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Biological Sex and Hormonal Contraceptive Associations with Drug Cue Reactivity in Cannabis Use Disorder

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Introduction

Cannabis Use Disorder (CUD) is associated with significant disability (Hasin et al., 2016) and increased in prevalence from 2.1% in 2002 to 2.6% in 2017 in the United States (Compton et al., 2019). CUD prevalence (Hasin et al., 2016) and chronicity (Khan et al., 2013) is higher in males, but females demonstrate accelerated progression to CUD (i.e., telescoping; Kerridge et al., 2018), worse cannabis withdrawal severity (Sherman et al., 2017), and worse CUD pharmacotherapy outcome (McRae-Clark et al., 2015, 2016). Unfortunately, no FDA-approved medications for CUD exist and psychosocial approaches have modest long-term abstinence rates (Gates et al., 2016). To improve CUD treatments, it is important to understand how biological sex and related variables affect mechanisms implicated in CUD maintenance, which will ultimately inform sex-specific treatment development.

Drug cue reactivity is a robust predictor of drug use behavior in substance use disorders, particularly among males (see Vafaie & Kober, 2022 for a meta-analysis). Further, reward-related brain region (i.e., vmPFC, striatum, amygdala) activation to drug cues is often greater in males compared to females across multiple substance use disorders (i.e., alcohol, nicotine, cocaine), whereas cue-induced craving comparisons typically reveal no sex differences or heightened craving in females (Doran et al., 2014; Dumais et al., 2017; Kaag et al., 2019; Kennedy et al., 2013; Kilts et al., 2004; Petit et al., 2013; Potenza et al., 2012; Robbins et al., 1999; Saladin et al., 2012; Wetherill et al., 2013). As in other substance use disorders, exposure to cannabis cues also activates neural reward-related circuitry (see Sehl et al., 2021 for a meta-analysis) and elicits craving (e.g., Lundahl & Johanson, 2011; McRae-Clark et al., 2011) in CUD. Only four studies to date have examined sex differences in drug cue reactivity in CUD (Henry et al., 2014; Prashad et al., 2020; Lundahl & Johanson, 2011; Wetherhill et al., 2015). The three studies that measured neural cannabis cue reactivity found no sex differences (Henry et al., 2014; Prashad et al., 2020; Wetherhill et al., 2015), whereas craving results were mixed with two showing no sex differences (Lundahl & Johanson, 2011; Wetherill et al., 2015) and one showing greater craving in females (Prashad et al., 2020). Interestingly, Prashad and colleagues (2020) found that sex differences in

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craving were driven by higher craving in the naturally-cycling female subsample in the follicular phase. This finding suggests that sex differences in cannabis cue reactivity may depend on the ovarian hormone milieu in female participants at the time of data collection, which will vary by menstrual cycle phase and hormonal contraceptive use.

A large preclinical literature has shown that greater addiction vulnerability in female relative to male animals is dependent on ovarian hormones (see Becker & Koob, 2016 for a review). Estrogen and progesterone typically have opposing effects on drug-seeking (e.g., Maher et al., 2021; Schmoutz et al., 2014). Although multiple mechanisms are likely involved, estrogen and progesterone are thought to influence drug cue reactivity via dopaminergic (exciting drug-seeking) and GABAergic (inhibiting drug-seeking) transmission, respectively (Hudson & Stamp, 2011). Consistent findings have also emerged in humans. For instance, progesterone administration reduced drug cue-induced craving in females with cocaine use disorder (Fox et al., 2013; Milivojevic et al., 2016). Relatedly, greater drug cue-elicited neural activation and craving was found in nicotine-dependent females in the follicular (estrogen > progesterone) vs. luteal (progesterone > estrogen) phase of the menstrual cycle (Franklin et al., 2015; Gray et al., 2010). In a study of regular alcohol-using women, attention bias to alcohol cues increased in the late (high estrogen) vs. early (low estrogen) follicular phase (Griffith et al., 2023). Overall, existing menstrual cycle and drug administration studies suggest that high estrogen/low progesterone may modulate neural drug cue reactivity and craving in females.

