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Sex Differences in Associations Between Cannabis Craving and Neural Responses to Cannabis Cues: Implications for Treatment

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Preclinical and clinical research indicates that there are sex differences in how men and women initiate, progress, respond to, and withdraw from cannabis use; however, neurophysiological differences, such as neural responses to cannabis cues, are not well understood. Using functional MRI and an event-related blood oxygen level-dependent backward-masking task, we compared neural responses to backward-masked cannabis cues to neutral cues in treatment-seeking, cannabis-dependent adults ($N = 44$; 27 males) and examined whether sex differences exist. In addition, functional MRI findings were correlated with cannabis craving. Backward-masked cannabis cues elicited greater neural responses than neutral cues in reward-related brain regions, including the striatum, hippocampus/amygdala, insula, anterior cingulate cortex, and lateral orbitofrontal cortex, $p < .01$, $k > 121$ voxels. Although no significant sex differences in neural responses to cannabis cues emerged, women showed a positive correlation between neural responses to cannabis cues in the bilateral insula and cannabis craving and an inverse correlation between neural responses to cannabis cues in the left lateral orbitofrontal cortex and cannabis craving. Men, however, showed a positive correlation between neural responses to cannabis cues in the striatum and cannabis craving. Given that cues and craving are important triggers and the focus on many behavioral treatment approaches, these findings suggest that treatment-seeking, cannabis-dependent men and women may benefit from sex-specific and tailored cannabis use disorder treatments.

Keywords: cannabis, dependence, cues, sex differences, craving

Cannabis is the most widely used illicit drug worldwide (United Nations Office on Drugs and Crime, 2014). In the United States, the number of individuals who meet criteria for cannabis-related disorders are two times higher than the number for any other illicit drug (Substance Abuse and Mental Health Services Administration, 2014). With a growing number of states legalizing cannabis for medicinal and recreational use (Cerdá, Wall, Keyes, Galea, & Hasin, 2012) and municipalities decriminalizing cannabis (Miech et al., 2015), the rates of cannabis use and cannabis use disorders (CUDs) will likely rise. Indeed, the escalation in use has already begun: In 2012, there were 18.9 million past month cannabis users, up from 14.5 million users in 2007 (Substance Abuse and Mental Health Services Administration, 2013). As such, improving our understanding of the neural and behavioral features associated with cannabis use and CUD is imperative in order to improve prevention and treatment.

The most studied and promising treatments for CUD include behaviorally based psychotherapeutic interventions, such as contingency management, motivational enhancement interviewing, or cognitive–behavioral therapy (CBT; Budney, Roffman, Stephens, & Walker, 2007; Davis et al., 2015). A recent meta-analysis of behavioral therapies for treatment-seeking cannabis users examined the overall impact of behavioral interventions (i.e., 10 randomized control trials) in the treatment of CUD and found that the effect sizes of behavioral therapies were superior to inactive waitlist control treatments; however, behavioral therapies did not outperform active control treatments (i.e., treatment as usual or psychological placebo; Davis et al., 2015). These findings are not surprising given that behavioral therapy achieves only a 50% abstinence rate during the first 2 weeks of treatment (Budney, Moore, Rocha, & Higgins, 2006; Budney et al., 2007), and of those who achieve abstinence during treatment, approximately 50% relapse within 1 year (Budney et al., 2007). Although behavioral therapies may be effective for some patients, individual differences, such as biological sex, may play an important role in cannabis use and treatment of CUDs.

Preclinical and clinical studies indicate sex differences in several aspects of cannabis use and CUD (Cooper & Haney, 2014; Craft, Marusich, & Wiley, 2013; Crane, Schuster, Fusar-Poli, & Gonzalez, 2013; Marusich, Lefever, Antonazzo, Craft, & Wiley, 2014). Specifically, men are more likely to initiate cannabis and

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subsequently develop a CUD than women (Wagner & Anthony, 2007), yet women progress from first use of cannabis to CUD faster than men (Hernandez-Avila, Rounsaville, & Kranzler, 2004; Khan et al., 2013). Sex differences have also been reported in the behavioral effects of cannabinioids. In rodents, females are more sensitive to the reinforcing, anxiogenic, and sedative effects of cannabinoids (Fattore, Fadda, & Fratta, 2009; Fattore et al., 2007; Harte-Hargrove & Dow-Edwards, 2012), and in humans, women report higher ratings of abuse-related effects (i.e., "Good" and "Take Again") following active cannabis administration than men (Cooper & Haney, 2014). Further, women exhibit greater physiological withdrawal symptoms than men (Copersino et al., 2010), which has been hypothesized to contribute to relapse (Haney et al., 2013) and could, in turn, influence treatment response. Although these findings suggest sex-specific differences in cannabis use, research has just begun to explore how these differences could influence treatment.

