Drug and Alcohol Dependence 200 (2019) 145–152

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Preliminary evidence that computerized approach avoidance training is not associated with changes in fMRI cannabis cue reactivity in non-treatment-seeking adolescent cannabis users

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ARTICLE INFO

Keywords:
Neuroimaging
Adolescence
Cannabis
Cognitive bias modification
Cue-Reactivity

ABSTRACT

Background: Cognitive Bias Modification (CBM) has garnered interest as a potential addiction treatment. CBM interventions such as Approach Avoidance Training (AAT) are designed to alter automatic tendencies to approach drugs or drug-related cues. In our previous work, the cannabis AAT (CAAT) reduced cannabis approach bias, which was related to reduced cannabis use, among 80 non-treatment-seeking cannabis-using youth (Jacobus et al., 2018). In this preliminary examination, a subsample of these youth underwent neuroimaging to explore CAAT's effect on cannabis cue-related neural activation.

Methods: Sub-study participants were 41 cannabis-using youth ages 17–21 (mean age = 18.83; 47.5% female). Participants completed a cannabis cue-reactivity task during a functional MRI scan pre- and post CAAT-training or CAAT-sham to examine CAAT-related neural changes.

Results: Thirty-seven youth completed all six CAAT (n = 19) or CAAT-sham (n = 18) training sessions and had usable neuroimaging data. The group*time interaction on cannabis approach bias reached trend-level significance (p = .055). Change in approach bias slopes from pre-to post-treatment was positive for CAAT-sham (increased approach bias) and negative for CAAT-training (change to avoidance bias), consistent with the larger study. No significant changes emerged for cannabis cue-induced activation following CAAT-training or CAAT-sham in whole brain or region of interest analyses. However, active CAAT-training was associated with small-to-medium decreases in amygdala (Cohen's d_z = 0.36) and medial prefrontal cortex (Cohen's d_z = 0.48) activation to cannabis cues.

Conclusions: Despite reducing cannabis use in the larger sample, CAAT-training did not alter neural cannabis cue-reactivity in the sub-study compared to CAAT-sham. More research is needed to understand neural mechanisms underlying AAT-related changes in substance use.

1. Introduction

Among adolescents in the United States, cannabis is the second-most commonly used substance after alcohol, with 11% of 8th graders, 28% of 10th graders, and 36% of 12th graders reporting cannabis use in the past year, and 14% of 8th graders, 33% of 10th graders, and 44% of 12th graders reporting cannabis use in their lifetime (Johnston et al., 2019). Notably, cannabis legalization in recent years has impacted adolescents' perceptions of cannabis-related harm, as rates of adolescents reporting that regular cannabis use is harmful decreased from 84% in 1990 to 27% in 2018 (Johnston, et al., 2019). Importantly, of the 4% of adolescents aged 12–17 who met criteria for a substance use disorder (SUD) in 2016, approximately half had a cannabis use disorder (CUD) (Substance Abuse and Mental Health Services Administration [SAMHSA], 2017). Thus, cannabis use represents a large proportion of problematic adolescent substance use, and in fact, CUD is the most common reason for referral to substance use treatment among youth (Substance Abuse and Mental Health Services Administration: Center for Behavioral Health Statistics and Quality, 2018).

Of the 5% of adolescents aged 12–17 who needed SUD treatment in

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https://doi.org/10.1016/j.drugalcdep.2019.04.007
Received 11 January 2019; Received in revised form 4 March 2019; Accepted 8 April 2019
Available online 14 May 2019

2016, only 3% received treatment. Among individuals aged 18–25, 16% needed SUD treatment in 2016, with only 12% of them actually receiving it (SAMHSA, 2017). Unfortunately, few adolescent SUD treatment options exist, and those that are available have demonstrated only modest effectiveness (Tripodi et al., 2010; Vandrey and Haney, 2009). Some studies suggest that up to 86% of substance-using adolescents return to using within 12 months of treatment (Brown et al., 1996; Winters et al., 2000). A recent meta-analysis indicated that patients with CUD who undergo behavioral treatments tend to have better outcomes (e.g., frequency and quantity of use, psychosocial functioning) compared to patients on a waitlist control (Davis et al., 2015). However, this meta-analysis also found that behavioral treatments did not outperform active control conditions, indicating that there is still significant room for improvement in terms of developing ideal behavioral treatment options for CUD. Overall, there is a growing need for the development of novel treatments for adolescent SUD, and behavioral treatments for CUD may be of particular value.

Recently, cognitive bias modification (CBM) has garnered interest as a potential SUD treatment. CBM is designed to alter approach biases (i.e., automatic action tendencies to approach substance cues) (Eberl et al., 2013, 2014; Wiers et al., 2011; Wiers et al., 2010) and subsequently decrease use of a particular substance (Eberl et al., 2013, 2014; Sharbanee et al., 2014; Wiers et al., 2015a, 2010). One type of CBM intervention is the computerized Approach-Avoidance Task (AAT), designed to alter approach biases through instructing participants to either pull a joystick towards themselves or push it away depending upon the stimulus presented. For example, participants are instructed to push the joystick away on the majority of trials when a substance cue is presented (e.g., to avoid substance cues) and pull the joystick toward them when a non-substance cue is presented (e.g., to approach non-substance cues). The AAT may be particularly relevant for adolescents, given its short duration, ability to be administered by non-clinicians thereby increasing its access, and potential for online use.

