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Dean, Andy
Moeller, Scott
Amir, Nader
et al.

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NO EFFECT OF ATTENTIONAL BIAS MODIFICATION TRAINING IN METHAMPHETAMINE USERS RECEIVING RESIDENTIAL TREATMENT

Andy C. Dean, Ph.D.[a,c], **Erika L. Nurmi, M.D., Ph.D.**[a], **Scott J. Moeller, Ph.D.**[d], **Nader Amir, Ph.D.**[e], **Michelle Rozenman, Ph.D.**[a], **Dara G. Ghahremani, Ph.D.**[a], **Maritza Johnson**[a], **Robert Berberyan**[a], **Gerhard Hellemann, Ph.D.**[a], **Ziwei Zhang**[a], and **Edythe D. London, Ph.D**[a,b,c]

[a]Department of Psychiatry and Biobehavioral Sciences, UCLA Semel Institute for Neuroscience, David Geffen School of Medicine, Los Angeles, CA, 90024, USA

[b]Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, Los Angeles, CA, 90024 USA

[c]Brain Research Institute, David Geffen School of Medicine, Los Angeles, CA, 90024, USA

[d]Department of Psychiatry, Stony Brook University School of Medicine, Stony Brook, NY 11794, USA

[e]Department of Psychology, San Diego State University, San Diego, CA 92120 USA

Abstract

Rationale: Attentional bias toward drug-related stimuli is a feature of drug addiction that is linked to craving and drug-seeking behavior.

Objectives/Method: An attentional bias modification (ABM) program was tested in 42 methamphetamine-dependent clients (DSM-IV criteria) receiving residential treatment for their drug use. Participants were randomly assigned to one of two groups (N = 21 each), receiving 12 sessions of either computerized ABM training (designed to train attention away from methamphetamine stimuli 100% of the time) or an attentional control condition (designed to train attention away from methamphetamine stimuli 50% of the time). Outcome measures included attentional bias to methamphetamine-related stimuli on a probe detection task, self-reported craving, and preferences to view methamphetamine-related images on a Simulated Drug-Choice Task. A subset of participants (N = 17) also underwent fMRI in a cue-induced craving paradigm.

Results: Poor split-half reliability was observed for the probe detection task. Using this task, attentional bias toward methamphetamine-related stimuli was greater after training than at baseline, irrespective of group ($p=0.037$). Spontaneous and cue-induced methamphetamine craving diminished with time ($ps<0.01$), but ABM training did not influence these effects (group by time interactions, $ps>0.05$). ABM training did not influence selection of methamphetamine-related pictures in the Simulated Drug Choice task ($p>0.05$). In the fMRI assessment, cue-induced

*Corresponding author: Edythe D. London, Ph.D., UCLA Semel Institute for Neuroscience and Human Behavior, 760 Westwood Plaza, Los Angeles, CA, United States of America 90095-1759, Tel: +1 310 825 5839; fax: +1 310 825 0812; elondon@mednet.ucla.edu.

activation in the ventromedial prefrontal cortex was reduced over time, without an effect of ABM training.

Conclusions: ABM training did not improve several clinically-relevant variables in treatment-seeking methamphetamine users. Additional research is needed to improve the measurement of attentional bias.

Keywords

stimulant; substance abuse; attentional bias; craving

1. INTRODUCTION

Despite the worldwide prevalence of Methamphetamine (MA) Use Disorder and substantial effort in medication development for treating the condition, there is no FDA-approved medication for this indication (Ballester, Valentine, & Sofuoglu, 2017; Substance Abuse and Mental Health Services Administration, 2013; UNODC, 2017). Behavioral approaches are therefore the mainstay of treatment. Yet improved therapeutic approaches are needed because dropout from treatment and relapse are common (Brecht & Herbeck, 2014; Brorson, Ajo Arnevik, Rand-Hendriksen, & Duckert, 2013; Chiang et al., 2006; Cook, Quinn, Heinzerling, & Shoptaw, 2017; McKetin et al., 2012).

