Published in final edited form as:

Exp Clin Psychopharmacol. 2011 June ; 19(3): 224–230. doi:10.1037/a0023030.

Cue-induced Craving for Marijuana in Cannabis Dependent Adults

Leslie H. Lundahl, Ph.D. and Chris-Ellyn Johanson, Ph.D.

Substance Abuse Research Division, Department of Psychiatry and Behavioral Neurosciences,
Wayne State University School of Medicine

Abstract

Recent interest in the development of medications for treatment of cannabis-use disorders indicates the need for laboratory models to evaluate potential compounds prior to undertaking clinical trials. To investigate whether a cue-reactivity paradigm could induce marijuana craving in cannabis dependent adults, 16 (eight female) cannabis dependent and 16 (eight female) cannabis-naïve participants were exposed to neutral and marijuana-related cues, and subsequent changes in mood, self-reported craving, and physiologic function were assessed. Significant group X cue interactions were found on all three VAS craving indices as well as on the Compulsivity scale of the Marijuana Craving Questionnaire-Brief Form (MCQ-BF). Cannabis dependent individuals responded to marijuana-related cues with significantly increased reports of marijuana craving compared to neutral cue exposure, although there were no cue-induced changes in any of the physiological measures. There were no significant gender differences on any of the measures. These results indicate that marijuana craving can be induced and assessed in cannabis dependent, healthy adults within a laboratory setting, and support the need for further research of the cue reactivity paradigm in the development of medications to treat cannabis-use disorders.

Keywords

Marijuana; cue-reactivity; craving; humans; gender differences

Marijuana is the most commonly used illegal drug in the United States, with approximately 104 million Americans (42% of the population) aged 12 and older having tried marijuana at least once (Substance Abuse and Mental Health Services Administration, 2009). The prevalence of marijuana dependence and recent interest in the development of medications for the treatment of this disorder translates into the need for controlled laboratory models to test novel compounds both alone and in conjunction with traditional treatment methods. There is much controversy in the research community as to the validity of craving as a construct (Witkiewitz & Marlatt, 2004) and the imprecision with which it traditionally has been conceptualized, defined, and assessed (e.g., Pickens & Johanson, 1992; Sayette, Shiffman, Tiffany, Niaura, Martic, & Shadel, 2000). However, craving continues to be considered a central feature of drug abuse with roles both in motivating drug use (e.g.,

O'Brien, Childress, Ehrman, & Robbins 1998; Wolfling, Flor & Grusser, 2008) and precipitating relapse (e.g., Lowman, Hunt, Litten, & Drummond, 2000). Craving also has been identified as a symptom both of cannabis dependence (Coffey, Carlin, Degenhardt, Lynskey, Sanci, & Patton, 2002) and cannabis withdrawal (Budney, Hughes, Moore, & Vandrey, 2004; Budney, Vandrey, Hughes, Thostenson, & Bursac, 2008; Haney, 2005; Vandrey, Budney, Hughes, Liguori, 2008). Thus, craving might be considered a key outcome variable in studies of medication efficacy. A laboratory model that reliably can induce craving and provide a strategy for measuring this phenomenon is vital to the evaluation of the efficacy of pharmacologic compounds in either blocking or attenuating craving for marijuana. The cue reactivity paradigm represents such a model.

The cue reactivity paradigm was developed to systematically induce and quantify craving across substances (Drummond, Tiffany, Glautier, & Remington, 1995). Cue reactivity refers to conditioned reactions to environmental and interoceptive substance abuse cues (Rohsenow, Niaura, Childress, Abrams, & Monti, 1990). While self-reports of craving often are the primary outcome, other types of reactivity are sometimes measured (e.g., physiological activity, other mood changes, latency to use drug). In these studies, substance dependent or abusing individuals are exposed both to cues that are thought to be associated with the taking of their preferred drug ("active" cues; e.g., drug taking paraphernalia, videotapes showing drug acquisition, preparation, and ingestion, etc.) and to cues that are not related to drug taking, or "neutral" cues (e.g., wood chips, water, etc.). Reports of craving and physiologic responses to these two types of cues are then compared. Numerous laboratory studies of cue reactivity indicate that this paradigm elicits robust levels of self-reported craving in both alcohol and drug dependent individuals as well as correlated changes in physiological activity following only the drug related cues (Carter & Tiffany, 1999).

