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# Neural responses to subliminally presented cannabis and other emotionally evocative cues in cannabis-dependent individuals

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## Abstract

**Rationale—**Addiction theories posit that drug-related cues maintain and contribute to drug use and relapse. Indeed, our recent study in cocaine-dependent patients demonstrated that subliminally presented cocaine-related stimuli activate reward neurocircuitry without being consciously

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perceived. Activation of reward neurocircuitry may provoke craving and perhaps prime an individual for subsequent drug-seeking behaviors.

**Objectives—**Using an equivalent paradigm, we tested whether cannabis cues activate reward neurocircuitry in treatment-seeking, cannabis-dependent individuals and whether activation was associated with relevant behavioral anchors: baseline cannabis craving (drug-seeking behavior) and duration of use (degree of conditioning).

**Methods—**Twenty treatment-seeking, cannabis-dependent individuals (12 males) underwent event-related blood oxygen level-dependent functional magnetic resonance imaging during exposure to 33-ms cannabis, sexual, and aversive cues presented in a backward-masking paradigm. Drug use history and cannabis craving were assessed prior to imaging.

**Results—**Participants showed increased activity to backward-masked cannabis cues in regions supporting reward detection and interoception, including the left anterior insula, left ventral striatum/amygdala, and right ventral striatum. Cannabis cue-related activity in the bilateral insula and perigenual anterior cingulate cortex was positively associated with baseline cannabis craving, and cannabis cue-related activity in the medial orbitofrontal cortex was positively correlated with years of cannabis use. Neural responses to backward-masked sexual cues were similar to those observed during cannabis cue exposure, while activation to aversive cues was observed only in the left anterior insula and perigenual anterior cingulate cortex.

**Conclusions—**These data highlight the sensitivity of the brain to subliminal reward signals and support hypotheses promoting a common pathway of appetitive motivation.

### Keywords

Addiction; Cannabis cues; Neuroimaging; Cannabis craving; Subliminal; Marijuana cues; Marijuana craving; Reward

## Introduction

Cannabis is the most widely used illicit substance in the USA (Substance Abuse and Mental Health Services Administration 2012). Although commonly considered a “soft option” drug (Raphael et al. 2005), chronic cannabis use is associated with several negative consequences, including an increased likelihood of experiencing depression and anxiety (Pacek et al. 2012), high-risk sexual behavior (Schuster et al. 2012), and a range of physiological, cognitive, and neural abnormalities (Crane et al. 2012; Jacobus et al. 2012). Despite these negative consequences, cannabis users often report multiple quit attempts without achieving prolonged abstinence (Budney et al. 2008).

According to theoretical models of addiction, one factor contributing to continued drug use and relapse is exposure to drug-related stimuli, or cues (Milton and Everitt 2012; O'Brien et al. 1998). Exposure to cannabis-related cues, such as seeing cannabis or cannabis-related paraphernalia, elicits increased physiological arousal (Wolfling et al. 2008), subjective craving (Lundahl and Johanson 2011; Nickerson et al.2011, and increased neural activity in reward-related brain regions (Cousijn et al. 2012; Filbey et al. 2009; Goldman et al. 2012. 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 part of many treatment approaches.

Although coping with conscious triggers may be effective for some individuals, it is possible that the brain's response to reward cues may begin outside conscious awareness (Berridge and Winkielman 2003; Winkielman et al. 2003) and, consequently, may not be amenable to existing cognitive treatment approaches (Asensio etal. 2010). Indeed, functional magnetic resonance imaging (fMRI) studies using subliminal paradigms (i.e., brief presentation of stimuli that are attended to but not consciously perceived) support the notion that exposure to drug-related cues, even when presented outside awareness, activates reward neurocircuitry (Childress et al. 2008; Zhang et al. 2009). Using fast event-related fMRI and a backward-masking paradigm, we previously demonstrated that cocaine cues activated the insula, ventral striatum (VS), and amygdala—without being consciously perceived (Childress et al. 2008). Though this study demonstrated that subliminal cocaine cues can trigger reward circuitry, it is not known whether these findings generalize to other drugs of abuse and populations, such as cannabis-dependent individuals.