Attentional bias toward drug-related stimuli is considered a key feature of drug addiction and likely presents a major barrier to the success of therapies for MA Use Disorder (Field & Cox, 2008). Attentional bias has been demonstrated in individuals with addictive disorders using several methods, including modified Stroop tasks [i.e., slower reaction time to identify ink color of drug-related vs. neutral words, indicating greater salience of the drug-related words (Cox, Fadardi, & Pothos, 2006)], modified probe detection tasks [i.e., faster response to a visual probe placed in the location of a drug-related stimulus rather than a neutral one (Field et al., 2007; T. Schoenmakers, Wiers, Jones, Bruce, & Jansen, 2007)], eye tracking [i.e., orienting visual gaze toward drug-related stimuli (Friese, Bargas-Avila, Hofmann, & Wiers, 2010)] and dual-task procedures [i.e., impaired performance during a decision-making task when simultaneously presented with drug-related stimuli (Waters & Green, 2003)]. Attentional bias for drug-related cues is thought to develop as a consequence of classical conditioning (Cox, Fadardi, Intriligator, & Klinger, 2014), in which drug-related cues (conditioned stimuli) are repeatedly paired with rewarding effects of drugs (unconditioned stimuli).

Attentional bias toward drug-related stimuli has been associated with clinically relevant variables, such as the quantity and frequency of drug use across different classes [e.g., alcohol, marijuana, heroin; for review, see (Field & Cox, 2008)]. Craving for addictive substances, particularly alcohol and nicotine, has been positively correlated with attentional bias [for review, see (Field, Munafo, & Franken, 2009)]. Increasing attentional bias by experimental manipulation also appears to increase craving for alcohol (Field et al., 2007). Attentional bias, measured through modified Stroop tasks, has been associated with treatment adherence and likelihood of relapse for individuals receiving treatment across a range of substances, including MA (Hester, Lee, Pennay, Nielsen, & Ferris, 2010), cocaine

(Carpenter, Schreiber, Church, & McDowell, 2006; DeVito, Kiluk, Nich, Mouratidis, & Carroll, 2018), alcohol (Cox, Hogan, Kristian, & Race, 2002; Diaz-Batanero, Dominguez-Salas, Moraleda, Fernandez-Calderon, & Lozano, 2018), cigarettes (Powell, Dawkins, West, Powell, & Pickering, 2010), and heroin (Marissen et al., 2006). However, negative findings regarding associations between attentional bias and treatment outcome have also been reported (Field, Mogg, Mann, Bennett, & Bradley, 2013; Kennedy, Gross, Ely, Drexler, & Kilts, 2014; Marhe, Luijten, van de Wetering, Smits, & Franken, 2013; Snelleman, Schoenmakers, & van de Mheen, 2015), and reviews of the literature conclude that attentional bias is not consistently related to outcome (Christiansen, Schoenmakers, & Field, 2015; Field, Marhe, & Franken, 2014).

Nonetheless, experimental therapeutic interventions have been designed to reduce attentional bias in order to improve treatment outcomes for addictions. A single session of training with a modified probe detection task reduced attentional bias in participants who were heavy alcohol drinkers (Field et al., 2007; Field & Eastwood, 2005; T. Schoenmakers et al., 2007) or cigarette smokers (Attwood, O'Sullivan, Leonards, Mackintosh, & Munafo, 2008; Field, Duka, Tyler, & Schoenmakers, 2009); but such studies showed limited effects on craving or consumption of alcohol or cigarettes (Christiansen et al., 2015). When multiple attention modification training sessions (typically 3 to 15) were administered using either probe detection tasks or Stroop paradigms, attentional bias to alcohol- and cigarette-related stimuli was reduced (Fadardi & Cox, 2009; Kerst & Waters, 2014; Lopes, Pires, & Bizarro, 2014; McGeary, Meadows, Amir, & Gibb, 2014; T. M. Schoenmakers et al., 2010), and there was also evidence of associated reductions in cue-induced craving (Kerst & Waters, 2014) and alcohol consumption (Fadardi & Cox, 2009; McGeary et al., 2014). Null findings for associations with craving and substance use, however, have also been reported (for review, see Christiansen et al., 2015). In individuals with Cocaine Use Disorder, five sessions of attentional bias training with a modified probe detection task did not significantly influence attentional bias, craving or cocaine use (Mayer et al., 2016).

