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# Magnitude and duration of cue-induced craving for marijuana in volunteers with cannabis use disorder

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ABSTRACT

*Aims:* Evaluate magnitude and duration of subjective and physiologic responses to neutral and marijuana (MJ)–related cues in cannabis dependent volunteers.
*Methods:* 33 volunteers (17 male) who met DSM-IV criteria for Cannabis Abuse or Dependence were exposed to neutral (first) then MJ-related visual, auditory, olfactory and tactile cues. Mood, drug craving and physiology were assessed at baseline, post-neutral, post-MJ and 15-min post MJ cue exposure to determine magnitude of cue- responses. For a subset of participants (n = 15; 9 male), measures of craving and physiology were collected also at 30-, 90-, and 150-min post-MJ cue to examine duration of cue-effects.
*Results:* In cue-response magnitude analyses, visual analog scale (VAS) items craving for, urge to use, and desire to smoke MJ, Total and Compulsivity subscale scores of the Marijuana Craving Questionnaire, anxiety ratings, and diastolic blood pressure (BP) were significantly elevated following MJ *vs.* neutral cue exposure. In cue-response duration analyses, desire and urge to use MJ remained significantly elevated at 30-, 90- and 150-min post MJ-cue exposure, relative to baseline and neutral cues.
*Conclusions:* Presentation of polysensory MJ cues increased MJ craving, anxiety and diastolic BP relative to baseline and neutral cues. MJ craving remained elevated up to 150-min after MJ cue presentation. This finding confirms that carry-over effects from drug cue presentation must be considered in cue reactivity studies.



## 1. Introduction

Marijuana is the most commonly used illicit drug in the United States and primary problem among substance abuse treatment seekers (SAMHSA, 2014). Psychosocial interventions are partially efficacious, but most cannabis dependent patients in treatment do not achieve abstinence (Copeland et al., 2001; Marijuana Treatment Project Research Group, 2004). Currently there are no FDA-approved medications for treating cannabis use disorder (CUD).

Craving is a central feature of drug abuse (O'Brien, 2005) associated with motivating use (O'Brien et al., 1998; Wolfling et al., 2008; Preston et al., 2009) and relapse (Childress et al., 1988; Lowman et al., 2000). As a symptom of CUD (American Psychiatric Association, 2013) and cannabis withdrawal (Budney et al., 2004; Haney, 2005; Vandrey et al., 2008), craving can be considered a significant target in studies of treatment efficacy.

The cue reactivity paradigm offers a means to induce and quantify craving in a controlled environment. Substance-abusing individuals are exposed to drug-related cues (*e.g.*, paraphernalia, videos depicting drug preparation or taking) and neutral cues (*e.g.*, wood chips, pencils, water). Craving and physiologic responses to these different cues are compared. An extensive literature demonstrates cue-induced craving across various substances including nicotine, alcohol, cocaine, heroin (reviewed by Carter and Tiffany, 1999), and marijuana (Haughey et al., 2008; Wolfling et al., 2008; Gray et al., 2008, 2011; Lundahl and Johanson, 2011; McRae-Clark et al., 2011; Nickerson et al., 2011; Charboneau et al., 2013; Lundahl and Greenwald, 2015). Cue-induced craving for marijuana has been found to be population-, cue-, and drug-specific. That is, only marijuana smokers (but not marijuana-naïve controls) responded to marijuana-related cues (but not neutral cues) with increased self-

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reported craving, and with increased craving only for marijuana but not nicotine (Lundahl and Johanson, 2011).

This paradigm has been used to evaluate potential anti-craving medications for cocaine (Kranzler and Bauer, 1992; Robbins et al., 1992; Hersh et al., 1995; Berger et al., 1996; Ehrman et al., 1996; LaRowe et al., 2007; Reid and Thakkar, 2009), nicotine (Reid et al., 2007; Rohsenow et al., 2008; Franklin et al., 2011; Ditre et al., 2012), alcohol (Rohsenow et al., 2000; Hutchison et al., 2001), and marijuana (Lundahl and Greenwald, 2015). Across studies, drug-related cues reliably induced drug-specific craving despite variable efficacy of the potential medications tested. In general, cue reactivity procedures provide a valuable set of outcomes for screening putative anti-craving medications, and may identify mechanisms relevant to pharmacotherapy even in the absence of medication efficacy (Berger et al., 1996).

