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Sex differences in stress reactivity after intranasal oxytocin in recreational cannabis users

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ABSTRACT

Cannabis is the most widely used illicit drugs and the changing legal, political and cultural climate will likely increase cannabis use further. One factor that may underlie the transition from recreational use to problematic use is stress. The hormone oxytocin (OXT) modulates stress and may have therapeutic efficacy for substance use disorders, but few studies have examined OXT in cannabis users. Another factor is sex; although more men smoke cannabis, the transition from recreational to problematic use is faster in women. Using a within-subjects design, the effects of intranasal (i.n.) oxytocin (OXT; 40 IU) administration on stress reactivity (using the Trier Social Stress Test; TSST) and cannabis (5.6% THC) self-administration was assessed in recreational cannabis using men (n = 31) and women (n = 32) relative to i.n. placebo (PBO) and no-stress (NST) conditions. The TSST produced expected subjective and cardiovascular effects compared to the NST. However, in the i.n. OXT-TSST condition, positive subjective effects were lower and negative subjective effects were higher in women compared to PBO administration and compared to men. Further, latency to self-administer cannabis was longer in women than men and women self-administered less cannabis than men regardless of stress condition. There were no differences in cannabis craving as a function of sex, stress, or medication. These results suggest that OXT administration may lead to greater stress reactivity in recreational cannabis users, particularly women, and support growing evidence that sex differences should be carefully considered when examining the therapeutic potential of OXT.

1. Introduction

Cannabis remains one of the most widely used drugs in the United States (U.S.) and its use has been steadily increasing since 2002 (Center for Behavioral Health Statistics and Quality, 2015). Importantly, the number of individuals initiating cannabis use, as well as the amount and frequency of cannabis use by current cannabis smokers, is likely to continue to increase, in part due to the changing political and legal landscape (Martins et al., 2016) and the changing medical and public perception of cannabis use (Okaneku et al., 2015). Cannabis use typically begins in adolescence or young adulthood (Horey et al., 2012; Miech and Koester, 2012), and escalates in a subset of individuals (Behrendt et al., 2009; Kerridge et al., 2017), which may lead to Cannabis Use Disorder (CUD). For example, Gorelick (2018) postulated that CUD develops in approximately 10% of cannabis users, though Hasin et al., (2015) posited that about 30% of cannabis users may have some level of CUD.

Little is known about the factors that contribute to the transition from recreational to problematic cannabis use, defined as heavy use in quantity and frequency, negative consequences such as health problems (e.g., respiratory), sleep disruption, learning and memory issues, and psychiatric disorders, including CUD (Kerridge et al., 2017; Khan et al., 2013; Schepis et al., 2011). Given the epidemiological data demonstrating continued increases in cannabis use, understanding this transition has heightened significance. In support of this, the most recent Monitoring the Future survey found that cannabis has generally increased over the past year among high school students (Johnston et al., 2018).

One factor that appears to influence the likelihood of developing CUD is sex. Similar to other drugs of abuse, there is preclinical (Cooper and Craft, 2018; Craft et al., 2013; Fattore and Fratta, 2010) and clinical (Cuttler et al., 2016; Fogel et al., 2017) evidence that the effects of

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cannabinoids differ between males and females. Although CUDs are more prevalent in men than women (Kerridge et al., 2017; Lev-Ran et al., 2013), women progress faster from first cannabis use to problematic use ("telescoping") compared to men (Kerridge et al., 2017; Khan et al., 2013; Schepis et al., 2011). Women with CUDs also report more cannabis withdrawal symptoms (Copersino et al., 2010; Herrmann et al., 2015), and have more co-morbid psychiatric disorders (Khan et al., 2013), than men with CUDs. Further, the use of cannabis for medical conditions is growing more rapidly among women (e.g., Ryan-Ibarra et al., 2015).

However, relatively few controlled studies have examined sex differences in the effects of cannabis use in humans. Our group found that women reported significantly greater positive, or abuse-related, subjective effects of 'Take Again' and 'Good Drug Effect' after smoking a single cannabis cigarette compared to men matched for cannabis use (Cooper and Haney, 2014). In a subsequent study examining cannabis-induced analgesia (Cooper and Haney, 2016), men showed decreased pain sensitivity after active cannabis administration, relative to placebo (PBO) cannabis, whereas women did not. Greater subjective ratings linked to positive effects or abuse coupled with potentially increased amounts needed to alleviate negative effects such as pain could potentially increase the likelihood of developing a CUD, particularly in women. These findings indicate that a better understanding of the effects of cannabis-related sex differences is needed.

Another factor that may be related to the transition from recreational use to CUD is stress: individuals may smoke cannabis as a coping mechanism to alleviate stress (Copeland et al., 2001; Fattore, 2013; Hyman and Sinha, 2009) and the relief from stress may in turn lead to increased cannabis use and risk of developing CUDs (Hyman and Sinha, 2009). Several studies have shown that stress exposure in controlled laboratory settings increases cannabis craving in cannabis users (Buckner et al., 2011, 2016; McRae-Clark et al., 2011, 2013), particularly among individuals with social anxiety (Buckner et al., 2016). For example, McRae-Clark et al. (2011) found that among cannabis-dependent individuals, those exposed to the standard laboratory stressor, the Trier Social Stress Test (TSST), reported greater cannabis craving than those exposed to a stress-free condition. In addition, sex differences in stress reactivity have been shown in drug users (e.g., Back et al., 2005; Fox and Sinha, 2009), including cannabis users (Buckner et al., 2011; Bujarski et al., 2012; Chao et al., 2018). Specifically, in cannabis users, Bujarski et al. (2012) found that problems with cannabis use in women were associated with lower tolerance for distress compared to men, Chao et al. (2018) found that women reported greater ratings of nervousness in response to the TSST, whereas men did not, and Buckner et al. (2011) reported that women had greater stress-induced cannabis craving after a social stressor than men. Thus, it appears that female cannabis users may be more vulnerable to stress exposure than male cannabis users; however, whether stress directly increases cannabis use is not known and cannot be assumed since ratings of drug "craving" do not always predict drug use (Haney et al., 2010), highlighting the need to directly examine the impact of stress on cannabis use.

Oxytocin (OXT) is a peptide hormone that has been well documented to modulate physiological stress in laboratory animals (Ježová et al., 1996; Laguna-Abreu et al., 2005; Lukas et al., 2011; see Lee and Weerts, 2016 for review). Further, there is some evidence in humans that administration of intranasal (i.n.) OXT, attenuates stress responsivity (see Sippel et al., 2017 for review), including TSST-induced stress in borderline personality disorder patients (Simeon et al., 2011) and in men with low, but not high, emotion regulation abilities (Quirin et al., 2011). Additionally, in healthy controls, i.n. OXT appears to decrease subjective negative affect scores after TSST exposure compared to PBO in men, though not in women (Kubzansky et al., 2012).

Since stress is an important contributor to drug relapse (e.g., Aguilar et al., 2013; Sinha et al., 2011; Goodman and Packard, 2016; Kaye et al., 2017), the potential therapeutic role of OXT in substance use disorders has gained attention and there are a number of recent reviews discussing the preclinical and clinical literature on OXT and substance use (Bisagno and Cadet, 2014; Bowen and Neumann, 2017a,b; Kim et al., 2017; Lee et al., 2016; Lee and Weerts, 2016; McGregor and Bowen, 2012; Pedersen, 2017). In fact, Bowen and Neumann (2017b) elegantly describe the potential role of OXT (both endogenous and exogenous) on a range of behaviors (including stress reactivity) and the underlying neurobiological systems involved in substance use disorders. While the preclinical evidence for OXT playing a therapeutic role in substance abuse is relatively strong, the evidence in humans has been limited, with mixed results. For instance, i.n. OXT decreased alcohol craving in alcohol abusers (Mitchell et al., 2016), decreased alcohol withdrawal in alcohol-dependent individuals (Pedersen et al., 2013), had no effect on heroin craving in opioid-dependent individuals (Woolley et al., 2016), decreased cocaine craving, but not heroin craving, in individuals with opioid use disorder who use cocaine (Stauffer et al., 2016), and increased cocaine craving in cocaine-dependent individuals (Lee et al., 2014).