Thus, the aim of the present study was to examine whether cannabis-dependent individuals respond to cannabis cues presented in the backward-masking paradigm with activation of reward neurocircuitry and to investigate the relationships between applicable behavioral end points (i.e., cannabis craving and years of cannabis use). Based on our previous findings, we hypothesized that cannabis-dependent individuals would show increased activity to backward-masked cannabis cues in the insula, VS, and amygdala (Childress et al. 2008) and potentially in additional regions involved in salience and reward, such as the anterior cingulate cortex, the medial prefrontal cortex, and the hippocampus. Given that an extensive literature suggests that heightened motivational/emotional states (e.g., hunger, drug craving) lead to heightened sensitivity to associated cues (Martens et al. 2013; Siep et al. 2009), we hypothesized that cannabis craving reported prior to the imaging session would positively correlate with these cannabis cue-related activations. Further, based on the principles of simple Pavlovian conditioning, we hypothesize that drug cues acquire the ability to trigger brain reward circuitry such that greater drug experience should lead to stronger responses. Support for these hypotheses would improve our understanding of the automatic processes underlying cannabis use and help guide treatment strategies.

A secondary aim was to examine whether cannabis-dependent individuals respond similarly to emotionally evocative cues. One hypothesis debated in the field is that chronic drug use leads to the devaluation of natural rewards; however, research in this area has provided mixed results (Cabeza de Vaca and Carr 1998; Goldstein et al. 2010; Grigson and Twining 2002; Klucken et al. 2013). In our previous work in cocaine-dependent patients (Childress et al. 2008), increased brain responses in reward neurocircuitry were observed to both backward-masked cocaine and sexually evocative cues. Thus, we examined whether chronic cannabis use altered reactivity to natural reward and emotionally evocative stimuli by including sexual and nonrewarding, aversive cues in our backward-masking paradigm.

## Methods

### Participants

Participants were cannabis-dependent individuals who were taking part in the neuroimaging cannabis outpatient treatment study of a larger, ongoing three-arm (i.e., cocaine, cannabis, prescription opiates) study examining neural and behavioral features predictive of treatment outcomes. For the current study, only baseline neuroimaging data from 23 chronic, heavy cannabis smokers (i.e., cannabis use on 10 or more days in the last month or >240 days in the past 2 years (Pope et al. 2001)) who responded to radio advertisements and local list serves describing a neuroimaging outpatient treatment study for cannabis dependence and met the DSM-IV (American Psychiatric Association 1994) criteria for cannabis dependence are presented. Data for the current study were collected at the baseline session, and as such, participants had not begun treatment nor had they set a quit date. Exclusion criteria included current DSM-IV Axis I diagnoses (other than cannabis or nicotine dependence), lifetime history of head injury with loss of consciousness for more than 3 min, contraindications for magnetic resonance imaging, current treatment for cannabis dependence, clinically significant medical conditions, and use of medication interacting with the central nervous system. Individuals were excluded due to structural artifact ($n$ =1) or experiencing claustrophobia upon entering the scanner ($n$ =2). The remaining data from 20 participants (12 males) were used in statistical analyses.

### Procedures

This study adhered to the Declaration of Helsinki and was approved by the University of Pennsylvania Institutional Review Board. After completing a detailed telephone screen, participants gave informed consent, completed psychological and medical screening, and participated in an MRI session. To minimize potential substance-induced cerebral blood flow changes, participants were asked to abstain from alcohol and illicit substances for 24 h prior to the MRI session (average self-reported abstinence of cannabis use was 1.5±1.5 days). Of note, urinalysis cannot detect 24-h abstinence of Δ9-tetrahydrocannabinol (THC) metabolites; however, urinalyses increase accuracy of self-reported substance use (Roese and Jamieson 1993). Thus, participants were tested for substance use with a urine drug test and alcohol breathalyzer. All participants were positive for cannabis use and negative for other substance use. Participants met with clinical staff prior to scanning to review MRI scanning tasks and to assess for acute cannabis effects. MRI scans were rescheduled for participants under the influence of drugs or alcohol ($n$ =1). Participants received $135 for completing the screening and MRI sessions.

### Clinical assessments

All participants were screened for the presence of Axis I psychiatric disorders using the Mini International Neuropsychiatric Interview (Sheehan et al. 1997). Cannabis and other drug use during the preceding 30 days was quantified using the Timeline Followback method (Sobell and Sobell 1991). Cannabis use and cannabis-related problems, as well as other illicit drug use and problems, were assessed with the Addiction Severity Index (ASI) (McLellan et al. 1992). The Marijuana Craving Questionnaire-Short Form (MCQ-SF) (Heishman et al. 2009) measured self-reported baseline cannabis craving before the

neuroimaging session. 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, purposefulness). The magnitude of cannabis craving was determined by summing all items for a total score, which results in a more reliable, internally consistent measure of the phenomenon. The Fagerstrom Test for Nicotine Dependence (FTND) measured nicotine dependence severity (Heatherton et al. 1991).

