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Approach bias modification for cannabis use disorder: A proof-of-principle study

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Abstract

Background—More effective treatments for cannabis use disorder (CUD) are needed. Evidence suggests that biases in cognitive processing of drug-related stimuli are central to the development and maintenance of addiction. The current study examined the feasibility and effect of a novel intervention—approach bias modification (ApBM) – on cannabis approach bias and cue-reactivity.

Methods—A randomized, double-blind, sham-controlled proof-of-principle laboratory experiment investigated the effect of a four-session computerized ApBM training protocol on cannabis approach bias and cue-reactivity in non-treatment seeking adults age 18–65 with CUD (N=33). ApBM procedures involved responding to cannabis or neutral stimuli using a computer joystick to model approach or avoidance behavior. Reactivity to tactile, olfactory, and auditory cue sets was assessed with physiological (blood pressure and heart rate) and subjective (cannabis craving) measures. Cannabis use was assessed via self-report.

Results—Participants receiving ApBM showed blunted cannabis cue-induced craving at the end of training compared to those in the sham-ApBM condition ($p=0.05$). A preliminary gender effect on cannabis use was also found; men receiving ApBM reported fewer cannabis use sessions per day at the end of training compared to women ($p=0.02$), while there were no differences between men and women in the sham condition. ApBM did not attenuate cannabis approach bias following training.

Conclusion—Preliminary results indicate that ApBM may be efficacious in reducing cannabis cue-reactivity and improving cannabis use outcomes. While encouraging, the results should be interpreted with caution. Investigation of ApBM as an adjunct to psychosocial treatments for treatment-seeking adults with CUD is warranted.

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Keywords

cannabis; approach bias modification; cognitive bias; marijuana; treatment

1.0 Introduction

Cannabis use and rates of cannabis use disorder (CUD) are increasing in the United States. From 2002 to 2013 the prevalence of CUD in the general population nearly doubled from 1.5% to 2.9% (Hasin et al., 2015). Myriad consequences of cannabis use have been identified (Hall, 2015; Volkow, Baler, Compton, & Weiss, 2014) including impairments in cognitive functioning. Cannabis use is associated with deficits in working memory, abstract reasoning, and attention (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013), and while evidence suggests recovery of neurocognitive deficits following prolonged abstinence (Schulte et al., 2014), cognitive impairment in treatment-seeking cannabis users is associated with poor treatment retention (Aharonovich, Brooks, Nunes, & Hasin, 2008). Likewise, implicit cognitive functions, such as automatic processing of drug cues, are associated with heavy cannabis use. Biased cognitive processing of cannabis cues is associated with increased cannabis use, dependence severity, and cannabis-related problems (Cousijn et al., 2012; Cousijn et al., 2013; Stacy & Wiers, 2010). Given that treatments for CUD demonstrate limited effectiveness and durability (Sherman & McRae-Clark, 2016), investigation of novel interventions is warranted and implicit cognitive processing may be an important treatment target.

Dual process models of addiction posit an override of executive control (top-down) processes by implicit-reward driven (bottom-up) processes following repeated drug exposure (Bechara, 2005; Stacy & Wiers, 2010). This imbalance helps explain the compulsive nature of addiction characterized by continued drug use despite insight into the negative consequences. Chronic drug use sensitizes the mesolimbic reward circuitry and increases the incentive-salience of drug cues (see *Incentive-Sensitization Theory*; Robinson & Berridge, 1993, 2003). A recent meta-analysis of cannabis cue-reactivity studies found moderate to intense psychophysiological (i.e. skin conductance, event-related potentials) and subjective (i.e. cannabis craving) reactivity among cannabis users compared to baseline, and to neutral stimuli (Norberg, Kavanagh, Olivier, & Lyras, 2016). In addition, cue-induced mesolimbic activation has been associated with increased cannabis craving (Charboneau et al., 2013) and activation of the dorsal striatum is associated with cannabis problem-severity at 3-year follow-up (Vingerhoets et al., 2016). Treatments that attenuate cue-reactivity and craving may help restore balance between top-down and bottom-up processing, and ultimately improve cannabis treatment outcomes.

Implicit biases in cognitive processing of drug cues play an important role in the maintenance of addictive behaviors and are associated with poor treatment outcomes (Cox, Pothos, & Hosier, 2007; Marhe, Waters, van de Wetering, & Franken, 2013; Waters et al., 2003). Approach bias is one form of cognitive bias and refers to the automatic action tendency to approach a drug or drug cue following exposure. Approach bias can be assessed using a computerized approach-avoidance task (AAT) (Wiers, Rinck, Dictus, & van den

Wildenberg, 2009) that indirectly measures an individual's tendency to approach rather than avoid drug-related stimuli. Approach bias to cigarette smoking cues has been associated with increased nicotine craving among heavy smokers (Wiers et al., 2013), while cannabis approach bias has been associated with increased cannabis use and greater cannabis-related problem severity among cannabis-dependent adults (Cousijn et al., 2012; Cousijn, Goudriaan, & Wiers, 2011).

Approach bias modification (ApBM) is a novel treatment approach that seeks to attenuate approach bias and dampen the incentive-salience of drug cues. A recent systematic review found positive effects of ApBM on consumption behavior and relapse across drugs of abuse and binge eating behaviors (Kakoschke, Kemps, & Tiggemann, 2017), with the largest effect sizes from studies that successfully attenuated approach bias. In contrast, a meta-analysis of cognitive bias interventions found limited efficacy (Cristea, Kok, & Cuijpers, 2016). Notably, this meta-analysis combined different cognitive retraining paradigms (approach bias, attentional bias, and inhibitory control) and combined experimental proof-of-principle studies in college students not motivated to change and randomized controlled trials in clinical samples (Wiers, Boffo, & Field, in press).

