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Sex Differences in the Subjective and Reinforcing Effects of smoked cannabis

Stephanie Lake[1,2], **Margaret Haney**[3], **Ziva D. Cooper**[1,2,4]

[1]UCLA Center for Cannabis and Cannabinoids, Jane and Terry Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, 760 Westwood Plaza, Suite 38-418, Los Angeles, CA, 90095

[2]Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California, Los Angeles, 757 Westwood Plaza, Los Angeles, CA, 90095

[3]Department of Psychiatry, Division on Substance Use Disorders, Columbia University Irving Medical Center, New York State Psychiatric Institute, 1051 Riverside Drive, Unit 120, New York, NY, 10032.

[4]Department of Anesthesiology and Perioperative Medicine, University of California, Los Angeles, 757 Westwood Plaza, Suite 3325, Los Angeles, CA, 90095

Abstract

Preclinical studies have shown sex-based differences in the reinforcing effects of cannabinoid 1 receptor agonists such as delta-9-tetrahydrocannabinol (THC). This study sought to test whether these sex differences translate to humans by assessing the subjective and reinforcing effects of smoked cannabis in male and female volunteers. We pooled data (n = 68; 55M, 13F) from two within-subject randomized controlled trials of healthy, ≥weekly cannabis users comparing the subjective and reinforcing effects of smoked active (~25 mg THC) versus placebo cannabis (0 mg THC). Subjective ratings of drug effects and mood were measured using visual analog scales and reinforcing effects were measured with a cannabis self-administration task. Sex-dependent outcomes were explored using generalized linear mixed models. Under active cannabis conditions, female participants reported greater reductions from baseline in cannabis craving, and significantly

Send correspondence to: Ziva D. Cooper, PhD, Director, UCLA Center for Cannabis and Cannabinoids, Jane and Terry Semel Institute for Neuroscience and Human Behavior, UCLA, Associate Professor, Departments of Psychiatry and Anesthesiology, UCLA, 760 Westwood Plaza, Suite 37-418, Los Angeles, CA, USA, 90025, **Tel:** (310) 206-8542, zcooper@mednet.ucla.edu.

Author Contributions:

ZDC and MH were responsible for the funding acquisition, study concept and design. ZDC and MH implemented and oversaw the primary research studies from which data were generated. SL developed the analytic approach and conducted the statistical analysis. SL drafted the manuscript. MH and ZDC provided critical revision of the manuscript. All authors critically reviewed content and approved final version for publication.

Conflict of Interest: Outside of this work, ZDC reports receiving study drug from Canopy Growth Corp and True Terpenes, and study-related materials from Storz & Bickel. MH has served on the scientific advisory board for Pleo Pharma.

Ethics approval statement: Both outpatient studies from which data were collected for this analysis were conducted in accordance with the Declaration of Helsinki and approved by the New York Psychiatric Institute Institutional Review Board.

Clinical trial registration: The primary studies from which data were derived for this secondary analysis were initiated and completed before existing regulations required that all human subjects research be registered on clinicaltrials.gov. We intentionally did not register our studies in clinicaltrials.gov, not simply because study outcomes were not clinical in nature, but because we did not want to expose prospective participants to our recruitment criteria, which included information that may be leveraged to gain study entry under false pretenses.

higher cannabis-specific ratings of strength, liking, willingness to take again, and good effect, compared to males (interaction $p<0.05$). Placebo and active cannabis were self-administered by 22% and 36% of male participants, respectively, and by 15% and 54% of female participants, respectively. Receipt of active cannabis significantly increased likelihood of self-administration ($p=0.011$), but a sex difference was not detected ($p=0.176$). Although females were more sensitive to certain positive subjective effects of active cannabis, they were not more likely than males to self-administer it. These findings highlight the need to test sex differences as a primary objective in experimental studies and may shed light on accelerated trajectories from initiation to cannabis use disorder observed among women.

Keywords

Cannabis; Tetrahydrocannabinol; Acute drug effects; Sex differences; Cannabis use disorder

1. INTRODUCTION

Cannabis is one of the most used psychoactive substances in the world. In the United States (U.S.), the prevalence of cannabis use has increased noticeably since the early 2000s (1); in 2020, over 49 million people (~18%) aged 12 or over in the U.S. were estimated to have used cannabis (2). More than 35 U.S. states and the District of Columbia have adopted regulatory approaches to medical and/or non-medical cannabis (3), signifying a societal shift away from criminalization and towards normalization of cannabis use.

Epidemiology of cannabis use is marked by important sex (biological) and gender (socio-cultural) differences (herein, we use “male” and “female” descriptors when referring to sex assigned at birth, and “men” and “women” when describing broader observations that span sex and gender). Historically, more men than women have used cannabis, but in the era of legalization, rates have increased among women (4) with evidence of a narrowing prevalence gap between males and females born after 1995 (5). Indeed, women make up the fastest growing consumer demographic in many legal markets in the United States (6, 7) and may differ from men in their motivations for using cannabis. For example, in samples of people using cannabis for therapeutic purposes, women more often report using cannabis for relief of anxiety (8, 9) and were more likely to increase their use of cannabis to manage anxiety after the onset of the COVID-19 pandemic (10).