Several recent AAT studies have shown promising results, particularly regarding alcohol treatment. In a clinical lab-based study, Alcohol AAT (A-AAT) was associated with decreased alcohol approach bias and reduced alcohol consumption (Wiers et al., 2010). In a follow-up randomized controlled trial in alcohol dependent adults ($N = 214$), the A-AAT was associated with a 13% reduction in alcohol relapse a year after treatment (59% of the control group relapsed vs. 46% of the A-AAT group) (Wiers et al., 2011). Two larger A-AAT replication studies have been completed (total $N = 1907$), and both found a 9% reduction in relapse one year post-treatment in the control group vs. the A-AAT group ($N = 502$; 51% of control group relapsed vs. 42% A-AAT group (Eberl et al., 2013) and $N = 1405$; 57% vs. 48% (Rinck et al., 2018)). Further, in detoxifying alcohol dependent adults ($N = 83$), the A-AAT was associated with a 30% reduction in relapse at 2 weeks post-detox (75% vs. 45%) (Manning et al., 2016).

However, it should also be noted that several meta-analyses suggest that CBM may not be effective, particularly among non-treatment-seeking individuals with alcohol use disorders. Notably, a Bayesian meta-analysis of studies investigating CBM interventions for alcohol and tobacco use disorders found that all effects of CBM on cognitive bias and relapse rates were associated with wide 95% confidence intervals, thereby indicating insufficient evidence in favor of or against the efficacy of CBM interventions in these populations (Boffo et al., 2019). Another recent meta-analysis of CBM interventions for alcohol and smoking addictions demonstrated that although there were small effects of CBM on cognitive biases, no significant effects were observed on craving or addiction (Cristea et al., 2016). Thus, the overall body of evidence on CBM interventions in the context of alcohol and smoking are mixed, and differences in study methodologies (e.g., inclusion of treatment-seekers vs. non-treatment-seekers) likely contributes to the discrepant findings (Wiers et al., 2018a, b).

Only two studies exist exploring CBM for cannabis use. One AAT study of adults with CUD found that individuals in the cannabis AAT (CAAT) condition showed decreased cannabis cue-induced craving post-intervention (Sherman et al., 2018). Given that approach bias exists in adolescents early in their substance use trajectory (Peeters et al., 2013, 2012), and that youth who use cannabis have shown approach biases for cannabis cues which predict future cannabis use (Cousijn et al., 2012), CBM (and in particular the AAT) may be an effective treatment option for this population. Thus, in our previous pilot study (Jacobus et al., 2018), 80 non-treatment-seeking adolescents (across two study sites in San Diego, CA, and Charleston, SC) were randomized to receive either six sessions of CAAT-training or CAAT-sham to examine the effectiveness of CAAT on reducing cannabis use in youth. Participants who completed CAAT-training reported a significant reduction in cannabis use days compared to individuals in the CAAT-sham group. Greater cannabis avoidance bias from baseline to post-treatment was related to decreased percent days of cannabis use during treatment, suggesting that CAAT may be an effective treatment for reducing adolescent cannabis use.

Regarding possible mechanism(s) of action for the AAT, several recent studies have suggested that AAT may be associated with altered neural activation in reward-related brain areas (Wiers et al., 2015a, b). Specifically, in a group of alcohol dependent males, CBM was associated with greater reductions in alcohol approach bias-related medial prefrontal cortex (mPFC) activation compared with individuals who did not receive CBM training, and these reductions in activation were correlated with reduced alcohol approach bias (Wiers et al., 2015a). Similarly, in a study of abstinent alcohol dependent patients, the A-AAT was associated with greater reductions in alcohol cue-induced activation in the bilateral amygdala as well as in behavioral arousal ratings for alcohol pictures. Decreases in activation in the right amygdala were associated with decreased craving in the A-AAT group but not the sham-training group (Wiers et al., 2015b). Findings suggest that AAT's potential mechanism(s) of treatment efficacy could involve modulation of certain behavioral correlates of addiction, such as craving and/or approach biases (O'Brien, 2015).

Cannabis-using youth demonstrate heightened motivational response to the presentation of cannabis-related cues (Henry et al., 2014); however, few studies have used fMRI to examine neural cue-reactivity in cannabis-using youth. We recently demonstrated that visual cannabis cues compared to visual control cues were associated with activation in brain regions underlying incentive salience, reward, and visual attention in adolescent cannabis users (Karoly et al., 2018). Further, research among cannabis-using adults indicates that reward-related brain areas show greater activation in response to tactile cannabis vs. non-cannabis cues (Filbey et al., 2009), as well as during visual cannabis vs. non-cannabis cues (Cousijn et al., 2013; Goldman et al., 2013) and subliminally presented cannabis vs. non-cannabis cues (Wetherill et al., 2014). These findings are consistent with a recent meta-analysis of neuroimaging studies of cannabis use, which demonstrated that cannabis use is associated with differential activation across a number of brain regions underlying reward and cognitive control (Yanes et al., 2018).