With respect to OXT and cannabis, rodent studies have suggested a complex interaction between CB1 receptors and oxytocin, particularly in terms of social behavior (e.g., Hillard, 2015; Wei et al., 2015), and the effect of oxytocin in human cannabis users and on cannabis-related behaviors appears equally complex. There is some evidence from two small pilot studies in cannabis users that i.n. OXT may be effective at (1) reducing self-reported cannabis use in cannabis-dependent individuals (Sherman et al., 2017), and (2) decreasing stress-induced cannabis craving and dehydroepiandrosterone (DHEA; a stress-related hormone) levels (McRae-Clark et al., 2013). Unfortunately these studies did not examine sex differences even though OXT is sexually dimorphic at the anatomical, neurochemical and behavioral levels (see reviews by Bisagno and Cadet, 2014; MacDonald and Feifel, 2013; Neumann and Slattery, 2016). However, a number of other studies in laboratory animals (Steinman et al., 2015) and humans (e.g., Cardoso et al., 2012; Flanagan et al., 2018; Kubzansky et al., 2012; Rilling et al., 2014; Xu et al., 2017) have demonstrated that the effects of i.n. OXT differ between males and females. Thus, sex likely plays a key role in the interaction between OXT, stress and drug use.

The present study used a within-subjects design to investigate the influence of stress and OXT on cannabis use and whether these effects varied as a function of sex. Specifically, we examined the effects of i.n. OXT, compared to PBO, on the response to the TSST and subsequent ad libitum cannabis self-administration in male and female recreational cannabis users. Based on the prevailing literature when this study was initiated, we hypothesized that 1) exposure to the TSST would increase cannabis self-administration (e.g. Buckner et al., 2011; McRae-Clark et al., 2011); 2) i.n. OXT would attenuate stress reactivity to the TSST and correspondingly decrease stress-induced cannabis self-administration (e.g. McRae-Clark et al., 2013); and 3) the effects of i.n. OXT on decreasing stress reactivity and decreasing cannabis self-administration would be more pronounced in women compared to men (e.g., Cardoso et al., 2012).

2. Methods

2.1. Participants

Men and women, ages 21–45, who participated in this study responded to online and newspaper advertisements soliciting male and female cannabis users. Individuals were told that the purpose of the study was to assess the role of the peptide hormone OXT on stress response, mood, vital signs, and cannabis use in men and women who smoke cannabis. The Institutional Review Board of the New York State Psychiatric Institute approved this study. Participants gave written informed consent before beginning the study and were paid for participation.

Men and women were carefully matched on a number of demographic variables. To be eligible, recreational cannabis users had to report smoking between 2 and 18 cannabis cigarettes per week (e.g., Moss et al., 2012) but could not meet moderate to severe DSM-5 (American Psychiatric Association, 2013) criteria for a CUD or report smoking cannabis daily. Individuals could meet criteria for mild CUD (but not a requirement), defined as endorsing 2–3 criteria; the most common symptoms endorsed by participants were using larger amounts of cannabis or using over a longer period than intended and cannabis craving.

Participants were medically and psychiatrically healthy based on a physical examination, a structured clinical interview, 12-lead electrocardiogram, clinical blood chemistries, heart rate (HR) and blood pressure (BP). Exclusion criteria included significant medical illness, regular use of medications (including hormonal contraceptives), pregnancy (verified by plasma chorionic gonadotropin hormone), and nursing. All women had regular menstrual cycles. In addition, no one endorsed any current psychiatric disorders or current moderate to severe criteria for any for substance use disorder and/or endorsed withdrawal symptoms, including cannabis (excluding caffeine and nicotine), based on the Mini International Neuropsychiatric Interview for DSM-5 (Sheehan, 2014). Individuals were excluded from the study if they were seeking treatment for their cannabis use and were given referrals for treatment providers.

2.2. General procedure

Individuals participated as outpatients at the New York State Psychiatric Institute for 2 Phases: an i.n. OXT phase and a PBO phase. Each phase was comprised of 3 sessions that were conducted on separate days: a sample session, a TSST-cannabis self-administration session, and a no stress (NST)-cannabis self-administration session. For women, sessions were scheduled during the follicular phase (days 3–10 after the onset of menstruation), as has been done in a number of our studies (e.g., Reed et al., 2010, 2012), since stress and OXT response, as well as cannabis effects, may differ as a function of menstrual cycle phase. For all participants, the two phases were conducted 4 weeks apart to allow for recovery of the effects of the TSST and to allow for women to be tested in the follicular phase of the menstrual cycle. The order of the TSST and NST sessions and i.n. OXT and PBO sessions were randomized and counterbalanced between groups and phases.

Each evening throughout the study, participants completed modified Daily Ratings Form (see Evans and Levin, 2003) using Qualtrics®, a web-based online survey. This 24-item questionnaire assessed daily mood, behavior, physical symptoms, amount of cannabis smoked (number of joints/blunts), other drug or alcohol use, and for women the onset and duration of menses. Women were instructed to call the laboratory when they started menstruating since sessions were scheduled during the follicular phase (e.g., Reed et al., 2010).

Participants were instructed not to take any medications or drugs (including cannabis), or drink alcohol, the day before each session, and they were instructed to refrain from smoking tobacco cigarettes after 8:00 pm the day before a session. To verify compliance, at the beginning of each session we assessed carbon monoxide and breath alcohol levels (Alco-Sensor III, Intoximeters, Inc., St. Louis, MO) and did a urine drug toxicology screen. If carbon monoxide levels were > 8 ppm, indicative that the participant had smoked cannabis or a cigarette prior to arrival, breath alcohol levels were positive, or a urine drug screen was positive for any drugs other than cannabis, the participant was sent home and the session was rescheduled. For women, blood samples were drawn for hormone assays to confirm that sessions were conducted in the follicular phase and a urine pregnancy test was performed.

At the end of each session, before leaving the laboratory, participants had to pass a field sobriety test and have stable mood and vital signs (BP ≤ 140/90 and HR ≤ 100). If the participant was impaired, they remained at the laboratory until the drug effects subsided. Participants were offered the choice between fare for mass transit or a car service each session and were instructed not to drive, take any medications, use any drugs including cannabis, or drink alcohol for the remainder of the day.

Table 1
Timeline of session study procedures.

TIME	EVENT
1100	Baseline Mood Q's[a]; BDI; BP & HR Light Lunch
1230	Food removed; HR monitor applied[b]
1315	I.N. OXT or PBO administration (counterbalanced)
1345	OXT, progesterone & estradiol levels Mood Q's; BP & HR
1400	TSST or NST (tests counterbalanced)
1420	Cannabis self-administration (3 h)
1720	Mood Q's; BP & HR
1750	Mood Q's; BP & HR
1820	Mood Q's; BP & HR
1830	Light dinner
1900	Mood Q's; BP & HR
1930	Mood Q's; BP & HR
End of session	Field sobriety test; end of session

BD I = Beck Depression Inventory; BP = Blood Pressure; HR = Heart Rate; I.N. OXT = Intranasal Oxytocin; PBO = Placebo; TSST = Trier Social Stress Test; NST = No Stress Test.
[a] Mood Q's = Questionnaires including State Anxiety Inventory, Positive & Negative Affect Schedule, Drug Craving Visual Analogue Scale, & Perceived Stress Scale.
[b] HR was continuously monitored throughout all sessions.

