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Marijuana Dependence Moderates the Effect of Posttraumatic Stress Disorder on Trauma Cue Reactivity in Substance Dependent Patients

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Abstract

Background—Individuals with posttraumatic stress disorder (PTSD) are at heightened risk for marijuana use. Although extant studies speak to the importance of examining the co-occurrence of PTSD and marijuana use as it relates to a variety of clinically-relevant outcomes, no studies have explored the way in which marijuana use may affect in-the-moment emotional responding among individuals with PTSD. Thus, the purpose of this study was to explore the role of marijuana dependence in the relation between PTSD and subjective and biological emotional reactivity in response to a trauma cue.

Methods—Participants were 202 patients with and without current PTSD consecutively admitted to a residential SUD treatment facility. Patients were administered diagnostic interviews, and subjective (negative affect) and biological (cortisol) reactivity to a personalized trauma cue were assessed.

Results—Whereas current PTSD was associated with greater subjective emotional reactivity among participants without marijuana dependence, there were no significant differences in subjective emotional reactivity as a function of PTSD status among participants with marijuana dependence. Moreover, marijuana dependent participants (with and without PTSD) reported less subjective emotional reactivity than participants with PTSD and without marijuana dependence. No significant findings were obtained for cortisol reactivity.

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Contributors

Drs. Tull and Gratz oversaw the study from which these data came. All authors were equally involved in study conceptualization, data analysis, and the writing of this manuscript.

Conclusions—Findings suggest that patients with co-occurring PTSD and marijuana dependence may experience alterations in their emotional processing in response to a trauma cue (i.e., dampening of arousal). Additional research is required to clarify the specific mechanisms through which marijuana use influences emotional reactivity and fear-related emotional processing, as well as how such effects may influence PTSD treatment.

Keywords

cannabis; cortisol; emotion regulation; experimental psychopathology; PTSD; substance use disorder

1. INTRODUCTION

Posttraumatic stress disorder (PTSD) is characterized by the presence of re-experiencing, avoidance, and hyperarousal symptoms, as well as negative alterations in cognition and mood, following exposure to a traumatic event (American Psychiatric Association [APA], 2013). The symptoms of PTSD have the potential to result in broad functional impairment (Rodriguez et al., 2012) and contribute to the development of other psychiatric disorders (Kessler et al., 1995), especially substance use disorders (SUD; Chilcoat and Menard, 2003). Within the extant literature, the majority of studies examining the co-occurrence of PTSD and SUD have focused on alcohol or cocaine use disorders (e.g., Coffey et al., 2007; Jakupcak et al., 2010; Waldrop et al., 2007); however, there is an emerging body of literature exploring the connection between PTSD and marijuana use.

Research has shown that individuals with PTSD are at heightened risk for marijuana use. For example, in the National Comorbidity Survey, current PTSD was found to be uniquely associated with increased rates of past year marijuana use and daily marijuana use (Cogle et al., 2011). Likewise, PTSD symptom severity demonstrates a significant positive association with frequency of marijuana use (Bonn-Miller et al., 2011; Bremner et al., 1996). Notably, the relation between PTSD and marijuana use is also clinically-relevant. Within a sample of military veterans with PTSD, Bonn-Miller et al. (2013) found that a pretreatment diagnosis of a marijuana use disorder was associated with weaker response to residential PTSD treatment even when other relevant factors (e.g., trauma severity) were considered. Similarly, PTSD symptom severity is positively associated with using marijuana to cope, marijuana use problems, and severity of marijuana withdrawal symptoms (Boden et al., 2013; Bonn-Miller et al., 2011, 2007; Earlywine and Bolles, 2014). Although these studies highlight the importance of examining the co- occurrence of PTSD and marijuana use as it relates to a variety of clinically-relevant outcomes, no studies to date have explored the way in which marijuana use may affect in-the-moment emotional responding among individuals with PTSD.