In this pilot neuroimaging study testing the CAAT-training intervention in a subsample of non-treatment-seeking, cannabis-using youth from a larger study (Jacobus et al., 2018), we hypothesized that participants who received CAAT-training would demonstrate changes in neural activation in reward-related regions such as the nucleus accumbens (NAcc), amygdala, and mPFC (Wiers et al., 2015b, 2014) during a visual cannabis cue task compared to participants who received CAAT-sham training.

2. Methods

2.1. Participants

Participants were a subsample of a larger multisite study (Jacobus et al., 2018) and comprised 41 non-treatment-seeking youth ages 17–21

(mean age = 18.83; 47.5% female) who reported regular (˜5 days/week) cannabis use. Inclusion and exclusion criteria were identical across the two sites. All 41 participants included in this sub-study were from the South Carolina site, and underwent neuroimaging pre- and post-treatment. Participants from the San Diego site did not undergo any neuroimaging procedures. Behavioral outcomes across the entire sample from both study sites were reported previously (Jacobus et al., 2018). Participants were recruited through media advertisement and flyers. All participants were required to be ≤21 years old and have > 52 lifetime cannabis use episodes and weekly cannabis use over the past year. All participants provided informed consent. If participants were under age 18, parental consent and adolescent assent were obtained. The Medical University of South Carolina Institutional Review Board approved all protocols.

Exclusion criteria included: not having a parent to consent if under age 18; MRI contraindications (e.g., braces, claustrophobia); known prenatal illicit drug or alcohol exposure (> 2 drinks on an occasion or > 4 drinks/week, based on youth self-report regarding knowledge of their mother's use of drugs or alcohol while pregnant with them); psychoactive medications; premature birth (< 34 weeks gestation or < 5 lbs. birth weight); history of major neurological or medical disorder or head trauma (loss of consciousness > 10 min) that could affect blood oxygen level dependent (BOLD) response; current DSM-5 major psychiatric disorder (e.g., bipolar disorder, psychotic disorder); history of learning disability or pervasive developmental disorder; inadequate comprehension of English; non-correctable sensory problems; illicit substance use other than cannabis or alcohol (> 100 times) in the past year; and current pregnancy.

2.2. Study procedures

2.2.1. Procedures

All youth (N = 41) enrolled in the study were scheduled for a baseline assessment involving collection of background information, substance use history, substance use self-report questionnaires, mental health functioning, and measurement of automatic action tendencies to approach cannabis. Following the baseline appointment, participants were randomized to complete six sessions of CAAT-training (n = 23) or CAAT-sham (n = 18) twice per week over three weeks. The study included six total training sessions based on prior research. Specifically, although some studies have demonstrated effects with only four sessions (e.g., Manning et al., 2016; Sherman et al., 2018; Eberl (2014) found in that six was the mean optimum number of sessions needed to change approach bias, when combined with regular treatment. In addition, Rinck (2018) found CBM effects using six sessions.

The study employed a double-blind procedure; thus, all research staff were kept blind to the condition to which the participant was assigned. Participants were scheduled for a final appointment to re-assess approach bias (i.e., automatic tendencies to approach cannabis) and complete follow-up self-report substance use questionnaires. The baseline and post-treatment visit included a 30-minute MRI scan, including a visual cannabis cue-reactivity task (Karoly et al., 2018). No other treatment was provided as part of the study.

2.2.2. Measures

Demographics. A youth interview was administered to collect information on sample demographics. The interview included questions about age, sex, race, ethnicity, lifetime drug use, education, maternal substance use during pregnancy, and medical history. Demographic information for the sub-study sample is included in Table 1.

Mental health. The MINI International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) version 7, a brief structured diagnostic interview for major Axis I disorders in DSM-5 and ICD-10, was administered by a trained researcher.

Table 1
Demographic characteristics of sample (N = 37).

Demographics	CAAT-Training M (*SD*) or % n = 19	CAAT-Sham M (*SD*) or % n = 18
Age, Baseline	18.89 (*.88*)	18.78 (*.88*)
% female	47.37%	50%
% Caucasian	94.73%	77.77%
Education (grade, in years)	12.68 (*.90*)	12.61 (*.70*)
BDI-II, baseline	5.95 (*6.80*)	4.89 (*3.34*)
BDI-II, post-treatment	4.16 (*5.01*)	3.95 (*5.21*)
STAI, baseline	28.84 (*8.07*)	30.17 (*9.24*)
STAI, post-treatment	29.79 (*8.87*)	29.39 (*7.75*)
Internalizing—Youth Self Report	47.32 (*10.40*)	48.89 (*9.57*)
Externalizing—Youth Self Report	51.26 (*8.43*)	54.22 (*8.54*)
% Alcohol Use Disorder (past 12 months; MINI)	57.90%	44.44%
% Cannabis Use Disorder (past 12 months; MINI)	78.95%	72.22%
Age of cannabis use onset	15.74 (*1.15*)	16.31 (*1.01*)
Age of cannabis use onset, regular use	17.05 (*1.24*)	17.44 (*1.04*)
Cannabis use episodes, past year	465.26 (*263.15*)	433.00 (*298.39*)
% cannabis use days, past 30 days, baseline	76.66 (*28.15*)	70.44 (*26.2*)
% cannabis use days, post-treatment	75.67 (*31.31*)	69.19 (*24.54*)
Days since last use of cannabis, baseline	1.00 (*1.37*)	2.28 (*3.27*)
Days since last use of cannabis, post-treatment[a]	.84 (*1.64*)	1.18 (*1.67*)
% alcohol use days, past 30 days, baseline	26.14 (*14.28*)	25.74 (*15.71*)
% alcohol use days, post-treatment	39.31 (*22.83*)	29.31 (*18.61*)
Days since last use of alcohol, baseline[a]	6.32 (*9.80*)	4.06 (*4.39*)
Days since last use of alcohol, post-treatment[*,b]	2.32 (*1.70*)	6.43 (*9.54*)
Total cigs past 30 days, baseline	4.74 (*20.64*)	2.22 (*8.45*)