Despite some evidence of benefit in individuals who misuse alcohol or smoke cigarettes, there has been no research on attentional bias modification (ABM) training in individuals with Methamphetamine Use Disorder. We therefore performed a 4-week (12 sessions) randomized control study of ABM in 42 participants who met DSM-IV criteria for Methamphetamine Dependence and presented for treatment at a residential facility (Cri Help, Inc.). Participants were randomly assigned to the active condition (ABM group) or an attentional control condition (control group) (N = 21 per group). Training was conducted using an established probe detection task procedure (Amir et al., 2009; MacLeod, Mathews, & Tata, 1986), in which MA-related and unrelated words were presented on a computer screen, followed by a probe requiring a response. In the ABM condition, the probe was always placed in the location of the MA-unrelated word, whereas in the control condition the probe replaced the MA-related word in half of trials and the unrelated word in the other half of the trials. Thus the ABM condition sought to always train attention away from MA-related stimuli. At baseline, post-training, and 1-month follow-up, participants were assessed on measures of self-reported MA craving, a pictorial probe detection task (using MA-related pictures rather than words) and the Simulated Drug Choice Task (Moeller et al., 2009). We hypothesized that, relative to the control group, participants in the ABM group would show

greater reductions in craving, attentional bias and choices to view methamphetamine-related images on the simulated drug choice task from baseline to the post-training measurements.

After the first 25 enrolled participants completed the study, functional magnetic resonance imaging (fMRI) was added to assess neural markers of potential changes in craving. The remaining participants (N = 17; 8 ABM and 9 control participants) were administered fMRI scans before and after training. In the scanner, they completed a cue-induced craving task in which they were presented with MA-related and neutral pictures and provided trial-by-trial self-reports of craving. Because activation in the striatum and ventromedial prefrontal (including orbitofrontal) cortex has been associated with exposure to drug-related cues (Chase, Eickhoff, Laird, & Hogarth, 2011; Kuhn & Gallinat, 2011), we hypothesized that ABM training would attenuate cue reactivity and lead to a greater reduction in these brain regions over time than the control condition.

2. METHODS AND MATERIALS

2.1 Participants (see Table 1)

The participants were clients at Cri-Help, Inc., a community-based residential drug treatment program that uses a combination of evidence-based practices, including cognitive behavioral therapy, 12-Step facilitation, motivational interviewing and group counseling. Upon admission to the residential program, potential participants received a flyer describing the study. Those who expressed interest met with a research staff member. Each participant received a thorough, lay-language explanation of the study and provided written informed consent, following the guidelines of the UCLA Office for Protection of Research. Security measures at Cri-Help ensure that drug use in the facility is very rare. Clients receive urine tests randomly and always after trips away from the facility.

All of the participants were fluent in English and were diagnosed with current MA Dependence, using DSM-IV criteria via the M.I.N.I. International Neuropsychiatric Interview (Sheehan et al., 1998). Most also met criteria for abuse or dependence of other substances, but all tested negative for drugs on urinalysis conducted randomly at Cri Help, Inc.; they also tested negative (Alpha Scientific Designs, Instant-View® test for amphetamine, benzodiazepine, cocaine, MA, morphine and cannabinoids) immediately preceding test sessions. The exclusion criteria were: (1) neurological disorders (e.g., multiple sclerosis, stroke, dementia); (2) head injury with loss of consciousness > 30 min; (3) untreated or unstable medical illness, including neuroendocrine, autoimmune, renal, hepatic, or active infectious disease that required immediate medical attention (stable HIV+ and hepatitis were allowed), (4) schizophrenia, psychotic disorder or bipolar I disorder; (5) any other illness, condition, or use of medications that, in the opinion of the PI and study physician, would preclude safe participation. The participants were randomized to one of two groups (N = 21 each) to receive either ABM or control training; they were not informed of their group assignment (i.e., single blind administration).