In the first proof-of-principle study of ApBM, heavy drinking college students who were trained to approach alcohol cues drank more in a taste test than those trained to avoid alcohol cues (Wiers, Rinck, Kordts, Houben, & Strack, 2010). In two subsequent largescale clinical trials, ApBM was effective in retraining alcohol-dependent individuals to avoid rather than approach alcohol cues, and was associated with 10–13% reduction in relapse rates at 1-year post-treatment (Eberl et al., 2013; Wiers et al., 2011). Likewise, two recent pilot studies found reductions in cigarette consumption and dependence severity among nicotine-dependent individuals who received ApBM compared to sham training controls (Kong et al., 2015; Wittekind, Feist, Schneider, Moritz, & Fritzsche, 2015). A recent fMRI study by Wiers and colleagues (2015) found decreased neural activity in mesolimbic brain regions among alcohol-dependent individuals who received ApBM compared to controls, suggesting that ApBM directly targets neurobiological mechanisms associated with addiction. ApBM has shown promise in the treatment of alcohol and nicotine use disorders, but to date, it has not been tested for cannabis use disorder.

The current proof-of-principle laboratory experiment tested the feasibility and effect of ApBM on cannabis approach bias and cue-reactivity among non-treatment seeking adults with CUD. The primary aims were to determine: 1) the feasibility of administering ApBM procedures with cannabis users, 2) whether ApBM would attenuate cannabis approach bias, and 3) whether ApBM would attenuate cannabis cue-reactivity. Exploratory aims were: a) to assess the impact of ApBM on cannabis use, and b) to explore whether gender moderated treatment effects.

2.0 Materials and Methods

2.1 Study Design

A randomized, double-blind, sham-controlled proof-of-principle study investigated the effect of a 4-session computerized ApBM training protocol on cannabis approach bias and

cannabis cue reactivity in non-treatment seeking adults with CUD. Study participants completed a pre-assessment, followed by four training (or sham-control) sessions over a two-week period, and a two-week follow-up assessment. All procedures were approved by the Medical University of South Carolina Institutional Review Board and were conducted in accordance with the Declaration of Helsinki.

2.2 Participants

Non-treatment-seeking adults age 18–65 who met DSM-5 criteria for moderate to severe CUD during the past 3 months were recruited through local print and online media advertising. Participants were told they would be participating in research study investigating the association between cognitive functioning and cannabis use. Additional inclusion criteria were the ability to provide informed consent and function at an intellectual level sufficient to allow accurate completion of all assessment instruments; and identification of cannabis as their primary substance of choice. Participants were excluded at screening for the following reasons: 1) history of or current psychotic disorder or bipolar affective disorder; 2) current major depressive disorder or post-traumatic stress disorder; 3) current suicidal or homicidal risk; 4) taking psychotropic medications (with the exception of non-MAOI antidepressants, and stimulants for ADHD), opiates or opiate antagonists; 5) women who were pregnant, nursing or of childbearing potential and not practicing an effective means of birth control; 6) evidence of or a history of significant hematological, endocrine, cardiovascular, pulmonary, renal, gastrointestinal, or neurological disease; 7) being unwilling or unable to maintain abstinence from alcohol and cannabis for 12 hours and other drugs of abuse (except nicotine) for three days prior to study procedures; 8) meeting DSM-5 criteria for moderate to severe SUD (other than nicotine or cannabis) within the past 60 days.

2.3 Assessment Instruments

2.3.1 Diagnostic instruments—The *Mini-International Neuropsychiatric Interview* (M.I.N.I.) (Sheehan et al., 1998) was used to assess DSM-5 psychiatric and substance use diagnoses. The M.I.N.I. is a brief structured interview that was designed to assess current diagnoses using a series of questions in dichotomous format (yes/no).

2.3.2 Substance-related instruments—Substance use during the two weeks prior to baseline, between each ApBM session, and between end of treatment and follow-up were assessed using the *Timeline Follow-Back* (TLFB) (Sobell & Sobell, 1992). The TLFB is a calendar-based instrument used with specific probes to ascertain detailed information about amounts of substance use. *Urine Drug Screening:* Drug screens were performed using the iScreen 5 Panel Multi-Drug Urine Dip Card Test Kit, an in vitro diagnostic test for the qualitative detection of drug metabolites in the urine. The iScreen profile (cut off) consists of amphetamines (1000ng/ml), cocaine (300 ng/ml), THC (50 ng/ml), benzodiazepines (300 ng/ml), and opiates (2000 ng/ml). Results were used to confirm abstinence prior to study procedures and to substantiate self-reports of all substance use except cannabis, which was assessed by saliva testing. *Saliva Drug Screening:* In addition to urine testing, participants were also asked to provide a saliva sample to verify abstinence from cannabis use through use of Oral-View™ testing (Noble Medical). This test is able to detect THC in saliva for up

to 14 hours, which allowed verification of abstinence in the past 12 hours as indicated in procedures. *Breathalyzer* (AlcoSensor III, Intoximeters, Inc., St. Louis): To ascertain abstinence from alcohol during the study period, subjects had their breath sampled for the presence of alcohol (Alco-Sensor III, Intoximeters Inc., St. Louis, MO).