Beck Depression Inventory-II (BDI-II); State-Trait Anxiety Inventory (STAI) Trait version.
* $p < .05$.
[a] n = 36.
[b] n = 35.

Substance use. The calendar-based Timeline Followback (TLFB) interview (Sobell et al., 1979) was used at baseline to assess quantity and frequency of cannabis, alcohol, cigarette, and other drug use at baseline and follow-up sessions. Other measures of substance use included in the study are listed in Table 2. See Jacobus et al. (2018) and Karoly et al. (2018) for detailed descriptions of these measures.

2.3. Approach bias assessment and CAAT intervention conditions

2.3.1. Approach bias assessment

The approach bias computerized assessment task measured automatic approach tendencies toward cannabis stimuli pre- and post-CAAT-training or CAAT-sham (see Jacobus et al., 2018 for further details). In the assessment task, participants were required to make an *equal number* of approach (pull) and avoidance (push) movements to both cannabis and neutral stimuli. An irrelevant feature version of the task was used (i.e., participants responded to the color of the image border rather than a particular aspect of the cue itself). A cannabis approach bias score was computed by subtracting each participant's median response latency for correct trials in the cannabis pull condition from his or her median response latency for correct trials in the corresponding cannabis push condition (i.e., cannabis push minus cannabis pull). A neutral image approach bias score was also computed. The comprehensive cannabis bias score was calculated by subtracting the neutral image bias score from the cannabis image bias score (i.e., cannabis bias minus neutral image bias) (Wiers et al., 2015b). Positive values indicate an approach bias (faster approach tendency) for cannabis cues whereas negative values indicate an avoidance bias.

Table 2
Substance use self-report questionnaires, N = 37.

Cannabis & Alcohol Use Questionnaires	CAAT-Training M (*SD*) or % n = 19	CAAT-Sham M (*SD*) or % n = 18
Marijuana Ladder, baseline	3.89 (*2.36*)	4.06 (*1.66*)
Marijuana Ladder, post-treatment	3.74 (*2.28*)	3.78 (*2.26*)
Cannabis Withdrawal Scale, baseline	21.47 (*17.12*)	27.33 (*24.58*)
Cannabis Withdrawal Scale, post-treatment	28.18 (*22.42*)	23.44 (*26.80*)
Marijuana Effect Expectancies, baseline:		
Cognitive and behavioral impairment	29.58 (*6.53*)	31.61 (*8.35*)
Relaxation and tension reduction	31.63 (*4.76*)	30.44 (*5.04*)
Social and sexual facilitation	29.95 (*5.03*)	28.22 (*4.97*)
Perceptual and cognitive enhancement	26.95 (*4.50*)	26.56 (*3.20*)
Global negative effect	14.74 (*4.39*)	14.33 (*4.23*)
Craving and physical effect	24.68 (*3.25*)	25.78 (*2.53*)
Marijuana Effect Expectancies, post-treatment:		
Cognitive and behavioral impairment	30.11 (*7.45*)	30.28 (*9.02*)
Relaxation and tension reduction	30.84 (*3.72*)	29.78 (*4.51*)
Social and sexual facilitation	29.37 (*5.26*)	27.94 (*5.23*)
Perceptual and cognitive enhancement	26.47 (*4.36*)	26.89 (*3.56*)
Global negative effect	15.53 (*4.35*)	14.17 (*3.70*)
Craving and physical effect	24.53 (*3.63*)	25.78 (*2.92*)
Self-Efficacy Questionnaire, baseline	3.78 (*1.04*)	4.01 (*1.41*)
Self-Efficacy Questionnaire, post-treatment	3.74 (*1.23*)	4.10 (*1.41*)
Marijuana Craving Questionnaire-SF, baseline	14.54 (*2.99*)	14.56 (*5.23*)
Marijuana Craving Questionnaire-SF, post-treatment	14.36 (*5.60*)	12.92 (*3.54*)
Marijuana Problem Scale, baseline	4.53 (*3.47*)	3.33 (*3.01*)
Marijuana Problem Scale, post-treatment	4.21 (*3.71*)	3.17 (*2.96*)
SOCRATES Drug Use Questionnaire, baseline	16.68 (*12.35*)	13.33 (*11.17*)
SOCRATES Drug Use Questionnaire, post-treatment	11.32 (*12.36*)	11.50 (*9.62*)
Rutgers Alcohol Problem Index, baseline	9.79 (*8.92*)	7.22 (*6.50*)

$^{*}p < .05$, $^{a}n = 36$.