2.2 Procedure

To allow for cessation of acute withdrawal (Zorick et al., 2009), all participants were abstinent for at least 14 days before baseline testing, which consisted of the following: diagnostic interview with the M.I.N.I., IQ estimation using the Wechsler Test of Adult Reading (Wechsler, 2001), and completion of questionnaires collecting demographic information, medical history, drug use history, depressive symptoms (Beck Depression Scale, (Beck, 1967)) and symptoms of nicotine dependence [to ensure groups were balanced on degree of nicotine dependence; Fagerström Test for Nicotine Dependence, (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991)]. Participants also completed baseline testing with the pictorial probe detection task and the Simulated Drug Choice Task; a subset completed fMRI (see Outcome Measures section).

Prior to initiation of ABM or control training, participants each provided six words that they associated with their MA use, three neutral-valence words, and three positive-valence words. These words were then implemented in the ABM or Control conditions used for training (see below). Experts have recommended the use of personalized stimuli selected by each individual participant, rather than using of a common set of stimuli for all participants, because personalized stimuli may more directly target an individual's cognitive schemas (Hakamata et al., 2010; Hallion & Ruscio, 2011).

The computerized intervention consisted of four weeks of training on a modified probe detection test, three times per week (total of 12 sessions). The probe detection task is a variant of one used previously (Amir et al., 2009; MacLeod et al., 1986) for patients with affective disorders. Each session consisted of 360 trials. All trials began with a fixation cross ("+") presented in the center of the screen for 500 ms. Immediately upon disappearance of the fixation cross, two words (previously generated by the participant) appeared on the screen — one on top and the other below. Each pair consisted either of an MA-related word and an MA-unrelated word (66% of trials) or two MA-unrelated words (33% of trials). Two MA-related words were never shown together. After presentation of the words for 500 ms, a probe (the letter E or F) appeared in the location of one of the two words. Participants were instructed to identify the probe as an E or F by left- or right-clicking a computer mouse. The probe remained on the screen until a response was given, after which the next trial began. During each session, the combination of probe type (E/F), probe position (top/bottom) and word type (MA-related vs. positive or neutral MA-unrelated) was counterbalanced. For participants in the ABM group, the probe was always placed (100% of the trials) at the location of the MA-unrelated word if a MA-related word was displayed. For participants in the control group, the location of the probe appeared with equal frequency in the position of the MA-related word or the MA-unrelated word.

2.3 Behavioral Outcome Measures

Pictorial Probe Detection Task.—This task was similar to the probe detection task used for ABM training, but included 288 trials and the pairs of stimuli presented were MA-related pictures and neutral pictures rather than words. The task was administered at baseline, post-training and at one-month follow-up. The methamphetamine-related pictures were selected from a larger set of 188 pictures that were rated by two MA-dependent participants whose

data were not included in this study. The participants rated how “interesting” the pictures were on a 5-point scale range from not at all (0) to extremely (5). The 48 pictures with the highest average ratings were selected for the task.

MA-related pictures (48 total) were visually matched to the neutral pictures (48 total) by color and shape; each picture was shown three times during the task, once in each of three blocks of trials. As when the stimuli were words (see above), pictures were shown in pairs and the participant had to respond to the subsequent probe (identify it as an E or F with a mouse click) as quickly as possible. Unlike the paradigm in the ABM training task, here the probe was placed in the location of the MA-related and unrelated pictures with equal frequency.

The task was scored in two ways, both of which excluded incorrect trials (errors in identifying the E or F), trials with reaction times (RTs) ≤ 350 ms or ≥ 2 sec, and trials with extreme RTs (> or < 2 SDs from each subject’s mean RT). This excluded an average of 31.7 trials per administration (SD = 21.5). The first scoring method considered only trials with picture pairs consisting of an MA-related picture and a neutral picture (see MacLeod & Mathews, 1988). While counterbalancing for location on the screen (top or bottom), this scoring method subtracted the average reaction time when the probe replaced the MA-related picture from the average reaction time when the probe replaced the neutral picture. Higher scores reflected faster responding when the probe was in the location of MA-related vs. neutral pictures; higher scores are considered to reflect greater bias (see MacLeod & Mathews, 1988).