From a public health standpoint, understanding sex and gender differences in cannabis’ subjective and reinforcing effects is critical. Along with higher overall prevalence rates (11), men tend to initiate use at a younger age, engage in higher frequency and quantity use (12, 13), and more often meet diagnostic criteria for cannabis use disorder (CUD) (14, 15). However, women have shown quicker progression from initiation to regular use (16) and CUD (14, 17, 18), and from onset of regular use to treatment for CUD (19), consistent with a “telescoping effect.” Notably, women with CUD report more severe cannabis withdrawal symptoms (20) and are more likely to experience comorbid anxiety (18, 21, 22), mood disorders (18, 21), and suicidality (22) relative to men. A recent study in patients licensed to use cannabis for chronic pain recorded significantly more adverse events among women,

including central nervous system and psychological problems (23), raising concerns of increased susceptibility to adverse effects from long-term use.

Sex differences in acute response to cannabinoid type 1 (CB1) receptor agonists like delta-9-tetrahydrocananbinol (THC), the primary psychoactive component of cannabis, have been documented in animal research. Females appear to: be more sensitive to CB1 receptor agonist acute analgesic and reinforcing effects, develop greater tolerance to the analgesic effects, and exhibit more severe withdrawal after chronic exposure including anxiety-like behaviors (24). The preclinical literature also provides important clues into the potential underlying mechanisms driving sex-based differences in relationships between THC exposure and adverse outcomes. These proposed factors include differences in CB1 receptor density and signaling, and increased production of THC's active metabolite (11-hydroxy-tetrahydrocannabinol, or 11-OH-THC) associated with circulating estradiol levels in females (24).

Human experimental studies testing sex differences in acute cannabis effects have been less consistent. For example, we conducted two placebo-controlled, double-blind studies involving smoked cannabis among people who use cannabis ≥weekly. In the first study, we found higher subjective ratings of drug strength, effect, liking, and willingness to take the drug again associated with cannabis administration among females relative to males (25), but we did not observe the same effect in the second study (26). Since then, studies involving healthy volunteers who use cannabis at moderate (27) or low frequencies (28, 29) have noted greater drug effect ratings among female relative to male participants, but only at lower doses; others reported no significant sex differences (30, 31). However, comparing sex effects between studies is rendered difficult by varying THC doses, preparations, modes of administration, levels of participant cannabis use experience, and subjective endpoints tested.

One limitation spanning previous human experimental research in this area is the reliance on subjective measures alone as an index of potential development of high-risk patterns of use (sometimes referred to as "abuse liability") (26, 27, 30). Self-administration models used in animal and human research are considered the "gold standard" to determine the reinforcing effects of psychoactive substances and to test potential effectiveness of pharmacotherapies for substance use disorders (32). Preclinical studies show that females self-administer CB1 receptor agonists at a higher rate than males (33), but no human studies to date have examined sex differences in cannabis self-administration.

Using data pooled from two within-subject, randomized placebo-controlled studies, we sought to explore sex differences in smoked cannabis' reinforcing effects via the completion of a self-administration task. We also compared subjective ratings of mood and drug effects over time after drug administration between male and female participants. Of note, some of the subjective measures data from a subset of participants in the current sample have been previously analyzed for sex differences (data from 19% of current participants were included in one study (25), and 18% in another (26)), and are included herein to provide supporting data to complement the self-administration analysis in this sample of individuals.

2. METHODS

2.1. Data sources

Data for this study came from two within-subject, double-blind, randomized placebo-controlled trials testing the acute effects of smoked cannabis. Study 1 (n = 49) was designed to measure the effect of naltrexone maintenance on cannabis self-administration and subjective drug effects (34). Study 2 (n = 19) was designed to measure the effect of cannabis on the analgesic, subjective, and reinforcing effects of two low doses of oxycodone (35). Details specific to the primary study objectives and design are available in their respective primary publications. For the present analysis, we retained data from two experimental sessions per participant in which placebo (0 mg THC) or active cannabis (~22 mg THC [study 1] or ~ 31 mg THC [study 2] was administered alone (i.e., without naltrexone [study 1] or oxycodone [study 2]).

Both outpatient studies were conducted at the New York State Psychiatric Institute in accordance with the Declaration of Helsinki and approved by the New York Psychiatric Institute Institutional Review Board.

2.2. Participants

Participants were healthy volunteers aged 21–50 years with recent cannabis smoking experience. All participants provided a detailed drug and medical history, received medical and psychiatric evaluations, and provided written informed consent to participate in the trial. Participants were eligible for inclusion in each study if they were deemed healthy (via physical examination, psychiatric assessment, electrocardiogram, urinalysis and blood chemistry), not regularly using drugs other than cannabis, alcohol, nicotine, or caffeine (determined through urine toxicology and self-report) and not seeking treatment for their cannabis use. Eligible participants smoked cannabis ≥weekly in the four weeks before screening (study 1: ≥4 times/week; study 2: ≥3 times/week), as determined through urine toxicology and self-report. Exclusion criteria included meeting DSM-IV revised criteria for Axis I psychopathology, problematic alcohol use, current use of unregulated drugs aside from cannabis, regular use of prescription or over-the-counter medication (except oral contraceptives), and current pain (study 2). In addition, pregnant or breastfeeding participants were excluded.