2.3.2. CAAT avoid cannabis and sham intervention conditions

To modify automatic action tendencies to approach cannabis stimuli, the approach bias assessment was modified for the CAAT-training (i.e., avoid cannabis condition) such that the majority of cannabis pictures (92%) were presented in the push-format and 8% in the pull-format, with reversed contingencies for neutral pictures; the overall number of push- and pull-trials each remained 50%. The CAAT-sham condition was identical to the CAAT-training condition in every respect except there was *no contingency* between the presentation of cannabis stimuli and push vs. pull movements. Thus, participants were required to make an *equal number* of approach (pull) and avoidance (push) movements to both cannabis and neutral pictures. Each CAAT training or sham session comprised 384 trials administered in two consecutive runs of 192 trials each with a short break in between: 8 pictures × 2 picture type (cannabis vs. neutral) × 2 border color (yellow vs. blue) × 12 repetitions. The duration of each training session was approximately 15 min. All participants received identical computerized training tasks and standardized instructions for completing the tasks. A brief practice (12 trials) preceded the task and included one cannabis and one neutral image not encountered during training; this practice trial was done before each of the six training sessions to ensure the participants understood the instructions before completing the training.

2.4. Cannabis cue-reactivity task

A visual fMRI cannabis cue-reactivity task was designed to examine differences in activation to cannabis vs. non-cannabis images (Karoly et al., 2018) and was administered twice: once before the participant was randomized to CAAT-training or CAAT-sham and again after their 6th session of CAAT-training or CAAT-sham. Participants completed the same task at each scan session. After the scan, participants rated each image as to whether or not it was cannabis-related. Details of the cannabis cue task have been described previously (Karoly et al., 2018). Throughout the scan session, participants responded using a hand pad in the scanner. Research assistants were trained to watch the hand pad responses. After 2 missed responses, the research assistant would remind the participant over the speaker to continue responding. This ensured that participants were awake and participating throughout the duration of the task.

2.5. Image acquisition, pre-processing and analysis

Functional images were acquired with a 12-m gradient-echo, echo-planar imaging (EPI) sequence on a 3-Tesla TIM Trio Scanner (Siemens, Erlangen, Germany). Acquisition parameters were: repetition/echo time (TR/TE) = 2200/35 ms; 328 volumes; flip angle (FA) = 90°; field of view (FOV) = 192 mm; matrix = 64 × 64; voxel size = 3.00 x 3.00 mm; 37 contiguous 3-mm-thick slices). A field map was also acquired to allow geometric unwarping and cost-function masking of EPI images induced by magnetic field inhomogeneities. Using FEAT (fMRI Expert Analysis Tool) v5.98, part of FSL (FMRIB's Software Library, Oxford) (Smith et al., 2004), functional images were first realigned to the middle volume to correct for motion during the task. A framewise displacement (FD) threshold of 0.9 mm (fewer than 10% of volumes censored at this threshold) was used. Using this threshold, no participants were excluded from the analysis based on motion. One participant was excluded due to falling asleep during the task. Images were subsequently stripped of non-brain tissue/skull, spatially smoothed (8-mm full-width-at-half-maximum kernel), intensity normalized by the mean of all volumes, high-pass filtered (sigma = 240 s), and resampled to 2-mm isotropic voxels. Explanatory variables were created by convolving stimulus presentation timing with a double gamma hemodynamic response function in FEAT. A multiple linear regression analysis was performed to estimate the hemodynamic parameters for each explanatory variable. To identify differences in the magnitude of the BOLD signal for cannabis vs. non-cannabis images, contrast maps were created by contrasting the parameter estimates from the multiple regression for these stimuli. Contrast maps were registered to each participant's high-resolution anatomical image, and subsequently to the Montreal Neurological Institute (MNI) 152-subject-average template. Next, we used fixed-effects models on all participants to examine differences between cannabis vs. non-cannabis activation at baseline and follow-up. These differences were then carried forward to test between-groups, random-effects differences in the magnitude of differences between baseline and follow-up scans. *Z* (Gaussianized *T/F*) statistic images were thresholded using clusters determined by $z > 3.1$ and a (corrected) cluster significance threshold of $p = 0.05$ (Eklund et al., 2016; Worsley, 2001).

2.6. ROI selection and analysis

In addition to whole brain analyses, several regions of interest (ROI) were examined based upon previous AAT studies. Specifically, bilateral amygdala, bilateral NAcc, and mPFC ROIs were selected based on prior work demonstrating that AAT training was associated with reduced visual alcohol-cue induced activation in the bilateral amygdala in abstinent alcohol-dependent patients (Wiers et al., 2015b) and that alcohol-approach bias was associated with activation in the NAcc and mPFC in alcohol dependent patients (Wiers et al., 2014). ROIs were created using the Harvard-Oxford probabilistic atlas (Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006). Linear mixed models were run in SPSS version 24 (IBM) to examine interactions between time and CAAT-training condition on activation within each ROI.