The second scoring method, measuring disengagement bias (Koster, Crombez, Verschuere, Van Damme, & Wiersema, 2006), examined trials in which MA-related and neutral pictures were paired, as well as trials where two neutral pictures were paired. This score subtracted the average reaction time when the probe replaced a neutral picture in a neutral/neutral pair from the average reaction time when the probe replaced a neutral picture in a neutral/MA-related pair (counterbalanced for location type). Higher scores are thought to reflect greater difficulty disengaging attention from MA-related vs. neutral stimuli (Koster et al., 2006).

Reliability of the pictorial probe detection task was very poor. When calculated for baseline, post-treatment and 1-month follow-up administrations, split-half reliability was low for the attentional bias index (as tabulated by MacLeod & Mathews, 1988) (Spearman-Brown coefficient range = −0.433 to 0.372) and disengagement bias index (Spearman-Brown coefficient range = −0.388 to 0.362). Similarly, when split-half reliability was calculated based on odd and even trials, rather than the first and second half of trials, poor reliability remained (Spearman-Brown coefficient range = −0.324 to 0.496).

Simulated Drug Choice Task.—Participants indicated their choice for viewing methamphetamine-related images in comparison to standardized pleasant, unpleasant, and neutral images. The latter three categories included images selected from the International Affective Image System (IAPS) (Lang, 2005): pleasant (e.g., smiling babies), unpleasant (e.g., mutilation), and neutral (e.g., household items) images. The methamphetamine-related images were selected from freely available image banks and online sources (and did not

overlap with those used in the visual dot probe task), and were matched to the IAPS images on size and ratio of human/non-human content. The drug-related images used in this task were originally designed for cocaine users (Moeller et al., 2009), but recently were adapted for methamphetamine users (Moeller et al., 2018).

On each trial, participants used continuous button-pressing to choose between two side-by-side images from the respective images categories (pleasant, unpleasant, neutral, methamphetamine). A choice enlarged the selected image to cover the screen, and participants could view that image for the 5000-msec trial duration by continued button pressing; 500 msec of non-response returned the side-by-side image display. After each trial, new images appeared. Each image category was represented an equal number of times throughout the task, and was displayed on the left or right side of the screen an equal number of times. The task was comprised of 70 trials (i.e., 7 repetitions of unique stimuli in each of 10 image category pairs). Button pressing (working) for images was a design feature to simulate drug-seeking.

Data were processed by summing the total number of button presses executed for each picture category across the entire task (Moeller et al., 2010; Moeller et al., 2009; Moeller et al., 2018). We then created a targeted, *a priori* methamphetamine-minus-pleasant (meth>pleasant) contrast score, which was used in the analyses. This meth>pleasant contrast has been the task variable that most consistently predicts clinical and biological outcomes and markers of severity in our studies (Moeller et al., 2010; Moeller et al., 2009; Moeller et al., 2018). More broadly, the direct comparison between the drug and positive reinforcer categories is consistent with drug-choice studies conducted in preclinical and clinical populations (Banks, Hutsell, Schwienteck, & Negus, 2015; Moeller & Stoops, 2015), which pit the choice for drugs against the choice for comparably valuable alternative reinforcers as a model of core addiction symptomatology (Ahmed, 2010; Goldstein & Volkow, 2011). The simulated drug choice task was administered at baseline, post-training and 1-month follow-up.

Spontaneous Craving.—Self-reported spontaneous MA craving (i.e., not cue-induced) was measured with the Brief Methamphetamine Craving Scale, which was adapted from the Brief Cocaine Craving Questionnaire (Sussner et al., 2006). The scale consists of 10 Likert-scale items and was administered prior to each training session, at post-training and at 1-month follow-up.