Hormonal contraceptives (HC) also impact ovarian hormones and are commonly used in the United States (Daniels et al., 2013). HCs suppress endogenous hormones to early follicular phase levels (i.e., low estrogen and progesterone; Hampson, 2020; Sahlberg et al., 1987), but contain synthetic progesterone/estrogen (i.e., progestins/estradiol) that act centrally and are similarly or more potent than their endogenous counterparts (Benagiano et al., 2004; Fishman & Norton, 1977; Gogos et al., 2014). No studies to date have examined drug cue reactivity differences in HC-using vs. naturally-cycling females. Further, most studies on sex differences in drug cue reactivity have used female samples with mixed hormonal status (i.e., HC users and non-users, naturally-cycling at different phases, peri- and post-menopausal) and/or do not present female hormonal status data. Variability in HC use and menstrual cycle phase may underlie mixed findings on sex differences in cannabis cue-induced craving (Lundahl & Johanson, 2011; Prashad et al., 2020; Wetherill et al., 2015), as well as the absence of sex difference in neural cannabis cue reactivity (Henry et al., 2014; Prashad et al., 2020; Wetherhill et al., 2015) often found in other substance use disorders.

The aim of the present study is to evaluate the roles of HC use and menstrual cycle phase in cannabis cue reactivity sex differences. As part of a larger study (Macatee et al., 2023), young adults reporting frequent cannabis use (89.5% with current DSM-5 CUD diagnosis) were exposed to cannabis-related and neutral images during electroencephalography (EEG) recording. Cannabis craving was measured after cue exposure. Neural drug cue reactivity was assessed using the late positive potential (LPP), an event-related potential typically enhanced to drug cues in substance use disorder compared to control groups (see Webber et al., 2022 for meta-analysis). Further, LPP modulation by drug cues covaries with drug

cue-elicited craving (Franken et al., 2003; Franken et al., 2008) and other indicators of drug use motivation (e.g., Versace et al., 2023; Dunning et al., 2011; Moeller et al., 2012), underscoring its validity. We hypothesized that male vs. female differences in the cannabis cue LPP and craving would depend on HC status. Because HCs contain only progestin or a high progestin to estradiol ratio, we reasoned that HC users would have reduced craving and cannabis cue LPP amplitude relative to males given the inhibitory effect of progesterone on drug cue reactivity (Fox et al., 2013; Milivojevic et al., 2016). However, HCs also suppress endogenous ovarian hormones to levels observed in the early follicular phase, a phase associated with heightened drug cue reactivity in females with nicotine dependence (Franklin et al., 2015; Gray et al., 2010). Given this ambiguity, our hypothesis was limited to a moderating role of HC status on sex differences in cannabis cue reactivity without specifying directionality. Finally, based on prior menstrual cycle phase findings in CUD (Prashad et al., 2020) and nicotine dependence (Franklin et al., 2015; Gray et al., 2010), as an exploratory analysis we compared cannabis cue LPP amplitude and craving in naturally-cycling females in the follicular vs. luteal phase.

Methods

Participants

As part of a larger study (Macatee et al., 2023), 154 adults reporting frequent cannabis were recruited from a large southeastern university and the surrounding community. Inclusion criteria included: (1) English fluency; (2) 18-30 years old; (3) ≥ 2/week cannabis use over past year. Two participants had to be excluded due to use of non-HC medications with effects on ovarian sex hormones (estrogen+progesterone for gender dysphoria, gonadotropic-releasing hormone antagonist for endometriosis). Of the remaining 152 participants (89.5% with current DSM-5 CUD), 74 and 78 were biologically male and female, respectively. Of the 78 females, 52 reported currently using a HC (FemaleHC+; see Supplemental material for specific HC descriptives) and 26 reported no current HC use (FemaleHC−).

Procedure

After providing informed consent, interested participants completed an online screening questionnaire to assess inclusion criteria. Eligible participants completed a CUD interview and were invited to a ~2.5 h laboratory visit. The lab visit began with a baseline cue reactivity task during EEG recording followed by a craving assessment (see Figure 1). Participants then completed a stress or neutral mood manipulation followed by a second administration of the cue reactivity task and craving assessment (see Macatee et al., 2023 for description of larger study). Only baseline cue reactivity and craving were examined in the present study to maximize sample size and test sex differences in drug cue reactivity in isolation, as done in prior work on this topic. To limit the impact of acute drug effects on cue reactivity, participants were instructed to abstain from alcohol/ illicit substances for at least 24 h and caffeine/nicotine for at least 1 h prior to the lab visit. Research assistants verbally confirmed participant adherence to these instructions. All study activities were done in accordance with the Declaration of Helsinki and approved by the Auburn University IRB.

Materials and Measures

Self-report and interview measures

Hormonal contraceptives and menstrual cycle.—Females were asked if they currently use a birth control medication. Participants who answered affirmatively were prompted to enter the medication name, dosage, and frequency of use. Female participants were also asked to report whether they were currently menstruating or indicate the onset date of their most recent menses.