2.4 Cannabis Cue-Reactivity

The cannabis cue-reactivity paradigm included physiological (heart rate and blood pressure) and subjective (cannabis craving) reactivity components assessed at 3 time points: prior to neutral cues (tonic), following neutral cues (neutral reactivity), and following cannabis cues (cannabis reactivity). Cannabis cues always followed neutral cues to account for drug cue carryover effects (Lundahl & Greenwald, 2016). Cue sets were matched on content characteristics and contained tactile (e.g. bowl, blunt wraps vs. sticky notes, pencil), auditory (e.g. guided visualization of a cannabis session vs. walk on the beach), and olfactory cues (e.g. 3 drops of cannabis sativa essential oil placed on a cannabis surrogate – motherwort vs. cedar wood chips), and have been shown to elicit reactivity in previous studies (McRae-Clark et al., 2011). Participants were instructed to interact with the cues by picking them up, smelling them, and handling them as they would their own paraphernalia, while visualizing a recent pleasurable cannabis using session. Cue-reactivity was assessed at baseline (BL), end of training (EOT), and at a 2-week follow-up (FU) and change in reactivity was compared between groups and within subjects. Heart rate and blood pressure were measured using GE Dynamap PRO 200, while cannabis craving was measure using the Marijuana Craving Questionnaire (MCQ) (Heishman, Singleton, & Liguori, 2001).

2.5 Approach Bias Modification

Approach bias assessment and modification procedures used the Cannabis Approach Avoidance Task (CAAT), a cannabis adaptation of the computerized Alcohol Approach-Avoidance Task (AAT), which was developed to assess and modify alcohol approach bias (Wiers et al., 2009; 2010).

2.5.1 Approach bias assessments—Participants were presented with cannabis (CB)-related and neutral images on a computer screen and asked to push or pull a joystick in response to a non-content related (i.e. irrelevant) stimulus feature (i.e. image border color – blue or yellow). Joystick movement activated a zooming feature, which has been shown to effectively model approach (pull: zoom in) and avoidance (push: zoom out) (Neumann & Strack, 2000). Participants were asked to respond to stimuli as quickly and accurately as possible. Reaction times were calculated from image onset to zoom off-screen, and median reaction times were used to compute approach bias scores in order to avoid outlier influence. Approach bias assessments occurred at three time points: BL, EOT, and FU. The assessment phases consisted of 2 blocks of 96 trials and participants were presented with an equal number of CB and neutral images across border color. After pre-assessment, the ApBM training phase began.

2.5.2 Approach bias modification protocol—The ApBM protocol consisted of four training sessions, separated by at least one day, over a two-week period. A four session protocol was chosen based on previous studies showing positive results (Kong et al., 2015;

Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011). Each training session consisted of two blocks of 192 trials. ApBM involves the manipulation of response contingencies (push vs. pull – CB vs. neutral) in order to retrain participants to avoid rather than approach CB stimuli. For participants in the active training condition, 90% of CB trials were presented in the push format (avoid) and 90% of neutral trials in the pull format (approach). Control participants (sham training) were presented with equally distributed (50%) push/pull CB pictures. Two stimulus sets of 16 CB and 16 neutral images were used and counterbalanced from pre-assessment to post-assessment and follow-up to test for generalizability. For example, if subject 101 received Set A for pre-assessment and trainings, their post-assessments used Set B; if subject 102 received Set B for pre-assessment and training, they were tested using Set A at post-assessments.

2.6 Procedures

2.6.1 Screening visit—All procedures took place in the Addiction Sciences Division at the Medical University of South Carolina. After all inclusion and no exclusion criteria were met, participants were randomly assigned to either the experimental (active ApBM) or control (sham ApBM) condition. Upon presentation for each study visit, participants were breathalyzed and a urine sample was collected and tested for the presence of cocaine, opiates, benzodiazepines, THC, and stimulants. A saliva sample was also collected to verify abstinence from cannabis for the past 12 hours. If all test results were within study inclusion/exclusion criteria, test day procedures began.

2.6.2 Intervention and follow-up—On study day 1, participants underwent baseline cue-reactivity procedures, followed by approach bias pre-assessment and the first ApBM training session. Three additional ApBM training sessions were then scheduled. At the last study visit (EOT), following the last ApBM training session, approach bias post-assessment was conducted and followed by the cue-reactivity procedures. To assess the durability of effects, participants returned to the clinic two weeks later for a FU visit where approach bias assessment and cue-reactivity procedures were again completed.

2.7 Statistical Procedures

Baseline clinical and demographic characteristics were collected and contrasts performed between training groups. Continuous and ordinal characteristics were compared using a Wilcoxon Rank-Sum test while categorical characteristics were compared using a Pearson Chi-Square test. Generalized linear mixed effects regression models (GLMMs) with appropriate distributional assumptions were used to test study hypotheses. Models were initially adjusted for visit, cue type (cannabis, neutral) where appropriate, and baseline measure of each outcome. Interaction terms of study training assignment with study visit and gender were independently added to each model and tested for evidence of effect modification. When evidence of a clinical interaction was present, pairwise comparisons within and across gender were examined to assess the direction and magnitude of the modification. Approach bias scores were calculated using differences in subject-level reaction times across stimulus group (neutral vs. cannabis), and computed by subtracting the subject-level median “pull CB cue” reaction times (RTs) from the subject-level median “push CB cue” RTs; a positive value thus indicates greater cannabis approach bias. Between

group differences in approach bias scores as calculated above were compared using GLMMs. Additionally, baseline approach bias was added to cue-reactivity and cannabis use outcomes models to determine if increased approach bias at study entry was associated with craving and use following training. All analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