Cue-induced Craving Paradigm (during fMRI).—Immediately before and after the 12-session course of training, a subset of participants completed a cue-induced craving paradigm paired with fMRI. Participants viewed images of MA-related paraphernalia (e.g., pipes) and neutral images that were matched with the MA stimuli on particular features (see below). Each image was presented for 8s. Following image presentation, a mean of 3s elapsed (jittered delay across trials taken from an exponential distribution with a range of 0.5s to 6s and intervals of 0.2s), and then participants were prompted to rate their urge to use MA (“How much do you feel like using meth right now?”). Ratings were made on a Likert-type scale ranging from 1 (“not at all”) to 4 (“very much”), using the right hand with a four-button button box in the scanner. Participants had up to 3s to respond on each trial. After

making a button press, their choice was highlighted on the screen (0.4s), followed by presentation of a fixation cross for a mean duration of 3s (jittered delay across trials taken from an exponential distribution with range of 0.5s to 6s and intervals of 0.2s). Five such trials were administered in a practice session outside the scanner before the first session began to familiarize participants with the task. Eighty trials in four runs (20 trials per run) were administered per scanning session. The primary dependent variable from the task consisted of contrast scores between craving ratings for the MA vs. neutral cues (MA minus neutral; to control for generalized craving that was not stimuli-specific).

The images used in the task were downloaded from the Internet using Google Image Search, and did not overlap with other tasks in the study. MA-related images consisted of glass pipes, MA in crystallized or powered form, people smoking MA (without faces shown), or any combination of these. MA-related and neutral images were matched by shapes, color content, and brightness. Example neutral images included pencils, close-up views of snow, and crystal glass vases. Images were equal in size (1024×768 with 72 pixels/inch resolution). One-hundred sixty unique images (80 MA-related, 80 neutral) were used in the study; one set of 80 (40 MA and 40 neutral) was used for the scan before training and a second set of 80 was used after training. The two image sets were matched for content. Each image was viewed only once by each participant. Across participants, image sets were counterbalanced for appearance before and after training (i.e., a given image set appeared before training for one participant and after training for another), and trial sequences were pseudorandomized across participants.

The presentation and timing of all stimuli and response events were programmed using Matlab (Mathworks, Natick, MA) and the Psychtoolbox www.psychtoolbox.org on an Apple MacBook Pro laptop running Mac OSX 10.6.8 (Apple Computers, Cupertino, CA). During scanning, visual stimuli were presented on MRI-compatible goggles (Resonance Technologies, Van Nuys, CA).

2.4 MRI Data Acquisition

Imaging was performed using a 3-T Siemens AG (Erlangen, Germany) Prisma MRI scanner with a 32-channel head coil at the Ahmanson-Lovelace Brain Mapping Center at UCLA. Multiband echoplanar imaging (EPI) (Xu et al., 2013) was used to acquire functional T2*-weighted images during performance of the cue-induced craving task [multiband acceleration factor, 8; slice thickness, 2 mm; 72 slices; repetition time (TR), 0.8 s; echo time (TE), 37 ms; flip angle, 52°; field of view (FOV), 208 mm]. For registration purposes, a T2-weighted matched-bandwidth high-resolution anatomical scan (same slice prescription as EPI with TR, 5000 ms; TE, 60 ms) and a T1 magnetization-prepared rapid-acquisition gradient echo (MPRAGE) high resolution scan [slice thickness, 0.8 mm; 208 slices per slab; TR, 2400 s; TE, 2.24 ms; flip angle, 8°; matrix, 256 × 256; FOV, 256 mm; sagittal orientation] were acquired for each participant. The orientation for matched bandwidth and EPI scans was oblique axial in order to maximize full brain coverage and to optimize signal from ventral prefrontal regions.