To date, very few studies have examined sex differences in CUD treatment. In a recent study of motivations to quit cannabis use in adult nontreatment seekers, researchers evaluated the influence of sex, among other factors, on risk of relapse over time and found that women were more likely than men to be motivated by self-image, self-control, health concerns, and social acceptability (Chauchard, Levin, Copersino, Heishman, & Gorelick, 2013). Interestingly, health concerns (e.g., worry that cannabis use is impacting health) were associated with higher risk of relapse after a quit attempt and social acceptability (e.g., hair and clothes would not smell of cannabis; using marijuana is becoming less socially acceptable) were associated with a lower risk of relapse among women (Chauchard et al., 2013). Sex differences in barriers and facilitators to cannabis treatment have also been explored. In one study, regular treatment users in treatment, in the community, and from an Internet sample completed surveys assessing perceived barriers and facilitators to entry to cannabis treatment, and findings indicate that women were more likely to report that seeking cannabis treatment is not necessary when reducing use (Gates, Copeland, Swift, & Martin, 2012). Men, however, were more likely to report that it would be hard to admit to having a problem with cannabis due to the perception that cannabis is a harmless drug, and men were more likely to report a need for current treatments to provide additional help with life skills than women (Gates et al., 2012). Together, these findings suggest cannabis use has important sex-specific effects on behavior, cognition, and perceptions about treatment, which likely influence all aspects of treatment and relapse.

Although behavioral and cognitive data indicate sex differences in cannabis use that might influence treatment response, sex differences in neural responses to cannabis cues may also be an important factor. Theoretical models of addiction indicate that exposure to drug-related stimuli, or cues, contributes to continued drug use and relapse in addicted individuals (Milton & Everitt, 2012; O'Brien, Childress, Ehrman, & Robbins, 1998). Among cannabis users, exposure to cannabis-related cues, such as seeing cannabis-related paraphernalia, increases physiological arousal (Wölfling, Flor, & Grüsser, 2008), subjective craving (Charboneau et al., 2013; Lundahl & Johanson, 2011), and neural activity in reward-related brain regions (Cousijn et al., 2013; Goldman et al., 2013). Further, cue-elicited craving predicts subsequent use up to 4 hr after exposure to cues (Fatseas et al., 2015). As such, cannabis cues are often defined as conscious triggers for cannabis craving and use, and strategies to avoid and manage exposure to cannabis cues are the focus of behavioral and cognitive treatment approaches. However, according to a recent study conducted by Wetherill and colleagues (2014) among treatment-seeking, cannabis-dependent individuals, even exposure to cannabis cues that are too brief to be consciously identified increase neural activity in brain regions supporting reward detection and interoception. Unfortunately, the sample size was not large enough to examine sex differences, but findings from the study suggest that the standard approaches to treating CUD by targeting conscious triggers may not be the optimal treatment approach.

In the current study, we have doubled our sample of treatment-seeking, cannabis-dependent individuals to explore whether sex differences exist in neural responses to cannabis cues presented in the backward-masking paradigm and to investigate the associations between neural activity and cannabis craving. Based on our previous findings and the growing body of research demonstrating sex differences in cannabis use, we hypothesized that sex differences would emerge with differences in neural activity to backward-masked cannabis cues in reward-related regions, including the insula, ventral striatum, medial prefrontal cortex, and amygdala/hippocampus (Childress et al., 2008; Wetherill et al., 2014). Given that an extensive literature suggests that heightened motivational/emotional states (e.g., craving) lead to heightened sensitivity to associated cues (Field, Munafò, & Franken, 2009), we hypothesized that cannabis craving reported prior to the imaging session would positively correlate with these cannabis cue-related activations and that different patterns of associations would emerge in women and men. Support for these hypotheses would improve our understanding of the neurobiological processes underlying cannabis use and help guide treatment strategies.