Marijuana Craving.—Current cannabis craving was quantified by summing 11 items measured on a scale of 1 (“strongly disagree”) to 7 (“strongly agree”) (Marijuana Craving Questionnaire; Heishman et al., 2009). The total score had excellent internal consistency (α=.91).

Substance use and mental health.—Substance use and mental health information was collected using the Timeline Follow-Back (Robinson et al., 2014), Drug Use Questionnaire (Hien & First, 1991), and Mood and Anxiety Symptom Questionnaire (MASQ; Wardenaar et al., 2010). DSM-5 Cannabis Use Disorder criteria were assessed using the Substance Use Disorder module of the Structured Clinical Interview for the DSM-5 Research Version (SCID-5-RV; First et al., 2015). Additional detail on these measures is provided in the Supplemental.

Cue Reactivity Task.—Participants were presented 40 cannabis and 40 neutral images on a computer screen. They were instructed to simply look at each image for the duration it was on the screen (3000ms). At the beginning of each trial, a blue fixation cross was presented as an attention check for 1000ms, followed by a 500-3000ms [500ms random step] black screen. Participants were required to press the spacebar at each fixation cross to view the image. Image presentation was organized into four category-specific blocks (two cannabis, two neutral) of 20 images each. Within-block image order and block order were randomized. Images were taken from a validated set of cannabis and matched neutral stimuli (Macatee et al., 2021). To maximize cue relevance, participants were presented with the cannabis image set that reflected their primary method of use (bowl, bong, blunt/joint, or vaporizer). One neutral image set (matched with cannabis image sets on presence of people) was used for all participants. All cannabis image sets were matched on arousal and significantly different from the neutral set on valence, arousal, and cannabis use urge ratings (Macatee et al., 2023).

Psychophysiology Data Acquisition.—EEG data was recorded using an active electrode system (ActiCHamp, Brain Products GmbH) with a 32-channel cap placed in accordance with the 10-20-system (ActiCAP, Brain Products GmbH). A ground electrode was placed at AFz and FCz served as the online reference. Impedances were reduced to 10kΩ or less using electrolyte gel. Vertical and horizontal electrooculograms were recorded from four electrodes on the outer canthi of both eyes and above/below the eye. All data was recorded with Brain Vision Recorder (Brain Products GmbH) at 1000Hz.

Data Preprocessing

Of the 152 participants, 148 and 150 had available EEG and craving data, respectively. Raw EEG data was downsampled to 250 Hz, re-referenced to the averaged mastoids, and high- (0.10 Hz) and low-pass (30 Hz) filtered. Eye movement artifacts were corrected using the algorithm developed by Gratton, Coles, and Donchin (1983). Data were segmented from −200 to 3000ms around picture onset and baseline-corrected. Automated artifact rejection of individual channels within segments and entire segments was performed using a modified version of the FASTER algorithm (Nolan, Whelan, & Reilly, 2010; see Macatee et al., 2023 for details). The remaining artifacts were identified and removed by visual inspection (*M* cannabis trials retained for averaging =37.04, *SD* =2.82; *M* neutral trials retained for averaging=37.45, *SD*=2.18). Based on inspection of the grand average difference wave and topographical maps (see Figure 2), cannabis and neutral cue LPP amplitudes were quantified from 600-3000ms using a central-parietal (Cz, CP1, CP2, Pz) pooling. To examine specificity to the LPP, the P3 was quantified from 250-600ms at Pz. Split-half reliabilities of the neutral (α=.70) and cannabis cue LPP (α=.78) were acceptable (see Macatee et al., 2023 for detail on split-half computation).

Data Analytic Plan

Covariate selection—To test if demographic, substance use, and/or mental health variables significantly differed across males, femalesHC+, and femalesHC−, Group (Male, FemaleHC+, FemaleHC−) was entered as a predictor in a generalized linear model. Variables that significantly differed by group were entered as predictors of craving, P3, and LPP outcomes in univariate analyses. Variables that significantly predicted outcomes were entered in corresponding covariate-adjusted analyses to test robustness of Group differences in these outcomes.

Sex and Hormonal Contraceptive Associations with Craving, P3, and LPP—For the craving outcome, a generalized linear model was conducted with Group entered as the predictor. For the P3 and LPP outcomes, a 3x2 multi-level model (compound symmetry covariance structure) was conducted with Group as a between-subjects factor and Cue (Cannabis, Neutral) as a within-subjects factor. Only fixed effects were entered in the model. Significant omnibus tests were followed with pairwise comparisons. All significance tests were two-tailed with α=.05.

