Holmes, A. (2008). Variation in mouse basolateral amygdala volume is associated with differences in stress reactivity and fear learning. *Neuropsychopharmacology*, 33(11), 2595-2604. doi: 10.1038/sj.npp.1301665

- Yücel, M., Solowij, N., Respondek, C., & et al. (2008). Regional brain abnormalities associated with long-term heavy cannabis use. *Archives of General Psychiatry*, 65(6), 694-701. doi: 10.1001/archpsyc.65.6.694
- Zvolensky, M. J., Marshall, E. C., Johnson, K., Hogan, J., Bernstein, A., & Bonn-Miller, M. O. (2009). Relations between anxiety sensitivity, distress tolerance, and fear reactivity to bodily sensations to coping and conformity marijuana use motives among young adult marijuana users. *Exp Clin Psychopharmacol*, 17(1), 31-42. doi: 10.1037/a0014961

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Contributors

Ariel Ketcherside and Francesca Filbey wrote the manuscript. Ariel Ketcherside conducted all analyses.

Conflict of Interest

All authors declare no personal or financial conflicts of interest, which could inappropriately influence this manuscript.

List of Figures

Figure 1. Anxiety mediates the relationship between Early Life Stress and Problematic Marijuana Use. ACME = Average causal mediation effect, ADE = Average direct effect.

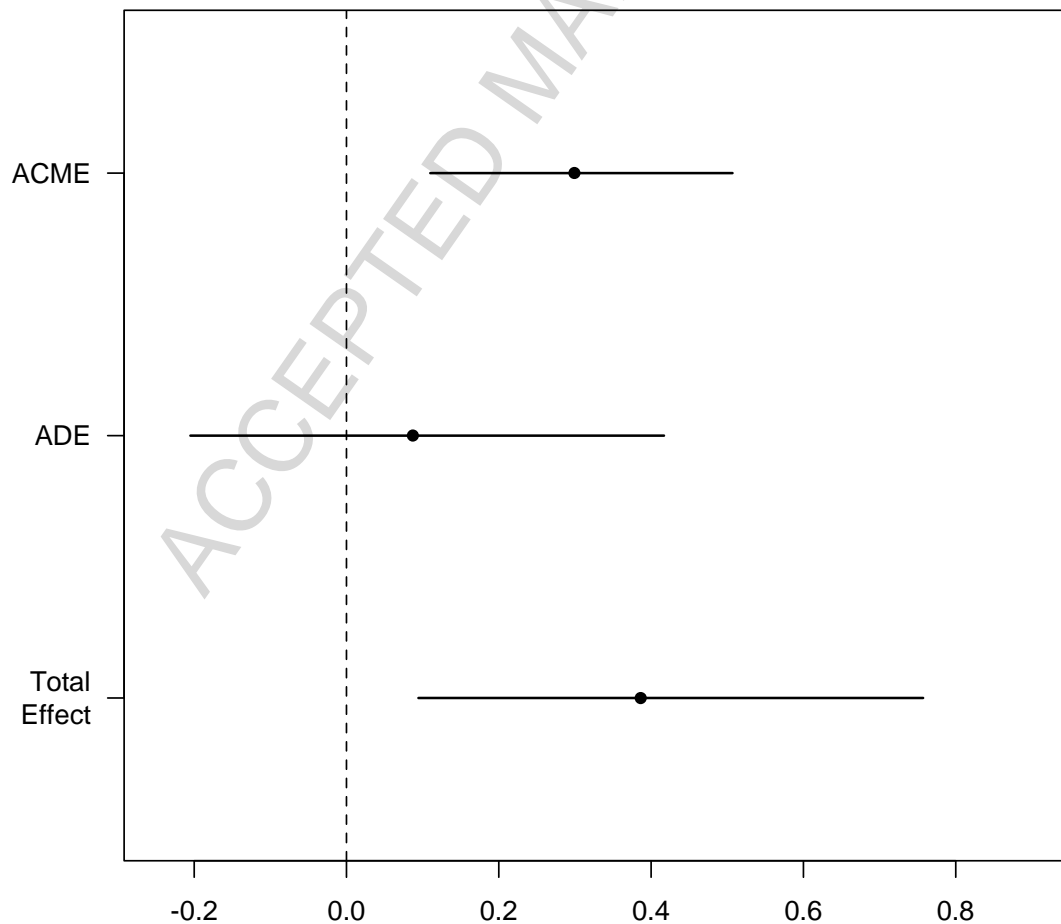


Figure 2: Depression mediates the relationship between early stress and problematic marijuana use. ACME = Average causal mediation effect, ADE = Average direct effect.