Materials and Method

Participants

In total, 157 individuals age 18–60 provided written informed consent and completed an in-person screening session to determine eligibility. To be eligible, individuals had to meet *DSM–IV* (American Psychiatric Association, 1994) criteria for cannabis dependence and express interest in reducing or stopping cannabis use. Individuals were excluded if they had clinically significant medical conditions; current *DSM–IV* diagnoses of drug and/or alcohol dependence (other than cannabis or nicotine dependence); lifetime history of head injury with loss of consciousness for more than 3 min; contraindications for MRI; current treatment for cannabis dependence; use of medication interacting with the central nervous system; and for women, pregnancy. Recruitment consisted primarily of radio advertisements, local list-serves, flyers, and word of mouth. Of the 157 individuals screened, 59 did not meet study criteria, and 34 were lost to follow-up or no longer wanted to participate. Of the 64 eligible participants, 54 completed the baseline imaging session. Ten baseline imaging datasets were unusable due to either subject distress during the scan session ($n = 2$), structural artifact ($n = 1$), excessive movement ($n = 3$), or falling asleep during the scan session ($n = 4$), resulting in a final sample size of 44. Twenty of the 44 participants included in this study are

reported on elsewhere (Wetherill et al., 2014). See Table 1 for participant demographics.

Procedures

All study procedures adhered to the Declaration of Helsinki and were approved by the University of Pennsylvania Institutional Review Board. Individuals who responded to advertisements underwent an initial telephone screening, after which eligible individuals were seen in person and gave written, informed consent. Interested individuals then underwent a medical and psychiatric evaluation to substantiate that they met study criteria.

Prior to starting treatment, participants completed baseline questionnaires, interviews, and an MRI session. Participants were asked to abstain from alcohol and illicit substances for the 24 hr prior to the MRI session (average self-reported abstinence of cannabis use was 21.1 hr ± 31.3 hr). Although urine analysis cannot detect 24-hr abstinence of Δ9-tetrahydrocannabinol (THC) metabolites, urine analyses increase accuracy of self-reported substance use (Roese & Jamieson, 1993). Thus, participants were tested for substance use with a urine drug screen and alcohol breathalyzer, and all participants were positive for cannabis use but were negative for other substance use. Prior to the scan session, an addiction therapist or licensed clinical psychologist met with each participant to review MRI scanning tasks, to assess for acute cannabis effects, and to administer two clinical scales of depression and anxiety, the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960) and the Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959). If assessments determined that participants were under the influence of any drug or alcohol, the MRI scan session was rescheduled ($n = 1$). Participants received $135 for completing the screening and baseline MRI session.

Measures

Sociodemographic/clinical information. Sociodemographic and clinical information included biological sex, age, race/ethnicity, and medical history.

Psychiatric diagnosis. The Mini International Neuropsychiatric Interview (Sheehan et al., 1997) was used to classify patients according to the presence or absence of standard psychiatric disorders according to *DSM–IV* criteria (American Psychiatric Association, 1994).

Substance use variables. Weekly cannabis consumption, cigarette smoking, and alcohol consumption was calculated using a 30-day Timeline Follow-Back interview (Sobell & Sobell, 1992), which allows for retrospective assessment of substance use. Research indicates that the Timeline Follow-Back interview has adequate test–retest reliability and is considered the gold standard for retrospective assessment of substance use. Typical weekly substance use (quantity and frequency) were included as covariates in all analyses. The Addiction Severity Index (McLellan et al., 1992) assessed lifetime cannabis, cocaine, amphetamine, heroin, opiate, barbiturate, hallucinogen, sedative, alcohol, and inhalant use.

Cannabis craving. The Marijuana Craving Questionnaire-Short Form (MCQ-SF; Heishman et al., 2009) measured self-reported baseline cannabis craving. The MCQ-SF is a four-factor structured scale covering behavioral experiences associated with aversive and appetitive aspects of drug motivation (i.e., compulsivity, emotionality, expectancy, and purposefulness). The magnitude of cannabis craving was assessed prior to the neuroimaging session and was determined by summing all items of the MCQ-SF for a total craving score. Immediately prior to the event-related backward-masked cue task, participants were also asked the following: "Using a scale of 0–9, with 0 meaning *none* or *not at all* and 9 meaning *extremely,* indicate to what degree you are now experiencing any craving or desire for marijuana?"