Although much evidence supports the utility of the cue reactivity paradigm with various drugs of abuse, to date there are few published, controlled laboratory studies of marijuana cue-elicited craving. In determining the reliability and validity of the Marijuana Craving Questionnaire (MCQ), Singleton, Trotman, Zavahir, Taylor, & Heishman (2002) exposed current marijuana users to three script conditions, no-urge (no mention of marijuana), low-urge (desire to smoke marijuana) and high-urge (strong desire to smoke marijuana), and found that marijuana craving increased as a function of marijuana-urge script content. More recently, Haughey, Marshall, Schacht, Louis, and Hutchison (2008) reported that exposure to the sight and smell of used marijuana paraphernalia (i.e., bong, pipe) significantly increased self-reported cannabis craving above levels of craving due to cannabis withdrawal in their sample of daily marijuana smokers. Similarly Wolfling, Flor, and Grusser (2008) found that chronic heavy cannabis users responded to presentation of cannabis-related pictures with increases in self-reported craving and skin conductance, and a larger late positivity of the visual event-related brain potential. In the first study to include adolescents, Gray, LaRowe, and Upadhyaya (2008) demonstrated that marijuana-related imagery, video, and *in vivo* cues elicited marijuana cue reactivity in older adolescents and young adults with cannabis use disorders. Finally, audio, visual, olfactory, and vibrotactile cannabis-related cues presented via virtual reality environments were found to increase subjective marijuana craving and attention to cues relative to neutral cues among current marijuana smokers (Bordnick et al.,

2009). Overall, these findings indicate that a variety of marijuana-related stimuli can reliably elicit marijuana craving responses.

Few studies of drug cue reactivity have investigated gender differences, and those that have demonstrate mixed results. For example, although one study of cocaine cue reactivity indicated that females reported more craving in response to cocaine cue exposure compared to males (Robbins, Ehrman, Childress, & O'Brien, 1999), other studies have not supported this finding (e.g., Avants, Margolin, Kosten, & Cooney, 1995). Results from the only published marijuana craving study (Zilberman, Tavares, Hodgins, & el-Guebaly, 2007) that included gender as a variable showed that the intensity of self-reported marijuana craving was greater among males than females. It is important to note that the cue reactivity paradigm was not used to elicit marijuana craving in that study. Thus, it is not clear whether there are gender differences in drug craving overall, or in cue-elicited craving for marijuana specifically.

The cue reactivity model represents a unique strategy to provide an initial screening of the potential efficacy of medications for the treatment of marijuana abuse and dependence. Pharmacologic agents that alter reactivity to cues presented in a laboratory setting also may be effective in decreasing reactivity to cues encountered in the patient's natural environment, potentially reducing the risk of relapse. Thus, eliciting urges to use, or craving, is a more powerful test of the ability of pharmacologic agents to attenuate craving than simply asking individuals to retrospectively self-report craving. However, this approach has not yet been utilized in marijuana treatment research, although its use in the cocaine (e.g., Robbins, Ehrman, Childress, & O'Brien, 1992; Berger, Hall, Mickalian, Reid, Crawford, Delucchi et al., 1996) and alcohol (e.g., Rohsenow, Monti, Hutchison, Swift, Colby & Kaplan, 2000; Hutchison, Swift, Rohsenow, Monti, Davidson, & Almeida, 2001) literature indicates it may be useful in identifying potential medications for the treatment of marijuana dependence that would warrant further investigation in controlled clinical trials.

Furthermore, none of the published studies that have compared reactivity to marijuana-related and neutral cues in a laboratory context under controlled conditions have included a cannabis-naïve control group, and most have excluded gender as a variable. The current study was conducted to assess the specificity of a marijuana cue-reactivity paradigm as a first step in using this laboratory model for assessment of anti-craving medications. A second aim was to explore gender differences in marijuana cue reactivity. It was hypothesized that: (1) exposure to marijuana-related but not neutral stimuli would result in increased craving for marijuana (cue specificity); (2) exposure to marijuana-related stimuli would result in increased craving for marijuana but not nicotine (drug specificity); and (3) individuals with cannabis use disorders would exhibit marijuana cue reactivity but cannabis naïve individuals would not (population specificity). Finally, it was hypothesized that males would demonstrate greater marijuana cue reactivity compared to females.

Method

Participants

Participants were recruited through local community newspaper advertisements. To be included in the study, potential participants had to be between the ages of 18 and 44 years, meet DSM-IV criteria for Cannabis Dependence but no other psychiatric or substance abuse disorder (with the exception of Nicotine Dependence) and be in good health. Females could not be pregnant or lactating. Potential participants had to be able to provide informed consent and demonstrate adequate cognitive functioning (i.e., estimated IQ greater than 85). They also could not have a history of or current major neurological, cardiovascular, pulmonary, or systemic diseases. The Wayne State University Human Investigation Committee approved all procedures and participants were enrolled in the study only after providing informed consent. Participants were paid for their participation and were provided with lunch.