2.3. Trier Social Stress Test session

Table 1 shows the timeline of stress (TSST/NST)-medication (OXT/PBO)-self administration sessions. The TSST (Kirschbaum et al., 1993) began at 1400, 45 min after i.n. OXT or PBO administration. Participants had a 10-min preparation period, during which they were brought into a conference room and introduced to a 2-person committee. Participants were told the topic of a speech that they would be giving during a 5-min public speaking task and that the committee would be giving them a second 5-min task (the mental arithmetic task) following their speech. They were also told that they would be audio and video recorded. They were then given time to prepare their speech. After the public speaking and mental arithmetic tasks, participants completed subjective questionnaires and then the 3-hr cannabis self-administration period began. Since the TSST was administered twice, participants were randomly assigned a different topic for their speech and different numbers for the arithmetic task each TSST session.

2.4. No stress test (NST)

Similar to the TSST session, NST sessions began at 1400, 45 min after i.n. OXT or PBO administration (Table 1). On NST sessions, participants read a randomly assigned New Yorker article of neutral content; they were instructed to quietly read the article at their own pace for 20 min (to match the 20 min required for a TSST), similar to a previously used control session (e.g., McRae-Clark et al., 2011). They were told that they would not be tested on the reading material.

2.5. Cannabis sample sessions

The first session of each phase (sessions 1 & 4) was a sample session to orient participants to study procedures and familiarize them with the effects of the cannabis strength that would be available during the self-administration sessions for that phase. For each Sample session, participants reported to the laboratory at 0900. They completed a baseline subjective effects battery, had vital signs monitored and were given lunch. To approximate the timing of the self-administration sessions, beginning at 1400, participants smoked 1/4 of a cannabis cigarette (5.6% THC) once per hour at 1400, 1500 and 1600 and were instructed to pay close attention to how the cannabis made them feel since on other days they would have the opportunity to choose how much of the same strength cannabis cigarettes they would like to smoke. The subjective effects battery and vital signs were measured each hour after cannabis administration.

2.6. Cannabis self-administration sessions

During the second and third sessions of each phase (sessions 2 & 3 and 5 & 6), participants had a TSST or a NST session (Table 1). These sessions were separated by at least 48 h. Upon arrival at 1100, participants completed baseline questionnaires and then had lunch. At 1230, participants had a HR monitor attached to continuously record HR throughout the session. Forty-five minutes before the TSST or NST, 40 IU of i.n. OXT or matching PBO was administered by a study physician, similar to the procedures used in previous studies (e.g., McRae-Clark et al., 2013). Thirty minutes later, blood samples were drawn to measure levels of oxytocin and, in women, progesterone and estradiol to confirm menstrual cycle phase. At 1400, participants took part in the TSST or NST, immediately followed by a 3-hr cannabis self-administration period, described below.

To alleviate boredom and to better model naturalistic smoking behavior during the self-administration period, participants were provided an iPad® with a selection of TV shows, games and music. There were one-way mirrors between the laboratory and testing rooms so research assistants could monitor participants. The subjective-effects battery was completed multiple times during the session (see below). Participants were given a light dinner at 1800. All sessions were similar in duration regardless of the amount of cannabis self-administered in order to eliminate the potential influence of session duration on the decision to self-administer cannabis. Participants remained at the laboratory until 1830 or, if still impaired, until they passed a field sobriety test and mood and vital signs stabilized.

2.7. Cannabis administration

Cannabis cigarettes (5.6% Δ^9-THC; w/w, approximately 800 mg), provided by NIDA, were smoked in a plastic cigarette holder, and the exposed end was pinched to cover the leaves (e.g., Haney et al., 2010). Participants had the opportunity to smoke cannabis ad-libitum on self-administration sessions. Over a 3-hr period, they could request to smoke cannabis by indicating a specific number of cannabis portions desired; cannabis cigarettes had lines marking 1/4 increments so that each cannabis cigarette provided 3 portions (the final 1/4 of each cigarette remained in the cigarette holder). An investigator delivered the number of cannabis cigarettes requested, a lighter, and a smokeless ashtray. Participants smoked self-administered cannabis alone to minimize the social aspects of smoking that might influence cannabis use independent of study conditions. Participants could smoke at their own pace, but they had up to 10 min to smoke the portions requested. Throughout the 3-hr period they could make additional requests. The maximum number of cannabis cigarettes available was 4 cigarettes for a maximum of 12 portions (4 cigarettes × 3 portions) over the course of 3 h. Participants were not informed of how many portions they could smoke; in the event a participant requested > 12 portions they were simply told that no more portions were available that session.

2.8. Intranasal oxytocin and placebo dosing

Nasal spray bottles of OXT and matching PBO (0.9% saline) were purchased from Pharmaworld International Pharmacy (Zurich, Switzerland). Active OXT (Syntocinon manufactured by Novartis) was administered as a dose of 40 IU/ml delivered as 5 alternating sprays per nostril (0.1 ml per spray, for a total of 1.0 ml) for a total of 10 sprays spaced 30 s apart. To ensure accurate and controlled delivery, the nasal sprays were administered by the study physician and one of the investigators was present to provide verbal instructions and coordinate the precise timing of nasal sprays. Intranasal PBO was administered in the same way. Lab Roten (Ochsen, Switzerland) manufactured the matching the PBO under GDP guidelines and was identical to the OXT formulation but did not contain OXT.

2.9. Measures

2.9.1. Cognitive tests

The Wechsler Adult Intelligence Scale 3rd edition (WAIS-III; Wechsler, 1997) provided scores for Verbal IQ, Performance IQ, and Full Scale IQ, along with four secondary indices (Verbal Comprehension, Working Memory, Perceptual Organization, and Processing Speed). For this study, only the Vocabulary subscale (for Verbal IQ) and Block subscale (for Performance IQ) scores were calculated. The Stroop color and word test (Golden, 1978) yielded three scores based on the number of items completed on each of three stimulus sheets (a Word Page with color words printed in black ink, a Color Page with ‘Xs’ printed in color, and a color-Word Page with words from the first page printed in colors from the second page). An Interference score, which is the extent of delay in naming the color of an incongruent color word relative to naming the color of a congruent color word or of a neutral non-color word, was calculated. These two cognitive tests were only completed during screening.

2.9.2. Subjective effects questionnaires

The subjective-effects battery consisted of a 100-point visual analogue scale (VAS) of (1) perceived stress (“Upset,” “Nervous,” “Stressed,” “Confident,” “Angered”; adapted from Cohen et al., 1983); (2) sociability (“Sociable,” “Loving,” “Playful,” “Insightful”; adapted from Bedi et al., 2010); (3) other medication/drug effects (“Stimulated,” “Bored,” Anxious,” “Nauseated,” “Dizzy,” “Confused,” “Lonely,” “Elated,” “Blank,” and “Restless”); and (4) cannabis craving, the State portion of the State-Trait Anxiety Inventory (STATE; Spielberger et al., 1983), the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988), and a 5-item Drug Effects Questionnaire (e.g., “like the drug,” “feel the drug”; adapted from Reed et al., 2010). On TSST and NST sessions, the subjective-effects battery was completed before i.n. OXT or PBO administration, after i.n. OXT or PBO administration, immediately after stress exposure (i.e., Time 0), every 45 min during the cannabis self-administration period, and then approximately every 30 min until the end of the session.