Event-related backward-masked cue task. To measure neural responses to subliminally presented cannabis cues, we used a backward-masking paradigm with a fast event-related functional MRI design, as described in detail previously (Childress et al., 2008; Wetherill et al., 2014; Young et al., 2014). Briefly, this passive viewing task consists of 192 trials, with each trial lasting 2,000 ms (i.e., 500-ms fixation cross, 33-ms cue stimulus, 467-ms

Table 1
Demographics by Biological Sex

Measure	Males ($n = 27$)		Females ($n = 17$)	
	M (*SD*)	Range	*M* (*SD*)	Range
Age	29.3 (8.2)	20–51	30.0 (6.8)	21–48
Race (% African American)	77.8		70.6	
Years of education	13.0 (1.5)	11–16	13.0 (2.2)	8–17
Cannabis use				
Days per week	6.3 (1.0)	2.3–7.0	5.7 (1.8)	2.1–7.0
Grams per smoking day	3.5 (5.4)	0.4–26.1	2.8 (2.4)	0.2–10.0
Years of cannabis use	11.4 (9.2)	3–38	10.8 (7.6)	0–32
Cannabis craving	42.1 (15.1)	17.0–74.0	43.6 (17.1)	17.0–64.0
Tobacco use				
# Daily smokers	16		8	
Cigarettes per day	7.5 (7.5)	2–30	8.0 (5.9)	2–30
Alcohol use				
# Weekly drinkers	20		7	
Days per week	1.3 (1.1)	0.0–4.2	0.8 (0.9)	0.0–2.8
Drinks per drinking day	5.1 (2.5)	2.4–12.2	5.3 (2.3)	2.6–8.5

Note. Male and female data represent mean group demographic characteristics (with standard deviations in parentheses). Sex differences emerged in the number of weekly drinkers per group, with males having more weekly drinkers than females, $\chi^2 = 4.8$, $p = .03$. No sex differences existed in any other demographic variables.

masking stimulus, and 1,000-ms fixation cross). As such, the stimulus-onset-asynchrony between cue and masking stimulus was 33 ms. This design prevents conscious processing of cue stimuli, as conscious visual processing of a very brief target (i.e., cue) stimulus (e.g., 20–33 ms) is eclipsed if a longer "masking" stimulus is presented immediately after the target (Brooks et al., 2012). Importantly, we have shown, using a forced-choice categorization task, that these backward-masking procedures prevent the conscious perception of cue stimuli (Childress et al., 2008). Total task time was approximately 8.5 min.

Imaging Parameters and Data Analysis

Prior to conducting analyses, all data were examined to ensure that data were usable and that there were no outliers. Imaging data were acquired on a 3.0 Tesla Trio whole-body scanner (Siemens AG, Erlangen, Germany) equipped with a standard 8-channel receive-only array head coil. Scan sessions began with shimming and sagittal localization. Three-dimensional T1-weighted magnetization-prepared rapid acquisition with gradient echo structural images were collected transaxially (repetition time, 1,510 ms; echo time, 3.7 ms; 160 slices; slice thickness 1 mm; field of view, 192 × 256 mm; flip angle 90°). Whole-brain gradient-echo echo planar images sensitive to blood oxygen level-dependent signal were acquired with the following parameters: repetition time, 2,000 ms; echo time, 30 ms; 32 slices; slice thickness 4.5 mm; field of view, 64 × 64 mm; flip angle 90°. Data were preprocessed and analyzed using Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London, United Kingdom). Images were slice-time corrected, realigned, motion corrected, and smoothed using an 8-mm full-width at half maximum Gaussian kernel. Next, functional data were registered to the participant's structural image and normalized to Montreal Neurological Institute standard space.

First level (within-subject) analyses were conducted individually for each participant with a general linear model to quantify the relationship between the observed event-related (blood oxygen level-dependent) signals and regressors encoding experimental conditions (i.e., cannabis cues, neutral cues). Regressors were created by convolving experimental condition functions with the canonical hemodynamic response function (Friston et al., 1998). The six motion estimates created during motion correction were entered as covariates of no interest. First-level (subject specific) contrast images were entered into the second-level (random effects) group-level analyses. In addition to the contrast of interest, correlations between subliminal cannabis-cue induced brain activity (relative to neutral cues) and baseline cannabis craving were computed by performing regression analysis within an a priori region of interest (ROI) mask to explore brain-behavioral associations. Age was included as a covariate of no-interest in all analyses. Frequency and quantity of alcohol and cigarette use did not differ between men and women in this sample, and therefore, these variables were not included in the final analyses. We did, however, conduct analyses with cigarettes per day and drinks per drinking day as covariates, and findings remained the same as those reported here.