2.5 Data Analysis

Behavioral data analysis.—Demographic differences between groups were evaluated using t-tests or Chi-square tests, as appropriate. Primary analyses were evaluated with the General Linear Mixed Model (GLMM), with separate GLMM models for each dependent variable (i.e., attentional bias, spontaneous craving and simulated drug choice). GLMM accounts for correlations due to repeated measurements, and automatically handles missing data such that incomplete data can be included in the model (e.g., missing one-month follow-up). In all models, the main effect of time, group and their interaction was tested, with the primary hypothesis that significant time by group interactions would reflect greater improvement in outcomes in the ABM group versus the control group after training than before training.

fMRI analyses.—Analysis of fMRI data was performed using the FSL (5.0.9) toolbox from the Oxford Centre for fMRI of the Brain (www.fmrib.ox.ac.uk/fsl). Image preprocessing included registration to compensate for head motion, skull-removal, spatial smoothing, and spatial registration to standard space (Montreal Neurological Institute (MNI) avg152 template). Whole-brain, voxel-wise statistical analyses were performed using a multi-stage approach to implement a mixed-effects model treating participants as a random effects variable. For all first level analyses, time-series statistical analysis was carried out using linear modeling with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001) after high-pass temporal filtering. Each of the two task conditions were modeled as separate regressors. Motion parameters were included as covariates of no interest to account for variance associated with residual motion. The contrast of interest included MA vs. neutral cues.

For each scanning session, first-level GLMM models were completed for each run to derive the contrast image for MA vs. neutral cues. These contrast images were then submitted to a second-level fixed effects analysis which combined the contrast images across scanning runs, resulting in a single contrast image per scanning session. To determine effects of ABM training (pre- vs. post-training scans by group), these session images were submitted to repeated measures ANOVAs (see below).

Non-parametric permutation testing (Nichols & Holmes, 2002) was used for all group-level analyses with the BROCCOLI toolbox (Eklund, Dufort, Villani, & Laconte, 2014) and RANDOMISE, FSL's tool for non-parametric inference (RANDOMISE, (Winkler, Ridgway, Webster, Smith, & Nichols, 2014)). Non-parametric approaches have been shown to more appropriately control the rate of false positives than cluster-based methods that rely on random field theory (Eklund, Nichols, & Knutsson, 2016). For evaluation of cue-induced activation in participants prior to undergoing the study treatment conditions, a one-sample t-test was performed using BROCCOLI on the contrast images of MA vs. neutral cues (using 5,000 permutations). The t-statistic image was thresholded using cluster-corrected statistics with a cluster-forming threshold of $t > 3.68$ (equivalent to $P<0.001$ for $N=17$). To examine main effects of group, time, and their interaction ($N=12$), a repeated measures ANOVA design was implemented in RANDOMISE using threshold-free cluster enhancement, which precluded the need for specifying an explicit a priori cluster-forming threshold (Smith &

Nichols, 2009). Post-hoc pair-wise comparisons (see Results section) to test the effect of time were performed with difference images (pre – post treatment) in BROCCOLI with a cluster-forming threshold of $t > 2.71$ (i.e., $P<0.01$). Anatomical locations of activations were identified using the Harvard-Oxford Probabilistic Atlas.

3. RESULTS

3.1 Group comparisons of demographic characteristics

The number of participants who dropped out of the study prior to completing training did not significantly differ between groups (ABM N = 1; Control N = 5; $p > 0.05$), resulting in 21 subjects in each group who completed all training sessions. Of these completers, the ABM and control groups were of similar demographic composition. The groups did not significantly differ (ps > 0.05) in age, gender, years of education, estimated IQ, years of mother's education, ethnicity, race, HIV status, self-ratings of depression, cigarette smoking (yes/no), comorbid substance use abuse/dependence diagnosis (see Table 1), nicotine dependence (smokers only), cigarettes per day (smokers only), days using alcohol per week, alcoholic drinks consumed per week, days using marijuana per week, grams of marijuana used per week, days using cocaine per week, grams of cocaine used per week, days using opiates per week and indices of MA use: days using MA per week, average grams consumed per day, age of onset of use, years of heavy use, days used in the month before treatment or preferred route of administration. The groups did not differ in baseline attentional bias (ps > 0.05) or the number of subjects who completed the one-month follow-up assessment (ABM N = 18; Control N = 16; $p > 0.05$).