3.0 Results

3.1 Participants

Forty-nine participants were randomized (Active ApBM $n=25$, Sham ApBM $n=24$; Table 1). The mean age was 24.7 ($SD=6.1$) years, 49% ($n=24$) were males and 74% were Caucasian ($n=36$). Although participants in both groups reported similar days of use during the two weeks prior to the study [ApBM=13.1(1.4) vs. Sham=12.2(2.4) days], participants randomized to the active ApBM group reported a greater number of cannabis use sessions over the same time period [ApBM=39.4(18.6) sessions vs. Sham=28.8(12.0) sessions, $p=0.05$]. Randomized groups did not differ on reported MCQ total score at baseline [ApBM=45.8(11.9) vs. Sham=40.6(13.7)]. Of the 49 randomized participants, 39 (79.6%) completed all four training visits, and 33 (67.3%) completed all study visits and FU (study completers). Study completion rates did not differ by group [ApBM=16(64%); Sham=17(71%)]. Study completers were 58% female ($n=19$), 85% Caucasian ($n=28$), and had a mean age of 24.3(5.8) years. One participant reportedly became pregnant six days before the FU visit and reported abstinence for those six days. No concerns regarding data integrity were found and her data was included in all analyses; this participant was in the Sham training condition.

3.2 Approach bias

Approach bias was assessed at BL, EOT, and FU. Overall, participants demonstrated an approach bias for cannabis cues compared to neutral cues at BL [14.2(5.9) vs. -1.2(5.9); $p=0.01$]. Baseline cannabis approach bias did not differ between training conditions ($p=0.31$). To test the training effect of ApBM over time, a three-way interaction between condition (active vs. sham), stimulus type (cannabis vs. neutral), and visit (BL, EOT, FU) was analyzed. The results did not show a training effect of ApBM on cannabis approach bias over time ($p=0.80$; Figure 1). Additional analysis did not reveal modification of the training effect by baseline approach bias ($p=0.43$), baseline cannabis use ($p=0.85$), or gender ($p=0.25$). Response accuracy rates were high and did not vary across groups over the course of the study (98.3% ApBM vs. 98.2% sham); the lowest overall accuracy rate was 92% ($n=1$) indicating a clear understanding of and adherence to ApBM instructions.

3.3 Cue-reactivity

Cannabis cue-reactivity was measured at BL, EOT, and FU. After adjusting for baseline MCQ total craving score, participants in the active training condition had lower MCQ total scores approaching statistical significance compared to the sham condition at EOT [ApBM 38.7(0.8) vs. sham 40.9(0.7); $p=0.051$], but not at FU [ApBM 39.5(0.8) vs. sham 39.8(0.8); $p=0.82$; Figure 2]. The difference noted at EOT was driven primarily by response to the cannabis cues [ApBM 39.5(1.0) vs. sham 43.2(1.0); $p=0.01$], rather than neutral cues

[ApBM 37.4(1.0) vs. sham 40.0(1.0); $p=0.08$] or tonic craving response [ApBM 39.5(1.0) vs. sham 39.4(1.0); $p=0.94$]. There results were not maintained at FU. No significant group differences were found on physiological cue-reactivity including heart rate ($p=0.68$) or blood pressure [diastolic ($p=0.76$), systolic ($p=0.59$)]. Baseline approach bias scores were significantly associated with self-reported craving following treatment ($p=0.02$) indicating greater approach bias at baseline was positively correlated with cue induced craving following training. There was no evidence that men and women had a differential craving response to the cues based on ApBM training assignment ($p=0.70$).

3.4 Cannabis use outcomes

Days of cannabis use and cannabis sessions per day were measured two weeks prior to BL, between BL and EOT, and between EOT and FU (2-week intervals, 6 weeks total). There was no main effect of ApBM on overall use sessions per day during the study ($p=0.45$), however, there was preliminary evidence that women and men responded differently to ApBM (gender $\times$ training, $p=0.03$; Figure 3). Men in the active ApBM condition reported fewer use sessions per day than women in the active condition [men 1.8(0.2) vs. women 2.3(0.2); $p=0.03$]; this difference did not exist in the sham condition [men 2.3(0.2) vs. women 2.1(0.2); $p=0.38$]. The difference between men and women was significant at EOT [men 1.9(0.2) vs. women 2.5(0.2); $p=0.022$], but not at FU [men 1.8(0.2) vs. women 2.1(0.2); $p=0.21$]. There was no gender difference in the number of reported using days during the same period [women 11.6(0.9) vs. men 12.1(0.6); $p=0.63$]. Baseline approach bias scores were not associated with use during the study or at FU ($p>0.10$).

4.0 Discussion

The current proof-of-principle study is the first to examine the effect of approach bias modification for cannabis use disorder. The study examined whether ApBM would attenuate cannabis approach bias and cannabis cue-reactivity among non-treatment seeking adults with CUD. Exploratory analyses examined the effect of ApBM on cannabis outcomes and tested gender as a potential moderator. The findings indicate that relative to sham, ApBM did not attenuate cannabis approach bias, but did blunt cannabis cue-induced craving. There was also preliminary evidence that men may respond better to ApBM as indicated by a reduction in cannabis use compared to women. Finally, compliance was high as 80% of the sample completed all four training sessions and 67% completed through the 2-week FU visit, suggesting ApBM is feasible to administer.