### Stimuli and fMRI backward-masking task

To measure neural responses to subliminally presented stimuli, we used fMRI during a backward-masking paradigm (Childress et al. 2008) designed to prevent conscious processing of targets. In backward-masking paradigms, conscious visual processing of a very brief target is eclipsed if a longer "masking" stimulus is presented directly after the target, causing a disruption in the relay of the original stimulus from the retina to the visual cortex (Brooks et al. 2012). The effectiveness of our backward-masking procedures for 33-ms targets and 467-ms masking stimuli was demonstrated with a forced-choice categorization test in our previous research (Childress et al. 2008). Consequently, in an event-related fMRI design (Fig. 1), each target image was displayed for 33 ms followed by a 467-ms masking stimulus, for a total of 500 ms of visual stimuli. Importantly, the stimulus-onset asynchrony (SOA) between target and mask was 33 ms (Brooks et al. 2012; Carlsson et al. 2004), with the mask immediately following the target. The interstimulus interval (ISI) was of random duration between 1,000 and 2,000 ms. As in Childress et al. (2008), target stimuli consisted of 24 drug-related (in this case, cannabis), 24 sexual, 24 aversive, and 24 neutral images. Cannabis images were pictures of cannabis, cannabis-related paraphernalia, and individuals engaged in cannabis smoking using various modes of administration. Sexual (mean arousal rating = 6.36) and aversive (mean arousal rating = 6.23) images were taken from the International Affective Pictures System (IAPS) (Lang et al. 2008). Neutral targets and masking stimuli were taken from our laboratory archive of nondrug images (e.g., building facades, people engaged in everyday activities, etc.). Images were matched on size, average luminosity, and context/complexity. Targets and masks were paired randomly, and each target–mask pair was presented quasi-randomly (no more than two targets of the same category in succession) without replacement until all target–mask pairs were shown (1 cycle: 24 target–mask pairs × 4 categories = 96 trials); a second cycle followed. Prior to the task, participants were told the following: "Pay attention to each picture. There is a small test later to see which pictures you remember."

Guided by *OptSeq*, 33 null stimuli (gray screens with a small black fixation cross) were inserted into each cycle of the stimulus sequence (quasi-random, no more than two in succession) to improve the efficiency of the event-related design, but were not part of the formal statistical analysis. Total task time was approximately 8.5 min.

### MR acquisition

Imaging data were acquired on a 3.0-T Trio whole-body scanner (Siemens AG, Erlangen, Germany) equipped with a standard eight-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 (MPRAGE) structural images

were collected transaxially (repetition time (TR) 1, 510 ms, echo time (TE) 3.7 ms, 160 slices, slice thickness 1 mm, field of view (FOV) 192×256 mm, flip angle 90°). Whole-brain gradient-echo, echo-planar images (EPI) sensitive to blood oxygen level-dependent (BOLD) signal were acquired with the following parameters: TR 2,000 ms, TE 30 ms, 32 slices, slice thickness 4.5 mm, FOV 64×64 mm, and flip angle 90°.

## Data processing and analysis

Imaging data were analyzed using Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London, UK). After slice timing correction, functional images of each participant were realigned and unwarped, co-registered to the structural MRI image, normalized to the Montreal Neurological Institute (MNI) standard space, and smoothed using an 8-mm full-width at half maximum Gaussian kernel. First-level (within-subject) analyses were conducted individually for each participant with a general linear model (GLM) to quantify the relationship between the observed event-related (BOLD) signals and regressors encoding experimental condition conditions (i.e., cannabis cues, sexual cues, aversive 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 (1) baseline cannabis craving and (2) years of cannabis use were computed for all subjects by performing regression analysis within an a priori region of interest (ROI) mask to explore brain-behavioral associations.

Imaging analyses were focused on ROIs associated with processing of reward-related stimuli, specifically the medial orbitofrontal cortex (mOFC), insula, perigenual anterior cingulate cortex (pgACC), VS, hippocampus, and extended amygdala (i.e., amygdala, bed nucleus of stria terminalis) (Brooks et al. 2012; Chase et al. 2011; Kuhn and Gallinat 2011a). These ROIs were joined into one mask of 9,602 (2× 2×2 $mm^3$) voxels (see Online Resource 1 or our interactive website: http://franklinbrainimaging.com). The ROI mask was created using the Harvard-Oxford probabilistic anatomical atlas provided with the FMRIB Software Library (FSL) (Smith et al. 2004). To control for type 1 error, neural activity within the ROI mask of each voxel was considered significant at a nominal alpha level of $p < 0.01$ and a cluster extent of 121 contiguous resampled voxels as determined via Monte Carlo simulations using *3dClustSim* Analysis of Functional NeuroImages (AFNI) software (Cox 1996) (http://afni.nimh.nih.gov/).