There is reason to believe that the presence of marijuana use could influence emotional responding to trauma cues among individuals with PTSD; however, the precise way in which emotional responding would be affected is unclear. For example, it is possible that individuals with PTSD may exhibit more intense emotional responses to a trauma cue in the context of marijuana use – consistent with findings that marijuana users report greater

emotion dysregulation than non-users (Bonn-Miller et al., 2008). Thus, it is possible that marijuana use may further exacerbate the heightened emotion dysregulation found in PTSD (Tull et al., 2007), contributing to greater trauma cue emotional reactivity within this population. Moreover, findings that individuals with marijuana dependence exhibit greater subjective reactivity to a biological challenge (CO₂ inhalation) than those with marijuana abuse (Bonn-Miller and Zvolensky, 2009) suggest that there may be a dose-response relationship with regard to the level of marijuana use and emotional reactivity.

Alternatively, an emerging body of research on the effects of marijuana use on emotional responding suggests that marijuana use may dampen emotional reactivity in response to a trauma cue among individuals with PTSD. The amygdala (an area of the brain implicated in the development and maintenance of pathological anxiety and PTSD; Liberzon and Sripada, 2007) includes a high density of CB1 cannabinoid receptors (Perra et al., 2008), activation of which diminishes anxiety responses and amygdala activation in response to aversive stimuli (Patel et al., 2005). Consequently, ingestion of Δ^9 -tetrahydrocannabinol (THC), the primary psychoactive ingredient in marijuana and a selective CB1 agonist, may correspond with attenuated threat-related emotional reactivity among individuals with PTSD. In support of this notion, studies have demonstrated that marijuana use is associated with reduced amygdala reactivity among individuals with comorbid marijuana dependence and major depression (Cornelius et al., 2010). Likewise, administration of THC in healthy recreational marijuana users (i.e., marijuana users who do not meet criteria for a marijuana use disorder) significantly reduced amygdala reactivity in response to threat signals (Phan et al., 2008). Moreover, van Leeuwen and colleagues (2011) found that repeated marijuana users exhibit lower stress reactivity levels (as indexed by cortisol levels) than individuals who have never used tobacco or marijuana in their lifetime. Finally, individuals with marijuana dependence have been found to exhibit a reduced subjective and biological sensitivity to negative emotion cues (i.e., unpleasant pictures), relative to abstinent marijuana users and healthy controls (Somaini et al., 2012).

The purpose of the current investigation was to explore the role of marijuana dependence in the relation between PTSD and subjective and biological emotional reactivity in response to personalized trauma cues. This investigation was carried out in a sample of substance dependent patients in residential SUD treatment – a clinical population at high-risk for both PTSD and marijuana dependence (Chen et al., 2011). Given the absence of research in this area, as well as conflicting evidence with regard to the particular impact of marijuana dependence on emotional responding in PTSD, no specific hypotheses were made.

2. METHOD

2.1. Participants

Participants for the current study included 202 patients (100 women) from a SUD inpatient treatment facility who reported exposure to at least one potentially traumatic event. Participants ranged from 18 to 60 years of age (*Mean* = 34.32, *SD* = 10.10) and were ethnically diverse (60.4% White; 36.6% African American; 1.5% Latina/o). With regard to educational attainment, 34.1% of participants reported receiving their high school diploma or GED and an additional 38.1% reported completing some form of higher education. The

majority of participants were unemployed (67.3%) and had an annual household income of less than \$20,000 (66.3%). Additional clinical and diagnostic data on the participants is presented in Table 1.

2.2. Measures and Stimuli

2.2.1. Diagnostic Assessment Measures—The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 1996) was used to assess for current SUD, including current marijuana dependence. To establish current PTSD diagnoses, all participants were interviewed using the DSM-IV version of the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1990). The CAPS is a structured PTSD diagnostic interview and the most widely used measure of PTSD (Elhai et al., 2005). It assesses the frequency and intensity of the 17 DSM-IV (APA, 2001) PTSD symptoms (plus eight associated symptoms). Frequency items are rated from 0 (never or none/not at all) to 4 (daily or almost every day or more than 80%). Intensity items are rated from 0 (none) to 4 (extreme). The Item Severity = 4 (ISEV4) rule, which requires that at least one re-experiencing, three avoidance/emotional numbing, and two hyperarousal symptoms have a severity rating (frequency + intensity) of 4, was used to establish PTSD diagnoses. Frequency and intensity ratings were also summed to create an overall PTSD symptom severity score (Weathers et al., 1999). The CAPS has adequate interrater reliability (.92–.99) and convergent validity with the SCID-I (First et al., 1996) and other established measures of PTSD (Weathers et al., 2001). In addition, the robust psychometric properties of the CAPS have been supported in a variety of combat and civilian samples, including patients with substance dependence (e.g., Blake, et al., 1990; Brown et al., 1996; Shalev et al., 1997; Weathers et al., 2001).