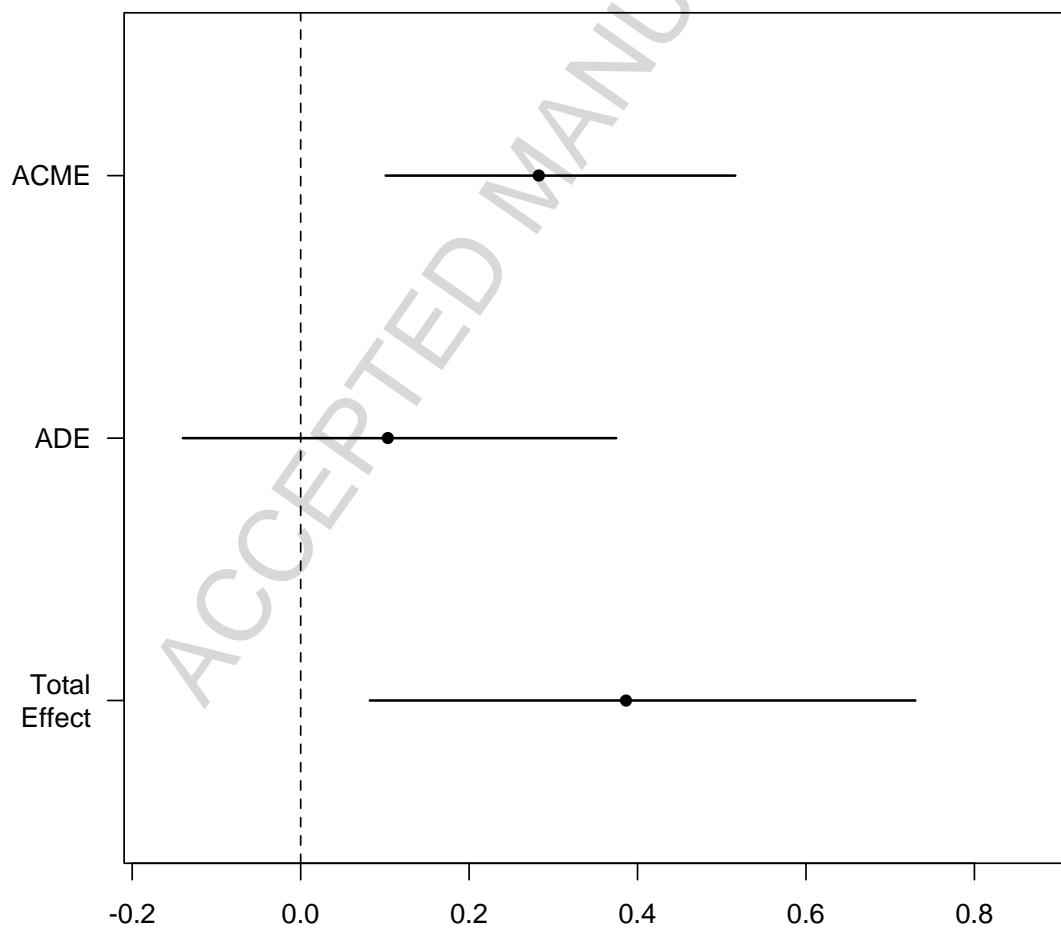
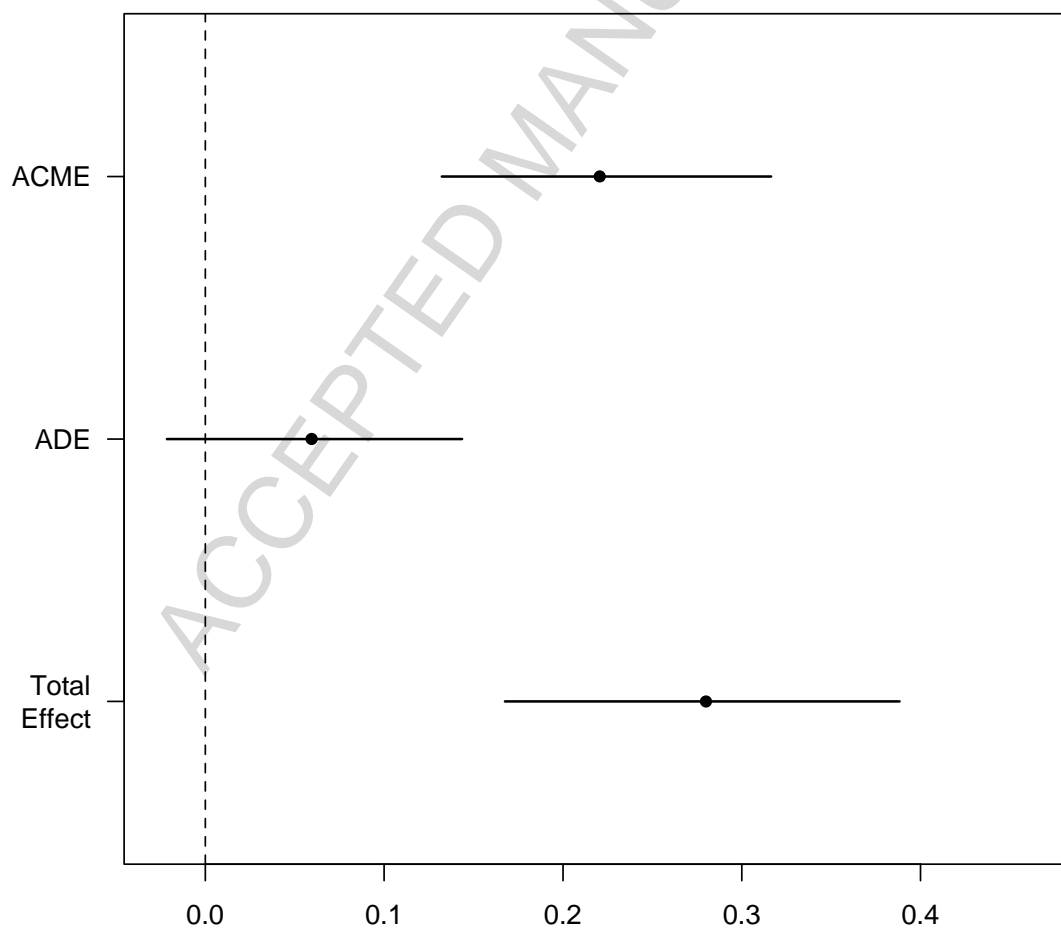