Secondary analyses examined neural responses to backward-masked cues using the following contrasts: (1) sexual versus neutral cues, (2) cannabis versus sexual cues, (3) aversive versus neutral cues, and (4) cannabis versus aversive cues, following the same first- and second-level analyses described above.

## Results

Demographic, self-report, and substance use characteristics are presented in Table 1. Subjects reported no illicit substance use other than cannabis in the past 30 days. Cannabis-dependent individuals displayed enhanced responses to backward-masked cannabis versus neutral cues in the left anterior insula, left VS/amygdala, and right VS (Table 2, Fig. 2). There were no areas wherein activation was greater to neutral cues relative to cannabis cues.

Next, we examined the extent to which MCQ-SF scores assessed just prior to the imaging session and number of years of cannabis use was correlated with neural activation to cannabis cues (compared to neutral cues). $\beta$ coefficients were extracted from significant clusters and averaged to calculate the association between behavioral scores and brain responses. Baseline cannabis craving scores were positively correlated with brain activation to backward-masked cannabis cues in the bilateral insula (right: $r$ =0.64, $p$ =0.002; left: $r$ =0.57, $p$ =0.008) and pgACC ($r$ =0.56, $p$ =0.01) (Fig. 3a, b). Number of years of cannabis use positively correlated with brain activation to cannabis cues in a cluster spanning the mOFC ($r$ =0.69, $p$ =0.001) (Fig. 3c). We observed no inverse correlations with the MSQ-SF craving scores or years of cannabis use. Cannabis craving and cannabis use history did not correlate with brain activation to sexually evocative or aversive pictures.

Secondary analyses examined neural responses to backward-masked sexual and nonrewarding, aversive stimuli compared to neutral cues and cannabis cues. Cannabis-dependent individuals displayed enhanced responses to backward-masked sexual cues relative to neutral cues in the left VS, bilateral anterior insula, right hippocampus/amygdala, and pgACC (Table 2, Fig. 2); however, there were no areas wherein activation was significantly different during subliminal exposure to cannabis cues compared to sexual cues. In the aversive cue versus neutral cue contrast, cannabis-dependent individuals displayed enhanced responses to backward-masked aversive cues in the left anterior insula and pgACC (Table 2, Fig. 2), but did not show VS activity that was observed during the subliminal cannabis and sexual cue contrasts. In the cannabis cue versus aversive cue comparisons, there were no significant differences in activation. Online Resource 2 provides a table of these whole-brain analyses.

## Discussion

Using visual backward masking of cannabis-related cues, we found additional evidence to support the hypothesis that drug-related cues presented outside awareness activate reward-related circuitry. Specifically, our data indicate that cannabis-related cues evoke neural activity in the left anterior insula, left VS/amygdala, and right VS. Thus, our results replicate and extend previous research in cocaine-dependent individuals (Childress et al. 2008) by using the same backward-masking task with cannabis-related cues and finding similar reward-related activations in a different patient population, specifically those who are cannabis dependent. Further, our findings provide further support for one role of the anterior insula, which is bottom-up detection of salient stimuli and drug craving (Menon and Uddin 2010; Naqvi and Bechara 2010). Our data also provide support for the involvement of the mOFC in reward learning and incentive salience, as evidenced by the positive correlation

between brain responses to cannabis cues presented outside awareness and years of cannabis use. Lastly, the demonstration that cannabis-dependent individuals display enhanced reward-related responses to sexually evocative cues supports hypotheses promoting a common pathway of appetitive motivation.

## Neural responses to backward-masked cues

Among treatment-seeking, cannabis-dependent participants, backward-masked cannabis cues (relative to neutral) elicited greater neural responses in the left anterior insula, left VS/amygdala, and right VS. The involvement of the VS in subliminal processing of drug-related cues is consistent with an extensive literature indicating that this region, as part of the mesolimbic dopamine (DA) pathway (i.e., DA cells in the ventral tegmental area project into the VS), plays a crucial role in reward processes (Koob and Volkow 2010; Wise 2009), especially cue reactivity (Caggiula et al. 2001; Franklin et al. 2007; Schacht et al. 2013). Drugs of abuse stimulate surges of DA in the VS, thus strengthening stimulus–drug associations (Berridge and Robinson 1998; Robinson and Berridge 2003). Through repeated drug use and stimulus–drug pairings, drug-related stimuli acquire powerful incentive properties and motivate drug-seeking behavior (Berridge and Robinson 1998; Robinson and Berridge 2003). As such, our findings suggest that even subliminal exposure to stimuli associated with one's drug of choice activates this conditioned salience and reward neurocircuitry, perhaps eliciting craving and “priming” an individual for subsequent drug-seeking behaviors.