We used the a priori ROI mask from our previous research (Wetherill et al., 2014), which included regions associated with reward and drug cue-reactivity, specifically the orbitofrontal cortex, insula, perigenual anterior cingulate cortex, ventral striatum, hippocampus, and extended amygdala (i.e., amygdala; bed nucleus of stria terminalis. These ROIs were joined into one mask of 9,602 ($2 \times 2 \times 2$ mm^3) voxels, which was created using the Harvard–Oxford probabilistic anatomical atlas provided with Functional Magnetic Resonance Imaging of the Brain Software Library (Smith et al., 2004). To control for Type I error, neural activity within the ROI mask of each voxel was considered significant at a nominal alpha level of $p < .01$ and a cluster extent of 121 contiguous resampled voxels as determined via Monte-Carlo simulations using *3dClustSim* (Analysis of Functional NeuroImages software; Cox, 1996; http://afni.nimh.nih.gov/).

Results

Neural Responses to Backward-Masked Cannabis Cues

As a group, cannabis-dependent, treatment-seeking individuals showed enhanced responses to backward-masked cannabis cues compared with neutral cues in the bilateral hippocampus/amygdala, bilateral insula, striatum, left lateral orbitofrontal cortex, and anterior cingulate cortex (see Figure 1). Analyses among women revealed greater responses to backward-masked cannabis cues compared with neutral cues in a cluster spanning the striatum, left hippocampus/amygdala, and left lateral orbitofrontal cortex. Similar analyses among men showed greater responses to backward-masked cannabis cues (vs. neutral cues) in the left striatum and left lateral orbitofrontal cortex (see Figure 2). Direct comparisons of neural activation to backward-masked cannabis cues compared with neutral cues between men and women revealed no significant differences.

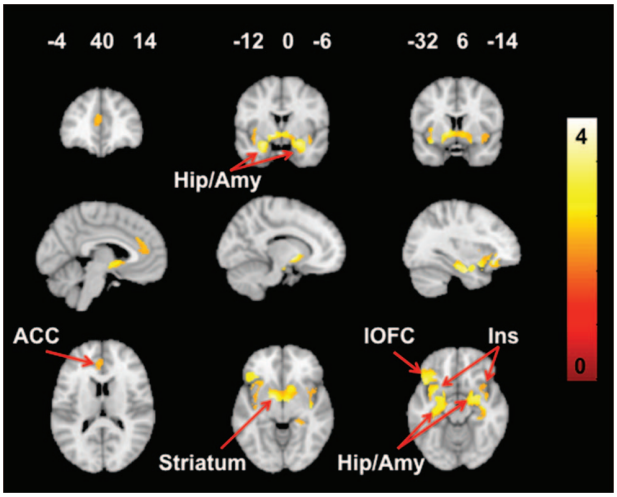

Figure 1. Neural responses to backward-masked cannabis cues compared with neutral cues in 44 treatment-seeking, cannabis-dependent adults, $p < .01$, $k > 121$ voxels. Representative functional MRI sagittal, axial, and coronal brain slices analyzed in SPM8 and overlain on the Montreal Neurological Institute brain. Data are displayed neurologically (left is left). The color bar represents *T* values. ACC = anterior cingulate cortex; Hip/Amy = hippocampus/amygdala; Ins = insula; lOFC = lateral orbitofrontal cortex. See the online article for the color version of this figure.