Although exposure to substance-related cues increases craving for that specific substance, duration of cue-responses has received little attention but is important for several reasons. First, establishing a timeline of craving could inform design of laboratory cue paradigms. To control for potential carry-over effects, it has been recommended (Monti et al., 1987; Hutchison et al., 1999) that the neutral cue should always precede active drug cue presentation; thus neutral and drug-related cues have not been counterbalanced in most cue reactivity studies (Carter and Tiffany, 1999). Few studies have investigated whether there are carry-over effects or when cue-induced craving returns to baseline levels. Heishman et al. (2010) found that male and female smokers responded to tobacco-related imagery and *in vivo* cues with greater tobacco craving and increased heart rate and blood pressure, elevations that were sustained for 30-min post-exposure (Heishman et al., 2010). If cue-induced craving persists for extended periods of time, then paradigms would need to account for carry-over effects by scheduling washout intervals between cue conditions to avoid confounding. Second, because craving is related to motivating drug use (Wolfling et al., 2008) and relapse (Lowman et al., 2000), from a safety perspective, participants should not leave the laboratory until craving levels return to baseline to minimize risk of iatrogenic drug use. Finally, when using the cue reactivity paradigm in medication development studies, it is essential to know the duration of induced drug craving. Even if a medication acutely attenuates craving, a longer-acting formulation may be necessary to be efficacious.

The present study investigated the magnitude and duration of marijuana cue-induced subjective and physiological reactivity in cannabis-dependent male and female adults. We hypothesized that marijuana cue exposure would increase craving relative to neutral cue exposure. We also examined the time course of marijuana cue-induced exposure until 150-min post-cue.

## 2. Methods

### 2.1. Participant selection

The local IRB approved all study procedures. Candidates from 18 to 44 years old were recruited through local newspaper ads and word-of-mouth referrals. Eligible participants had to be in good health based on history and physical exam, standard laboratory studies, electrocardiogram, and psychiatric interview. Participants were not seeking treatment, met DSM-IV (APA, 1994) criteria for Cannabis Dependence, and submitted a cannabinoid-positive (cut-off $\geq$50 ng/ml) urine sample at screening. Candidates with positive urine tests for non-cannabinoid drugs were excluded. Additional exclusion criteria were any current DSM-IV axis I disorder except Cannabis or Nicotine Dependence (assessed using the Structured Interview for DSM-IV; First et al., 1996); neurologic, cardiovascular, pulmonary or systemic diseases; and cognitive impairment. Females could not be pregnant or lactating, and had to be using medically approved contraceptives. All participants had to provide sober (BAC < 0.02%) informed consent and demonstrate adequate cognitive functioning (*i.e.*, estimated IQ > 85; Zachary, 1986). Participants also completed questionnaires regarding their drug and alcohol use. Volunteers were paid for their participation.

### 2.2. Design and procedure

*2.2.1. General procedures.* Participants were admitted to a university-affiliated inpatient unit at 9:00 pm and spent the evening prior to their session to control for alcohol and drug use for the 12-h prior. After eating breakfast at 7:30 a.m., they were and transported to the laboratory *via* taxicab with staff escort. Participants provided breath and urine samples for toxicology testing upon their arrival at the laboratory. While on the inpatient unit, participants were offered periodic tobacco cigarette breaks during which they could smoke cigarettes. At the laboratory, cigarette breaks were allowed only when participants were not completing questionnaires or experimental tasks.

*2.2.2. Experimental session procedures.* Participants were seated in a recliner in a light- and sound-attenuated private testing room each participant underwent the marijuana cue exposure procedure described below. A telemetric (Mini-Mitter Co, Inc., Bend, OR) was used to collect skin temperature and heart rate data, and a blood pressure cuff was fitted to each participant to monitor blood pressure. The experimental session consisted of three, 10-min phases (*i.e.*, baseline, neutral cue, marijuana cue), followed by a 30-min recovery period. Each phase was separated by 10 min. Following advice of Monti et al. (1987), the order of cue presentation was not counterbalanced to avoid possible carry-over effects from marijuana cues. All experimental instructions to the participants were delivered *via* speaker in the chamber to minimize distraction during cue exposures.

*2.2.2.1. Baseline.* While seated in the recliner, participants were asked to "relax" for 10-min while pre-cue subjective and physiological measures (see below) were recorded. The neutral phase began immediately after the baseline phase.

*2.2.2.2. Neutral-cue 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 floral scented potpourri in a small bowl. Participants were next instructed to handle and smell these items while viewing a videotaped film clip containing nature scenes set to classical music. Following this 10-min cue period, participants were instructed to return the items to the table and to replace the cover. Subjective and physiological measures were recorded. They were then asked to "sit back and relax" for 10-min until the next phase began.

*2.2.2.3. Marijuana-cue phase.* Immediately following the neutral cue exposure, participants were asked to remove the inverted 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 were instructed to handle and smell these items while viewing a videotaped film clip depicting of individuals smoking marijuana. Set to dance music, video scenes depicted preparing marijuana for smoking (*i.e.*, rolling joints and blunts), and smoking marijuana in a variety of ways (*i.e.*, joint, blunt, bong, pipe) in different settings (*i.e.*, party, on a date, in a living room). At the end of the 10-min exposure, participants were asked to return the items to the table and replace the opaque cover over the items. Subjective and physio-