Figure 3: Depression mediates the relationship between perceived stress and problematic marijuana use. ACME = Average causal mediation effect, ADE = Average direct effect.



List of Tables

Table 1: Demographic characteristics of the participants. All values are represented as mean (SD) unless otherwise indicated. Participants with excessive missing data were excluded.

	N	Mean	SD
Total	151	-	-
Male/Female	109/42	-	-
Age	151	24.73	7.50
Years of education	149	13.48	2.31
Full scale IQ*	110	105.73	15.59
Use Marijuana Daily	110	-	-
Use Marijuana Weekly	151	-	-
Marijuana Problem Scale Score	128	4.02	4.46
Years regular marijuana use	151	7.01	7.03
Age of onset of regular use	151	17.37	3.73
Alcoholic beverages per day	150	1.25	1.84
Cigarettes/day, if smoker	48	11.08	6.25
Total Beck Depression Inventory Score	146	6.95	6.94
Total Beck Anxiety Inventory Score	151	7.52	8.77
Early Life Stress Questionnaire Score	151	3.46	2.89
Perceived Stress Scale Score	112	34.55	8.59

* IQ was assessed using the Wechsler Adult Scale of Intelligence (WASI)

Table 2: Zero-order correlations among variables of interest. ES = total Early Life Stress Questionnaire score, PS = total Perceived Stress Scale score, BAI = total Beck Anxiety Inventory score, BDI = total Beck Depression Inventory score, Cigs/day = number of reported cigarettes smoked per day in a typical week, ETOH/day = average number of alcoholic beverages per day, as calculated according to the Timeline Follow Back.

[illegible]

Highlights

- The relationship between early life stress and problematic marijuana use is mediated by Depression.
- Depression and anxiety mediate the relationship between perceived stress and problematic marijuana use in heavy marijuana users
- The presence of depression and anxiety in problematic marijuana users should be addressed in treatment for marijuana use.