SUD patients with (vs. without) PTSD exhibit more severe clinical presentations, including elevated rates of co-occurring mood, anxiety, and personality disorders (Najavits et al., 1998; Mills et al., 2006; Tull et al., 2013a). Therefore, to ensure that any observed relations are unique to PTSD rather than elevated levels of psychopathology in general, diagnostic interviews were administered to assess for the presence of mood and anxiety disorders and borderline personality disorder. Specifically, the Mini International Neuropsychiatric Interview, Version 6.0 (MINI; Sheehan et al., 2009) was used to assess for current DSM-IV Axis I disorders with the exception of PTSD and SUD, and the borderline personality disorder module of the Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV; Zanarini et al., 1996) was used to assess for the presence of current borderline personality disorder (Zanarini et al., 2000). The MINI has shown adequate reliability and validity in the assessment of psychiatric disorders, as well as strong test-retest and inter-rater reliability (Sheehan et al., 1997). Likewise, past research indicates that the DIPD-IV demonstrates good inter-rater and test-retest reliability for the assessment of BPD (Zanarini et al., 2000), with an inter-rater kappa coefficient of .68 and a test-retest kappa coefficient of .69.

Interviews were conducted by bachelors- or masters-level clinical assessors trained to reliability with the principal investigator (MTT) and co-investigator (KLG). All interviews were reviewed by the principal investigator, with diagnoses confirmed in consensus meetings.

2.2.2. Personalized Trauma Script—During the initial assessment session, participants were asked specific questions regarding their most traumatic life event. For the PTSD group, this consisted of their index traumatic event (i.e., the event from which their PTSD diagnosis stemmed). Participants without a current diagnosis of PTSD were asked to describe the potentially traumatic event that was currently associated with the most distress. This portion of the session was tape recorded so that a research assistant affiliated with the study could create a script using the participant's own language. Participants were asked to picture the situation in their mind and try to remember as vividly as possible what the event entailed and their feelings at the time. Participants were then asked to describe the incident in as much detail as possible. The interviewer probed for key aspects of the event (e.g., time and place of the event, as well as emotions, thoughts, and bodily sensations experienced during the event). Prior to the first experimental session, a script consisting of a series of autobiographical statements, appraisals, and emotional responses generated from the interview was recorded onto an audiotape. This script was approximately one minute in length and the narrator was consistent across all scripts.

The method for generating this personalized trauma script followed the procedures originally developed by Lang and colleagues (see Lang and Cuthbert, 1984; Levin et al., 1982) and adapted by Pitman et al. (1987) and Keane et al. (1998) to examine PTSD-relevant arousal within the laboratory. The script is designed to maximize emotional responses by depicting the events in a salient, emotion-focused form in second person, present tense. This procedure is well-established in the PTSD literature and has been found to reliably induce emotional responses across a range of populations (Lang et al., 1983; Miller et al., 1987; Orr et al., 1993; Pitman et al., 1987). Moreover, these procedures have been used to elicit PTSD-related emotional responses in SUD patients with PTSD (Coffey et al., 2002; Saladin et al., 2003; Tull et al., 2011).

2.2.3. Assessment of Subjective Emotional Reactivity—To assess subjective emotional reactivity to the trauma script, participants were administered the negative affect (NA) subscale of the Positive and Negative Affect Scales (PANAS; Watson et al., 1988) immediately prior to and following presentation of the trauma script. Specifically, participants were asked to rate the extent to which they were currently ("right now, at this very moment") experiencing 10 forms of NA on a scale from 1 (very slightly or not at all) to 5 (extremely). Overall NA was calculated by summing all items. Internal consistencies of NA subscale of the PANAS pre- ($\alpha = .86$) and post-trauma script ($\alpha = .89$) were adequate.