At baseline, there was a samplewide bias for cannabis cues compared to neutral cues. This is an important finding as it validates the construct of cannabis approach bias, as assessed with the CAAT, in our sample of non-treatment seeking adults with CUD. However, there was no training effect as ApBM did not attenuate cannabis approach bias from BL to FU compared to sham-ApBM. Several possible explanations are notable. First, ApBM is a novel intervention that has shown very positive results in clinical trials for alcohol use disorder (AUD), but a standardized protocol has not been established and it has never been tested for cannabis use. In the AUD trials, ApBM protocols ranged from 4 to 12 sessions and included a psychosocial treatment component (Eberl et al., 2013; Wiers et al., 2011), while the

current study used a 4-session protocol without psychosocial treatment. In addition, those samples were treatment-seeking inpatients, and thus, abstinent during ApBM procedures, while the current sample was non-treatment seeking and non-abstinent. Ongoing cannabis use may have undermined the efficacy of the intervention. Second, cognitive factors such as response inhibition, working memory, and regulatory control are important moderators that have been shown to impact the effectiveness of cognitive modification tasks (Grenard et al., 2008; Houben & Wiers, 2009; Peeters et al., 2013; Salemink & Wiers, 2012). These factors would be important to consider in a fully-powered clinical trial.

Participants receiving ApBM demonstrated blunted cannabis cue-induced craving at EOT compared to sham controls. This effect was transient and not maintained at the two-week follow-up. ApBM did not engender blunted physiological cue-reactivity. These results are consistent with evidence from alcohol-dependent patients who showed reduced subjective craving following ApBM for alcohol use disorder (Wiers et al., 2015). Craving plays a critical role in drug relapse and is an important treatment target (Fatseas et al., 2015; O'Brien, 2005). Further, baseline approach bias was positively correlated with cue-induced craving at end of treatment, which implies a mechanistic link between the two constructs. Thus, ApBM may target reward driven processes on both the implicit (approach bias) and subjective (craving) levels. While physiological cue-reactivity did not evidence significant reductions following ApBM, more sensitive measures (i.e. skin conductance) may prove fruitful in future studies.

Though preliminary in nature, results indicate potential gender-informed clinical application of ApBM. In our sample, men reported fewer cannabis sessions per day at EOT compared to women. Previous work on subliminal cannabis cue-reactivity has demonstrated that men show an association between craving and cue-induced activation in the mesolimbic region (Wetherill et al. 2015); it is possible that men may be more responsive to treatments such as ApBM, which has been shown to target reward-related brain regions (Cousijn et al., 2012; Wiers et al., 2015). Gender differences in personality traits may also influence these results. A recent meta-analysis found that men consistently show greater sensation-seeking and impulsivity (Cross, Copping, & Campbell, 2011), traits that are likely associated with implicit action tendencies towards drug stimuli and may be important covariates to consider.

The current study is the first to test ApBM for adults with CUD. While results were encouraging, important limitations are worth noting. First, as a proof-of-principle study power to detect a training effect was limited due to small sample size, making it difficult to draw firm conclusions. Gender results are to be interpreted with particular caution. Second, cognitive retraining procedures have not been standardized and study protocols have ranged from 1 to 12 sessions (Kakoschke et al., 2017), with the most effective including a psychosocial treatment component. The current study used a 4-session ApBM protocol, so a larger dose combined with psychotherapy may improve treatment outcomes. Relatedly, although this is the first study published using the CAAT, other studies are ongoing and will provide additional evidence as to the most effective procedures. Third, the sample was comprised of non-treatment seekers. Motivation is an important construct to consider in SUD treatment as treatment-seeking individuals may be more responsive to treatments at both the conscious and pre-conscious level. Moreover, ongoing cannabis use during the

study likely limited our ability to attenuate approach bias given that each use episode reinforces the mechanism of interest. Fourth, the order of the cue-reactivity and approach bias assessments was reversed from BL to EOT/FU. This design was chosen to limit transitions from computer task to cue task. While randomization would account for individual differences, having the cue-induction prior to BL approach bias assessment may have contributed to systematic error, thus limiting our findings on approach bias. Lastly, since there was no effect of ApBM on cannabis approach bias, findings may be better explained by another unknown factor, rather than as an effect of ApBM.

5.0 Conclusion

Cannabis use continues to increase in the United States, yet existing treatments have shown limited effectiveness. The current proof-of-principle study investigated a novel behavioral treatment that seeks to attenuate action tendencies to approach drug stimuli, and demonstrated feasibility and potential efficacy in reducing cannabis cue-induced craving in adults with CUD. Future research on ApBM with motivated, treatment-seeking individuals is needed to assess the treatment effect and optimal treatment duration. Potential mediators including response inhibition, working memory, and personality traits should also be considered. Approach bias modification is an innovative treatment strategy for CUD and may be an effective adjunct to psychosocial interventions. Replication and extension of the current findings in fully-powered clinical trials is needed in order to test the true efficacy of ApBM for CUD.