2.9.3. Vital signs

Heart rate (HR) was measured continuously throughout each session using a heart rate monitor (Polar RCX 5™ or Polar S610i™ Heart Rate Monitor, Polar Electro Inc., Woodbury, NY). Systolic (SP) and diastolic (DP) blood pressure were measured each session at baseline and immediately after the stress test (and after the self-administration period for safety reasons) using a ADC e-Sphyg 2 (American Diagnostic Corporation, Hauppauge, NY, USA) or Sentry II vital signs monitor (Model 6100; NBS Medical Services, Costa Mesa, CA).

2.9.4. Estradiol and progesterone levels

Estradiol and progesterone levels were analyzed by a commercial CLIA-approved laboratory (Labcorp, Inc.). Estradiol and progesterone were measured at a single time point each session (at the same time that blood samples were drawn for OXT levels) to confirm the menstrual cycle phase.

2.9.5. Oxytocin radioimmunoassay analysis

Two blood samples were obtained in BD Vacutainer® spray-coated EDTA blood collection tubes to obtain plasma (0.5–1.0 ml final plasma volume) 30 min after administration of i.n. OXT or PBO. Following plasma preparation, plasma samples were added to tubes containing 50 µl 1.0% acetic acid, followed by freezing and storage at −20 °C until the day of analysis. On the day of the analysis, samples were applied directly to two sequentially attached pre-equilibrated sample preparation cartridges: QMA Plus Light anion exchange cartridge (Waters, Milford, MA, USA), with the non-retentate collected directly onto an Oasis HLB solid phase extraction cartridge (Waters, Milford, MA, USA). The combined cartridges were then washed with 4.5 ml of distilled deionized water, and the QMA cartridge was then discarded. The solid phase HLB cartridge was washed further with 4.5 ml 5% methanol, 1% acetic acid, 94% H_2O. The retained OXT was then eluted with 2 × 0.5 ml 70% ethanol, 1% acetic acid, 29% H_2O fractions, which were combined. Solvent was evaporated overnight via vacuum centrifugation. Samples were re-suspended with 250 µl buffer, and 100 µl was used in each of two duplicates to OXT analysis via [^{125}I]-oxytocin radioimmunoassay, according to manufacturer's instructions (Bachem, Torrance, CA, USA). In parallel with samples (all of which were run together for any given participant's sessions), a standard curve was obtained using serial dilutions of OXT standard.

The radioimmunoassay kit utilizes a polyclonal antibody raised in rabbits, immunized with a synthetic peptide as the immunogen. The antibody has < 0.1% crossreactivity with other neuropeptides, including the closely related arginine vasopressin. The assay has detection limits of 2.5 pM, with 1 ml of plasma analyzed. Intraassay coefficient of variation, calculated within replicates over days, is 7.8%; interassay coefficient of variation, calculated using standards across days, is 14.0%.

A subset of samples (~35%) could not be properly analyzed, due to aberrant results, with similar aberrance observed in the standard curve, and were likely due to problems in the specific batch of either the antibody or the [^{125}I]-oxytocin radiotracer. Levels of OXT were determined using the standard curve, with corrections for dilution and concentration.

OXT plasma levels were only measured at a single time point, 30 min after i.n. OXT (or PBO), but before the TSST (or NST), to confirm i.n. OXT vs. PBO administration.

2.10. Debriefing

At the conclusion of the study, a study investigator explained to participants the purpose of the stress exposure and that they were not actually audio or videotaped. In addition, the study team discussed the health and financial benefits of cannabis cessation. Although individuals were not included if they were seeking treatment and/or met criteria for moderate to severe CUD, they were encouraged to consider treatment for their cannabis use, and provided appropriate referrals for treatment.

2.11. Data analysis

Eighty-three recreational cannabis users (44 women and 39 men) met all inclusion/exclusion criteria, however 10 participants never started the study and 9 participants started but did not complete the study (6 had scheduling conflicts or lost interest, 1 had irregular periods, and 2 had high blood pressure during the first session and were discontinued for safety reasons). In addition, one male participant was not included in the final analyses since he did not self-administer any cannabis during the study. Therefore, data from 63 recreational cannabis users (32 women and 31 men) who met full study criteria and completed the study were used in these analyses.

For all analyses, results were considered statistically significant if $p \leq 0.05$. To reduce the potential for Type I errors due to unequal sample sizes and to avoid reporting results that were too liberal or too conservative (i.e., underestimate or overestimate sphericity), the Huynh-Feldt correction was reported when epsilon was > 0.75 and the Greenhouse-Geisser correction when epsilon was < 0.75 (Girden, 1992). Effect sizes were reported as partial eta squared calculations.

2.11.1. Demographics

t-Tests were used to compare demographics and data collected during screening.

2.11.2. Subjective and cardiovascular effects

The difference between baseline and Time 0 (i.e., the first time point after the completion of the TSST or NST) for each test session was calculated (i.e., change from baseline) for analysis of post-stress/pre-cannabis self-administration subjective effects, SP and DP. Since HR was continuously recorded during the entire session, HR was calculated as the difference between baseline and the peak HR reading during the TSST or NST each test session. Mean Time 0 change from baseline data were then analyzed using a 2 × 2 × 2 mixed-model ANOVA with a between groups comparison (males vs. females) and within groups comparisons of medication (i.n. OXT vs. PBO) and stress condition (TSST vs. NST). Since drug effects would not be present at baseline, mean Time 0 ratings of “like the drug” and “feel the drug” were analyzed using the same 2 × 2 × 2 mixed-model ANOVA as above.

2.11.3. Cannabis self-administration

Cannabis self-administration (i.e., number of portions requested and smoked), total gram amount of cannabis smoked during the self-administration period and latency to request the first portion of cannabis were analyzed using a 2 × 2 × 2 mixed-model ANOVA with a between groups comparison (males vs. females) and within groups comparisons of medication (i.n. OXT vs. PBO) and stress condition (TSST vs. NST). Additionally, for the TSST sessions only, the number of cannabis portions smoked during each 45-min block over the course of the 3-hr self-administration period was analyzed using a 2 × 2 × 2 mixed-model ANOVA with a between groups comparison (males vs. females) and within groups comparisons of medication (i.n. OXT vs. PBO) and time (45 min block).

3. Results

3.1. Demographics

Participant characteristics are presented in Table 2. There were no significant sex differences in demographics, depression or anxiety self-report scores (*ps* ≥ 0.05). Moreover, drug use history, including cannabis and other drug use were remarkably similar between men and women (*ps* ≥ 0.05), except for cigarette smoking. Of those who reported cigarette smoking, men smoked significantly more cigarettes/day than women (7.0 vs. 1.8, respectively; $p < 0.05$); however, both groups met the criteria for “light” cigarette smoking, defined as < 10 tobacco cigarettes/day (i.e., Schane et al., 2010).

3.2. Hormone levels

On average, women had a mean menstrual cycle length of 28.9 days (±2.9). On the test session days, mean estradiol levels were 52.38 pg/ml (±3.30) and mean progesterone levels were 0.55 ng/ml (±0.02), confirming that sessions were conducted during the follicular phase of the menstrual cycle.

Plasma oxytocin levels were obtained from a subset of 42 participants (18 men and 24 women); these levels were significantly higher after i.n. OXT compared to PBO administration (50.45 pg/ml (±5.8) vs. 30.14 pg/ml (±4.7); Medication effect: $F(1,39) = 5.26$, $p = 0.03$, $\eta_p^2 = 0.12$). Oxytocin plasma levels were also higher in women compared to men (54.20 pg/ml (±6.21) vs. 23.14 pg/ml (±2.4); Sex Effect: $F(1,39) = 12.59$, $p = 0.001$, $\eta_p^2 = 0.24$), particularly after i.n. OXT (68.43 pg/ml (±9.17) vs. 27.97 pg/ml (±3.79); $p = 0.0003$).