2.3 Study drug

Each study used 800 mg dried cannabis (0% THC or 5.5–6% THC) cigarettes obtained from the National Institute of Drug Abuse. Cigarettes were stored frozen in an airtight container and humidified at room temperate for 24 hours prior to the session. Both studies followed a puffed paced-smoking procedure (36) in which participants inhaled one puff (5-second inhalation, 10-second hold) every minute until 50% (study 1) or 70% (study 2) of the cigarette had been smoked.

2.4. Experimental sessions

Details specific to the experimental sessions are available in each study's primary publication. In brief, participants provided a baseline measure for all Subjective Effects-

Visual Analog Scale (SE-VAS; see "Assessments") items. Heart rate and blood pressure were measured using a Sentry II vital signs monitor (Model 6100: NBS Medical Services, Costa Mesa, CA). After active or placebo cannabis administration (see "Study drug"), cardiovascular measures and subjective effects were measured at 15, 30, 60, 90, and 120 minutes. At one time-point post-administration (150 minutes in study 1; 195 minutes in study 2), participants completed the cannabis self-administration task (Table 1).

2.5. Assessments

2.5.1. Subjective Effects-Visual Analog Scale (SE-VAS)—Participants rated their mood and physical symptoms on a modified 44-item, computerized VAS measuring affective and physical subjective drug effects (37).

Cannabis Rating Form (Cannabis-RF): Subjective cannabis-related effects were assessed with a 5-item VAS asking participants to rate the strength of the drug effect, good drug effect, bad drug effect, drug liking, and willingness to take the drug again (38).

2.5.2. Cannabis reinforcing effects—Participants had the opportunity to purchase up to 3 puffs ($1 per puff) of the same strength of cannabis that they had smoked in the morning (~3 hours earlier). The money used to purchase cannabis came out of the participants' study earnings. Participants smoked the number of puffs purchased via the paced puffing procedure.

2.6. Data analysis

Participants' sex was collected upon study screening. Demographic characteristics between male (n = 55) and female (n = 13) participants were compared using Mann-Whitney U tests (continuous variables) or Fisher's test (categorical variables).

To minimize likelihood of Type I errors, we examined a subset of SE-VAS measures that we hypothesized to differ as a function of sex based on previous findings. These were: "High", "Crave cannabis", "Tired", "Stimulated", "Anxious", and "Good Effect" (25, 29, 39, 40). Change from baseline scores were calculated. We examined four Cannabis-RF measures (strength of drug, liking of drug, willingness to take again, and good drug effect), all recorded post-drug administration (not baseline-subtracted). We used generalized linear mixed models to test the effects of drug condition (active cannabis and placebo cannabis), sex (male and female), and time since drug administration on subjective effects. Based on visual inspection of the data, time was entered as a continuous variable for all outcomes except "Crave cannabis" and "Anxious", for which five post-administration categorical time-points were entered. We incorporated random intercepts per person to account for repeated measures over time and across drug conditions within subjects. We tested for interactions between treatment condition, sex, and time (i.e., a three-way interaction and all possible two-way interactions). Type III F-tests were used to determine significance of interactions and main effects. Categorical variables (drug condition, sex) were assigned deviation contrasts to allow for a main effects interpretation of all lower-order model parameter estimates and for correspondence with Type III F-test results (41). In cases of significant three-way interaction, we conducted post hoc tests to compare estimated

marginal means of linear time trends (where appropriate) for males and females across active and placebo drug conditions. We also computed estimated marginal means from a model with categorical time-points to identify data collection times in which males and females differed under each drug condition. In cases of no significant three-way interaction, we checked for significance of lower-order sex interactions (i.e., sex*drug or sex*time) and conducted post hoc pairwise tests to compare estimated marginal means collapsed across time (sex*drug) or marginal means of linear trends collapsed across condition (sex*time) between males and females.

We dichotomized the number of self-administered puffs into ≥1 vs. 0 and modelled sex-dependent effects of drug condition on self-administration with a generalized linear mixed model with binomial distribution, specifying random intercept per person. As self-administration was only assessed once per study session, only drug condition, sex, and a two-way interaction term were included in this model.

For each outcome, we tested whether the model results were robust to the inclusion of body mass index (BMI; continuous) and study of origin (trial 1 and trial 2; accounting for slight differences in active THC dose between trials) as covariates. Since the inclusion of these variables did not meaningfully change the model estimates, we report only the results of the unadjusted models.

All statistical analyses were conducted in R using RStudio (“lmertest” and “emmeans” packages). Significance tests were two-tailed and alpha was set to 0.05.

3. RESULTS

3.1. Participant characteristics

Characteristics of the study sample (n = 68) are summarized in Table 2. We compared characteristics between males (n = 55) and females (n = 13) and noted a few differences including a higher percentage of females who identified as non-Hispanic white and mixed race/other and a higher percentage of males who identified as non-Hispanic Black. Females reported higher median number of years of education (14.0, interquartile range [IQR]: 13.0 – 15.0) than males (12.0, IQR: 11.0 – 13.0). The median weight among males (77.1 kg, IQR: 68.5 – 84.1) was also significantly higher than females (67.1, IQR: 52.6 – 74.8), but BMI did not differ between sexes.