One hypothesis debated in the field is that chronic drug use leads to the devaluation of natural rewards; however, research in this area has provided mixed results (Cabeza de Vaca and Carr 1998; Goldstein et al. 2010; Klucken et al. 2013). Secondary analyses of neural responses to backward-masked sexual cues versus neutral cues revealed robust limbic activations, including the left VS, bilateral anterior insula, right hippocampus/amygdala, and pgACC. In addition, direct comparisons between neural activation to backward-masked cannabis cues relative to sexual cues revealed no significant differences, suggesting that in this sample of cannabis-dependent individuals, responses to natural rewards are not diminished. These findings are consistent with our previous research examining neural responses to backward-masked sexual cues among cocaine-dependent patients (Childress et al. 2008). Further, we observed a substantial anatomical overlap in the brain response to subliminal cannabis and sexual cues, which may be expected given that both cannabis and sexual cues are known to evoke reward-related responses and evidence suggesting common substrates for both drug and natural rewards (Pessiglione etal. 2007; Schroeder et al. 2001; Tang et al. 2012), although see Zombeck et al. (2008). These results are also in line with the findings of Versace et al. (2011) that showed cigarette-dependent individuals who showed brain responses to smoking cues also showed similar brain responses to sexually evocative stimuli. Although these data suggest a common substrate for drug and natural rewards, firmer conclusions could be drawn if an association between craving for sex and presentation of backward-masked sexual stimuli was observed; however, craving to sexual cues was not assessed.

Additional analyses explored neural responses to backward-masked aversive versus neutral cues and revealed greater responses in the left insula and pgACC; however, aversive cues did not activate the VS. Thus, cannabis-dependent individuals showed specific ventral striatal responses to both drug and natural subliminal reward cues, whereas aversive cues elicited responses in the brain regions involved in interoception and behavioral regulation (Menon and Uddin 2010). Studies have shown activation of the amygdala and/or VS during exposure to aversive stimuli (Klucken et al. 2009), yet others have not (Klucken et al. 2012). Indeed, comparisons of neural activation to backward-masked cannabis cues versus aversive cues revealed no areas wherein cannabis cues elicited greater activity relative to aversive cues. While there are many potential explanations for this null finding (e.g., conditioning and personal histories), our findings should be examined further in a in a larger, more generalizable sample prior to drawing definitive conclusions.

The insula, particularly the anterior portion, is a highly interconnected brain region that detects and integrates emotionally salient sensory and visceral stimuli and, as such, is associated with feeling states and interoceptive awareness (Craig 2009, 2011). For example, anterior insula activation has been observed during the presentation of fearful stimuli (Klucken et al. 2009), sexual stimuli (Kuhn and Gallinat 2011b), and drug-related stimuli (Franklin et al. 2009b; Potenza et al. 2012). Consistent with these findings, the anterior insula showed enhanced responses to cannabis, sexual, and aversive subliminal stimuli compared to neutral stimuli and, consequently, may reflect bottom–up detection and internal somatosensory responses to backward-masked emotionally relevant stimuli.

### Correlations with cannabis craving and years of cannabis use

Brain activation does not provide information about hedonic tone or reward value. For example, regions that typically activate in response to rewarding stimuli also activate to fearful stimuli (Klucken et al. 2009). Thus, to test whether the brain activation is related to these important properties, we utilized relevant behavioral anchors, such as craving and years of use. Cannabis craving prior to the imaging session was positively correlated with activation in the bilateral insula and pgACC. These findings are consistent with research indicating that drug-related cues activate the insula and that activity in the insula is positively correlated with drug craving (Bonson et al. 2002; Franklin et al. 2009b). The anterior cingulate cortex is involved in several monitoring, decision-making, and cognitive control processes (Isomura and Takada 2004; Rushworth et al. 2011), and the correlation between subliminal cannabis cue reactivity in the pgACC and cannabis craving may reflect interindividual variability in attempts to regulate responses to subliminal cannabis cues detected by the anterior insula. Indeed, a recent theoretical model (Menon and Uddin 2010) posits that the insula and anterior cingulate cortex form a “salience network” that detects externally salient stimuli, modulates subsequent autonomic reactivity, and prepares for appropriate behavioral responses.

In addition, the total number of years of cannabis use was positively correlated with activation in a cluster spanning the mOFC. The mOFC is implicated in reward processing, which includes reward valuations (Diekhof et al. 2012; Elliott et al. 2000). Thus, our findings may suggest that the longer an individual has used cannabis, which suggests a

greater number of “pairings” between cannabis cues and drug reward, the greater opportunity there is for conditioned modifications to occur in reward-related brain regions. Together, our data provide support for theories purporting that drug dependence is a disorder of aberrant learning and modification of neural pathways due to repeated pairings of drug-related stimuli and drug use outcomes (Milton and Everitt 2012).