Results

Sample Characteristics

Group descriptives and omnibus tests are presented in Table 1. Groups were comparable on most demographic, substance use, and psychiatric variables. Significant group differences were found in educational attainment, past-week anxiety symptoms, past-year nicotine use, past-year sedative use, past-year hallucinogen use, and lifetime CUD symptoms. None of these variables significantly predicted the cannabis vs. neutral P3 or LPP contrast (all interactions with Cue had *p*s≥.15 with the exception of past-year nicotine year and education at *p*=.052 and *p*=.084 for the LPP, respectively);[1] thus, no covariates were included in the LPP or P3 analyses. Past-week anxiety symptoms, lifetime CUD symptoms, and past-year

sedative use significantly predicted cannabis craving (χ^2s>4.34, *p*s<.038); thus, these three variables were included in the covariate-adjusted craving analysis.

Sex and Hormonal Contraceptive Associations with Craving and Neurophysiological Drug Cue Reactivity

In the unadjusted craving analysis, the omnibus Group effect was non-significant, χ^2=5.63, *p*=.060, Males *M* =41.79, *SD*=14.08, FemaleHC+ *M*=42.27, *SD*=15.70, FemaleHC− *M*=49.54, *SD*=15.77, though pairwise comparisons were consistent with the hypothesized moderating role of HC use such that males reported significantly lower craving than FemaleHC−, χ^2=5.55, *p*=.018, but not FemaleHC+, χ^2=0.03, *p*=.86. The FemaleHC− vs. FemaleHC+ pairwise comparison did not reach significance, χ^2=3.77, *p*=.052. In the covariate-adjusted craving analysis, the omnibus Group effect remained non-significant, χ^2=1.80, *p*=.41; past-week anxiety and lifetime CUD symptoms were significantly predictive of higher craving, χ^2s>6.77, *p*s<.010, whereas past-year sedative use was non-significant, χ^2=1.07, *p*=.30.

In the P3 analyses, the expected Cue effect was significant, *F*(1,290)=7.33, *p*=.007, *Mdiff* =0.84μV, *SE*=0.31), but the Group*Cue interaction was non-significant, *F*(2, 290)=2.37, *p*=.095. In the LPP analysis, the omnibus Group*Cue interaction was significant, *F*(2,290)=5.81, *p*=.003. Pairwise comparisons revealed a significant cannabis > neutral LPP effect in males (*Mdiff* =1.66μV, *SE*=0.30, *t*=5.59, p<.001) and femalesHC− (*Mdiff*=1.32μV, *SE*=0.51, *t*=2.61 *p*=.010), but not femalesHC+ (*Mdiff*=0.09μV, *SE*=0.36, *t*=0.26, *p*=.79). Compared to femalesHC+, the cannabis > neutral LPP effect was significantly larger in males, *F*(1,242)=11.68, *p*<.001, and femalesHC−, *F*(1,146)=4.46, *p*=.036, who did not significantly differ, *F*(1,192)=0.29, *p*=.59 (see Figure 3). Pairwise comparisons of individual cannabis and neutral LPPs between groups did not reveal any significant differences (*p*s>.10) with the exception of a significantly decreased neutral LPP in males relative to femalesHC+ (*Mdiff*=−1.04 μV, *SE*=0.52, *t*=−2.00, *p*=.046).

Menstrual cycle phase associations with the LPP and craving

24 of the 26 femaleHC− participants reported the date of their last cycle (i.e., onset of most recent menses). Of these 24 participants, 13 and 6 were categorized as being in the follicular (days 0-13) and luteal (days 16-35) phases, respectively, at the time of data collection (see Supplemental for additional detail). An additional 3 participants were categorized as being in the ovulatory phase (days 14-15) and the remaining 2 participants reported a last cycle date > 35 days; these 5 participants were excluded from the follicular vs. luteal phase analyses. Cannabis vs. neutral LPP contrasts were comparable in the follicular (*Mdiff*=1.39μV, *SE*=0.68) and luteal (*Mdiff*=1.85μV, *SE*=1.09) phase participants, Phase*Cue *F*(1,16)=0.13, *p*=.73. Craving was also non-significantly different in the follicular (*M*=54.54, *SD*=12.06) and luteal (*M*=48.33, *SD*=13.81) phase participants, χ^2=1.11, *p*=.29, though it was numerically higher in follicular phase participants as expected.