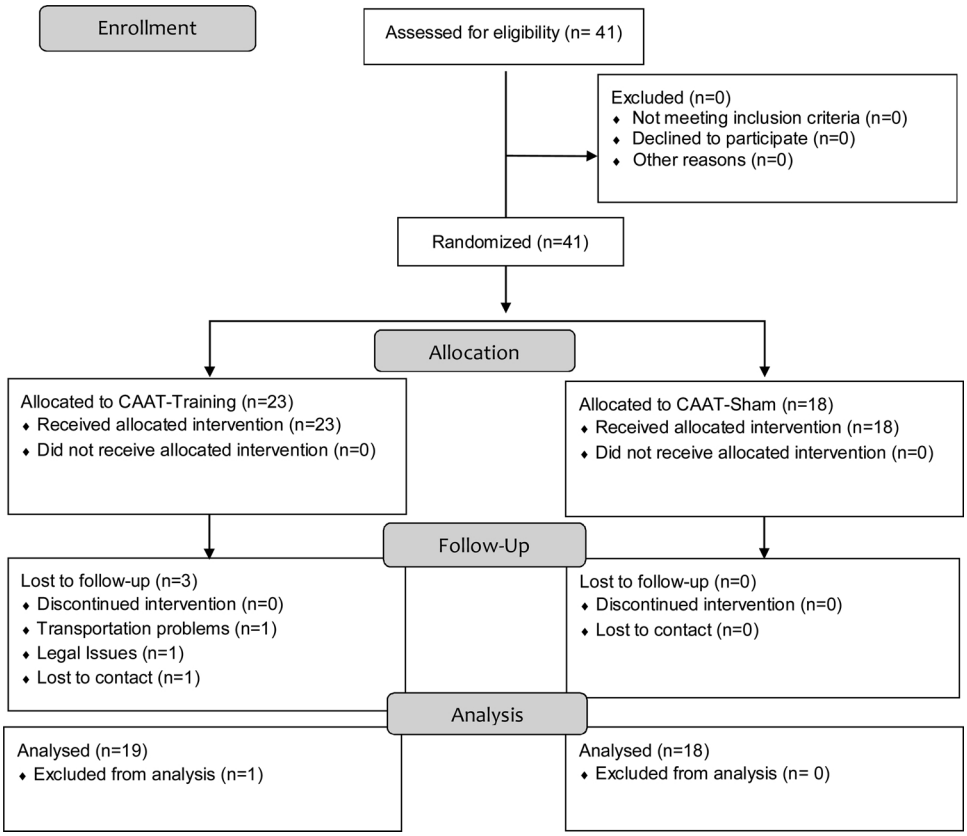

Fig. 1. Flow of participants through each phase of the study.
*Note that the participants included in this report comprise a subsample of a larger study published previously (see Jacobus et al., 2018). These participants were recruited from the Medical University of South Carolina recruitment site, as part of a multisite collaboration with the University of California, San Diego. None of the participants from the University of California, San Diego underwent the neuroimaging protocol.

3. Results

3.1. Demographic and substance use characteristics

Of the 41 participants included in the sub-study, 37 had usable scan data and were included in all analyses (see Fig. 1). Specifically, three participants did not complete all six sessions of CAAT (Fig. 1), and one was excluded due to falling asleep during the follow-up cue-reactivity task. No significant baseline differences were observed between CAAT-training and CAAT-sham groups on demographic (see Table 1) or substance use (see Table 2) characteristics.

3.2. Behavioral outcomes

All behavioral and substance use findings from the full sample are available in our prior paper (Jacobus et al., 2018). Thus, in terms of behavioral outcomes, we only examined the two primary outcomes of interest from the Jacobus (2018) study: change in cannabis approach bias tendencies and change in cannabis use following CAAT- or sham-training. It should be noted that, in general, the participants from the Charleston sample reported more severe cannabis use than individuals from the San Diego site. Specifically, individuals from the Charleston site reported more cannabis craving at baseline $t(78) = -2.738$, $p = .004$, and a greater percentage of cannabis use days in the past 30 days at baseline compared to individuals from the San Diego site $t(78) = -3.404$, $p = .001$ (San Diego = 52% cannabis use days; Charleston = 76% cannabis use days). However, to ensure that any potential differences in cannabis use patterns between the two sites did not contribute to findings across the whole sample, treatment site was previously explored (Jacobus et al., 2018) as a moderator of CAAT effects, but it did not significantly interact with treatment condition and/or time across the sample of individuals from both sites.

3.2.1. Change in cannabis approach bias tendencies and cannabis use

Examining the relationship between treatment group, time, and their interaction, the group by time interaction effect on comprehensive approach bias scores (cannabis image bias minus neutral image bias) demonstrated trend-level significance ($p = .055$), which was consistent with findings from the larger sample. Table 3 provides parameter estimates, significance levels, and confidence intervals, and suggests that change in cannabis approach bias slopes from baseline to post-treatment is positive for CAAT-sham (i.e., an increased approach bias) and negative for CAAT-training (i.e., change to avoidance bias) ($ß = -32.84$, SE = 16.55, 95% CI: -66.39, .72, $p = .055$).