3.2. Subjective drug and mood effects

3.2.1. SE-VAS measures—There was a significant main effect of drug condition on change-from-baseline ratings for all SE-VAS measures except “Tired” (p=0.643; Table 3). However, for “Tired”, there was a significant three-way interaction between drug condition, sex, and linear time (p=0.043) such that females became more tired over time under active cannabis conditions relative to males. There was also a significant three-way interaction between drug condition, sex, and time in baseline-subtracted SE-VAS ratings of “High” (p=0.003; Table 3). Under the active cannabis condition, peak ratings of “High” were similar for males and females, but subsided at a faster linear rate for females (p<0.001 for trend test; Figure 1). Significant interactions between drug condition and sex emerged

for ratings of “Crave cannabis”, “Anxious”, and “Good Effect” (Table 3). Relative to placebo, active cannabis also acutely decreased ratings of “Crave cannabis” in males and females ($p<0.001$; Table 3), with a significantly greater reduction in ratings among females, collapsed across time ($p=0.014$); differences were most prominent in the first hour following administration (Figure 1). Post hoc analysis of “Anxious” suggests that the sex interaction reflected larger, yet statistically non-significant ($p=0.101$), reductions in females under placebo cannabis conditions, collapsed across time (data not shown). Post hoc analysis of “Good Effect” suggests that the interaction reflected larger, yet statistically non-significant ($p=0.177$), increases from baseline in ratings among females under active cannabis conditions, collapsed across time (Figure 1).

3.2.2. Cannabis-RF measures—There was a significant drug condition by sex interaction for each measure (strong drug effect, drug liking, willingness to take the drug again, and good drug effect; all $p<0.001$; Table 1). Post hoc analyses revealed that, relative to males, females reported significantly greater ratings for all measures under active cannabis conditions, collapsed across time (all $p<0.05$). Specific time points at which ratings under active cannabis differed significantly between males and females are displayed in Figure 2. Of note, males also appeared slightly more sensitive to drug effects under placebo cannabis condition, with a trend towards higher scores collapsed across time for all measures (p-value range: 0.051 – 0.197; Figure 2).

3.2.3. Self-administration—Any self-administration (1–3 puffs) of drug by sex is displayed in Figure 3. Placebo cannabis was self-administered by 15 (21.8%) males (20% 1 puff, 6.7% 2 puffs, 73.3% 3 puffs) and 2 (15.4%) females (100% 2 puffs). Active cannabis was self-administered by 22 (36.4%) males (9.1% 1 puff, 18.2% 2 puffs, 72.7% 3 puffs) and 7 (53.8%) females (28.6% 2 puffs, 71.4% 3 puffs). In the generalized linear mixed model, active cannabis smoking was significantly associated with later self-administration ($p=0.012$) relative to placebo, but females were not more likely than males to self-administer active cannabis (interaction $p=0.176$; Table 3).

4. DISCUSSION

We pooled data from two within-subject, randomized, placebo-controlled trials to explore sex differences in the acute subjective and reinforcing effects of smoked cannabis in people who use cannabis near-daily. Active cannabis significantly increased subjective ratings of “High”, “Stimulated”, “Anxious”, and “Good Effect” and decreased ratings of “Crave cannabis”, relative to placebo. Females reported greater reductions from baseline in “Crave cannabis” following active cannabis administration compared to males. Active cannabis also increased ratings of the cannabis effects, such as “Strong,” “Like,” “Take again,” and “Good Effect” relative to placebo cannabis, and females reported significantly higher ratings relative to males on all four measures after smoking active cannabis. However, with the current sample, consisting of a relatively small sample of female participants, we did not detect a significant sex difference in cannabis self-administration.

The cannabis self-administration task as a measure of reinforcement sets the current study apart from previous research testing sex differences in acute effects of cannabis.

Self-administration has been used in preclinical studies to suggest that females are more sensitive to the reinforcing effects of CB1 receptor agonists, like THC, compared to males (for review, see (24)). We hypothesized that these sex differences would translate to humans. As expected, we found that active cannabis increased likelihood of self-administration relative to placebo, but this effect did not differ significantly between males and females. Given the low number of females available for the current analysis, and the relatively large proportional difference observed between sexes for active cannabis self-administration, it will be important to follow up this finding in future research specifically powered to detect a sex difference in this outcome. Importantly, as preclinical experiments demonstrate reduced cannabis self-administration in ovariectomized relative to intact female rodents (33), future research should also test whether sex differences vary as a function of menstrual cycle phase. Such studies would also help elucidate the underlying biological mechanisms that may contribute to sex differences in cannabis' rewarding effects.

