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Stress responding in cannabis smokers as a function of trauma exposure, sex, and relapse in the human laboratory

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ABSTRACT

Background: Stress responding is linked to drug use, but little is known about stress responses in cannabis smokers. We investigated acute stress responding in cannabis smokers as a function of trauma exposure and sex, and relationships between stress responses and cannabis relapse.

Methods: 125 healthy, non-treatment-seeking daily cannabis smokers (23F, 102 M) completed the Trier Social Stress Task (TSST), a standardized laboratory stressor; subsets also completed a trauma questionnaire (n = 106) and a laboratory cannabis relapse measure (n = 54). Stress responding was assessed with heart rate (HR), salivary cortisol (CORT), and self-rated mood.

Results: Cannabis smokers reporting at least one trauma exposure had higher CORT and anxiety overall compared to those reporting no trauma. Stress responding did not differ as a function of binary trauma exposure, although total number of exposures correlated positively with CORT and anxiety during stress. Females reported increased nervousness after stress relative to males matched to the females for cannabis and cigarette use. An interactive effect of sex and trauma on HR suggested that females with trauma exposure have increased cardiovascular stress responding relative to those without such exposure, with no differential effect in males. Stress responding did not predict laboratory cannabis relapse.

Conclusion: We report differences in acute stress responding as a function of trauma, sex, and their interaction in a large sample of relatively homogenous cannabis smokers. Further investigation of how trauma impacts stress responding in male and female cannabis smokers, and how this relates to different aspects of cannabis use, is warranted.

1. Introduction

Cannabis is the most widely used illicit drug internationally (UNODC, 2016). Between 2002 and 2014 there was a 28% increase in use in the US (Compton et al., 2016), with prevalence expected to continue to rise amid legal changes (Hall and Lynskey, 2016). An understanding of individual risk factors for problematic cannabis use could valuably guide prevention and intervention.

Stress exposure and dysregulated stress responding contribute to problematic use of other drugs. In rodents, exposure to acute stressors (e.g., social stress, foot shock) increases self-administration of cocaine (Goeders and Guerin, 1994; Haney et al., 1995; Miczek and Mutschler, 1996; Ramsey and van Ree, 1993), amphetamines (Vezina et al., 2002), opioids (Alexander et al., 1978; Shaham et al., 1992; Shaham et al., 1993; Shaham and Stewart, 1995), and alcohol (Pohorecky, 1990). In healthy humans, acute stress increases alcohol consumption (de Wit et al., 2003; Magrys and Olmstead, 2015; McGrath et al., 2016). Drug cravings also covary with responses to acute laboratory stress in alcohol and cocaine users (Fox et al., 2007; Fox et al., 2008; Fox et al., 2005; Sinha et al., 1999; Sinha et al., 2000; Sinha et al., 2003).

There is some evidence that dysregulated stress responding also contributes to vulnerability for drug misuse. Stress responding during withdrawal predicts relapse in alcohol- (Adinoff et al., 2005; Brady et al., 2006; Breese et al., 2011) and cocaine- (Back et al., 2010; Sinha et al., 2006) dependence. Moreover, stress-induced anxiety predicts lower engagement in aftercare following inpatient treatment in alcohol-

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dependent patients (Sinha, 2012). Thus, certain patterns of stress responding may increase drug taking and hinder treatment compliance.

Despite this existing research, little is known about stress responding in cannabis users. One study found that adolescents who had used cannabis ≥5× in the past year had blunted HPA-axis stress responses relative to those reporting less frequent use (van Leeuwen et al., 2011). Blunted cortisol and subjective distress ratings have similarly been observed in adult cannabis users compared to non-users (Cuttler et al., 2017). Further, social stress increased cannabis craving relative to a neutral task in cannabis users (Buckner et al., 2016; McRae-Clark et al., 2011). Thus, consistent with other drug-using groups, stress responding appears to be dysregulated in some cannabis smokers, and this may be related to clinical outcomes. To date, little is known about variability in stress responding in cannabis users.

Diverse factors may affect stress responses in cannabis smokers. Cannabis may acutely affect stress responding, given that oral THC modulates subjective stress responding (Childs et al., 2017). Adverse life experiences, such as trauma can have long-term effects on stress responding (Carpenter et al., 2007; Gutman and Nemeroff, 2003; Heim et al., 2008; McLaughlin et al., 2010; Nemeroff, 2004; Shea et al., 2005). Cannabis smokers who have experienced traumatic events may thus have altered stress responses and an increased risk for problematic cannabis use.