Changes in cannabis use following the CAAT or sham-training were examined. In contrast with findings from the larger study, at post-treatment follow-up, no significant differences in percentage of cannabis use days emerged between groups over the course of study enrollment in the Charleston participants ($ß = -.005$, SE = 4.25 95% CI: -8,61 8.60, $p = .999$). Note that percentage of cannabis use at baseline was calculated by dividing the number of days the participant reported using cannabis by 30, and at follow-up it was calculated by dividing the number of days the participant used cannabis by the number of days they were enrolled in the treatment phase of the study (enrollment was equal to 21 days, on average; Jacobus et al., 2018). At baseline, the CAAT-training group reported using cannabis on 76.67% of the past 30 days and the CAAT-sham group reported using cannabis on 70.18% of days. At follow-up, the CAAT-training group reported using cannabis on

Table 3
Final linear mixed model estimation of comprehensive cannabis approach bias score by time and treatment group (N = 37).

Independent Variables	*ß*	*SE*	*p*	95% CI	
Time	9.5	11.8	0.43	−14.45	33.45
Treatment Group	12.83	12.07	0.3	−11.62	37.29
Time × Treatment Group	−32.84	16.55	0.055	−66.39	0.72

75.67% of the days during which they were in treatment and the CAAT-sham group reported using cannabis on 69.19% of days.

3.3. Neuroimaging outcomes

3.3.1. Whole brain result

Baseline cue-reactivity in the sample has been reported previously (Karoly et al., 2018). Among individuals with neuroimaging data (n = 37), there were no significant differences between CAAT-training and CAAT-sham groups in terms of changes in cannabis cue-induced activation at pre-treatment compared to post-treatment.

3.3.2. ROI results

No significant interactions emerged for time by CAAT condition on any ROIs. However, findings suggest the experimental manipulation generated small-to-medium sized reductions in amygdala (Cohen's d_z = 0.363) and mPFC (Cohen's d_z = 0.478) activation (but not NAcc activation, Cohen's d_z =-.076) for those randomized to the CAAT-training condition, even though group by time effects failed to reach significance (amygdala p =. 44, NAcc p =.63 and mPFC p = .90). Note that left and right NAcc and amygdala were also tested separately, and no significant interactions emerged for the left and right hemisphere ROIs (left NAcc p = .45, right NAcc p = .85, left amygdala p = .59, right amygdala p = .33). Fig. 2 shows time by CAAT condition results from each model.

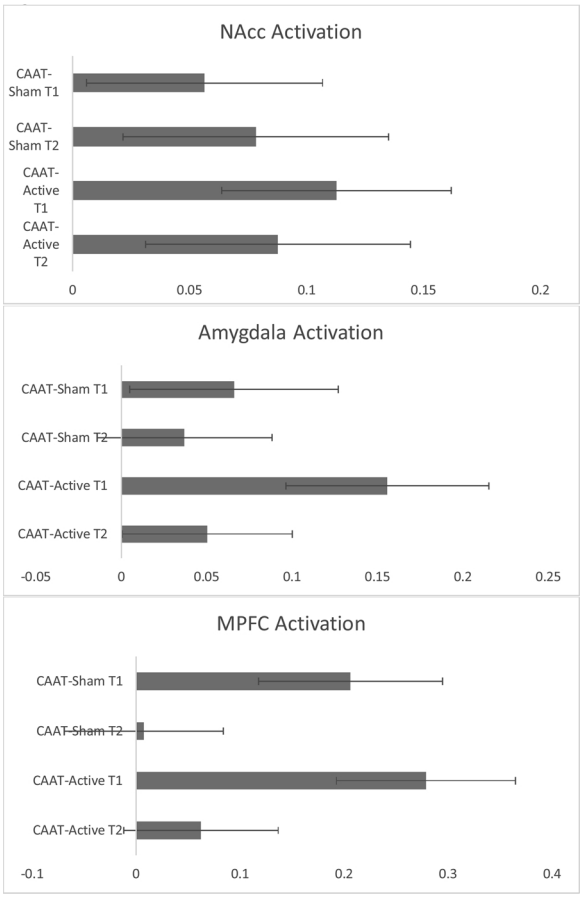

Fig. 2. Percent signal change in each ROI by group (CAAT-Sham vs. CAAT-Active) and time (T1, or pre-treatment, and T2, or post-treatment). For ease of visualization, graphed signal change values represent the average percent signal change for cannabis vs. non-cannabis cues in the left and right hemispheres for NAcc and amygdala.

4. Discussion

This proof-of-concept study involved a subset of participants from a larger pilot CBM study, which previously demonstrated a significant reduction in cannabis use in the CAAT-training group compared to the CAAT-sham group (Jacobus et al., 2018). This preliminary investigation was designed to examine whether changes in neural activation to cannabis cue-reactivity may explain these prior results. In contrast to findings from the larger proof-of-concept study, no significant changes in cannabis use were observed in the CAAT-training group compared to the CAAT-sham group, perhaps due to smaller sample size, lower power, and the more severe cannabis use patterns of the Charleston subsample compared to the San Diego subsample. No significant differences were observed in neural activation to cannabis cues following CAAT-training compared with CAAT-sham among non-treatment-seeking adolescent cannabis users. These preliminary results stand in contrast to significant differences observed in adult alcohol users (Wiers et al., 2015a, b). However, adolescents are earlier in their substance use trajectories compared to adults, and this difference in substance history and overall substance exposure may contribute to the null findings.