References

- Aharonovich E, Brooks AC, Nunes EV, Hasin DS. Cognitive deficits in marijuana users: Effects on motivational enhancement therapy plus cognitive behavioral therapy treatment outcome. *Drug Alcohol Depend.* 2008; 95(3):279–283. DOI: 10.1016/j.drugalcdep.2008.01.009 [PubMed: 18329188]
- Bechara A. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nat Neurosci.* 2005; 8(11):1458–1463. DOI: 10.1038/nn1584 [PubMed: 16251988]
- Charboneau EJ, Dietrich MS, Park S, Cao A, Watkins TJ, Blackford JU, ... Cowan RL. Cannabis cue-induced brain activation correlates with drug craving in limbic and visual salience regions: preliminary results. *Psychiatry Res.* 2013; 214(2):122–131. DOI: 10.1016/j.psychres.2013.06.005 [PubMed: 24035535]
- Cousijn J, Goudriaan AE, Ridderinkhof KR, van den Brink W, Veltman DJ, Wiers RW. Approach-bias predicts development of cannabis problem severity in heavy cannabis users: Results from a prospective fMRI study. *PLoS One.* 2012; 7(9)doi: 10.1371/journal.pone.0042394
- Cousijn J, Goudriaan AE, Wiers RW. Reaching out towards cannabis: Approach-bias in heavy cannabis users predicts changes in cannabis use. *Addiction.* 2011; 106(9):1667–1674. DOI: 10.1111/j.1360-0443.2011.03475.x [PubMed: 21518067]
- Cousijn J, Watson P, Koenders L, Vingerhoets WAM, Goudriaan AE, Wiers RW. Cannabis dependence, cognitive control and attentional bias for cannabis words. *Addictive Behaviors.* 2013; 38(12):2825–2832. DOI: 10.1016/j.addbeh.2013.08.011 [PubMed: 24018225]
- Cox WM, Pothos EM, Hosier SG. Cognitive-motivational predictors of excessive drinkers' success in changing. *Psychopharmacology (Berl).* 2007; 192(4):499–510. DOI: 10.1007/s00213-007-0736-9 [PubMed: 17333136]
- Crane N, Schuster R, Fusar-Poli P, Gonzalez R. Effects of Cannabis on Neurocognitive Functioning: Recent Advances, Neurodevelopmental Influences, and Sex Differences. *Neuropsychology Review.* 2013; 23(2):117–137. DOI: 10.1007/s11065-012-9222-1 [PubMed: 23129391]

- Cristea IA, Kok RN, Cuijpers P. The Effectiveness of Cognitive Bias Modification Interventions for Substance Addictions: A Meta-Analysis. *PLoS One*. 2016; 11(9):e0162226.doi: 10.1371/journal.pone.0162226 [PubMed: 27611692]
- Cross CP, Copping LT, Campbell A. Sex differences in impulsivity: A meta-analysis. *Psychological Bulletin*. 2011; 137(1):97–130. DOI: 10.1037/a0021591 [PubMed: 21219058]
- Eberl C, Wiers RW, Pawelczack S, Rinck M, Becker ES, Lindenmeyer J. Approach bias modification in alcohol dependence: Do clinical effects replicate and for whom does it work best? *Developmental Cognitive Neuroscience*. 2013; 4:38–51. [PubMed: 23218805]
- Fatseas M, Serre F, Alexandre JM, Debrabant R, Auriacombe M, Swendsen J. Craving and substance use among patients with alcohol, tobacco, cannabis or heroin addiction: a comparison of substance- and person-specific cues. *Addiction*. 2015; 110(6):1035–1042. DOI: 10.1111/add.12882 [PubMed: 25688760]
- Grenard JL, Ames SL, Wiers RW, Thush C, Sussman S, Stacy AW. Working memory capacity moderates the predictive effects of drug-related associations on substance use. *Psychol Addict Behav*. 2008; 22(3):426–432. DOI: 10.1037/0893-164x.22.3.426 [PubMed: 18778136]
- Hall W. What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? *Addiction*. 2015; 110(1):19–35. DOI: 10.1111/add.12703
- Hasin DS, Saha TD, Kerridge BT, Goldstein RB, Chou SP, Zhang H, ... Grant BF. Prevalence of Marijuana Use Disorders in the United States Between 2001–2002 and 2012–2013. *JAMA Psychiatry*. 2015; 72(12):1235–1242. DOI: 10.1001/jamapsychiatry.2015.1858 [PubMed: 26502112]
- Heishman SJ, Singleton EG, Liguori A. Marijuana Craving Questionnaire: development and initial validation of a self-report instrument. *Addiction*. 2001; 96(7):1023–1034. DOI: 10.1080/09652140120053084 [PubMed: 11440613]
- Houben K, Wiers RW. Response inhibition moderates the relationship between implicit associations and drinking behavior. *Alcohol Clin Exp Res*. 2009; 33(4):626–633. DOI: 10.1111/j.1530-0277.2008.00877.x [PubMed: 19183132]
- Kakoschke N, Kemps E, Tiggenmann M. Approach bias modification training and consumption: A review of the literature. *Addict Behav*. 2017; 64:21–28. DOI: 10.1016/j.addbeh.2016.08.007 [PubMed: 27538198]
- Kong G, Larsen H, Cavallo DA, Becker D, Cousijn J, Salemink E, ... Krishnan-Sarin S. Retraining automatic action tendencies to approach cigarettes among adolescent smokers: a pilot study. *Am J Drug Alcohol Abuse*. 2015; 41(5):425–432. DOI: 10.3109/00952990.2015.1049492 [PubMed: 26186485]
- Lundahl LH, Greenwald MK. Magnitude and duration of cue-induced craving for marijuana in volunteers with cannabis use disorder. *Drug Alcohol Depend*. 2016; 166:143–149. DOI: 10.1016/j.drugalcdep.2016.07.004 [PubMed: 27436749]
- Marhe R, Waters AJ, van de Wetering BJM, Franken IHA. Implicit and Explicit Drug-Related Cognitions during Detoxification Treatment are Associated with Drug Relapse: An Ecological Momentary Assessment Study. *J Consult Clin Psychol*. 2013; 81(1):1–12. DOI: 10.1037/a0030754 [PubMed: 23231572]
- McRae-Clark AL, Carter RE, Price KL, Baker NL, Thomas S, Saladin ME, ... Brady KT. Stress- and cue-elicited craving and reactivity in marijuana-dependent individuals. *Psychopharmacology (Berl)*. 2011; 218(1):49–58. DOI: 10.1007/s00213-011-2376-3 [PubMed: 21710170]
- Neumann R, Strack F. Approach and avoidance: The influence of proprioceptive and exteroceptive cues on encoding of affective information. *Journal of Personality and Social Psychology*. 2000; 79(1):39–48. DOI: 10.1037/0022-3514.79.1.39 [PubMed: 10909876]
- Norberg MM, Kavanagh DJ, Olivier J, Lyras S. Craving cannabis: a meta-analysis of self-report and psychophysiological cue-reactivity studies. *Addiction*. 2016; 111(11):1923–1934. DOI: 10.1111/add.13472 [PubMed: 27239052]
- O'Brien CP. Anticraving Medications for Relapse Prevention: A Possible New Class of Psychoactive Medications. *American Journal of Psychiatry*. 2005; 162(8):1423–1431. DOI: 10.1176/appi.ajp.162.8.1423 [PubMed: 16055763]