2.2.4. Assessment of Biological (Cortisol) Reactivity—Saliva samples were obtained at two time points during the study: (a) before trauma script presentation, and (b) 20-minutes post- trauma script presentation (given evidence that cortisol levels do not peak for approximately 20 min following presentation of an emotionally-evocative cue; Nicolson, 2007). Saliva samples were collected by having participants place a swab under their tongue for at least 1 min. Once the swab was saturated with saliva, participants were asked to place the swab into a plastic vial that was then sealed and stored in a freezer. All samples were assayed in duplicate for salivary cortisol off-site by Salimetrics, LLC using a highly sensitive enzyme immunoassay (Salimetrics, State College, PA). The test used 25 μ L of

saliva per determination, with a lower limit of sensitivity of 0.003 µg/dL, standard curve range from 0.012 µg/dL to 3.0 µg/dL, an average intra-assay coefficient of variation (CV) of 3.8%, and an average inter-assay CV of 5.1%.

Salivary cortisol data were available for only a subset of participants ($n = 168$). Samples for 34 participants were missing or excluded due to: (a) errors in collection; (b) inadequate volume of saliva for analysis; or (c) refusal to provide a saliva sample. Participants who provided saliva samples did not differ from those who did provide such samples on any demographic or diagnostic variables ($ps > .05$).

Saliva samples for most participants (70.3%) were collected between 1:00 and 5:00 pm (*mean* time of day for collection of first saliva sample = 1:13 pm). There were no between-group differences (across PTSD and/or marijuana dependence status) in the time of day of saliva sample collection ($p = .53$).

2.2.5. Additional Measures—Following the SCID-I, participants completed a self-report measure assessing 28 withdrawal symptoms associated with the discontinuation of a variety of different substances (e.g., sedatives, alcohol, opioids, cocaine). The severity of each withdrawal symptom was rated on a 5-point Likert-type scale ranging from 0 (not at all) to 4 (extremely severe). Six of these items were used to create a composite score reflecting the severity of DSM-5 (APA, 2013) current marijuana withdrawal symptoms (e.g., sleep problems, depression, restlessness, nervousness, physical symptoms, etc.). This score was used to evaluate and confirm the absence of current marijuana withdrawal symptoms among participants.

To assess frequency of marijuana use in the past year, participants completed the Drug Use Questionnaire (DUQ; Hien and First, 1991), a self-report measure of the past-year frequency of alcohol and drug use. Participants rate the frequency with which they have used a variety of substances, including marijuana, on a 6-point Likert-type scale (0 = never; 1 = one time; 2 = monthly or less; 3 = 2–4 times per month; 4 = 2–3 times per week; 5 = 4 or more times per week). In support of the measure's construct validity, scores on this measure have been found to be associated with a number of constructs theoretically and empirically linked to SUD, including cravings (Tull et al., 2013b) and impulsivity (Lejuez et al., 2007). Further, scores on this measure demonstrate convergence with SCID-I SUD diagnoses in associations with relevant outcomes (Lejuez et al., 2007).

2.3. Procedure

All procedures were reviewed and approved by the relevant Institutional Review Boards. Data were collected as part of a larger study examining risky behaviors among substance dependent patients. To be eligible for inclusion in the larger study, participants were required to: 1) be dependent on cocaine and/or alcohol; 2) have a Mini-Mental Status Exam (Folstein et al., 1975) score of ≥ 24 ; and 3) have no current psychotic disorder (as determined by the psychosis screener from the SCID-I; First et al., 1996). Eligible participants were recruited for this study no sooner than 72 hours after entry into the facility (to limit the possible interference of withdrawal symptoms on study engagement). Those who met inclusion

criteria were provided with information about study procedures and associated risks, following which written informed consent was obtained.

This study involved two sessions conducted on separate days. The average amount of time between the initial assessment session and the second session was 6.23 days ($SD = 2.98$). During the initial assessment session, participants completed the previously-described interviews and a series of questionnaires (including a form that assessed demographic characteristics and current use of psychotropic medication). Upon completion of this session, participants scheduled a second session and were reimbursed \$25. In the second session, all participants were asked to report the time since last food intake and caffeine consumption, and female participants were asked if they were currently menstruating (in order to examine the potential influence of these variables on cortisol reactivity). Participants then rated their current NA and provided a saliva sample. Afterwards, they listened to the one-minute tape describing their potentially traumatic event. Once the tape was finished, participants were instructed to close their eyes and imagine vividly the event taking place in real-time for one-minute (consistent with Keane et al., 1998). Afterwards, participants again completed the PANAS-NA. Participants then provided another saliva sample 20 min later. Participants were reimbursed \$15 for the second session.