Design and Procedure

Potential participants who responded to advertisements underwent an initial telephone screening and those who met criteria for the study were invited to the laboratory for additional screening. During the screening portion of the visit, participants were asked to provide a breath sample to assess expired alcohol levels (using Alco-Sensor Model III; Intoximeters; St. Louis, MO) and a urine sample was requested to test for recent use of THC, amphetamines, cocaine metabolites, opioids, barbiturates and benzodiazepines. To qualify for the study, urine samples had to be positive for THC and negative for all other substances. The Structured Interview for the DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1996) was then administered to assess substance use disorders, and possible co-occurring Axis I psychiatric disorders and antisocial-personality disorder. Following the interview, participants completed several questionnaires regarding their drug and alcohol use. Those who were not excluded based on results of the screening were invited to participate in the study.

Participants were required to spend the evening prior to their scheduled session on a university-affiliated inpatient research unit. This was done to control for alcohol and drug use prior to the experimental session. Participants were admitted at 9PM and discharged the following morning after breakfast. They were transported to the laboratory via taxicab with a staff escort. Upon arrival at the laboratory, participants were asked to provide breath and urine samples for toxicology screening.

Experimental session—Participants were seated in a recliner within a light- and sound-attenuated testing room. Each participant was fitted with a blood pressure cuff and a telemetric (Mini-Mitter Co., Inc.) physiologic recording device that collected skin temperature and heart rate. The session consisted of three, 10-min phases (i.e., baseline, neutral cue exposure, marijuana cue exposure) followed by a 30-min recovery period. The order of neutral and marijuana-related cues was not counterbalanced so as to allow for the most conservative assessment of cue-related reactivity (e.g., Monti et al., 1987). An experimenter debriefed participants following the conclusion of the session. All instructions

to the participants during the three phases were delivered over a speaker in the chamber to minimize disturbance during cue exposure.

Baseline—Participants were seated in the recliner and were instructed to “relax” for 10-min while skin temperature and heart rate were recorded. After these assessments, blood pressure was monitored and participants responded to questionnaires (described below). Approximately 5-mins were required for questionnaire completion, and the neutral phase immediately followed.

Neutral Phase—Participants were instructed to remove the inverted opaque cover marked “A,” which revealed a variety of school supplies, including pencils, erasers, a ruler, and scented floral potpourri in a small bowl. The participants were instructed to handle and smell these items as they viewed a videotaped film clip depicting nature scenes set to classical music. At the end of the 10-min neutral cue exposure, participants were instructed to return the items to the table and replace the opaque cover over the items. Blood pressure was measured, then participants were instructed to complete the next questionnaire set, and then to “sit back and relax” until the next phase began.

Marijuana-related Phase—The 10-min marijuana-related cue exposure followed the neutral exposure. Participants were instructed to remove the opaque cover marked “B,” which revealed various marijuana-related paraphernalia, including a recently used bong, pipe, rolling papers, hollowed-out blunts, and a roach clip. Participants then were instructed to handle and smell the items while viewing a videotaped film clip of young adults smoking marijuana. Various scenes depicted preparing marijuana for smoking (i.e., rolling blunts, joints), smoking marijuana in a variety of ways (i.e., joint, bong, blunt, pipe), and in several different settings (i.e., party, bedroom, on a date, etc.). The video scenes were set to popular dance music. At the end of the 10-min marijuana cue exposure, participants were instructed to return the items to the table and replace the cover over the items. Following a blood pressure assessment they completed the next questionnaire set. At no time was marijuana available to any of the participants.

Recovery Period—Following the marijuana-related cue phase participants were escorted to the recreation room where they could watch television or read for 30-min or until their self-reported craving and vital signs returned to baseline levels. Participants were then debriefed and allowed to leave the laboratory.

Physiologic Dependent Variables

Heart rate and skin temperature were monitored continuously and recorded at 1-min intervals throughout the session. Blood pressure was measured at baseline, immediately after neutral and marijuana cue exposure, and periodically before discharge (i.e., recovery period). Physiologic data collected during the recovery period were not included in the analyses.

Subjective Effects Questionnaires

Mood—Participants were presented with a series of computerized visual analog scales (VAS) and instructed to place a vertical mark on a 100-mm line anchored on the left by the words *not at all* and on the right by the word *extremely* that corresponded with their responses to the following mood-related items: “How (“Anxious”, “Upset”, “High”, “Happy”, “Sedated”, “Down”, and “Stimulated”) do you feel right now?”