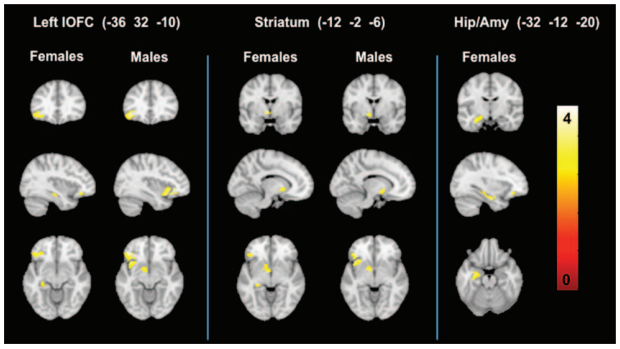

Figure 2. Neural responses to backward-masked cannabis cues compared with neutral cues in treatment-seeking, cannabis-dependent adults separated by sex (females: $n = 17$; males: $n = 27$), $p < .01$, $k > 121$ voxels. Representative functional MRI sagittal, axial, and coronal brain slices analyzed in SPM8 and overlain on the Montreal Neurological Institute brain. Data are displayed neurologically (left is left). The color bar represents T values. Hip/Amy = hippocampus/amygdala; lOFC = lateral orbitofrontal cortex. See the online article for the color version of this figure.

Correlations Between Cannabis Craving and Neural Activation to Backward-Masked Cannabis Cues

Overall, baseline cannabis craving scores assessed just prior to the imaging session did not show significant correlations with neural activation to backward-masked cannabis cues.

However, among women, baseline cannabis craving scores showed a positive correlation with neural activation to backward-masked cannabis cues in the bilateral anterior insula, right: $r(14) = 0.49$, $p = .05$; left: $r(14) = 0.50$, $p = .05$, and an inverse correlation to neural activation to backward-masked cannabis cues in the left lateral orbitofrontal cortex, $r(14) = -0.65$, $p = .008$ (Figure 3a and 3b). Cannabis craving among men was positively correlated with neural activation to backward-masked cannabis cues in a cluster spanning the striatum, $r(24) = 0.47$, $p = .01$ (Figure 3c). Cannabis craving among men did not show inverse correlations with neural activation to backward-masked cannabis cues.

Post Hoc Analyses

Given that only women exhibited greater neural responses to cannabis cues compared with neutral cues in the hippocampus/amygdala and that the hippocampus and amygdala have been implicated in other clinical states, such as depression (MacQueen & Frodl, 2011; McKinnon, Yucel, Nazarov, & MacQueen, 2009) and anxiety (Cominski, Jiao, Catuzzi, Stewart, & Pang, 2014), we conducted post hoc analyses to explore whether sex differences in depression and/or anxiety may have influenced our findings. Specifically, the HAM-D and HAM-A, which were administered prior to the scanning session, were scored, and the scores were then used to examine differences between men and women. Analyses revealed that men and women did not differ on clinical scales of depression, $t(42) = 1.32$, $p = .20$, or anxiety, $t(42) = 1.17$, $p = .25$. In addition, the HAM-D and HAM-A scores were entered in the neuroimaging analyses as covariates to see if the results were affected by clinical symptoms, and results were unchanged.

Discussion

Over the past three decades, there has been increased recognition of sex differences in drug use and treatment outcomes. Indeed, the National Institute on Drug Abuse launched the first program