## Potential limitations

A limitation to consider when interpreting the findings is the small sample size, 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, 40 % of the cannabis-dependent smokers in the current study also smoked cigarettes, and although it has not been shown that cannabis cues can mimic cigarette cues, it is conceivable. As such, the inclusion of cigarette smokers may confound the findings; however, the low dependence on cigarettes in subjects who participated in this study suggests that any potential confounding influence of cigarette smoking is minimal. It is also conceivable that greater response to the cannabis cues could be contributed to greater complexity of cannabis cues compared to the other emotionally evocative cues; however, all images were carefully matched on context, complexity, size, and luminosity. This study did not assess cannabis withdrawal symptoms on all subjects, and as such, it remains unclear as to whether withdrawal symptoms could have influenced findings. Additional studies are needed in order to examine the effects of withdrawal on cannabis cue reactivity. In addition, this study did not include a non-cannabis-using control group to explicitly show specificity of response to cannabis cues; however, it has been shown repeatedly that nonusers do not exhibit neural responses to drug cues (Childress et al. 1999; George et al. 2001; Grant et al. 1996). Consequently, we did not acquire data on nonusing controls. It is important to note that attention may influence our findings. As such, future research should examine attentional processes during the backward-masking task or following the scan session through an image recollection test. Finally, participants in this study were not immediately tested with a forced choice recognition task, but remained in the scanner for additional data acquisition required as part of a larger, ongoing three-arm study. We have previously shown that our backward-masking paradigm is effective in masking brief drug cues (Childress et al. 2008), and further support is provided by a recent meta-analysis across 12 studies showing that backward-masked stimuli were not consciously perceived even when presentations last for up to 50 ms (Brooks et al. 2012).

## Clinical implications

One of the most commonly used evidence-based behavioral treatments for drug dependence is cognitive behavioral therapy (CBT), in which an individual learns how to identify triggers (e.g., cues) for drug use and how to reduce craving and drug use through specific strategies and skills (Carroll 1998). Although there is empirical evidence that CBT and other behavioral treatments are effective, they yield modest effect sizes and outcomes vary widely across individuals (Dutra et al. 2008). Based on our findings, behavioral treatment approaches that focus on the conscious identification of cues for drug use and/or feeling states may face an inherent limitation: cue-triggered reward neurocircuitry may be activated outside conscious awareness. Thus, in some cases, reward neurocircuitry is already

stimulated before triggers can be consciously identified or avoided, and in other cases, cognitive control circuitry is recruited too slowly for effective management of emergent craving. Alternative or supplemental interventions to standard treatments might aim to address the neuropsychological mechanisms underlying the rapid, automatic neural response to reward-related stimuli through cognitive training and pharmacological interventions. For example, a recent study of cognitive bias modification (CBM), an approach that aims to modify automatic action tendencies, showed that four brief sessions of retraining automatic action tendencies (from approach bias to avoidance bias) improved treatment outcomes at 1-year follow-up in alcohol-dependent patients (Wiers et al. 2011). Similarly, a pharmacological intervention with a medication such as the purported anti-craving/anti-relapse agent baclofen, which blocks drug-motivated behaviors in animals (Brebner et al. 2002; Fattore et al. 2009) and humans (Addolorato et al. 2011; Franklin et al. 2009a) and reduces “resting” brain activity in reward-related circuitry in humans (Franklin et al. 2011, 2012), may prove effective in drug-dependent individuals who are responsive to subliminal cues. Thus, cognitive and pharmacological interventions aimed at altering or reversing the automatic, aberrant learning processes associated with repeated drug use may provide tailored, comprehensive relapse protection and improve drug use outcomes.

### Summary and conclusions

Our findings represent the first evidence that cannabis-dependent individuals exhibit increased brain responses to backward-masked cannabis cues in the left anterior insula, left VS/amygdala, and right VS. Reactivity to cannabis cues was associated with relevant behavioral anchors including cannabis craving and years of cannabis use. These findings are consistent with, and extend, previous research demonstrating that drug cues presented outside awareness can activate the brain's reward network. The data highlight the sensitivity of the brain to reward-related cues, and the brain response to such cues may be both a meaningful target for cannabis-dependence treatments and a screening tool for the discovery of therapeutics that address unconscious drug motivation. Ongoing research will help establish the link between the brain response to subliminal drug cues and subsequent drug use/relapse.