Our findings related to Cannabis-RF ratings are in line with Cooper and Haney's 2014 study, which included a small subset (n = 13; 7M, 6F) of the current sample (25), but contrast a subsequent study (also involving a small subset of the current sample [n = 12; 6M, 6F]) in which CRF measures did not differ between sexes (26). The presently observed heightened sensitivity to cannabis' positive subjective effects in females also differed from findings reported in recently conducted studies with varying cannabis doses and administration procedures. For example, a within-subject study compared peak subjective effects of 13.75 mg vaporized THC versus placebo among volunteers with moderate (<2 days/week) cannabis use and did not detect any differences (including in "strength of drug effect," "liking of drug effect") between males and females (30). Another study randomized participants with light-moderate (1–4 days/week) cannabis experience to smoke either a 750 mg cannabis cigarette (12.5% THC) or placebo (0% THC) ad libidum and did not find sex differences in subjective ratings of positive drug effects (e.g., "I like cannabis," "I feel the good effects") following active cannabis smoking; importantly, however, female participants smoked less active cannabis (73.3 mg vs. 86.0 mg) (31). A critical consideration in comparing our findings to existing research is that cannabis was used daily by most of our sample. Tolerance may play an important role in influencing THC's sex-specific acute effects, with preclinical literature showing accelerated tolerance to THC's antinociceptive effects in females (24). Matching male and female participants for their level of cannabis use should be incorporated into the design of future sex-based investigations of cannabis' effects to control for the influence of tolerance. Studies with a primary objective of testing sex differences could also match males and female participants on other socio-demographic factors that may influence cannabis use experience and/or incentive for or against purchasing additional puffs of the study drug, including those that differed in the current study (i.e., race and education).

As the current study only tested one dose of active cannabis (approximately 25 mg) against a placebo, another important feature of future work in this area will be to examine dose-dependent sex differences across a range of positive and negative subjective effects. Some human experimental research has demonstrated greater sensitivity in females to certain effects at low THC doses (27–29). For example, a within-subject study among infrequent cannabis users found that females reported increased "drug effect" relative to males at

the lower oral and vaporized THC doses (5–10 mg); yet, at higher doses (20–25 mg; vaporized only), females experienced more negative effects including anxiety/nervousness, restlessness, and heart racing, suggesting that potential dose-dependent sex differences may be outcome-specific (29). Another within-subject study tested a range of oral doses (0 to 30 mg THC) in ≥ weekly cannabis users and found that female participants reported significantly higher scores on several measures assessing the drug's abuse liability (e.g., "good effect", "pay for", "like drug", "take again") under the lowest active dose (5 mg THC), whereas males reported higher scores of drug liking only at the 15 mg dose; however, a higher expectancy effect among female participants could not be ruled out as an underlying explanation for differences observed at the lower dose (27). Interestingly, the current study presents a contrasting picture of expectancy to positive drug-specific subjective effects, with males tending to report higher ratings on Cannabis-RF measures under placebo conditions.

Another finding of the current study was the interaction of drug condition and sex with time such that males and females reached similar acute levels of intoxication, but effects were shorter in duration in females compared to males. Of note, we also observed a similar trend for ratings of cannabis strength (Figure 2). Preclinical studies show higher levels of 11-OH-THC in females compared to males after THC administration (42–45), suggesting a possible mechanism by which intoxication effects degrade at a faster rate for females. Pharmacokinetic analysis was not included in the present study, limiting our ability to determine a sex-dependent relationship with THC metabolism. More research is needed to further probe time course of THC's pharmacokinetic effects in males and females, with close attention to differences by cannabis use experience.

To our knowledge, this is the first study reporting greater reductions in spontaneous craving scores among females relative to males after smoking active cannabis. However, one within-subject study has previously shown that cue-induced increases in compulsivity (ability to control cannabis use) following oral administration of dronabinol (10 and 20 mg) were attenuated in females but not males (40). Our finding is worthy of follow-up, especially as treatment-seeking women report more withdrawal symptoms, higher severity of symptoms, and greater interference with quality of life compared to men (20, 46). However, the role of cannabis craving in driving sex differences in treatment or recovery outcomes is not clear given that craving did not differ significantly between males and females in these studies (20, 46). It will be important to probe potential sex differences in treatment effects including craving, withdrawal, and relapse in ongoing efforts to understand the therapeutic potential of cannabinoid receptor 1 agonists as a pharmacological strategy to treat CUD.

Certain limitations should be taken into consideration when interpreting the findings of this study. First, data were pooled from two placebo-controlled, randomized studies for the purpose of secondary data analysis and the sample included a relatively low number of females, most of whom have contributed subjective ratings data to previous analyses. Power to detect a true sex difference due to limited availability of data from female participants may have especially affected the self-administration measure, as it relied on one observation per participant smoking session in contrast to the other measures that were captured repeatedly throughout the session. Investigation into sex differences in subjective

responses that predict self-administration was also not feasible given the lower number of females, and this should be explored in future studies. Second, we did not administer varying strengths of cannabis and could not assess potential dose-dependent effects between sexes. Third, we were restricted in our ability to understand potential underlying metabolic or hormonal factors driving our findings; pharmacokinetics was not assessed nor were hormonal variations across the sessions. Finally, we did not analyze differences by gender identity. This is an important area for future work given that socio-cultural norms likely play a role in the changing landscape of cannabis use across the gender spectrum.

The current study limitations and the heterogeneity of results yielded through previous studies illuminate some key avenues for future research. Sex differences in the acute effects of cannabis have generally been tested as a secondary study objective—often assessed by pooling together data from several studies with differences in doses administered and routes of administration (as was done here). The underrepresentation of female participants within these seed studies means reduced precision and study power in secondary explorations of sex differences. There is a critical need for studies that are designed with the primary purpose of investigating sex differences in the acute subjective and reinforcing effects of cannabis at difference doses and modes of administration in humans. This research would be optimized by designing studies to prospectively assess sex-dependent effects and probe variables that account for differences including monitoring pharmacokinetics, controlling for menstrual cycle phase at the time of drug administration, and testing across levels of tolerance.