[1]When past-year nicotine use and education were included as covariates in the LPP analyses, the Group*Cue interaction remained significant, *F*(2,282)=4.57, *p*=.011. Therefore, only unadjusted LPP analyses are presented for interpretability.

Associations between HC characteristics and drug cue reactivity

45 participants using HC provided the name of the medication (see Supplemental for detail). Exploratory analyses testing differences in those using a progestin-only vs. combination HC, monophasic vs. triphasic pill, oral vs. non-oral HC, and IUD vs. non-IUD HC were non-significant (see Supplemental Material).

Discussion

The present study's hypotheses were partially supported. As hypothesized, sex differences in neurophysiological cannabis cue reactivity significantly varied by female hormonal contraceptive status. Significant group differences were found for the LPP but not P3. Females using hormonal contraceptives did not show significant LPP enhancement to cannabis vs. neutral cues, whereas cannabis cue enhancement of the LPP was significantly larger in both males and naturally-cycling females who did not differ from each other. In contrast to the LPP findings, sex differences in craving did not significantly vary by female hormonal contraceptive status after covariate adjustment, though unadjusted analyses showed higher craving in naturally-cycling but not HC-using females relative to males. Neurophysiological cannabis cue reactivity and craving did not significantly differ by menstrual phase, though phase-specific subsamples were small and only 8.3% of the sample was in the early/mid-luteal phase. Overall, the findings indicate that hormonal contraceptives may impact drug cue reactivity in CUD, potentially contributing to the mixed findings on sex differences in drug cue reactivity.

Greater cannabis cue enhancement of the LPP in males relative to females using hormonal contraceptives is consistent with sex difference studies on neural drug cue reactivity in alcohol (Kaag et al., 2019; Petit et al., 2013), cocaine (Kilts et al., 2004; Potenza et al., 2012), and tobacco use disorder (Dumais et al., 2017; Wetherill et al., 2013) samples, but inconsistent with three studies in CUD (Henry et al., 2014; Prashad et al., 2020; Wetherill et al., 2015). Given that cannabis cue enhancement of the LPP was comparable in males and naturally-cycling females in the present study, it may be that the female samples in the three CUD studies were predominantly not using HCs. Only Prashad and colleagues (2020) reported hormonal status and, consistent with the present study's findings, the majority of the female sample was not using hormonal contraceptives. The absence of significant sex differences in craving is consistent with most studies in other substance use disorders (Dumais et al., 2017; Kaag et al., 2019; Potenza et al., 2012; Wetherill et al., 2015; but see Robbins et al., 1999) and two of three CUD studies (Lundahl & Johanson, 2011; Wetherill et al., 2015; but see Prashad et al., 2020). However, it is noteworthy that craving was significantly higher in naturally-cycling females relative to males in the unadjusted analyses and numerically higher among females in the follicular vs. luteal phase, a pattern consistent with Prashad and colleagues (2020) findings. Nevertheless, the divergence of hormonal contraceptive moderation of sex differences for neural vs. subjective cannabis cue reactivity underscores the distinctiveness of these drug cue reactivity measures.

Speculatively, reduced cannabis cue modulation of the LPP in females using HC compared to males and naturally-cycling females may be driven by heightened central progestin-related activity in females using HC. The progestins used in HCs are known to cross

the blood-brain barrier and exert central effects,[2] with most showing higher potency than endogenous progesterone (Benagiano et al., 2004; Gogos et al., 2014). A progestin account is supported by several findings. First, 39 of the 45 HC-using females providing specific medication data used a preparation containing only a progestin or a consistently high progestin to estradiol ratio. Second, females using a progestin-only vs. combination HC did not have significantly different LPPs. Third, 20 of the 24 naturally-cycling participants that reported menstrual data were in a *lower* progesterone phase of their cycle.

Interestingly, HC-using and naturally cycling females had comparable cannabis cue LPPs, indicating that the HC group difference in cannabis cue modulation of the LPP was driven by an altered LPP to neutral cues. Many studies on cue reactivity sex differences do not report separate drug and neutral cue findings, but one that did found the late > early follicular phase effect on alcohol cue reactivity was driven by change in neutral cues (Griffith et al., 2023). It may be that the putative progestin-related effects on cannabis cue reactivity occur via modulation of non-drug stimuli salience, a contention supported by evidence that exogenous progesterone administration improves cognitive functioning and reduces negative affect in females with a substance use disorder (Fox et al., 2013; Milivojevic et al., 2016; Sofuoglu et al., 2011). Moreover, observational and experimental data suggest a reduced LPP to neutral images may indicate motivational disengagement (e.g., as observed in depression; Granros et al., 2022; Nelson et al., 2015) and/or off-task cognition (Barley et al., 2021; MacNamara et al., 2019). Thus, HC-related neural cannabis cue reactivity differences may occur via progestin-mediated effects on emotional salience of non-drug stimuli and/or overall cognitive functioning rather than direct amplification of drug cue incentive salience. Regardless of the specific mechanism, these findings suggest that variability in HC use across studies may contribute to the mixed findings on sex differences in drug cue reactivity.