Craving—VAS items that specifically addressed craving for marijuana included the phrase “How strong is your...” followed by “desire to smoke marijuana right now?”, “desire not to smoke marijuana right now?”, “urge to smoke marijuana right now?”, and “craving for marijuana right now?”. Responses were recorded identically to the Mood items described above.

Marijuana craving also was assessed using the Marijuana Craving Questionnaire – Brief Form (MCQ-BF). This instrument is comprised of 17 items thought to represent four specific constructs that were found to characterize marijuana craving in the 47-item MCQ (Heishman et al., 2001). These constructs include: 1) Compulsivity, the inability to control marijuana use; 2) Emotionality, the use of marijuana in anticipation in relief from withdrawal or negative affect; 3) Expectancy, the anticipation of positive consequences from smoking marijuana; and, 4) Purposefulness, the intention and planning of marijuana use for positive consequences.

Nicotine craving was measured using the Questionnaire of Smoking Urges (QSU) Brief Form (Cox et al., 2001). This instrument consists of 10 items representing the two factors contained in the 32-item QSU (Tiffany & Drobes, 1991). Items are scored on a seven-point Likert-type scale. Factor 1 items represent desire and intention to smoke cigarettes, and Factor 2 items reflect anticipation of relief from negative affect with an urgent desire to smoke cigarettes.

Statistical Analysis

All data were analyzed using the Statistical Package for the Social Sciences, Version 17 for Mac (SPSS, Inc. 2008). The ten 1-min samples immediately preceding the first cue phase were averaged to yield baseline heart rate and skin temperature values. Group differences at baseline were investigated using one-way analysis of variance (ANOVA). For variables on which significant baseline group differences were found, change from baseline scores were calculated by subtracting the baseline from the neutral and active cue values. Heart rate and skin temperature data were averaged over the 10-min of each cue exposure to yield a mean value for each condition. Change scores were analyzed using 2 (group: cannabis/control) x 2 (gender) x 2 (cue: neutral change/active change) repeated measures ANOVA, with cue type as the repeated factor. Raw data were used in analyses unless otherwise specified, and were analyzed using 2 (group) x 2 (gender) x 3 (cue: baseline/neutral/active) repeated measures ANOVA, with cue as the repeated factor. Simple contrasts were used to further examine significant interactions. All effects were tested at the .05 level of significance. Effect sizes also were calculated (Cohen, 1988).

Results

Participants

The participants (mean age = 27.7 ± 4.8 yrs) were classified as cannabis dependent (cannabis group: $n=16$; 8 male) or cannabis-naïve (control group: $n=16$; 8 male). All individuals in the cannabis group met DSM IV criteria for Cannabis Dependence but no other current or past Axis I psychiatric or substance abuse disorder. None of the controls met DSM-IV criteria for any current or past Axis I psychiatric or substance use disorder.

Cannabis group—Mean age at first marijuana use was $16.6 \pm (2.8)$ yrs and participants reported a mean of $80.3 (\pm 60.5)$ months of daily marijuana use. Estimated mean lifetime marijuana use was approximately 10,399 ($\pm 10,038$) episodes. Participants reported smoking an average of $2.8 (\pm 1.4)$ blunts per day and all provided urine samples that were positive for THC. Thirteen subjects reported smoking cigarettes, with nine reporting regular use (defined as 3x/wk). All subjects reported alcohol use, and four reported regular use (i.e., 3x/wk). Three subjects reported lifetime use of MDMA (mean = 2.70 episodes), and two reported lifetime cocaine use (intranasally, mean = 3.1 episodes). Thirteen of the participants were African American, one was Caucasian and two described themselves as multiracial.

Control group—All controls reported never having smoked marijuana and all provided urine samples negative for THC. Seven reported smoking cigarettes, with one reporting regular (3x/wk) use. Of the fourteen who reported alcohol use, only one reported regular use (3x/wk). There was no other reported drug use among the controls. Fourteen of the participants were African American and two were Caucasian.

Demographic and Drug Use Variables

One-way ANOVAs used to examine group and gender (within each group) differences indicated that the two groups did not differ in age, years of education, MDMA use, or cocaine use, but differed significantly on all marijuana use variables (Table 1). Within the cannabis group, males and females did not differ in age at first use of marijuana, current daily use, duration of daily use, estimated lifetime episodes of marijuana use, or number of times they used MDMA or cocaine. Within the control group there were no gender differences on any demographic or drug use variables.