Table 2
Demographic characteristics of study participants.

	Women	Men
N	32	31
Age (Yrs)	29.1 (6.1)	27.9 (7.1)
Race (Blk/Wht/Other)	14/9/9	18/9/4
Ethnicity (Hisp/Non Hisp)	11/21	10/21
Education (Yrs)	14.7 (1.8)	14.1 (1.6)
Beck Depression (BDI) Score	3.6 (4.8)	4.1 (3.8)
State Anxiety inventory Score	27.6 (5.9)	28.0 (5.2)
Trait Anxiety Inventory Score	31.5 (4.7)	33.6 (5.7)
WAIS		
Vocabulary Subscale Score	39.6 (7.6)	38.0 (9.4)
Block Subscale Score	37.3 (10.7)	40.9 (12.0)
Stroop Interference Score	3.1 (8.6)	2.6 (6.6)
Cannabis		
# days/week	3.6 (1.2)	3.7 (1.0)
# joints/week	5.4 (2.9)	5.7 (3.5)
# joints/occasion	1.8 (1.5)	1.6 (1.0)
Alcohol		
# drinkers	28	25
#drinks/week	3.1 (0.6)	5.0 (1.5)
Tobacco cigarettes		
# smokers	5	7
# smoked/day	1.7 1.8 (0.8)	7.0 (4.8)

Note: All demographics are presented as means ± SD unless otherwise denoted. Raw scores are reported for the WAIS and Stroop Test. Cigarette smokers were defined as those smoking ≥1 cigarette/day.

3.3. Post-stress/pre-cannabis effects

3.3.1. Subjective effects

Fig. 1 shows negative subjective effects (State Anxiety scores, PANAS Negative Affect scores, and ratings of Angered; depicted as Time 0 change from baseline) as a function of stress condition, medication and sex. In general, negative subjective effects were highest in women when pretreated with OXT and exposed to the TSST (i.e., OXT-TSST condition). Specifically, State Anxiety scores and PANAS Negative Scores (Medication x Stress x Sex interaction: $Fs(1,61) \geq 5.20$, $ps \leq 0.03$, $\eta_p^2 \geq 0.08$; Fig. 2) and self-reported ratings of Nervous and Confused (Medication × Stress × Sex interactions: $Fs(1,61) \geq 4.59$, $ps \leq 0.04$, $\eta_p^2 \geq 0.07$; data not shown) were significantly higher in women in the OXT-TSST condition when compared to the PBO-TSST condition, both NST conditions, and men in the OXT-TSST condition ($ps \leq 0.05$). Of note, State Anxiety scores tended to be *lower* in men in the OXT-TSST condition compared to the PBO-TSST condition ($p = 0.09$; Fig. 1), though this did not reach statistical significance. In addition, ratings of Angered were significantly higher in women than men, particularly in the OXT condition (Medication × Sex interaction: $F(1,61) = 6.90$, $p = 0.01$, $\eta_p^2 = 0.10$; Fig. 1).

Fig. 2 shows several positive subjective effects (ratings of Loving, PANAS Positive Affect scores, and ratings of Sociable; depicted as Time 0 change from baseline) as a function of stress condition, medication and sex. Corresponding to the increase in negative subjective effects in women in the OXT-TSST condition, ratings of Loving (Medication x Stress x Sex interaction: $F(1,61) = 4.34$, $p = 0.04$, $\eta_p^2 = 0.07$; Fig. 2) and PANAS Positive Affect scores (Stress × Sex interaction: $F(1,61) = 7.49$, $p = 0.008$, $\eta_p^2 = 0.11$; Fig. 2) were significantly lower in women in the OXT-TSST condition when compared to the other medication and stress conditions and compared to men ($ps \leq 0.05$). In addition, ratings of Sociable were significantly lower (Medication × Sex interaction: $F(1,61) = 6.08$, $p = 0.02$, $\eta_p^2 = 0.09$; Fig. 2) in women than men, particularly in the OXT condition.

Exposure to the TSST significantly increased ratings of Angered, Anxious, Bored, Lonely, Sedated, Stressed and Upset (Stress effects: $Fs(1,61) \geq 6.90$, $ps \leq 0.01$, $\eta_p^2 \geq 0.10$) and significantly decreased ratings of Sociable, Confident and Elated (Stress effects: $Fs(1,61) \geq 7.69$, $ps \leq 0.007$, $\eta_p^2 \geq 0.11$) compared to the NST condition, regardless of medication condition or sex (data not shown). There were no significant medication or stress condition effects or group differences in cannabis craving or ratings of Blank, Dizzy, Nauseated, Playful, Restless, Stimulated, Upset, Like the drug and Feel the drug (all $ps > 0.05$; data not shown). With respect to overall sex differences, ratings of Insightful were significantly lower in women compared to men (Sex Effect: $F(1,61) = 4.97$, $p = 0.03$, $\eta_p^2 = 0.08$), regardless of medication or stress condition (data not shown).

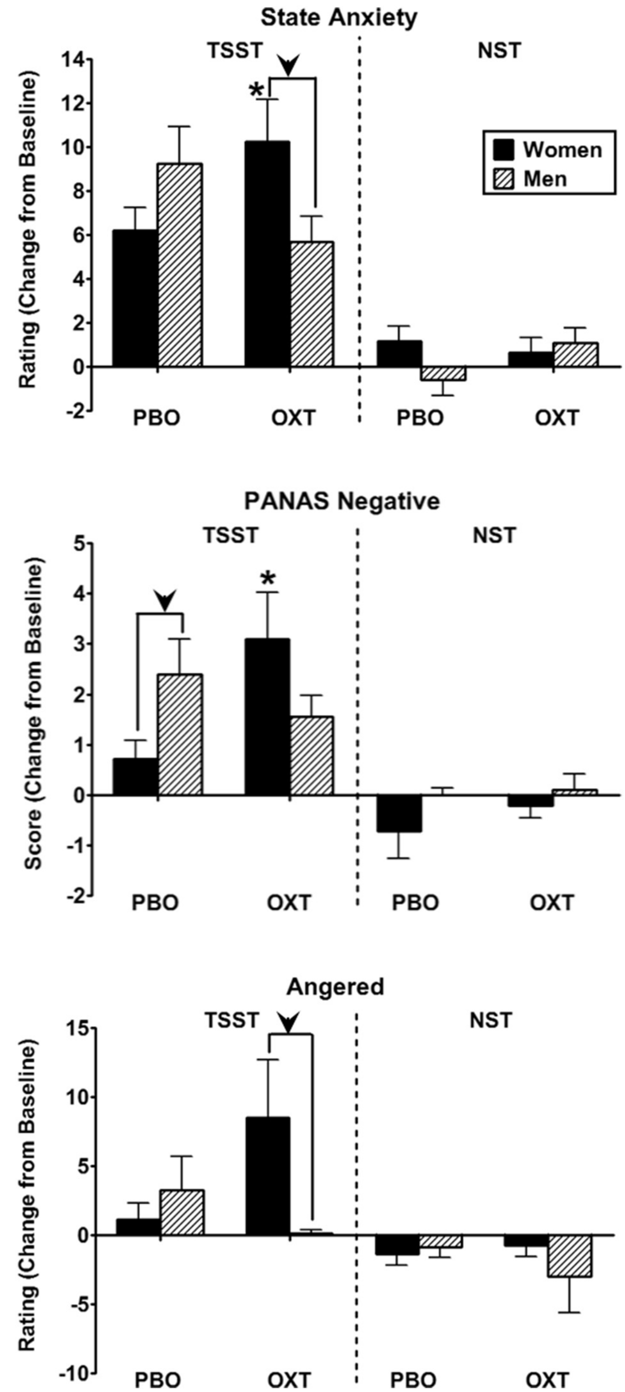

Fig. 1. Change from baseline ratings of State Anxiety, Negative Affect and Angered as a function of stress condition, medication condition and sex. * denotes a significant medication difference (PBO vs. OXT) within group ($p \leq 0.05$) and ▼ denotes a significant group difference (women vs. men) within medication condition ($p \leq 0.05$). Error bars represent +1 SEM.