The present study had several limitations. First and most importantly, ovarian hormones were not measured directly. Further, menstrual cycle phase in naturally-cycling participants was estimated based on self-reported date of last menses onset, which is an imprecise measure due to recall error and between-subjects variability in phase duration. Future research should measure ovarian hormone levels to validate cycle phase and directly test hypothesized hormone associations with drug cue reactivity. Second, non-drug emotional stimuli were not included in the cue reactivity task, which complicates interpretation of LPP enhancement by cannabis vs. neutral cues as reflective of drug cue incentive salience, non-specific emotional arousal, or general reward sensitivity. Third, participants using oral contraceptives were not asked what time they took their last pill, which likely introduced variability in peak hormone concentrations at the time of the lab visit. Although the absence of LPP differences in those using oral vs. constant hormone-releasing (i.e., IUD, implant, shot, vaginal ring) contraceptives suggests that this variability likely had little influence on our results, time since last pill should be measured in future research. Fourth, the naturally-cycling female subsample was relatively small, which may have impacted

[2] 11 of the 49 HC-using participants that provided enough information to discern IUD vs. alternative contraceptive use were using a hormonal IUD. Although IUD-released hormones were thought to only act locally, recent findings suggest that they have systemic effects akin to oral contraceptives (Huck et al., 2022).

statistical power. Fifth, the observed effect sizes are small in magnitude, which makes their clinical significance unclear. However, even small effects can inform theory and the mixed findings on sex differences in drug cue reactivity.

The present study's findings suggest that sex differences in neural cannabis cue reactivity in CUD may depend on female HC use. Cannabis cue enhancement of the LPP was larger in males and naturally-cycling females than HC-using females, who did not show a significant drug cue effect on the LPP. The predominant menstrual cycle phase and HC characteristics in the naturally-cycling and HC-using female subsamples, respectively, suggest a progesterone-related mechanism may contribute to HC group differences in cannabis cue modulation of the LPP. Given that cannabis cue modulation of the LPP has been linked with clinically-relevant CUD outcomes (Macatee et al., 2022, 2023), the present study's results can inform efforts to better understand sex differences in CUD maintenance and treatment response, ultimately paving the way for sex-specific treatment development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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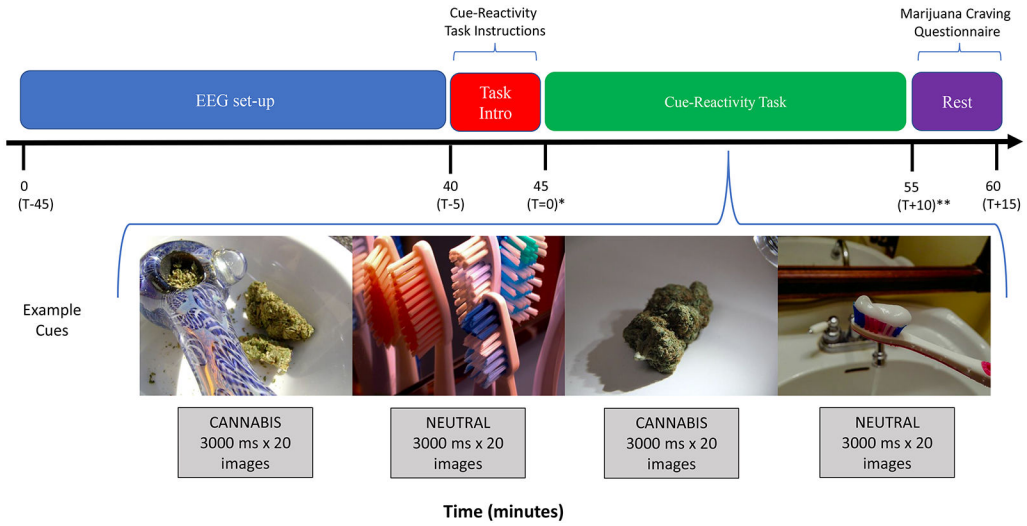

T=minutes relative to cue-reactivity task onset. *=Onset of cue-reactivity task. **Offset of cue-reactivity task.