- Peeters M, Monshouwer K, van de Schoot RA, Janssen T, Vollebergh WA, Wiers RW. Automatic processes and the drinking behavior in early adolescence: a prospective study. *Alcohol Clin Exp Res*. 2013; 37(10):1737–1744. DOI: 10.1111/acer.12156 [PubMed: 23763261]
- Robinson TE, Berridge KC. The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Research Reviews*. 1993; 18(3):247–291. DOI: 10.1016/0165-0173(93)90013-P [PubMed: 8401595]
- Robinson TE, Berridge KC. Addiction. *Annual Review of Psychology*. 2003; 54:25–53. DOI: 10.1146/annurev.psych.54.101601.145237
- Salemink E, Wiers RW. Adolescent threat-related interpretive bias and its modification: the moderating role of regulatory control. *Behav Res Ther*. 2012; 50(1):40–46. DOI: 10.1016/j.brat.2011.10.006 [PubMed: 22093764]
- Schulte MH, Cousijn J, den Uyl TE, Goudriaan AE, van den Brink W, Veltman DJ, ... Wiers RW. Recovery of neurocognitive functions following sustained abstinence after substance dependence and implications for treatment. *Clin Psychol Rev*. 2014; 34(7):531–550. DOI: 10.1016/j.cpr.2014.08.002 [PubMed: 25240109]
- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, ... Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*. 1998; 59(Suppl 20):22–33.
- Sherman BJ, McRae-Clark AL. Treatment of Cannabis Use Disorder: Current Science and Future Outlook. *Pharmacotherapy*. 2016; 36(5):511–535. DOI: 10.1002/phar.1747 [PubMed: 27027272]
- Sobell, L., Sobell, M. Timeline Follow-Back. In: Litten, R., Allen, J., editors. *Measuring Alcohol Consumption*. Humana Press; 1992. p. 41-72.
- Stacy AW, Wiers RW. Implicit cognition and addiction: A tool for explaining paradoxical behavior. *Annual Review of Clinical Psychology*. 2010; 6:551–575. DOI: 10.1146/annurev.clinpsy.121208.131444
- Vingerhoets WA, Koenders L, van den Brink W, Wiers RW, Goudriaan AE, van Amelsvoort T, ... Cousijn J. Cue-induced striatal activity in frequent cannabis users independently predicts cannabis problem severity three years later. *J Psychopharmacol*. 2016; 30(2):152–158. DOI: 10.1177/0269881115620436 [PubMed: 26645206]
- Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med*. 2014; 370(23):2219–2227. DOI: 10.1056/NEJMr1402309 [PubMed: 24897085]
- Waters AJ, Shiffman S, Sayette MA, Paty JA, Gwaltney CJ, Balabanis MH. Attentional Bias Predicts Outcome in Smoking Cessation. *Health psychology: official journal of the Division of Health Psychology, American Psychological Association*. 2003; 22(4):378–387. DOI: 10.1037/0278-6133.22.4.378
- Wetherill RR, Jagannathan K, Hager N, Childress AR, Franklin TR. Sex differences in associations between cannabis craving and neural responses to cannabis cues: Implications for treatment. *Experimental and Clinical Psychopharmacology*. 2015; 23(4):238–246. DOI: 10.1037/pha0000036 [PubMed: 26237321]
- Wiers CE, Kuhn S, Javadi AH, Korucuoglu O, Wiers RW, Walter H, ... Bermpohl F. Automatic approach bias towards smoking cues is present in smokers but not in ex-smokers. *Psychopharmacology (Berl)*. 2013; 229(1):187–197. DOI: 10.1007/s00213-013-3098-5 [PubMed: 23604335]
- Wiers CE, Stelzel C, Gladwin TE, Park SQ, Pawelczack S, Gawron CK, ... Bermpohl F. Effects of cognitive bias modification training on neural alcohol cue reactivity in alcohol dependence. *The American Journal of Psychiatry*. 2015; 172(4):335–343. DOI: 10.1176/appi.ajp.2014.13111495 [PubMed: 25526597]
- Wiers RW, Boffo M, Field M. What's in a Trial? On the Importance of Distinguishing between Experimental Lab-Studies and Randomized Controlled Trials; the Case of Cognitive Bias Modification and Alcohol Use Disorders. *Journal of Studies on Alcohol and Drugs*. (in press).
- Wiers RW, Eberl C, Rinck M, Becker ES, Lindenmeyer J. Retraining automatic action tendencies changes alcoholic patients' approach bias for alcohol and improves treatment outcome.