3. RESULTS

3.1. Preliminary Analyses

Of the study sample, 26.7% ($n = 54$) met criteria for current PTSD and 29.2% ($n = 59$) met criteria for current marijuana dependence. Data on the distribution of participants across the different groups are presented in Table 2. Pre- and post-script descriptive data for subjective emotional reactivity and cortisol reactivity as a function of PTSD and marijuana dependence status are presented in Table 3. There was no significant difference in rates of marijuana dependence between participants with (39%) and without (26%) PTSD, $\chi^2 = 3.34$, $p = .07$. There was also no significant difference in the frequency of marijuana use within the past year between participants with (mean = 2.80, $SD = 2.00$) and without (mean = 2.73, $SD = 2.07$) PTSD, $t(195) = -0.21$, $p = .83$. However, as would be expected, participants with marijuana dependence reported using marijuana significantly more often in the past year (mean = 3.88, $SD = 1.78$) than those without marijuana dependence (mean = 2.27, $SD = 1.97$), $t(195) = -5.36$, $p < .001$. Notably, however, participants with marijuana dependence reported negligible symptoms of marijuana withdrawal (mean item response = 0.36, $SD = 0.80$) at the time of the initial assessment session.

To identify potential covariates for the primary analyses (Tabachnick and Fidell, 2007), correlation analyses were conducted to explore associations between subjective and biological emotional reactivity and demographic factors (i.e., age, racial/ethnic background, income, education level, and employment status), diagnostic variables (major depression, number of anxiety disorders, number of SUD besides marijuana dependence, and borderline personality disorder), psychotropic medication use (yes vs. no), and number of potentially traumatic events reported. We also examined the zero-order associations between other potential covariates (i.e., time of day, time since last meal, time since last caffeine consumption, and [for female participants] current menstruation status) and salivary cortisol.

Subjective and biological emotional reactivity were represented by standardized residual scores created by conducting two linear regressions of post-trauma script NA and cortisol variables on pre-trauma script NA and cortisol variables, respectively. Given the small number of participants in many of the demographic categories, these variables were collapsed into dichotomous variables of: (1) White (60.4%) versus non-White (39.6%); (2) past year income of < \$20,000 (66.3%) versus > \$20,000 (33.7%); (3) a high school education or less (61.9%) versus some post-high school education (38.1%); and (4) unemployed (72.3%) versus employed (27.7%). Age ($r = 0.14$, $p = .04$), number of anxiety disorders ($r = 0.19$, $p = .006$), number of potentially traumatic events experienced ($r = 0.28$, $p < .001$), and borderline personality disorder ($r = 0.15$, $p = .03$) were significantly associated with subjective emotional reactivity to the trauma cue. In addition, White (vs. non-White) racial/ethnic background ($r = .16$, $p = .04$) and time since last caffeine consumption ($r = -.15$, $p = .05$) were significantly correlated with cortisol reactivity; menstrual cycle ($r = -.02$, $p = .76$), time since last meal ($r = .02$, $p = .84$), and time of day ($r = -.14$, $p = .07$) were not significantly associated with cortisol reactivity.

3.2. Primary Analyses

To determine the potential moderating effect of marijuana dependence on the relation between PTSD and trauma cue reactivity, a series of 2 (pre- vs. post-trauma script) $\times$ 2 (PTSD vs. no PTSD) $\times$ 2 (marijuana dependence vs. no marijuana dependence) repeated measures analyses of variance (ANOVAs) were conducted. Pre- and post-trauma script self-reported NA and salivary cortisol levels served as the dependent variables. Significant interactions were explored using the Tukey HSD test. To provide a more conservative test of our model, these analyses were then repeated including the covariates relevant to each dependent variable identified above. Specifically, for analyses examining subjective emotional reactivity, age, number of anxiety disorders, number of potentially traumatic events, and borderline personality disorder were included as covariates. For analyses examining cortisol reactivity, racial/ethnic background and time since last caffeine consumption were included as covariates.