Figure 1. Study Procedure

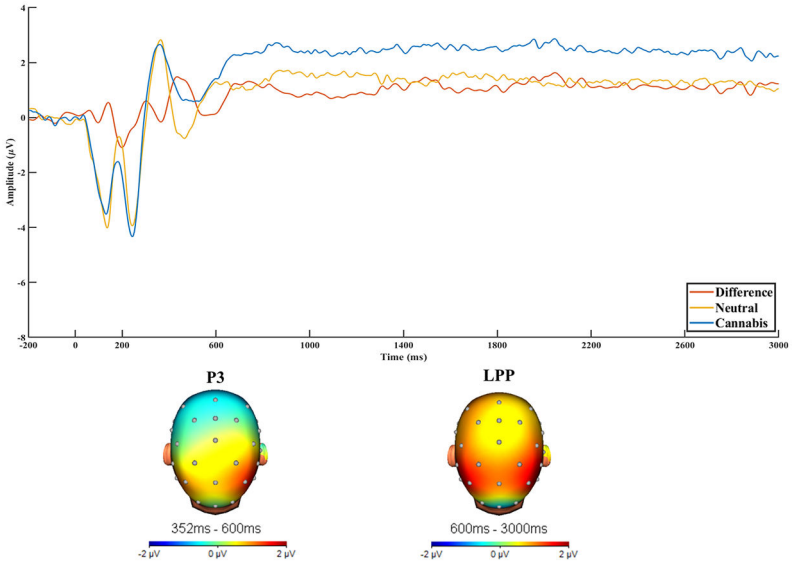

Figure 2. Grand average ERPs

ERPs to cannabis stimuli, neutral stimuli, and their difference in the whole sample are presented. Time relative to image onset is presented on the x-axis and amplitude in microvolts is presented on the y-axis. A 15Hz low-pass filter was applied to the difference wave for display purposes only. Topographical maps display the mean amplitude from 350-600ms (P3 window) and 600-3000ms (LPP window) in each group.

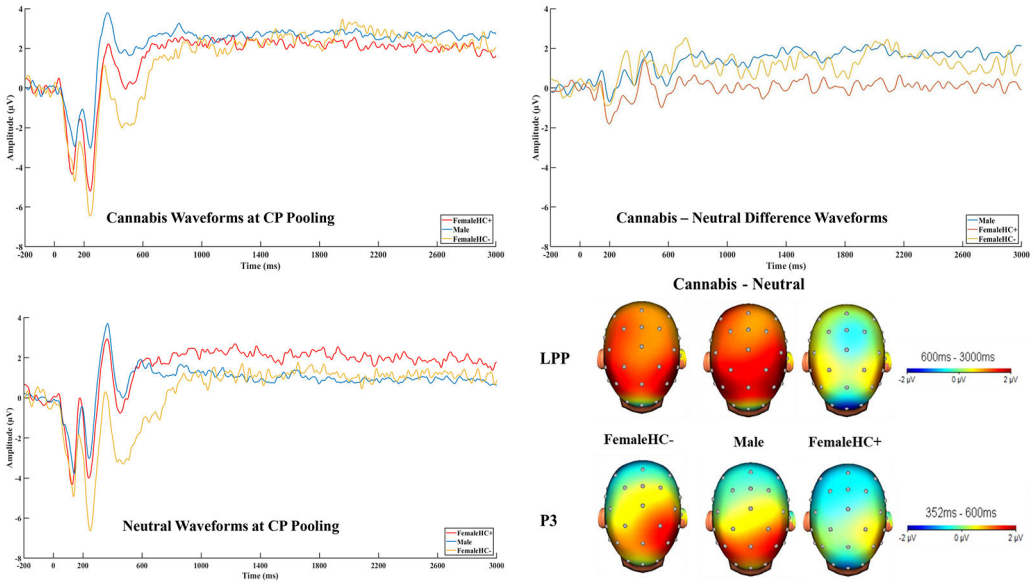

Figure 3. ERP modulation by cannabis cues in males, HC-using females, and naturally-cycling females

ERPs to cannabis stimuli (top left), neutral stimuli (bottom left), and their difference (top right) in males, naturally-cycling females (FemaleHC−), and hormonal contraceptive-using females (FemaleHC+) are presented. Time relative to image onset is presented on the x-axis and amplitude in microvolts is presented on the y-axis. A 15Hz low-pass filter was applied to the difference waves for display purposes only. Topographical maps display the mean amplitude from 350-600ms (P3 window) and 600-3000ms (LPP window) in each group.