5. CONCLUSION

As more women are initiating and increasing use of cannabis, determining sex-based differences in cannabis' subjective and reinforcing effects may provide help tailor interventions for cannabis harm reduction and education, prevention and treatment of cannabis use disorder, and guidance for medical cannabis use. Female participants in the current study experienced greater reductions in cannabis craving and reported higher ratings of positive cannabis-specific effects relative to males after smoking active cannabis (~25 mg THC). These findings are in line with sex differences reported in the preclinical literature and contribute to our ongoing understanding of this complex topic in humans. Notably, greater subjective ratings of positive cannabis-specific effects may provide a signal into possible underlying drivers for accelerated trajectories towards problematic cannabis use among women; however, research specifically designed to test sex differences is needed to confirm these findings. In addition to addressing existing limitations, future studies assessing sex differences in cannabis' subjective and reinforcing effects should include examination of outcomes across varying cannabis strengths, modes of administration, and individual tolerance level.

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Data availability statement:

The data that support the findings of this study are available upon reasonable request from the corresponding author.

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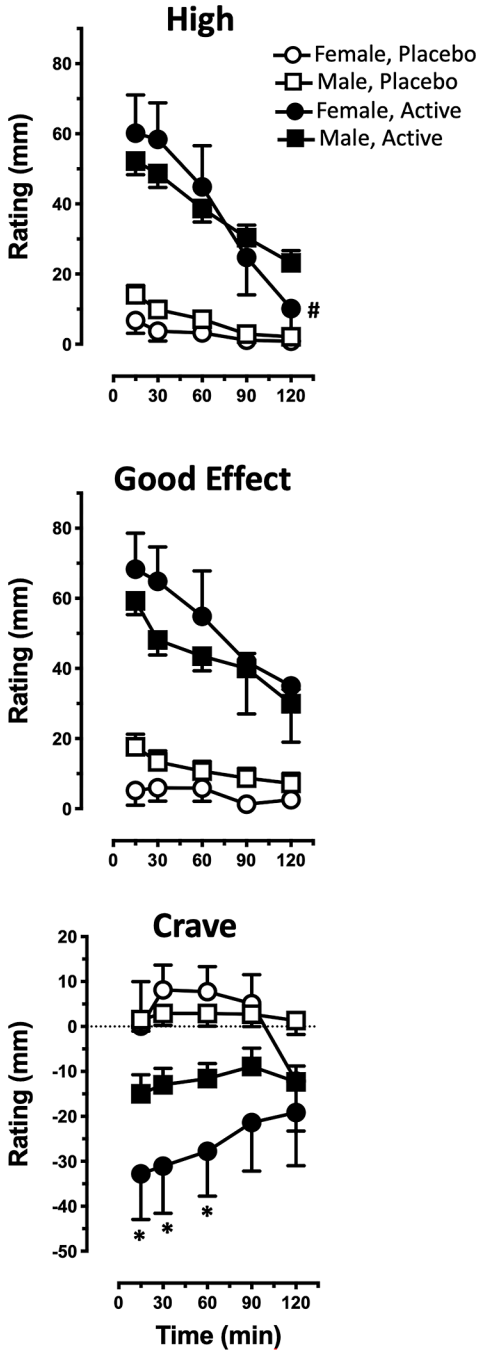

Figure 1.

Baseline-subtracted SE-VAS ratings under placebo (white symbols) and active cannabis (black symbols) conditions for males (squares) and females (circles). Data are plotted as raw mean (+1 SE) by drug condition, sex, and time (−1 SE removed for ease of visibility). *Indicates $p<0.05$ for time-point difference in estimated marginal means between males and females under active cannabis condition; # Indicates $p<0.05$ for linear time trend difference in estimated marginal means between males and females under active cannabis condition. Change in “High” and “Good Effect” are plotted on scale 0–80 mm; change in “Crave”

is plotted on scale −40–30 mm. Maximum change score = 100 mm. SE-VAS = Subjective Effects Visual Analog Scale; SE = Standard Error.