Psychological Science. 2011; 22(4):490–497. DOI: 10.1177/0956797611400615 [PubMed: 21389338]

Wiers RW, Rinck M, Dictus M, van den Wildenberg E. Relatively strong automatic appetitive action-tendencies in male carriers of the OPRM1 G-allele. *Genes, Brain & Behavior*. 2009; 8(1):101–106. DOI: 10.1111/j.1601-183X.2008.00454.x

Wiers RW, Rinck M, Kordts R, Houben K, Strack F. Retraining automatic action-tendencies to approach alcohol in hazardous drinkers. *Addiction*. 2010; 105(2):279–287. DOI: 10.1111/j.1360-0443.2009.02775.x [PubMed: 20078486]

Wittekind CE, Feist A, Schneider BC, Moritz S, Fritzsche A. The approach-avoidance task as an online intervention in cigarette smoking: A pilot study. *Journal of Behavior Therapy and Experimental Psychiatry*. 2015; 46:115–120. DOI: 10.1016/j.jbtep.2014.08.006 [PubMed: 25306247]

Highlights

- Implicit cognitive biases are critical to the maintenance of addictive behaviors
- A proof-of-principle lab-experiment of ApBM for adults with CUD was conducted
- ApBM engendered blunted cannabis cue-induced craving compared to sham
- ApBM may be an effective adjunct to traditional psychosocial treatments for CUD

Figure 1. Approach bias scores by condition, valence, and visit

Note: Data show raw approach bias scores across condition, valence (cue type), and visit. Results indicate overall cannabis approach bias, compared to neutral cue bias, across groups at baseline. Three-way interaction Condition $\times$ Valence $\times$ Visit was not significant. Active = ApBM training condition, Sham = control condition; BL = baseline visit; EOT = end of training visit; Follow-Up = two-week follow-up visit. darkest (left) columns: BL, lightest (middle) columns: EOT, and grayish columns (far right): Follow Up

Figure 2. Cannabis cue-induced craving by group and visit

Note: Adjusted for baseline cannabis cue-induced craving (MCQ Total score). EOT = end of training; Active indicates ApBM training condition; Sham indicates control condition. Compared to sham (n=17), active ApBM participants (n=16) showed blunted cue-reactivity at EOT, but not at follow-up.

Figure 3. Cannabis use during the study by gender and condition

Note: Adjusted for baseline cannabis use levels. Active indicates ApBM training condition; Sham indicates control training condition. Male participants in the active condition (n=7) showed fewer cannabis sessions per day compared to females in the active condition (n=9). This gender difference was not significant among sham participants.

Table 1

Demographic and clinical characteristics for overall sample and by training condition.

Characteristic	Training Condition			p-value
	Overall (n=49)	ApBM (n=25)	Sham N=24	
Age (M, SD)	24.7 (6.1)	25.9 (6.6)	23.5 (5.5)	0.18
Male Gender (%; n)	49.0 (24)	52.0 (13)	45.8 (11)	0.67
Caucasian (%; n)	73.5 (36)	72.0 (18)	75.0 (18)	0.81
Education (%; n)				0.36
Less than HS	2.0 (1)	4.0 (1)	0.0 (0)	
HS/Some College	75.5 (37)	68.0 (17)	83.3 (20)	
4 year degree or more	22.5 (11)	28.0 (7)	16.7 (4)	
Cigarette smoker (%; n)	38.8 (19)	48.0 (12)	29.2 (7)	0.18
Cigarettes per day (M, SD)	5.7 (5.9)	6.5 (6.5)	4.0 (4.7)	0.27
Any Alcohol Use past 30 days (%; n)	73.5 (36)	72.0 (18)	75.0 (18)	0.81
Drinks per day (M, SD)	3.6 (2.2)	3.4 (2.6)	3.8 (1.8)	0.25
Baseline Cannabis Approach Bias (M, SD) ⁺	12.2 (52.9)	20.4 (64.8)	8.2 (40.0)	0.31
Marital Status (%; n)				0.72
Married or living as such	8.2 (4)	8.0 (2)	8.3 (2)	
Divorced / Separated	8.2 (4)	8.0 (2)	8.3 (2)	
Never Married	83.7 (41)	84.0 (21)	83.3 (20)	
MCQ total score (M, SD)	43.1 (13.0)	45.8 (11.9)	40.6 (13.7)	0.15
Cannabis Use Days (14 days prior to BL)	12.6 (2.0)	13.1 (1.4)	12.2 (2.4)	0.23
Cannabis Use Sessions (14 days prior to BL)	34.1 (16.4)	39.4 (18.6)	28.8 (12.0)	0.05

Note:

⁺ Mean (M) and standard deviation (SD) of subject-level median RTs.