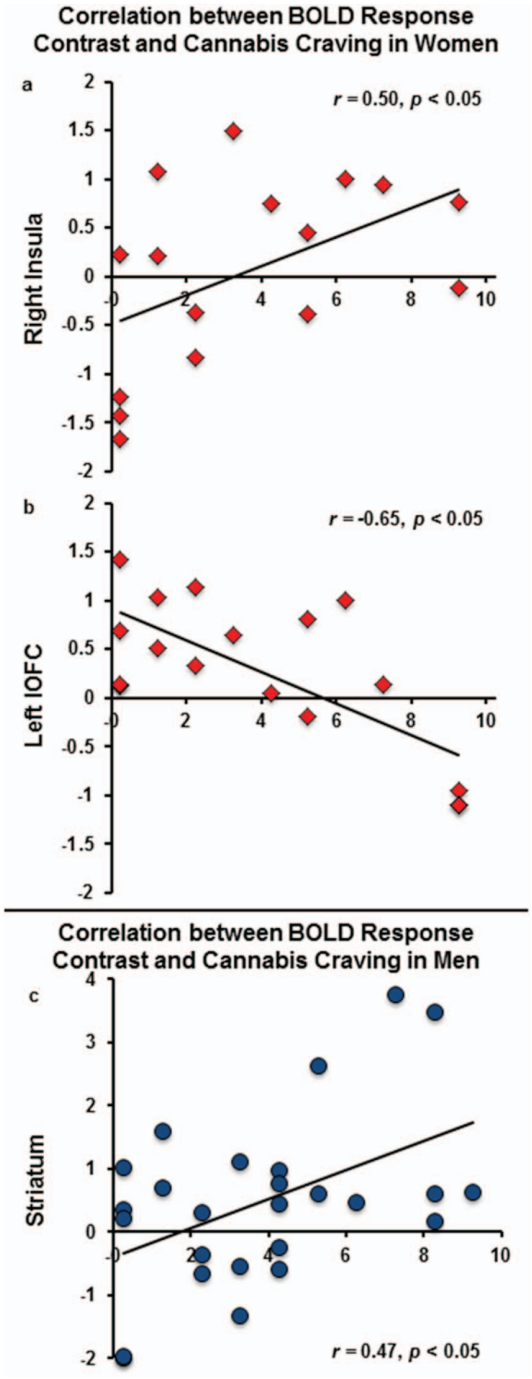

Figure 3. Correlations between blood oxygen level-dependent (BOLD) response contrast to backward-masked cannabis cues (vs. neutral cues) and cannabis craving in women (a, b) and men (c). lOFC = lateral orbitofrontal cortex. See the online article for the color version of this figure.

designed to treat women with substance use problems in 1973–1974 (Beschner, Reed, & Mondanaro, 1981) and developed an Office of Research on Women's Health to ensure the inclusion of women and minorities in clinical research. Consequently, a growing body of literature has identified considerable differences in various phases of the addiction cycle, with recent research suggesting that treatment processes and outcomes are influenced by sex/gender in complex ways (Green, 2006). To date, however, the majority of clinical treatment studies use a universal, gender-neutral approach and have found that women and men respond to psychological and pharmaceutical treatments for drug use disorders differently, with women typically showing poorer treatment outcomes than men (Ali, Seitz-Brown, & Daughters, 2015; DeVito, Babuscio, Nich, Ball, & Carroll, 2014; Litt, Kadden, & Tennen, 2015). Given the well-documented sex differences across various phases of the addiction cycle, research has started to focus on sex differences in the brain. As such, to improve our understanding of the neurobiological processes underlying cannabis use and to help guide treatment strategies, the present study aimed to examine sex differences in neural responses to backward-masked cannabis cues.

Here, we identified a network similar to that of previous studies examining neural responses to backward-masked drug cues in substance-dependent individuals (Childress et al., 2008; Wetherill et al., 2014). Furthermore, direct comparisons of neural responses to backward-masked cannabis cues compared with neutral cues between treatment-seeking, cannabis-dependent men and women revealed no significant statistical differences in neural activation. Among women, however, exposure to backward-masked cannabis cues elicited neural responses in the left hippocampus/amygdala, yet males did not show this pattern of hippocampal/amygdalar activation. With regard to behavioral data, we found sex-specific associations between neural responses to backward-masked cannabis cues and cannabis craving. Specifically, women showed a positive correlation between cannabis craving and neural responses to backward-masked cannabis cues in the bilateral insula, and an inverse correlation between cannabis craving and neural responses in the left lateral orbitofrontal cortex. In men, cannabis craving showed a positive correlation with neural responses to backward-masked cannabis cues in the striatum. These findings have potential implications for CUD treatments, as the association between cannabis craving and neural responses to backward-masked cannabis cues in women suggest that women could already possess top-down cognitive control skills, whereas males may need a more top-down treatment approach. Thus, men and women would likely benefit from sex-specific treatment approaches.

Although treatment-seeking, cannabis-dependent men and women showed increased neural responses to backward-masked cannabis cues in the striatum and left lateral orbitofrontal cortex, only women exhibited greater neural responses to cannabis cues compared with neutral cues in the left hippocampus/amygdala. Given that the hippocampus/amygdala have been implicated in depression (MacQueen & Frodl, 2011; McKinnon et al., 2009) and anxiety (Cominski et al., 2014), we conducted post hoc analyses to examine whether differences in depressive and/or anxiety symptomatology could account for the observed differences and found groups did not differ. Further, depression and anxiety scores did not influence our neuroimaging findings. Thus, our findings are likely related to other cognitive and clinical factors associated with cannabis use. For example, several neuroimaging studies have demonstrated that the hippocampus and amygdala are involved in emotion regulation and drug-related memory (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008; Wells et al., 2011; Zarrindast, Meshkani, Rezayof, Beigzadeh, & Rostami, 2010). Specifically, the amygdala plays an important role in both cue-associative learning and cue-induced relapse (Luo, Xue, Shen, & Lu, 2013), and the hippocampus is involved in establishing episodic memory for autobiographical events (Lipton & Eichenbaum, 2008). As such, females could be recruiting the hippocampus and amygdala while detecting salient cannabis cues and trying to regulate their emotions. Although speculative, this interpretation is consistent with recent research indicating that men have a greater ability to regulate emotions than women (Kong et al., 2014). If so, treatment approaches that include emotion regulation skill training components may be particularly helpful for treating CUD in women.