3.2.1. Subjective Emotional Reactivity—The repeated measures ANOVA produced a significant time $\times$ PTSD interaction, $F(1, 198) = 5.22$, $p = .02$, with post-hoc analyses demonstrating that participants with PTSD exhibited a significantly greater increase in NA from pre- to post-trauma script presentation compared to those without PTSD ($p = .01$). However, this main effect was qualified by a significant time $\times$ PTSD status $\times$ marijuana dependence status interaction, $F(1, 198) = 4.30$, $p = .04$. Post-hoc analyses revealed that among participants without marijuana dependence, those with PTSD exhibited a significantly ($p < .001$) greater increase in NA from pre- to post-trauma script presentation than those without PTSD. However, among participants with marijuana dependence, there was no significant difference in NA reactivity as a function of PTSD status ($p = .99$, $d = .04$). Given the absence of a significant difference in NA reactivity between marijuana dependent participants with and without PTSD, the small effect size associated with the difference, and the desire to reduce the risk for Type I error by reducing the number of comparisons conducted, the marijuana dependence groups were combined and complex contrasts (McHugh, 2011; Thompson, 2006) were conducted between this combined group and the

non-marijuana dependent PTSD and non-PTSD groups. Marijuana dependent participants (with and without PTSD) had significantly less NA reactivity than participants with PTSD and without marijuana dependence ($p = .049$). The comparison between the marijuana dependent groups and participants without PTSD or marijuana dependence was not significant ($p = .12$; see Figure 1).

When controlling for age, number of anxiety disorders, number of potentially traumatic events, and borderline personality disorder, no main effect of PTSD was obtained, $F(1, 194) = 1.67$, $p = .20$. However, the significant time $\times$ PTSD status $\times$ marijuana dependence status interaction remained, $F(1, 194) = 3.97$, $p = .048$.

To ensure that these findings were not simply an artifact of greater PTSD symptom severity among participants with PTSD and no marijuana dependence, we conducted an independent t-test examining differences in continuous PTSD symptom severity scores (derived from the CAPS) as a function of marijuana dependence among participants with PTSD. No significant between-group differences were found for overall PTSD symptom severity, $t(52) = 0.49$, $p = .62$.

3.2.2. Cortisol Reactivity—The repeated measures ANOVA for change in salivary cortisol levels from pre- to post-trauma script produced no significant main effects or interactions, $F_s(1, 164) < 0.92$, $p_s > .33$. These findings did not change when relevant covariates (e.g., racial/ethnic background, time since last ingestion of caffeine) were included in the model, $F_s(1, 164) < 0.84$, $p_s > .35$.

4. DISCUSSION

The goal of this study was to examine the moderating role of marijuana dependence on the relation between PTSD and subjective and biologically-indexed emotional reactivity to a personalized trauma cue. Results revealed that current PTSD was associated with greater subjective emotional reactivity to the trauma script only among participants without marijuana dependence; among those with marijuana dependence, subjective emotional reactivity did not differ as a function of PTSD status. Moreover, marijuana dependent participants (with and without PTSD) reported less subjective emotional reactivity than participants with PTSD but without marijuana dependence. Contrary to expectations, however, no significant differences were found for cortisol reactivity. Although preliminary, findings suggest that participants with co-occurring PTSD and marijuana dependence may exhibit a dampened subjective emotional response to trauma cues. This finding is even more notable when one considers that we did not find any differences in the severity of PTSD symptoms between PTSD participants with and without marijuana dependence. There are two possible explanations for our findings.

First, given the high density of CB1 cannabinoid receptors in the amygdala, repeated intake of THC, a selective CB1 agonist, may lead to reduced amygdala activation in response to negative emotional stimuli among individuals with PTSD. This reduced activation may then correspond to reduced subjective distress. Such an explanation is consistent with studies that have found that marijuana use is associated with reduced amygdala reactivity and a reduced

sensitivity to negative emotion cues (Cornelius et al., 2010; Phan et al., 2008; Somaini et al., 2012; van Leeuwen et al., 2011). Nonetheless, it is important to note that the observed differences in subjective emotional reactivity in this study did not correspond to any group differences in cortisol reactivity (which may be expected with this explanation).