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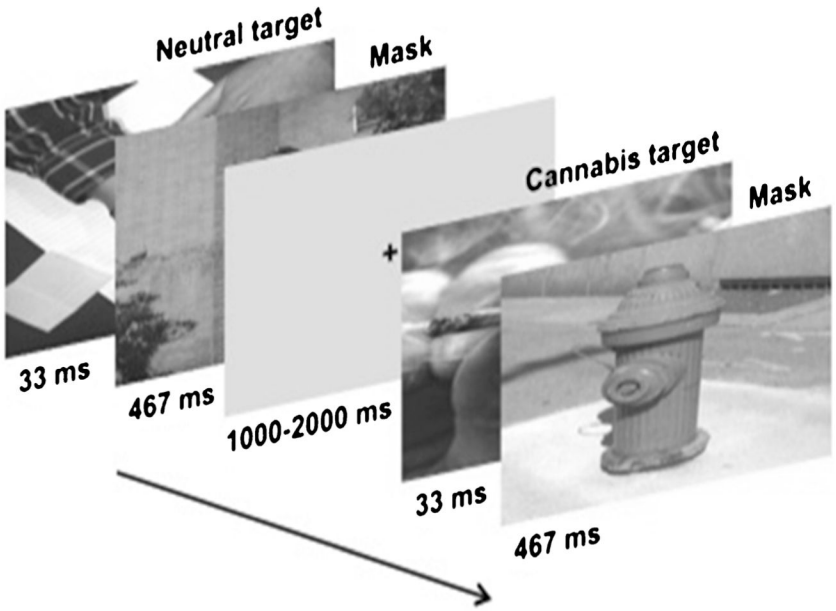


**Fig. 1.**

Backward-masking cue paradigm. Twenty-four targets from four categories (i.e., cannabis, aversive, sexual, neutral) and neutral masks were paired randomly, and each target–mask pair was presented quasi-randomly (no more than two targets of the same category in succession) without replacement. Targets were presented for 33 ms followed by a 467-ms neutral mask. As requested by the International Affective Picture System (IAPS), sexual and aversive images are not depicted. All task images are presented in color, but are shown here in grayscale

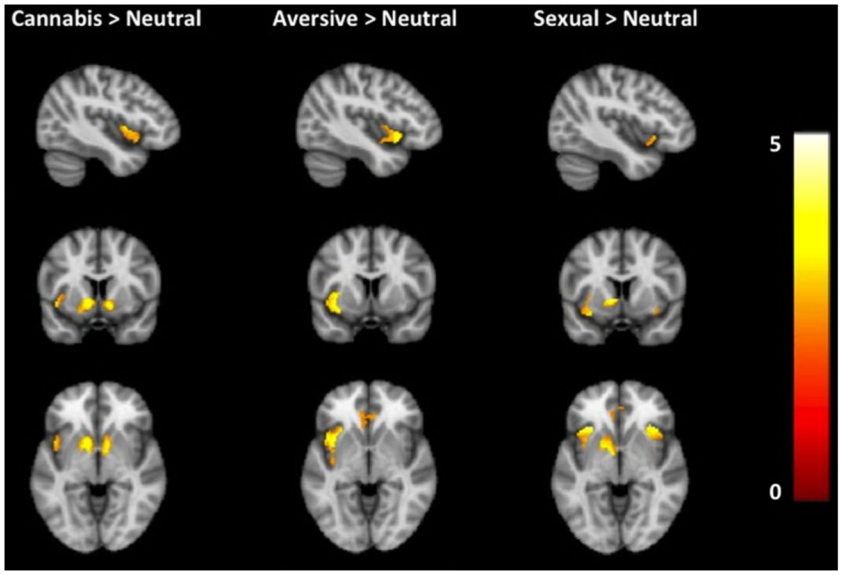


**Fig. 2.**

Neural activation during exposure to backward-masked cannabis, sexual, and aversive cues in cannabis-dependent treatment seekers. Cannabis cues (versus neutral) elicited greater activation in the left anterior and bilateral ventral striatum. Sexual cues (versus neutral) elicited greater activation in the left ventral striatum, bilateral anterior insula, right hippocampus/amygdala, and left perigenual anterior cingulate cortex. Aversive cues (versus neutral) elicited greater activation in the left insula and perigenual anterior cingulate cortex. Data are displayed neurologically (left is left). The *color bar* represents *T* values. MNI coordinate of all images displayed at −42, 8, and −4. An interactive visual display of unmasked brain data in all three planes at $p = 0.01$ can be found at http://franklinbrainimaging.com