Physiological Measures

There were no significant differences in heart rate, skin temperature, or systolic or diastolic blood pressure as a function of group, gender, or cue condition (data not shown).

Subjective Measures

Mood and craving states—Baseline group differences were found on the variables “anxious”, “craving for marijuana”, “urge to smoke marijuana”, “desire to smoke marijuana”, all four scales of the MCQ, and the QSU, with the cannabis group having higher scores than the control group on all measures. Thus, these variables were analyzed using change from baseline values as described above.

Significant group X cue interactions were found for the variables “craving for marijuana” (Hotelling’s $T=.462$, $F(1,28)=12.94$, $p=.001$), “urge to smoke marijuana” (Hotelling’s $T=.470$, $F(1,28)=13.15$, $p=.001$), “desire to smoke marijuana” (Hotelling’s $T=.495$, $F(1,28)=13.87$, $p=.05$), and on the Compulsivity Scale of the MCQ (Hotelling’s $T=.200$, $F(1,28)=5.61$, $p=.025$). Simple contrasts indicated that all of these measures significantly increased from baseline following marijuana cue relative to neutral cue exposure, but only for the cannabis group. Cohen’s D for the craving measures was 1.36, which corresponds to a very large effect size. The group X cue interaction on “craving for marijuana” is shown in Figure 1. There were no other significant differences on the remaining mood or nicotine craving scales as a function of gender or cue exposure.

Discussion

This is the first known study to compare marijuana cue reactivity in daily marijuana smokers to a control group of marijuana-naïve individuals, and to investigate gender differences in marijuana cue reactivity. Results of the current study indicate that the cue reactivity model provides a valid and reliable means for inducing and measuring craving for marijuana in cannabis-dependent individuals. Further, marijuana cues appear to elicit comparable levels of marijuana craving in males and females.

The cannabis dependent individuals in this sample responded to marijuana cues with increased self-reported urge to smoke marijuana, craving for marijuana, and desire to smoke marijuana. They also received higher scores on the Compulsivity scale of the MCQ-BF, a measure of an inability to control marijuana use. Thus, marijuana cues produced a significant increase in self-reported craving and compulsivity to use marijuana. These results are consistent with those reported by others who found that exposure to visual and olfactory marijuana cues significantly increased self-reported cannabis craving in similar samples (e.g., Haughey et al., 2008; Wolfling, Flor, & Grusser, 2008; Gray, LaRowe, and Upadhyaya, 2008; Bordnick et al., 2009). The current study builds on these findings by demonstrating that the marijuana cue craving response is population-, cue-, and drug-specific. That is, only marijuana smokers responded to marijuana cues with increased self-reported craving, and they responded to marijuana cues with increased craving only for marijuana and not for nicotine.

The lack of gender differences in this cue-elicited marijuana craving study is not surprising given that results from similar studies involving other drugs have been mixed. Although there is some evidence that females report more craving for cocaine in response to cocaine cue exposure than males (Robbins et al., 1999), other studies have not shown this (e.g., Avants et al., 1995). Rubonis et al. (1994) reported that females exhibit greater alcohol cue reactivity compared to males, but only when experiencing negative mood. Studies of non-cue elicited craving also are equivocal. Elman, Karlsgodt, & Gastfriend (2001) found that non-treatment seeking female cocaine abusers reported greater cocaine craving than males. Conversely, Zilberman et al. (2007) showed that in their sample of 16 cannabis users, self-reported craving was greater among males compared to females. While further research is needed in this area, it appears that there are no gender differences in marijuana cue reactivity.

The failure to find significant differences in blood pressure, heart rate, and skin temperature was not unexpected, as numerous studies of cue reactivity with other drugs of abuse have failed to show physiologic effects. In their meta-analytic review of 41 alcohol, nicotine, cocaine, and opiate cue reactivity studies, Carter and Tiffany (1999) reported a large effect size (i.e., .92) for craving, and smaller effect sizes for physiological indices (i.e., .26 for heart rate and $-.24$ for skin temperature). The authors concluded that self-reported craving represents a focused and specific reaction to the cue manipulation, whereas only a fraction of physiologic reactivity derived from general physiologic responses may be reflective of cue manipulations. That is, craving responses have a very high level of signal variance, or cue specificity relative to noise variance, whereas physiologic responding contains a great deal of noise variance and is less cue specific (Carter & Tiffany, 1999). To put the current findings in context with other drug cue reactivity studies, effect sizes of self-reported craving responses to other drugs of abuse range from a low of .53 (alcohol) to a high of 1.29 (opiates), with nicotine (1.18) and cocaine (1.26) falling near the higher end of the range. The effect size of the craving measures in the current study was 1.36, which is considered robust (Cohen, 1988).