Alternatively, the reduced emotional reactivity observed among marijuana dependent participants with PTSD may reflect a greater tendency to avoid negative emotions within this group. Research by Bonn-Miller and colleagues has shown that PTSD symptom severity is positively related to the use of marijuana to cope with negative internal experiences (Bonn-Miller et al., 2007; 2011), and a recent study by Bordieri et al. (2014) revealed a positive association between PTSD symptom severity and marijuana dependence only among individuals with average to high levels of experiential avoidance (i.e., the tendency to avoid unwanted internal experiences; Hayes et al., 1996). If our findings are due to heightened emotional avoidance among marijuana dependent patients with PTSD, such disruptions in the emotional processing of fear-relevant information may ultimately inhibit extinction of the fear and anxiety response among these individuals, contributing to the maintenance of PTSD (Foa and Kozak, 1986; Rauch and Foa, 2006). Given the current lack of clarity surrounding the precise consequences of marijuana use for reactions to stressors and emotional processing (Moreira and Lutz, 2008), as well as the specific explanation for our findings, prospective studies examining the long-term consequences of frequent marijuana use on PTSD symptoms are needed. Likewise, additional research is required to clarify the mechanisms through which marijuana use influences emotional reactivity and fear-related emotional processing.

Despite highlighting the potential relevance of marijuana dependence to subjective emotional responding to trauma cues among individuals with PTSD, this study is not without limitations. First, several of our groups included a relatively small number of participants, potentially reducing power to detect between-group differences. Studies with larger samples are needed. Moreover, although the use of a clinical sample of SUD patients is a strength of this study, this population is characterized by a high level of psychiatric comorbidity (Chen et al., 2011) and functional impairment (Hasin et al., 2007). Consequently, it is possible that findings may not generalize to other clinical populations (e.g., psychiatric outpatient populations) or nonclinical populations. For example, it is not clear if marijuana dependence in and of itself moderates the effect of PTSD on trauma cue reactivity outside the context of co-occurring psychopathology, including other SUD. Future studies that emphasize internal validity are needed to isolate the effect of marijuana use and dependence on the relation between PTSD and trauma cue reactivity. Likewise, given that all participants were abstinent from marijuana when completing this study (due to their recruitment from a residential SUD treatment facility), findings do not speak to the effect of acute marijuana intoxication on emotional reactivity.

The absence of data on the time since last marijuana use is another limitation. Indeed, although participants were not using marijuana at the time of the study and reported negligible marijuana withdrawal symptoms, they may still have had THC in their system (which could influence emotional responding). Future research assessing the time since last use of marijuana, as well as levels of THC in the urine or blood, are needed to examine the

impact of THC levels on emotional responding among individuals with and without PTSD. Future studies examining differences in emotional responding as a function of the frequency, severity, and history of marijuana use are also needed. Such studies will assist in determining whether emotional processing among individuals with PTSD is differentially affected by recreational versus chronic marijuana use.

In addition, only two modes (i.e., cortisol and self-report) of emotional responding were examined in the present study. Although the multimodal assessment of emotional responding provides us with a more complete understanding of the ways in which marijuana use may influence trauma cue reactivity among individuals with PTSD, these measures are associated with some limitations. For example, responses to self-report measures may be influenced by an individual's willingness and/or ability to accurately report on emotional experiences (Tull et al., 2008) – a particularly relevant concern for individuals with PTSD who exhibit low levels of emotional clarity and heightened emotional avoidance (Roemer et al., 2001; Tull et al., 2007). Likewise, although analyses of cortisol reactivity controlled for several factors found to influence cortisol levels (e.g., psychotropic medication use, time since last food intake/caffeine), we did not assess for all relevant factors that may influence biological responding in general or cortisol reactivity in particular, including non-psychotropic medication use (Granger et al., 2009), physical health (Rimmele et al., 2009), and dissociation (Simeon et al., 2007). In addition, although we attempted to collect saliva samples at a time when diurnal fluctuations are relatively stable (Clow et al., 2004), there was still some variability in collection times. Participants who provided saliva samples before noon would be expected to have higher cortisol levels at baseline, which could limit their observable cortisol reactivity (due to a restricted range). Future research using uniform saliva collection times (preferably later in the day when cortisol levels are relatively low and stable) are needed. Future studies also would benefit from the assessment of physiological emotional reactivity, as well as the use of more sophisticated assessments of biologically-based emotional reactivity (e.g., fMRI, affective startle response). Finally, in interpreting our findings, it is important to consider that we utilized a diagnostic interview designed to assess the DSM-IV diagnostic criteria for PTSD. The symptoms associated with PTSD and the criteria for determining a PTSD diagnosis were modified in the DSM-5 (see APA, 2013). Future studies should attempt to replicate our findings among individuals meeting criteria for PTSD in the DSM-5.