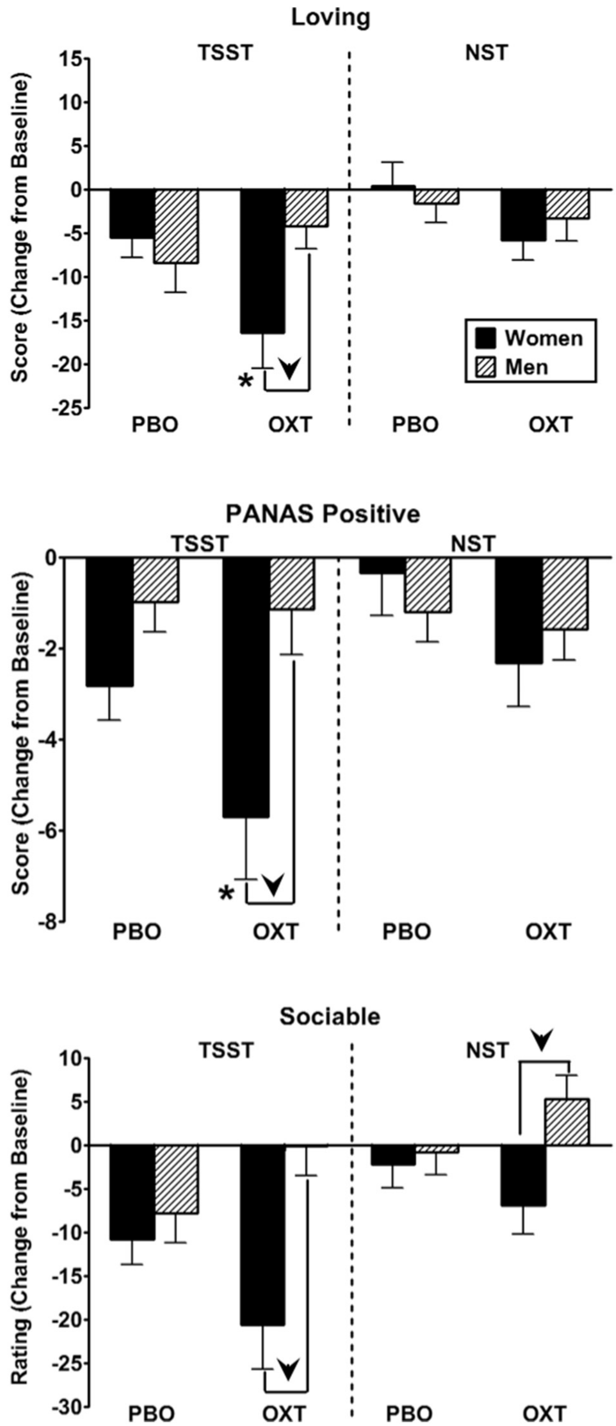

Fig. 2. Change from baseline ratings of Loving, Positive Affect and Sociable as a function of stress condition, medication condition and sex. * denotes a significant medication difference (PBO vs. OXT) within group ($p \le 0.05$) and ⮟ denotes a significant group difference (women vs. men) within medication condition ($p \le 0.05$). Error bars represent +1 SEM.

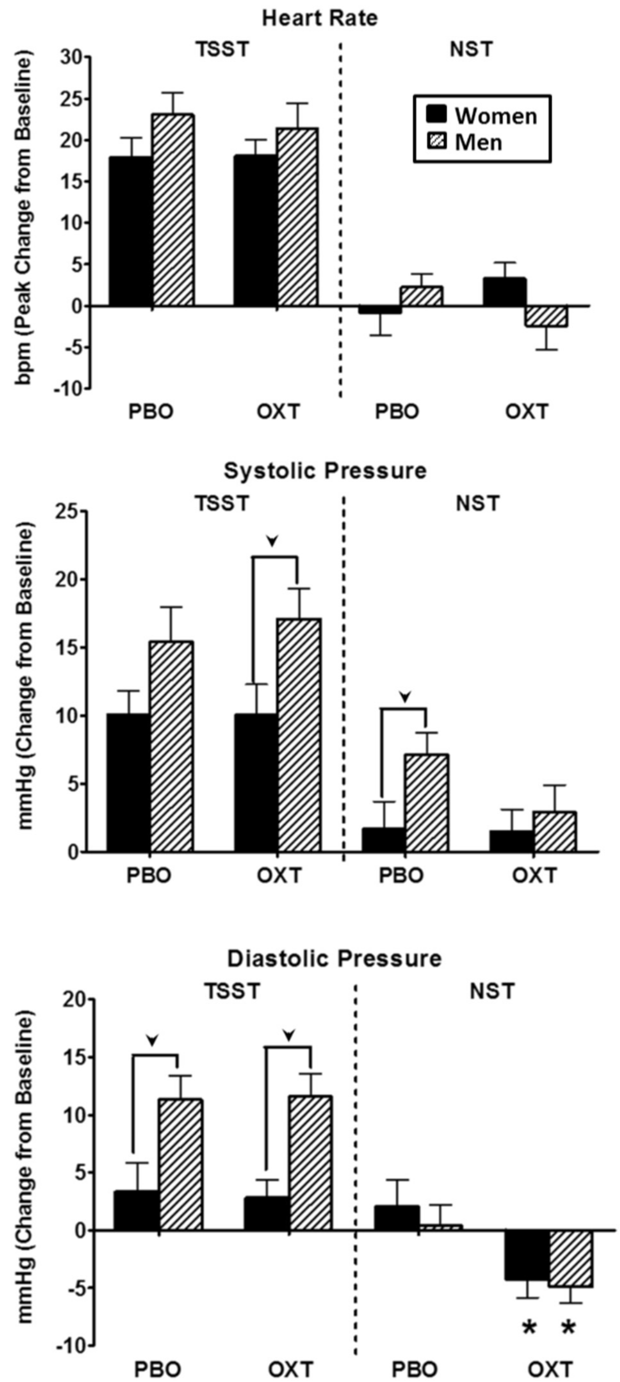

Fig. 3. Change from baseline measures of HR, SP and DR as a function of stress condition, medication condition and sex. * denotes a significant medication difference (PBO vs. OXT) within group ($p \le 0.05$) and ⮟ denotes a significant group difference (women vs. men) within medication condition ($p \le 0.05$). Error bars represent +1 SEM.

3.3.2. Cardiovascular effects

Fig. 3 shows HR, SP and DP as a function of stress condition, medication and sex. HR was significantly greater in the TSST condition than the NST condition (Condition effect: $F(1,61) = 130.17$, $p < 0.001$, $\eta_p^2 = 0.68$), regardless of medication condition or group. SP and DP were also significantly greater in the TSST condition than the NST condition (Condition effect: $Fs(1,61) \ge 20.92$, $ps < 0.05$, $\eta_p^2 \ge 0.47$), and men had significantly greater SP and DP compared to women in general (Group effect: $F(1,61) \ge 5.42$, $ps \le 0.02$, $\eta_p^2 \ge 0.08$).