The primary limitation of the present study is the relatively small sample size, leading to concerns about generalizability of the study findings. Another limitation is the potential confound of the fixed-order presentation of the cues. Monti et al. (1987) suggested that neutral cues always be presented prior to active (i.e., drug related) cues, due to potential carry over effects from the drug cues that do not dissipate prior to presentation of the neutral cues. Although one way to minimize potential carry over effects from a counterbalanced cue presentation is to introduce an inter-cue interval of sufficient duration (e.g., 30 min), this solution is less than ideal for a model that is to be used to test medications because the model may have to accommodate medications with relatively short duration of action. Future studies should investigate inter-cue intervals to determine when carry-over effects are absent.

In this controlled laboratory investigation of marijuana cue reactivity we demonstrated that cannabis dependent males and females responded to tactile, olfactory, and visual marijuana-related cues with significant increases in self-reported craving for, urge and desire to smoke marijuana. Craving, at least for other substances such as cocaine, is associated with use during daily life (Preston et al., 2009), and predicts treatment drop-out and use during treatment (Heinz et al., 2006) as well as time to relapse (Paliwal, Hyman, & Sinha, 2008). Thus, craving is a reasonable target for medication development efforts. The cue reactivity paradigm may be useful in evaluating pharmacological interventions because of its ability to induce an observable increase in marijuana craving in response to marijuana-related cues. This allows for detection of a drug effect signal on cue-specific craving. Individuals are confronted with olfactory, tactile, and visual drug-related cues in their natural environments and one focus of pharmacologic and/or behavioral interventions is reduction of craving in response to these cues. Results from this study indicate that the cue reactivity model could be used to test the effects of potential medications on responses to cues in a controlled environment prior to undertaking large, costly, and time-consuming clinical trials.

Acknowledgments

The authors gratefully acknowledge the efforts of many contributors: Cheryl Aubie, Kelty Berardi, Robert Kender, Lisa Ficker, Heather Durdle, Nancy Lockhart, Manny Tancer, MD, Michael Eadie, MD, Ken Bates, Laura Strathdee, Deb Kish, and the staff at the Psychiatric and Addiction Research Center. This research was supported by NIH grant # DA-019236 (LHL), and Joe Young, Sr. funds from the State of Michigan.

References

- Avants SK, Margolin A, Kosten TR, Cooney NL. Differences between responders and nonresponders to cocaine cues in the laboratory. *Addictive Behaviors*. 1995; 20:215–24. [PubMed: 7484315]
- Berger SP, Hall S, Mickalian JD, Reid MS, Crawford CA, Delucchi K, et al. Haloperidol antagonism of cue-elicited cocaine craving. *Lancet*. 1996; 347:504–508. [PubMed: 8596268]
- Bordnick PS, Copp HL, Traylor A, Grap KM, Carter BL, Walton A, Ferrer M. Reactivity to cannabis cues in virtual reality environments. *Journal of Psychoactive Drugs*. 2009; 41:105–112. [PubMed: 19705672]
- Budney AJ, Hughes JR, Moore BA, Vandrey R. Review of the validity and significance of cannabis withdrawal syndrome. *American Journal of Psychiatry*. 2004; 161:1967–1977. [PubMed: 15514394]
- Budney AJ, Vandrey RG, Hughes JR, Thostenson JD, Bursac Z. Comparison of cannabis and tobacco withdrawal: Severity, and contribution to relapse. *Journal of Substance Abuse Treatment*. 2008; 35:362–368. [PubMed: 18342479]
- Carter BL, Tiffany ST. Meta-analysis of cue-reactivity in addiction research. *Addiction*. 1999; 94:327–340. [PubMed: 10605857]
- Childress, AR.; McLellan, AT.; Ehrman, R.; O'Brien, CP. NIDA Research Monograph. Vol. 94. Supt. Of Docs., U.S. Gov. Print Office; Washington, DC: 1988. Classically conditioned responses in opioid and cocaine dependence: A role in relapse? *Learning Factors in Substance Abuse*; p. 25-43.
- Coffey C, Carlin JB, Degenhardt L, Lynskey M, Sanci L, Patton GC. Cannabis dependence in young adults: an Australian population study. *Addiction*. 2002; 97:187–194. [PubMed: 11860390]
- Cohen, J. Statistical power analysis for the behavioral sciences. 2. Hillsdale, NJ: Erlbaum; 1988.
- Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings.[comment]. *Nicotine & Tobacco Research*. 2001; 3:7–16. [PubMed: 11260806]
- Drummond, DC.; Tiffany, ST.; Glautier, S.; Remington, B. Cue exposure in understanding and treating addictive behaviours. In: Drummond, DC.; Tiffany, ST., et al., editors. *Addictive behaviour: Cue exposure theory and practice*. Oxford, England: John Wiley & Sons; 1995. p. 1-17.
- Elman I, Karlsgodt KH, Gastfriend DR. Gender differences in cocaine craving among non-treatment-seeking individuals with cocaine dependence. *American Journal of Drug and Alcohol Abuse*. 2001; 27:193–202. [PubMed: 11417935]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis Disorders - Patient Edition (SCID-I/P, Version2.0). 1996.
- Gray KM, LaRowe SD, Upadhyaya HP. Cue reactivity in young marijuana smokers: A preliminary investigation. *Psychology of Addictive Behaviors*. 2008; 22:582–586. [PubMed: 19071985]
- Haney M. The marijuana withdrawal syndrome: diagnosis and treatment. *Current Psychiatric Reports*. 2005; 7:360–366.
- Haughey HM, Marshall E, Schacht JP, Louis A, Hutchison KE. Marijuana withdrawal and craving: influence of the cannabinoid receptor 1 (CNR1) and fatty acid amide hydrolase (FAAH) genes. *Addiction*. 2008; 103:1678–1686. [PubMed: 18705688]
- Heinz AJ, Epstein DH, Schroder JR, Singleton EG, Heishman SJ, Preston KL. Heroin and cocaine craving and use during treatment: measurement validation and potential relationships. *Journal of Substance Abuse Treatment*. 2006; 31:355–364.
- Heishman SJ, Singleton EG, Liguori A. Marijuana Craving Questionnaire: development and initial validation of a self-report instrument. *Addiction*. 2001; 96:1023–1034. [PubMed: 11440613]