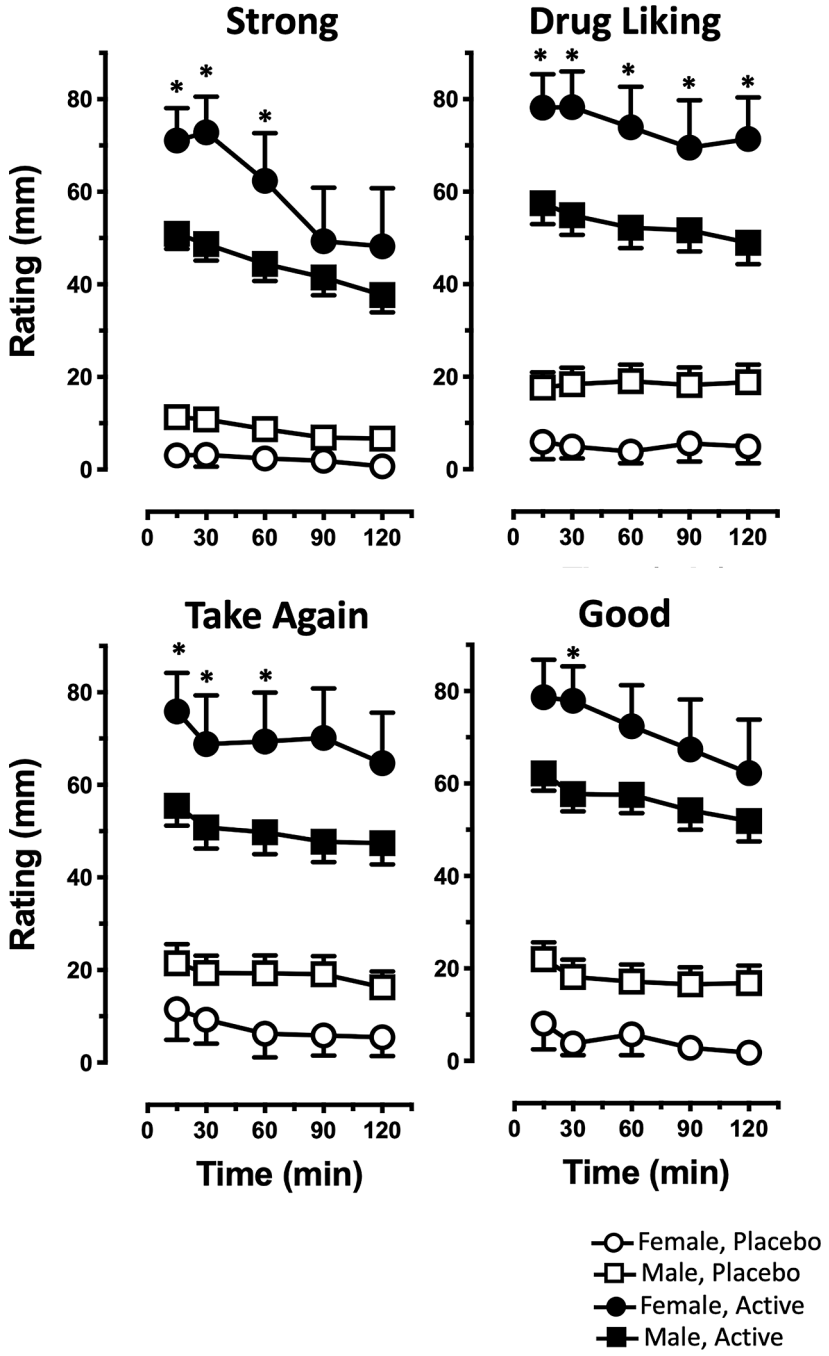

Figure 2.

Cannabis-RF ratings under placebo (white symbols) and active cannabis (black symbols) conditions for males (squares) and females (circles). Data are plotted as raw mean (+1 SE) by drug condition, sex, and time (−1 SE removed for ease of visibility). *Indicates $p<0.05$ for time-point difference in estimated marginal means between males and females under active cannabis condition. Cannabis-RF = Cannabis Rating Form; SE = Standard Error.