3.3.3. Cannabis self-administration

Fig. 4 shows the number of cannabis portions requested and smoked during the self-administration period as a function of stress condition, medication and sex. Women requested fewer cannabis portions than men in the TSST condition regardless of medication condition (Stress × Sex interaction: $F(1,61) = 3.91$, $p = 0.05$, $\eta_p^2 = 0.06$; Fig. 3). There was also a significant sex difference in the number of portions

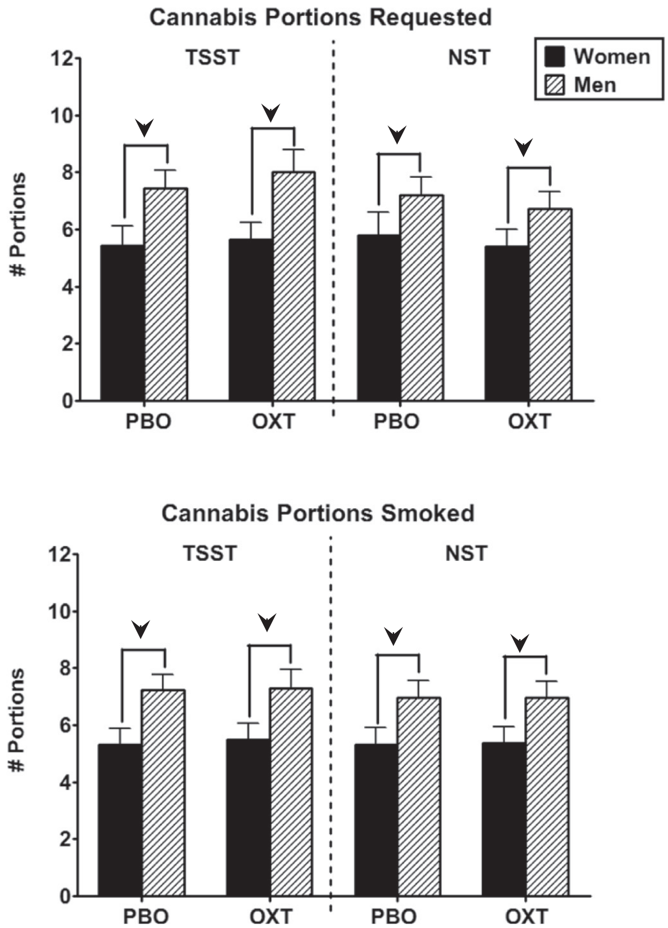

Fig. 4. Number of cannabis portions requested and smoked as a function of stress condition, medication condition and sex. ➤ denotes a significant group difference (women vs. men) within medication condition ($p \leq 0.05$). Error bars represent +1 SEM.

smoked (Sex Effect: $F(1,61) = 5.51$, $p = 0.02$, $\eta_p^2 = 0.08$; Fig. 4), where women smoked fewer cannabis portions than men (~5.4 vs. ~7.1, respectively) regardless of medication or stress condition. In addition, women in the OXT-TSST condition waited longer (~14 min) to request the first portion of cannabis than in any other condition (~7 min) and compared to men (~4 min) (Medication x Stress x Sex interaction: $F(1,61) = 5.35$, $p = 0.02$, η_p^2 0.08; data not shown). Of the portions smoked, there were no significant differences in the amount of cannabis smoked in grams ($p > 0.05$; data not shown) as a function of sex, stress or medication condition.

Fig. 5 shows the number of cannabis portions smoked during each 45-min block of the 3-hr self-administration period after TSST exposure as a function of medication condition and sex. Men smoked more than women during the first 45 min of the self-administration period (Time Effect: $F(5,305) = 49.59$, $p < 0.05$, $\eta_p^2 = 0.54$; Sex Effect: $F(1,61) = 6.34$, $p = 0.02$, $\eta_p^2 = 0.09$), and this was particularly evident in the OXT-TSST condition ($p = 0.02$).

4. Discussion

The most important and striking finding from the present study was that OXT produced an increase in TSST-induced subjective stress (greater negative subjective ratings and lower positive subjective ratings) compared to PBO in female cannabis users. By contrast, in male cannabis users, OXT produced small but non-significant decreases in TSST-induced negative subjective effects. These results contrast with our hypothesis that OXT would decrease stress reactivity to the TSST

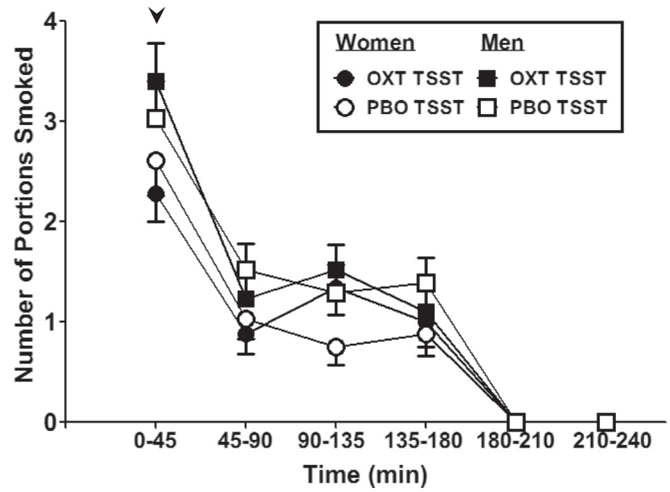

Fig. 5. Number of cannabis portions smoked in each 45-min block of the 3-hr self-administration period after the TSST as a function of medication condition and sex. ➤ denotes a significant group difference (women vs. men) within medication condition ($p \leq 0.05$). Error bars represent ± 1 SEM.

based on previous studies suggesting that OXT is a prosocial and anti-stress neuropeptide in animals, including humans (e.g., Kim et al., 2017; Smith and Wang, 2014; see Sippel et al., 2017 for review). For example, OXT (24 IU) has been shown to reduce cortisol levels and subjective stress in men in response to the TSST if participants also had social support (Heinrichs et al., 2003). OXT (24 IU) has also been shown to decrease ratings of anxiety in men before the TSST, but not during or after the TSST (de Oliveira et al., 2012), decrease stress-induced increases in salivary cortisol in men with low, but not high, emotion regulation, using a variant of the TSST (Quirin et al., 2011), and reduce negative self-appraisal among men with high trait anxiety subjected to a speech task (Alvares et al., 2012). Further, in a study comparing mixed gender samples of patients with Borderline Personality Disorder (BPD) and healthy controls, 40 IU OXT, compared to PBO, prevented stress-induced dysphoria in patients with BPD, but not in healthy controls (Simeon et al., 2011).

Our results are also discordant with the only other study that examined the effects of OXT on stress in cannabis users. McRae-Clark et al. (2013) found that OXT (40 IU) produced a decrease in ratings of anxiety and DHEA (but not cortisol) levels after the TSST relative to cannabis users who received PBO in eight cannabis users, predominately male (75%), who met criteria for cannabis dependence. Even though that study administered the same dose of OXT and employed the TSST to induce stress in cannabis users, it differed considerably from the present study in several respects (i.e., sample size, gender breakdown, and level of cannabis use), and, notably, there may be important differences between heavy users who are cannabis-dependent (or have a CUD) and recreational users.