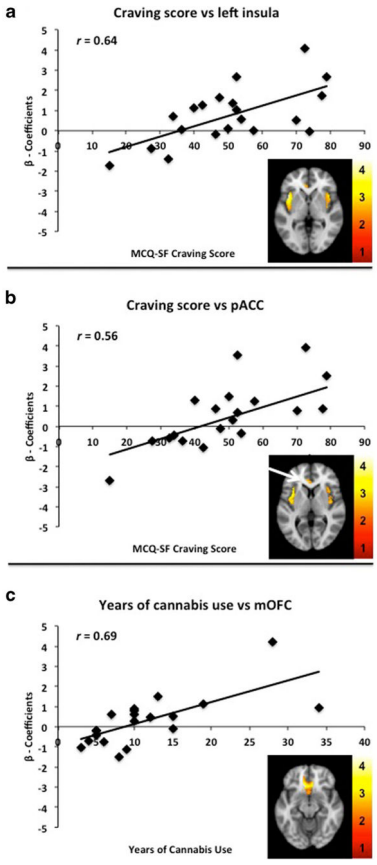


**Fig. 3.**

Correlations between brain responses during backward-masked cannabis cues and cannabis craving or years of cannabis use. Scatterplots showing significant correlations between MCQ-SF craving scores and $\beta$ coefficients extracted from the cluster and averaged. Illustrated are statistical maps in the axial view: **a** Cannabis craving versus left insula, $x = -40$; **b** cannabis craving versus perigenual anterior cingulate cortex (pgACC), $x = -4$; and **c** years of cannabis use versus medial orbitofrontal cortex (mOFC), $x = 8$. Data are displayed neurologically (left is left). The *color scale* represents the $T$ values. An interactive visual display of unmasked brain data in all three planes at $p = 0.01$ can be found at http://franklinbrainimaging.com

**Table 1**

Participant characteristics

| | ***N*=20** | **Means (SD)** |
|---|---|---|
| Sex | 12 males (60 %) | |
| Race | 18 African American (90 %) | |
| Report drinking alcohol | 7 (35 %, 7 males) | |
| Cigarette smokers | 8 (40 %, 5 males) | |
| Age | | 29.1 (9.7) |
| Years of education | | 12.4 (3.0) |
| Alcohol use (days/past 30 days) | | 1.5 (2.3) |
| Alcohol use (drinks/drinking day) | | 1.3 (0.5) |
| Cigarette dependence (FTND) | | 1.5 (2.2) |
| Duration of heavy cannabis use (years) | | 11.4 (7.9) |
| Cannabis use (days/30 days) | | 27.8 (3.7) |
| Cannabis use (g/day) | | 2.3 (2.7) |
| Cannabis craving (MCQ-SF)[a] | | 40.5 (14.0) |
| ASI Composite Scores[b] | | |
| Alcohol | | 0.05 (0.05) |
| Drug | | 0.20 (0.10) |
| Family/social | | 0.16 (0.20) |

*SD* standard deviation, *FTND* Fagerstrom Test for Nicotine Dependence, *MCQ-SF* Marijuana Craving Questionnaire-Short Form

[a]MCQ-SF craving scores can range from 12 to 84 (minimal to maximal intensity). Current sample ranged from 12 to 63

[b]Addiction Severity Index Composite Scores in each domain range from 0 (no problems) to 1 (severe problems)

**Table 2**

Neural activation to backward-masked cannabis, sexual, and aversive cues in a priori regions

| Region | Cluster size (voxels) | MNI coordinates | | | *T* values |
|---|---|---|---|---|---|
| | | *x* | *y* | *z* | |
| Cannabis cues > neutral cues | | | | | |
| L ventral striatum/amy | 579 | −10 | 10 | −4 | 4.25 |
| R ventral striatum | 209 | 10 | 8 | −6 | 4.14 |
| L insula | 150 | −42 | 2 | 4 | 3.52 |
| Sexual cues > neutral cues | | | | | |
| L ventral striatum | 893 | −8 | 6 | 2 | 4.40 |
| L insula | 378 | −30 | 26 | −6 | 4.71 |
| R insula | 287 | 36 | 22 | −8 | 4.42 |
| R hippo/amy | 187 | 18 | −14 | −24 | 3.86 |
| L perigenual ACC | 745 | −10 | 36 | 12 | 3.84 |
| Aversive cues > neutral cues | | | | | |
| L insula | 591 | −32 | 12 | −8 | 4.35 |
| L perigenual ACC | 344 | −10 | 28 | 20 | 3.50 |

MNI coordinates and *T* values of local maxima are shown for each cluster. Significant regions of interest level, $p < 0.01$; cluster was corrected at $p < 0.05$ (k >121 voxels)

*MNI* Montreal Neurological Institute, *L* left, *R* right, *amy* amygdala, *hippo/amy* hippocampus/amygdala, *ACC* anterior cingulate cortex