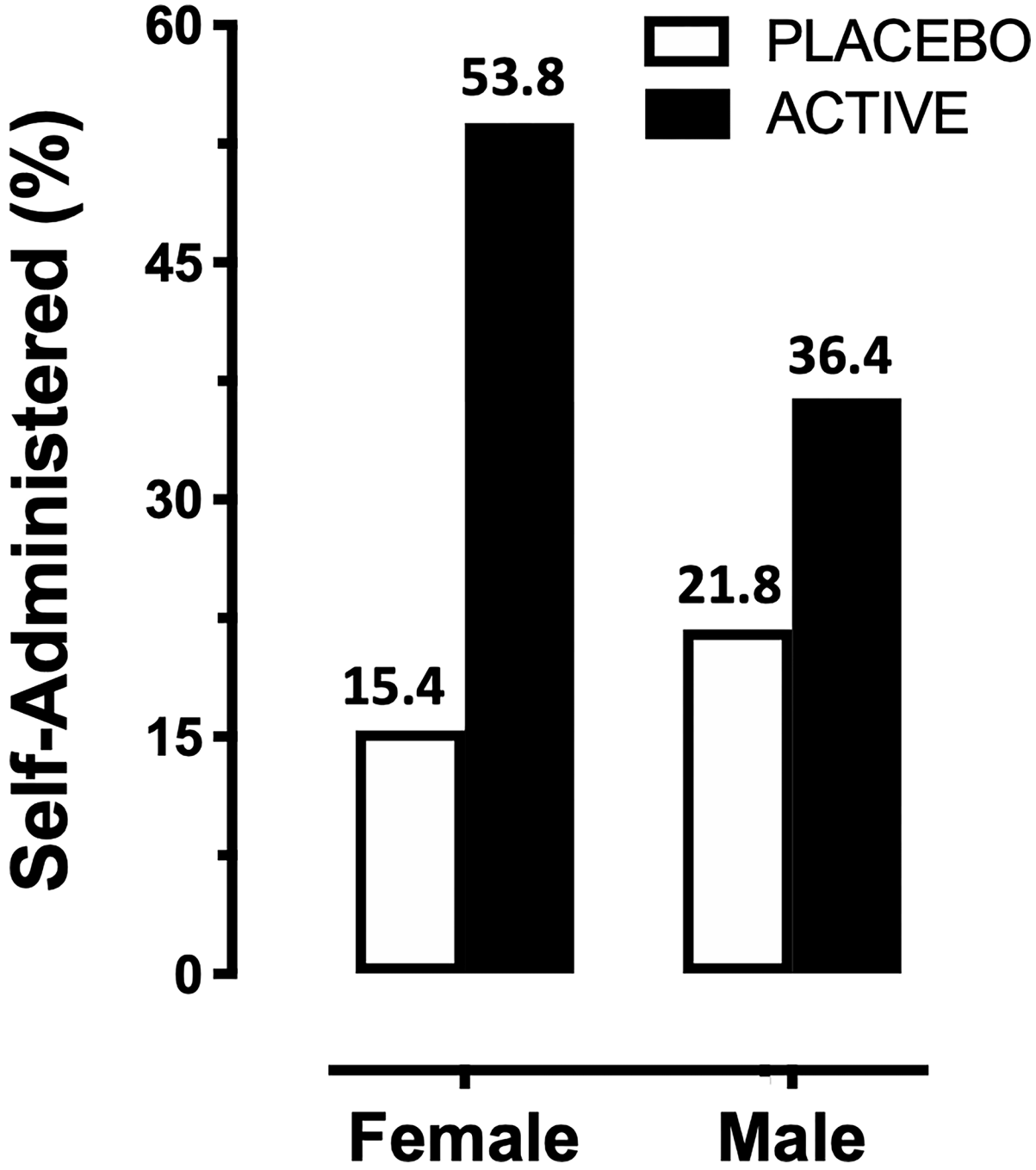

Figure 3.
Proportion of females (left) and males (right) who self-administered placebo (white bars) and active cannabis (black bars).

Table 1.

Session time course of relevant study procedures

Time (min)	Event
−90	Baseline SE-VAS (Study 1)
−60	Baseline SE-VAS (Study 2)
0	Cannabis administration
15	Cannabis-RF, SE-VAS
30	Cannabis-RF, SE-VAS
60	Cannabis-RF, SE-VAS
90	Cannabis-RF, SE-VAS
120	Cannabis-RF, SE-VAS
165	Cannabis self-administration (Study 1)
195	Cannabis self-administration (Study 2)

Note: Table lists only the seed studies' procedures relevant to the current analysis. Cannabis-RF = Cannabis Rating Form; SE-VAS = Subjective Effects Visual Analog Scale

Table 2.

Sociodemographic characteristics of the study sample (n = 68)

Characteristic	Males (n = 55)	Females (n = 13)	*p*-value
Age [1]	28.0 (24.0, 33.0)	29.0 (23.0, 32.0)	0.381
Race/ethnicity [2]			
% Non-Hispanic White	7.3	23.1	**0.001**
% Non-Hispanic Black	70.9	15.4	
% Other / Mixed race	21.8	61.5	
Education [1]			
Years of education	12.0 (11.0, 13.0)	14.0 (13.0, 15.0)	**<0.001**
Weight (kg) [1]	77.1 (68.5, 84.1)	67.1 (52.6, 74.8)	**<0.001**
BMI [1]	24.2 (21.9, 26.3)	24.4 (21.4, 24.6)	0.507
Past-month cannabis use			
Days per week [1]	7.0 (6.0, 7.0)	7.0 (6.0, 7.0)	0.630
% Daily [2]	65.4	69.2	0.844
Years of cannabis use [1]	11.0 (7.50, 16.0)	7.0 (2.5, 16.0)	0.182
Past-month alcohol use [2]			
Days per week [1]	1.0 (0.25, 2.5)	0.5 (0.0, 1.5)	0.134
% Weekly	54.5	46.2	0.759

Note:

[1] Median (IQR) reported, p-value derived from Wilcoxon rank-sum test;

[2] p-value derived from Fisher's exact test.

Table 3.

Generalized linear mixed model results for subjective effects as a function of drug condition, sex, and time since cannabis administration

Measure	Drug condition	Sex	Time	Drug condition x Sex	Drug condition x Time	Sex x Time	Drug condition x Sex x Time
SE-VAS							
High	<0.001	0.537	<0.001	<0.001	<0.001	0.087	**0.003**
Crave cannabis	<0.001	0.165	0.367	**0.001**	0.072	0.911	0.168
Tired	0.643	0.598	<0.001	0.183	0.128	0.125	**0.043**
Stimulated	<0.001	0.294	<0.001	0.197	0.035	0.425	0.973
Anxious	<0.001	0.324	0.944	**0.037**	0.555	0.537	0.756
Good Effect	<0.001	0.778	<0.001	**0.002**	<0.001	0.714	0.188
Cannabis-RF							
Strong	<0.001	0.141	<0.001	**<0.001**	<0.001	0.198	0.058
Like	<0.001	0.555	0.112	**<0.001**	0.095	0.834	0.987
Take again	<0.001	0.553	0.022	**<0.001**	<0.001	0.821	0.906
Good	<0.001	0.701	<0.001	**<0.001**	0.113	0.446	0.539
Self-administration							
≥1 puff purchased	0.011	0.725	NA	0.176	NA	NA	NA

Note: SE-VAS measures were analyzed as change from baseline; time was entered as a continuous variable for all outcomes except Crave cannabis and Anxious; bold indicates highest-order significant sex effect. SE-VAS = Subjective Effects Visual Analog Scale; Cannabis-RF = Cannabis Rating Form.