- Hutchison KE, Swift R, Rohsenow DJ, Monti PM, Davidson D, Almeida A. Olanzapine reduces urge to drink after drinking cues and a priming dose of alcohol. *Psychopharmacology*. 2001; 155:27–34. [PubMed: 11374333]
- Lowman C, Hunt WA, Litten RZ, Drummond DC. Research perspectives on alcohol craving: an overview. *Addiction*. 2000; 95(Supplement 2):S45–S54. [PubMed: 11002901]
- Monti PM, Binkoff JA, Abrams DB, Zwick WR, Nirenberg TD, Liepman MR. Reactivity of alcoholics and nonalcoholics to drinking cues. *Journal of Abnormal Psychology*. 1987; 96:122–126. [PubMed: 3584660]
- O'Brien CP, Childress AR, Ehrman R, Robbins SJ. Conditioning factors in drug use: can they explain compulsion? *Journal of Psychopharmacology*. 1998; 12:15–22. [PubMed: 9584964]
- Paliwal P, Hyman SM, Sinha R. Craving predicts time to cocaine relapse: further validation of the Now and Brief versions of the cocaine craving questionnaire. *Drug and Alcohol Dependence*. 2008; 93:252–259. [PubMed: 18063320]
- Pickens RW, Johanson CE. Craving: consensus of status and agenda for future research. *Drug and Alcohol Dependence*. 1992; 30:127–131. [PubMed: 1633752]
- Preston KL, Vahabzadeh M, Schmittner J, Lin JL, Gorelick DA, Epstein DH. Cocaine craving and use during daily life. *Psychopharmacology*. 2009; 207:291–301. [PubMed: 19777216]
- Robbins SJ, Ehrman RN, Childress AR, O'Brien CP. Using cue reactivity to screen medications for cocaine abuse: a test of amantadine hydrochloride. *Addictive Behaviors*. 1992; 17:491–499. [PubMed: 1332435]
- Robbins SJ, Ehrman RN, Childress AR, O'Brien CP. Comparing levels of cocaine cue reactivity in male and female outpatients. *Drug and Alcohol Dependence*. 1999; 53:223–230. [PubMed: 10080048]
- Rohsenow DJ, Martin RA, Eaton CA, Monti PM. Cocaine craving as a predictor of treatment attrition and outcomes after residential treatment for cocaine dependence. *Journal of Studies on Alcohol and Drugs*. 2007; 68:641–648. [PubMed: 17690796]
- Rohsenow DJ, Monti PM, Hutchison KE, Swift RM, Colby SM, Kaplan GB. Naltrexone's effects on reactivity to alcohol cues among alcoholic men. *Journal of Abnormal Psychology*. 2000; 109:738–42. [PubMed: 11195999]
- Rohsenow DJ, Niaura RS, Childress AR, Abrams DB, Monti PM. Cue reactivity in addictive behaviors: theoretical and treatment implications. *International Journal of the Addictions*. 1990; 25(7A-8A):957–993.
- Rubonis AV, Colby SM, Monti PM, Rohsenow DJ, Gulliver SB, Sirota AD. Alcohol cue reactivity and mood induction in male and female alcoholics. *Journal of Studies on Alcohol*. 1994; 55:487–494. [PubMed: 7934057]
- Sayette MA, Shiffman S, Tiffany ST, Niaura RS, Martin CS, Shadel WG. The measurement of drug craving. *Addiction*. 2000; 95(Supplement 2):S189–210. [PubMed: 11002914]
- Singleton EG, Trotman AJ, Zavahir M, Taylor RC, Heishman SJ. Determination of the reliability and validity of the Marijuana Craving Questionnaire using imagery scripts. *Experimental and Clinical Psychopharmacology*. 2002; 10:47–53. [PubMed: 11871362]
- SPSS. Statistical Package for the Social Sciences. SPSS, Inc; Chicago: 2008. Version 17.0 for Mac OS X
- Substance Abuse and Mental Health Services Administration. Results from the 2009 National Survey on Drug Use and Health: Summary of National Findings. Office of Applied Studies; Rockville, MD: 2009. NSDUH Series H-38A, DHHS Publication No. SMA 10–4586 Findings
- Tiffany ST, Drobos DJ. The development and initial validation of a questionnaire on smoking urges. *British Journal of Addiction*. 1991; 86:1467–1476. [PubMed: 1777741]
- Vandrey RG, Budney AJ, Hughes JR, Liguori A. A within-subject comparison of withdrawal symptoms during abstinence from cannabis, tobacco, and both substances. *Drug and Alcohol Dependence*. 2008; 92:48–54. [PubMed: 17643868]
- Witkiewitz K, Marlatt GA. Relapse prevention for alcohol and drug problems: That was zen, this is tao. *American Psychologist*. 2004; 59:224–235. [PubMed: 15149263]
- Wolfling K, Flor H, Grusser SM. Psychophysiological responses to drug-associated stimuli in chronic heavy cannabis use. *European Journal of Neuroscience*. 2008; 27:976–983. [PubMed: 18333968]