Stress responding also differs as a function of sex. In non-drug users, laboratory stress elicits greater heart rate and negative affect increases in women (Kelly et al., 2008; Kudielka et al., 2004; Ordaz and Luna, 2012), whereas men show higher blood pressure increases (Childs et al., 2010; Kajantie and Phillips, 2006; Kudielka and Kirschbaum, 2005; Lepore et al., 1993; Matthews et al., 2001). Findings related to sex differences in cortisol responses are inconsistent, however studies using the Trier Social Stress Task (TSST; Kirschbaum et al., 1993), a standardized stress assay, have reported heightened cortisol stress responses in males compared to females (Childs et al., 2010; Uhart et al., 2006). As noted above, social stress increases cannabis craving in cannabis users (Buckner et al., 2016; McRae-Clark et al., 2011); this effect appears to be particularly pronounced in women (Buckner et al., 2011). Women are also more likely than men to report use of cannabis for the purpose of alleviating anxiety (Cuttler et al., 2016), which can be a symptom of stress (Temple et al., 2014).

There may also be interactive effects of trauma and sex on stress responding in cannabis users. In non-drug users, trauma-exposed women display hyperactive HPA-axis and autonomic system reactivity to stress (Heim et al., 2000), whereas trauma-exposed men have blunted cortisol stress responding (Janusek et al., 2017). Such interactions may have important implications, given that trauma exposure in women predicts earlier cannabis use initiation and rapid progression to dependence (Werner et al., 2016a).

In this study, we aimed to investigate individual variability in response to standardized laboratory stress in a sample of regular cannabis smokers. We focused on differences as a function of trauma exposure and sex and their interaction. Given the possibility that stress responding may be linked to intractable cannabis use, we also investigated the relationship between acute stress responding and relapse to cannabis, as measured in a human laboratory model. We expected that: (1) cannabis smokers with trauma exposure would show greater stress reactivity than those without exposure; (2) female cannabis smokers would have greater mood and heart rate stress reactivity whereas males would have increased cortisol; and (3) cannabis smokers who relapsed to cannabis in the laboratory would show increased stress responding relative to those who remained abstinent, regardless of trauma exposure.

2. Methods

2.1. Participants

This analysis included data from cannabis smokers recruited in NYC, NY. Participants were healthy males and non-pregnant females between 18 and 50 years old reporting current, heavy cannabis use (defined as ≥2 cannabis cigarettes/day, ≥4 days/week). A PhD-level researcher assessed mental health status and drug use. Positive THC urine toxicology tests at all screening visits were required to biochemically verify current regular cannabis use. Estimates of number of cannabis cigarettes used were based on a rate of 1 'blunt' = 2 cannabis cigarettes (Mariani et al., 2011). Participants could not: (1) be regularly (> 2×/week) using other illicit drugs; (2) meet DSM-IV criteria for an Axis I disorder requiring intervention (APA, 1994); (3) be taking medication daily; (4) be seeking treatment; (5) have prior adverse cannabis effects; or (6) have a health condition contraindicating participation. Volunteers underwent psychiatric and physical examination and electrocardiogram, urinalysis, and blood panels before admission. All participants provided informed consent as approved by the New York State Psychiatric Institute (NYSPI) Institutional Review Board. Volunteers were compensated and fully debriefed at discharge.

2.2. Experimental protocol

Data were collected across 5 studies, all using an inpatient human laboratory model of cannabis withdrawal and relapse: (1) effects of cannabis cues and primes on cannabis relapse after withdrawal (not published); (2) effects of tobacco cigarette cessation versus smoking as usual on cannabis withdrawal and relapse in cigarette-smoking cannabis users (Haney et al., 2013a); (3) effects of nabilone on cannabis withdrawal and relapse (Haney et al., 2013b); (4) effects of zolpidem, alone or with nabilone, on cannabis withdrawal and relapse (Herrmann et al., 2016); and (5) effects of varenicline, alone or with nabilone, on cannabis withdrawal and relapse in cigarette smoking cannabis users (Herrmann et al., under review). For studies 2 and 5, participants also smoked at least 4 nicotine cigarettes daily.

2.2.1. Trier social stress task (TSST)

Before admission and any medication administration, participants attended a single session in which they completed the TSST, a standardized assay of social stress responding (Kirschbaum et al., 1993). We aimed to test participants in their 'normal' daily state i.e., not acutely intoxicated by cannabis and not in withdrawal. Thus, we did not provide specific instructions regarding abstinence before the session. Acute cannabis intoxication was minimized by keeping participants in the laboratory (where they could not smoke cannabis) for at least an hour before the TSST. The TSST was conducted in the afternoon to control for diurnal cortisol variations. Baseline measurements (see *Assessments*) were recorded approximately 25 min before the TSST (see Fig. 1). After baseline measurements, participants were informed that they would make a 5-min speech outlining their job qualifications in front of a committee rating their body language for signs of stress. They were also informed that they would complete a second task with instructions provided after the speech. Participants were shown the room and alerted to a video camera that they were told was recording (no recordings were made). They were given 10 min to prepare (the introduction phase). During the speech, the committee (two confederates) provided minimal instruction and no encouragement. Following the speech, participants completed complex mental arithmetic for 5 min. They were informed of errors and asked to begin again. The TSST reliably but transiently increases markers of stress across populations (Allen et al., 2014). Following the stressor, participants remained in the laboratory for 90 min completing assessments.