It is important to note that in the present study the TSST reliably induced stress as indicated by increased negative subjective ratings and cardiovascular effects in recreational cannabis users relative to the NST, replicating previous studies across a range of populations (e.g., Kirschbaum et al., 1993; Dickerson and Kemeny, 2004; Foley and Kirschbaum, 2010; Maki et al., 2015; McQuaid et al., 2016; McRae-Clark et al., 2013; Childs et al., 2017; Sack et al., 2017). However, as discussed above, strong sex differences in stress response emerged in the OXT condition, but few differences were found in the PBO condition. Other studies have found inconsistent results regarding sex differences in subjective and neuroendocrine response to stress (Back et al., 2005; Brady et al., 2006; Kelly et al., 2008; Kirschbaum et al., 1999; Reschke-Hernández et al., 2017; see review by Kudielka and Kirschbaum, 2005). A previous study by our group (Chao et al., 2018) in heavy cannabis users, found that women had an enhanced subjective and physiological stress response to the TSST compared to men. In the present study among recreational cannabis users, there were only modest sex differences in response to the TSST in cannabis users when PBO OXT was administered, and in contrast to previous studies, HR, BP and negative subjective effects were increased more in men relative to women. The primary difference between these two studies was the level of cannabis use. Regardless, these findings suggest that the increased stress response after i.n. OXT in women in the present study cannot be attributed solely to exposure to the TSST.

Further, few studies examining the role of OXT in humans have adequately examined sex differences (see MacDonald, 2013; MacDonald and Feifel, 2013; Bolea-Alamanac et al., 2018). One study that examined sex differences in OXT's effects on the response to the TSST found that 24 IU OXT increased ratings of anger in women yet decreased negative subjective effects in men (Kubzansky et al., 2012), similar to the current study despite differences in the dose of OXT tested (24 IU vs. 40 IU). In addition, in a study examining sex differences in the effects of 40 IU OXT on couples' conflict resolution, Flanagan et al. (2018) found that OXT increased negative attributions (e.g., statements of blame) and decreased positive attributions in women, whereas, in men, OXT decreased negative attributions and both PBO and OXT decreased positive attributions. Similarly, 24 IU i.n. OXT reduced the relevance of positive social interactions in women (Xu et al., 2017). These findings are consistent with recent studies in rodents indicating that OXT may produce anxiogenic effects in females (Duque-Wilckens et al., 2018; Steinman and Trainor, 2017; Steinman et al., 2016). Taken together, these studies indicate that OXT has differential effects in males and females and supports the growing evidence that OXT can exaggerate the effects of stress, particularly in females.

We also did not see differences in cannabis craving in men and women as a function of stress or medication condition, in contrast with other laboratory studies demonstrating that stress exposure increases drug craving (see Hyman and Sinha, 2009; Jones and Comer, 2013; Sinha et al., 2011). For example, in cannabis users with social anxiety disorder, social stress increased cannabis craving relative to a control condition (Buckner et al., 2016). Similarly, in cannabis-dependent individuals, cannabis craving increased in response to the TSST, and OXT (40 IU) attenuated this effect (McRae-Clark et al., 2013). However, in cocaine users, OXT (24 IU) *increased* the desire to use cocaine relative to placebo (Lee et al., 2014). Several factors may have obscured our ability to detect any potential effect of stress or OXT on cannabis craving, including the fact that participants with social anxiety were excluded and our sample consisted of recreational cannabis smokers who did not meet moderate to severe criteria for CUD.

To our knowledge, this is the first controlled laboratory study in humans to examine sex differences in cannabis self-administration using an ad libitum procedure. On average, participants smoked approximately 6 portions of cannabis on the self-administration sessions, with the greatest number of portions smoked within the first 45 min of cannabis availability. Despite similar self-reported levels of cannabis use before the study, men smoked more cannabis portions than women regardless of stress or medication condition, contrary to our hypothesis that stress would increase cannabis craving and self-administration. Given that we did not observe stress-induced changes in cannabis self-administration and there were minimal sex differences in stress reactivity when PBO was administered, it is not surprising that OXT also did not decrease cannabis self-administration.

However, there was evidence that OXT and stress interacted with cannabis self-administration. As mentioned above, women experienced the greatest TSST-induced subjective stress after OXT administration, and it was under these conditions that women also took significantly longer to initiate cannabis smoking. Further, in the TSST-OXT condition, men smoked the greatest number of portions within the first 45 min of the cannabis self-administration period, whereas women smoked the least number of portions under the same conditions. It is possible that given the short half-life of OXT and the transient stress response to the TSST, the 3-hour self-administration period may have hampered our ability to detect a direct effect of stress and OXT on cannabis self-administration. Additionally, a more robust effect may have emerged with a different group of cannabis users, such as heavier users or those with CUD.

4.1. Strengths and limitations

This study had a number of strengths, including: 1) directly comparing a large sample of men and a large sample of women who were carefully matched on cannabis use (quantity and frequency), 2) using a standard psychological stressor, 3) measuring cannabis self-administration and 4) controlling for the potential confound of fluctuations across the menstrual cycle by testing women exclusively in the follicular phase of the menstrual cycle.

In terms of limitations to the study design: Only a single dose of i.n. OXT was tested and neuroendocrine indices of stress responsivity were not obtained; however, our primary goal was to examine the effects of OXT on stress-induced cannabis self-administration and we did not want to confound this primary behavioral outcome measure with repeated collection of neuroendocrine samples via blood or saliva. Another potential limitation is that the timing of the OXT administration prior to the TSST may have precluded our ability to observe an effect on cannabis self-administration, which occurred over an hour later. This study was designed to be consistent with previous studies that have examined the effects of OXT on stress reactivity; OXT was administered before exposure to the TSST in all of those studies. We hypothesized that OXT would decrease stress reactivity, thus the proximity of OXT administration to TSST exposure was key, and that a reduction in stress reactivity would lead to a reduction in cannabis self-administration even if OXT did not directly alter cannabis self-administration. Future research would benefit from examining the direct effect of OXT on cannabis self-administration. Additionally, expectations of using cannabis after stress exposure, such as stress relief or a perceived socially desirable response bias in cannabis self-administration (particularly in women), may be of interest to explore during cannabis self-administration in the future to better understand stress-related cannabis use.

Regarding the measurement of OXT levels following OXT administration, the radioimmunoassay yields oxytocin-like immunoreactivity, and although there is no known crossreactivity, non-OXT binding cannot be ruled out. However, it is also important to note that OXT plasma levels were only assessed at a single time point since the objective of this measure was to simply confirm that the i.n. OXT spray was absorbed and increased plasma levels of OXT relative to placebo.

5. Conclusions

In summary, there was no evidence that stress induced by the TSST altered cannabis craving or cannabis self-administration among a group of recreational cannabis users when cannabis was available immediately after stress exposure. Further, there was no evidence that OXT attenuated the response to stress; instead OXT increased stress reactivity in women but not in men. While OXT did not appear to directly alter cannabis self-administration, there was some evidence that OXT and stress interacted with cannabis self-administration since, in the OXT-TSST condition, women waited longer to begin smoking cannabis and smoked less cannabis than men in the first 45 min of the self-administration session. Taken together, while there is growing preclinical evidence that OXT may have therapeutic benefits for addiction (Lee and Weerts, 2016; McGregor and Bowen, 2012; Pedersen, 2017), there is also increasing evidence that the effects of OXT on stress, and other behaviors, are more complex than initially assumed (e.g., Shamay-Tsoory and Young, 2016; Szymanska et al., 2017), and OXT may actually exacerbate stress response (e.g., Eckstein et al., 2014;

Kubzansky et al., 2012) rather than ameliorate it (e.g., McRae-Clark et al., 2013) in certain circumstances, particularly in females. Given the potential role of stress in drug use, clearly more clinical OXT research is needed (e.g., Insel, 2016). This is emphasized by Bowen and Neumann (2017b) in their recent review of the role of OXT in substance use, where it is noted that though there may be a potential utility for OXT in substance use treatment, there is a paucity of clinical studies and the results of the existing literature are mixed. Therefore, there are overarching issues that still need to be addressed, such as a better understanding of OXT in the brain. The results of the present study confirm this gap and highlight the importance of including women and examining sex differences in future studies evaluating the therapeutic potential of exogenous OXT for substance use disorders, as well as other treatment indications.

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