Emotional processing through engagement with fear-eliciting stimuli and the subsequent activation of emotional arousal plays a central role in the treatment of PTSD (Foa and Kozak, 1986; Rauch and Foa, 2006). Indeed, reduced fear activation and difficulties engaging emotionally with a traumatic memory may interfere with the effectiveness of PTSD treatment (Foa et al., 1995). Although the results of the current study are preliminary and require replication, they provide suggestive evidence that the heavy use of marijuana is associated with altered emotional responding to trauma-related cues. Thus, when treating individuals with PTSD, the assessment of marijuana use and dependence may provide insight into a potential factor that could influence the successful treatment of PTSD. In such cases, clinicians may enhance the effectiveness of PTSD treatment through procedural modifications such as encouraging increased emotional engagement, querying into specific feelings and thoughts associated with the traumatic event, and facilitating a present moment

focus (Hembree et al., 2003). Our findings may also suggest that the regulated use of endocannabinoid receptor agonists could assist in the treatment of PTSD. For example, Fraser (2009) found that nabilone, a synthetic cannabinoid, resulted in either a cessation of nightmares or a significant reduction in nightmare intensity among PTSD patients with treatment-resistant nightmares. Of course, as this area of research progresses, it is important that the endocannabinoid receptor agonists examined have limited abuse potential given the elevated risk of SUD among individuals with PTSD (Trezza and Campolongo, 2013).

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Highlights

- Examined moderating role of marijuana dependence on trauma cue reactivity in post traumatic stress disorder (PTSD).
- In absence of marijuana dependence, PTSD patients had more subjective reactivity.
- No differences in reactivity for marijuana dependent patients as a function of PTSD.
- Marijuana dependent PTSD patients less reactive than PTSD-no marijuana patients.
- Marijuana dependence may lead to a dampening of reactivity in patients with PTSD.

Figure 1. Interaction showing the moderating role of marijuana dependence on the effect of PTSD on subjective negative affect reactivity in response to the trauma script.

Table 1

Diagnostic and clinical data across all participants.

	% Present
Posttraumatic Stress Disorder	26.7%
Major Depressive Disorder	29.2%
Panic Disorder with/without Agoraphobia	26.7%
Social Anxiety Disorder	24.8%
Obsessive-Compulsive Disorder	12.9%
Generalized Anxiety Disorder	33.7%
Alcohol Dependence	66.3%
Cocaine Dependence	59.4%
Opioid Dependence	25.2%
Marijuana Dependence	29.2%
Sedative Dependence	21.8%
Stimulant Dependence	21.8%
Hallucinogen Dependence	3.5%
Borderline Personality Disorder	35.6%
Psychotropic Medication Use	51.0%

Note. All diagnoses are current.

Table 2

Distribution of participants across groups.

	PTSD	No PTSD
Marijuana Dependence	21 (18)	38 (32)
No Marijuana Dependence	33 (27)	110 (91)

Note. The number of participants across groups for analyses involving cortisol are presented in parentheses.

Descriptive Data for Pre- and Post-Script Subjective Negative Emotional Reactivity and Cortisol Reactivity as a Function of Group Status

Table 3

Marijuana Dependence	PTSD	Subjective NA Reactivity		Cortisol Reactivity	
		Pre-script	Post-script	Pre-script	Post-script
No	No	14.26 (6.20)	19.39 (8.04)	.21 (.19)	.19 (.16)
	Yes	16.82 (6.92)	27.69 (11.02)	.30 (.49)	.25 (.32)
Yes	No	13.82 (3.96)	21.40 (8.53)	.20 (.13)	.20 (.12)
	Yes	13.91 (5.62)	21.76 (8.10)	.23 (.13)	.22 (.12)

Note. Standard deviation presented in parentheses following means. NA = negative affect.