Zilberman ML, Tavares H, Hodgins DC, el-Guebaly N. The impact of gender, depression, and personality on craving. *Journal of Addictive Diseases*. 2007; 26:79–84.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.

Group X Cue interaction on self-reported “craving for marijuana” change from baseline scores on a 0–100 scale. Error bars represent standard errors of the mean. * indicates significant differences at the $p < .05$ level, where ratings following marijuana cue exposure were elevated compared to neutral cue exposure for the cannabis group only. ** indicates significant differences at the $p < .05$ level, where ratings for the cannabis group were greater than for the control group, following marijuana cue exposure only.

Table 1

Subject demographic and drug use variables

Participant Demographics and Drug Use Variables by Group and Gender

	Cannabis Group			Control Group			
	Males (n=8) Mean (SD)	Females (n=8) Mean (SD)	Gender Contrasts	Males (n=8) Mean (SD)	Females (n=8) Mean (SD)	Gender Contrasts	Group Contrasts
Years of Education	13.63 (2.83)	12.88 (1.36)	ns	14.75 (2.71)	12.88 (1.36)	ns	ns
Age at Study (years)	27.25 (5.50)	28.50 (4.14)	ns	27.25 (5.18)	27.88 (5.14)	ns	ns
Age at First Use of Marijuana (years)	16.38 (2.50)	16.75 (3.20)	ns	N/A	N/A	--	--
Duration of Daily Marijuana Use (months)	79.50 (66.64)	81.00 (58.35)	ns	0 (0)	0 (0)	ns	< .001
Current Daily Use (# blunts/day)	2.88 (1.46)	2.75 (1.34)	ns	0 (0)	0 (0)	ns	< .001
Estimated Lifetime Episodes of Marijuana Use	11659.00 (1329.71)	9193.00 (5959.63)	ns	0 (0)	0 (0)	ns	< .001
Episodes of MDMA Use	1.00 (2.45)	4.38 (12.37)	ns	0 (0)	0 (0)	ns	ns
Episodes of Cocaine Use	0 (0)	6.25 (13.50)	ns	0 (0)	0 (0)	ns	ns

Note: Group and Gender contrasts were tested by one-way ANOVAs.