Table 1.

Sample Characteristics (N=152)

	Male		FemaleHC+		FemaleHC−		Group Comparison	
	M or n	*SD*	*M or n*	*SD*	*M or n*	*SD*	χ^2	*P*
Demographics								
Age	21.70	2.74	21.63	2.39	21.77	3.22	0.05	0.98
Race							7.74	0.26
Black (Not Hispanic)	7		6		4			
White (Not Hispanic)	60		41		21			
Hispanic	6		1		1			
Asian or Pacific Islander	1		4		0			
Sexual Orientation							9.93	0.13
Heterosexual	60	---	30	---	19	---		
Homosexual	1	---	1	---	0	---		
Bisexual	10	---	18	---	7	---		
Other	2	---	2	---	0	---		
Income	6.67	3.41	6.67	3.12	5.00	3.45	5.17	0.08
Education							**14.79**	**0.02**
High school	12		5[a]		9[a]			
Some college	58		37		16			
Bachelor's degree	4		9		1			
Post-graduate degree	0		1		0			
Marital Status							3.65	0.46
Married	6		4		3			
Single/Never Married	67		47		21			
Divorced	1		1		2			
Cannabis Use								
Current CUD Dx	69		43		24		3.88	0.14
Lifetime CUD Dx	72		46		24		3.94	0.14
Past 12-Month CUD Criteria	4.81	2.46	4.23	2.35	5.62	2.67	5.69	0.06
Lifetime CUD Criteria	5.92[a]	2.66	4.83[ab]	2.49	6.38[b]	2.97	**7.87**	**0.02**
Past-month cannabis use sessions	45.38	36.61	44.60	33.86	47.00	40.18	0.03	0.99
Past-month cannabis use days	21.82	7.90	20.52	8.05	21.00	8.28	0.25	0.89
Age at first use	16.38	2.07	16.56	2.10	16.77	2.44	0.70	0.71
Age at regular use onset	18.27	2.38	18.56	1.81	18.62	3.16	0.67	0.72
# of years of regular smoking	3.44	2.51	3.46	3.59	4.07	4.79	0.75	0.69
Days since last cannabis use	3.14	4.66	2.38	2.02	2.35	2.08	0.94	0.62
Other Substance Use								
Past-month nicotine use days	10.64	12.43	9.25	12.74	11.69	13.51	1.24	0.54
Past-month alcohol use days	5.07	6.43	3.56	3.87	5.54	7.25	0.30	0.86

	Male		FemaleHC+		FemaleHC−		Group Comparison	
	M or n	*SD*	*M or n*	*SD*	*M or n*	*SD*	χ^2	*P*
Past-year nicotine use	3.36[a]	1.76	2.50[a]	2.12	3.35	1.90	**7.07**	**0.03**
Past-year alcohol use	2.95	1.03	2.73	0.97	2.96	1.06	1.61	0.45
Past-year cocaine use	0.35	0.69	0.27	0.63	0.38	0.80	0.65	0.72
Past-year amphetamine use	0.86	1.41	0.88	1.55	1.08	1.55	0.42	0.81
Past-year opioid use	0.36	0.87	0.17	0.51	0.31	1.01	1.83	0.40
Past-year hallucinogen use	1.04[a]	0.94	0.62[a]	0.82	0.85	1.16	**6.34**	**0.04**
Past-year sedative use	0.23[a]	0.56	0.54	1.21	0.77[a]	1.07	**7.89**	**0.02**
Mental Health								
Psychotropic Medication Use	16		20		11		5.96	0.05
MASQ-AA	16.43[a]	4.61	17.62	6.98	20.54[a]	6.66	**9.60**	**0.01**
MASQ-AD	30.85	8.00	28.35	6.36	29.62	5.91	3.85	0.15
MASQ-GD	23.68	7.88	24.67	7.87	27.62	9.33	4.60	0.10

[ab]Pairwise group comparison significant at $p<.05$. MASQ-AA/AD/GD=Mood and Anxiety Symptom Questionnaire – Anxious Arousal/Anhedonic Depression/General Distress. CUD= Cannabis Use Disorder. Past-year substance use is rated using the Drug Use Questionnaire. Past-month substance use and days since last cannabis use data are derived from the Timeline Follow-back; raw values were log-transformed for the omnibus group effect test.