There are several other potential explanations for these unexpected results. First, it is possible that the relatively small sample size limited our ability to observe significant group differences in neural activation. For example, Fig. 2 shows that a group by time difference may be present in the amygdala and mPFC, which could emerge with a larger sample size. The small to medium effect sizes that emerged for the CAAT-training group in these two regions supports this possibility. However, other studies have used similar or smaller sample sizes and observed differences in cue-elicited craving by CBM group (Wiers et al., 2015a, b). Notably, these alcohol-focused studies included treatment-seekers (i.e., abstinent inpatients) who had more substantial and prolonged use histories, were receiving additional behavioral treatment, and likely were more motivated to reduce their substance use compared to the non-treatment seeking adolescents included in the present study (Wiers et al., 2018a). Thus, differences between alcohol and cannabis users, and between treatment-seekers and non-treatment-seekers (who potentially have different goals, such as abstinence vs. reduction) may explain why the present results differ from several previous studies. It is also notable that, in contrast to the larger study, there were no significant reductions in cannabis consumption over the course of the study in the CAAT group or the sham group, which could also explain the lack of observed group by time differences in neural activation post-treatment in this non-treatment-seeking subsample.

It is also plausible that the cannabis cues used in the AAT task in the present study were not perceived by adolescents as personally relevant enough to precipitate a change in approach bias. Specifically, given that adolescents tend to be opportunistic drug users (Mokrysz et al., 2016), and may thus be somewhat more limited in their typical modes of cannabis consumption compared to adults, the cues from the CAAT may be salient or rewarding but not sufficiently personally relevant to each individual if they depict modes of consumption that are not regularly or readily available to certain adolescents. Thus, future CBM research with adolescents should explore the use of individualized cues for the CAAT, as they may be associated with more generalized alterations in cannabis cue-reactivity in adolescents, and may be more useful in the context of altering approach tendencies.

Although we did not observe significant changes in cue-reactivity related to CBM training in this sample, the study had numerous strengths. First, the study demonstrates the feasibility of a CBM intervention among adolescent cannabis users. It is worth noting that a high percentage (e.g., 37 out of 41, or 90%) of individuals enrolled in the study completed all six sessions of CAAT as well as baseline and follow-up scans, through which we acquired high-quality longitudinal neuroimaging data. Overall, results from the larger pilot project underscore the potential for CBM as a feasible treatment option for adolescents, and highlight the need for future studies to examine the efficacy of CBM in

decreasing cue-reactivity and substance use in adolescent cannabis users. For example, the AAT can be administered online, and this mode of administration could be potentially relevant for adolescents, as they are already well-connected to electronic interfaces. However, in one study of an online AAT among adult problem drinkers, both the AAT and sham-conditions reduced drinking over the course of the study, with no significant between-group differences (Wiers et al., 2015c). It is unclear how these results might translate across age groups and for different substance using populations. Thus, future work is needed to explore how online CBM interventions may impact adolescent cannabis users.

4.1. Limitations and future directions

In addition to the small sample size, the study had several other limitations of note. First, participation did not require meeting criteria for CUD, and only 75% of participants met CUD criteria. Relatedly, these adolescents were not treatment-seeking, whereas the Wiers (2015) study included alcohol-dependent inpatients. However, the Sherman et al. (2018) study included non-treatment-seeking adults with CUD. Treatment-seeking substance users have been shown to differ from non-treatment-seeking substance users across a number of clinically-relevant characteristics, including severity of dependence and symptoms, longer history of substance use, and greater consumption, and most of these characteristics predict clinical outcomes (Ray et al., 2017). Given the conflicting evidence, the efficacy of CBM interventions among treatment-seeking and non-treatment-seeking individuals with CUD should be further explored (Wiers et al., 2018a, b). Another important limitation of note is the fact that the AAT is known to have potential reliability concerns, (Rodebaugh et al., 2016), and the irrelevant feature version used here tends to have lower reliability than a relevant feature version of the task.

Overall, results from this pilot study are inconsistent with prior research suggesting altered neural responses to substance-related cues in reward-related brain regions following AAT. While not statistically significant, there were small-to-medium decreases in cue reactivity in the amygdala and mPFC in the active vs. sham CAAT groups, suggesting these regions may be affected by the intervention; however, findings are preliminary and replication would be necessary before reaching any conclusions. Reductions in cannabis use observed among the larger sample (Jacobus et al., 2018) may have occurred through some other mechanism, or the subsample included in the present study may have been underpowered to detect modest changes in neural activation and cannabis use. Future research is needed to better understand the potential mechanism(s) of action of AAT as a treatment for SUDs across adult and adolescent populations.

Contributors

HCK and LMS organized and prepared the manuscript. JPS, HCK, LRM and LMS conducted neuroimaging analyses. JJ and LMS were involved in study design. CTT, SFT and KMG were involved in advising regarding study design, analyses, and manuscript preparation. LRM assisted with running the study, working with data, and editing the manuscript. All authors have read and approved the final manuscript.

Conflict of interest

No conflict declared.

Role of funding source

Funding was provided by NIDA grant K12 DA031794 (Brady), NIAAA grant K23 AA025399 (Squeglia), NIAAAK99/R00 AAO21419 (Schacht) and NIH/NCATSKL2 TR001444 (Jacobus). Additional funding was also provided by the South Carolina Clinical and Translational Institute at the Medical University of South Carolina (UL1TR000062). The funding source had no role other than financial support.

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