Cannabis craving in women showed a positive correlation with neural activation in the bilateral insula and an inverse correlation with neural activation in the left lateral orbitofrontal cortex during exposure to backward-masked cannabis cues. The insula has reciprocal connections with cortical and subcortical brain regions (Naqvi, Gaznick, Tranel, & Bechara, 2014) and is involved in the experience of body awareness, emotional processing, regulating autonomic functions, and drug craving (Garavan, 2010; Naqvi et al., 2014), whereas the lateral orbitofrontal cortex is implicated in regulating impulses, reevaluating previously rewarding behavior, and in modulating downstream limbic regions involved in motivated behavior (Elliott, Dolan, & Frith, 2000; Rolls, 2004). Therefore, cannabis craving may heighten interoceptive awareness to cannabis cues while also activating brain regions involved in avoidance behaviors in women. Although speculative, these findings suggest that treatment-seeking, cannabis-dependent women appear to engage cognitive control processes even before starting CUD treatment. As such, women may benefit from treatment approaches that include emotion regulation components (as stated above) and cognitive bias modification training, which retrains approach bias, or automatic attention and action, toward alcohol and drug cues (Wiers et al., 2015). Specifically, cognitive bias modification training may help decrease craving and associated neural responses in the insula, while also increasing cognitive control and devaluation of rewards associated with lateral orbitofrontal cortex activity.

Cannabis craving in men showed a positive correlation with neural responses to backward-masked cannabis cues in the striatum. The striatum, as part of the mesolimbic dopamine (DA) pathway, is involved in several reward processes (Daniel & Pollmann, 2014; Koob & Volkow, 2010), including drug-cue associations (Robinson & Berridge, 2003) and reactivity (Volkow et al., 2008; Vollstädt-Klein et al., 2010; Wetherill et al., 2013). As such, the observed correlation between cannabis craving and neural responses to backward-masked cannabis cues is consistent with previous research and suggests that even exposure to drug cues that are not consciously perceived activates neural regions associated with reward and craving. These findings could suggest that men may benefit from treatment approaches that include several approaches to enhance prefrontal cognitive control, reduce reactivity, and attenuate the observed reward-related striatal activity. Specifically, men might benefit from a combination of cognitive–

behavioral therapy and mindfulness approaches, which have been found to enhance cognitive control activity and attenuate subcortical and craving-related activity and reactivity (Kober, Kross, Mischel, Hart, & Ochsner, 2010; Westbrook et al., 2013).

Conclusions and Limitations

In summary, treatment-seeking, cannabis-dependent individuals exhibited reward-related neural responses to backward-masked cannabis cues with sex-specific patterns and correlations between cannabis craving and neural activity. Although additional research is warranted, findings suggest that men and women seeking treatment for CUD might benefit from sex-specific and tailored approaches.

Limitations should be considered when interpreting the findings. First, sample size for each sex is moderate, with most participants identifying themselves as African American. To this end, future studies should include a larger sample with greater diversity to validate these findings and ensure generalizability. In addition, greater response to the backward-masked cannabis cues could be attributed to greater complexity of cannabis cues compared with the neutral cues; however, all images were carefully matched on context, complexity, size, and luminosity. This study did not assess or control for the influence of menstrual cycle phase/gonadal hormones, cannabis withdrawal symptoms, or motivations for treatment, and as such, it remains unclear as to whether hormone levels, withdrawal symptoms, or treatment motivation could have influenced findings. Additional studies are needed in order to examine the effects of these factors on cannabis cue reactivity. It is important to note that attention may influence findings, and future research should examine attentional processes during the backward-masking task.

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