3.2 Intercorrelation between Dependent Variables

Intercorrelations between dependent variables at baseline are shown in Table 2. The attentional bias index and the disengagement index were modestly correlated ($r = 0.37$, $p = 0.02$), but these two attentional bias measures were unrelated to the other dependent variables of interest (ps > 0.05). The Simulated Drug Choice task was positively correlated with spontaneous and cue-induced craving (ps < 0.05). These findings contribute to concerns regarding the ecological validity of the attentional bias measure and are considered in more detail in the Discussion section.

3.2 Effect of ABM on clinical variables

When attentional bias on the pictorial probe detection task was measured according to the method of MacLeod and Mathews (MacLeod & Mathews, 1988), there was no significant interaction between group and time ($F (1, 80.50) = 0.248$, $p > 0.05$), nor was there a main effect of group ($F (1, 98.55) = 0.574$, $p > 0.05$), but there was a significant effect of time ($F (1, 98.55) = 4.478$, $p = 0.037$) (see Figure 1); both groups (ABM and Control) exhibited greater attentional bias after training than before training. Posthoc analysis revealed that attentional bias measured at post-training was greater than when measured at baseline ($p = 0.001$); however, attentional bias at baseline and one-month follow-up did not differ significantly ($p > 0.05$).

When disengagement bias was measured on the pictorial probe detection task, there was not a significant interaction between group and time (F (1, 78.756) = 0.001, p > 0.05), nor were there significant effects of group (F (1, 97.159) = 0.100, p > 0.05) or time (F (1, 78.756) = 0.295, p > 0.05; see Figure 2).

On the Simulated Drug Choice Task (using the *a priori* meth>pleasant contrast score as the dependent variable), there was a main effect of group ($\chi^2(1) = 4.25$, p=0.039), showing fewer presses for methamphetamine-related images (versus pleasant images) in the ABM condition than in the control condition across the three study sessions. There was no main effect of time ($\chi^2(2) = 2.19$, p > 0.05) and no time × group interaction ($\chi^2(2) = 0.90$, p > 0.05; see Figure 3).

Spontaneous craving did not exhibit a significant interaction between group and time (F (1, 535.117) = 0.467, p > 0.05) or a main effect of group (F (1, 54.785) = 1.529, p > 0.05), but did reveal a significant effect of time (F (1, 535.117) = 33.525, p < 0.001), in which craving decreased for all participants (Figure 4).

On the cue-induced craving task in the fMRI scanner (using the *a priori* meth>neutral cue contrast score as the dependent variable), a significant effect of time was observed ($\chi^2(1) = 12.472$, p < 0.0005), with no main effect of group or interaction of group and time. Cue-induced craving decreased for both groups over time (Figure 5).

fMRI Results—Among the 17 participants (8 ABM, 9 control) who participated in the fMRI portion of the study, 12 had useable data for both the pre- and post-intervention scans (1 ABM and 3 control participants withdrew from the study; 1 control did not complete MRI scanning). Overall, 7 ABM and 5 control participants completed both pre- and post-intervention scans. Assessment of task results from the baseline scan across groups (N=17) showed greater activation in ventromedial PFC, right caudate, bilateral dorsolateral prefrontal cortex, superior frontal gyrus, bilateral posterior parietal cortex, and the precuneus when participants were presented with MA-related vs. neutral cues (Figure 6). There were no significant clusters of activation for the reverse contrast of neutral vs. MA-related cues.

In the evaluation of pre and post-intervention scans, no clusters survived a significance threshold of p < 0.05 for tests of main effects of group and time, nor for their interaction. Given small sample size and results indicating reduction of both spontaneous and cue-induced craving with time, we performed an exploratory post-hoc paired t-test analysis with time as the single independent variable, without group (thereby providing more degrees of freedom). At a cluster-determining threshold of t > 2.17 (i.e., p < 0.01), we observed reduction of activation over time in ventromedial PFC, including the orbitofrontal cortex (Supplementary Figure S1). No regions showed increases in activation over time, even at this statistical threshold.

4. DISCUSSION

The results indicate that ABM training did not lead to reductions in craving for MA or in attentional bias to MA-related stimuli. Although spontaneous craving and cue-induced craving for MA reduced over time with treatment, ABM training did not facilitate these

effects. Likewise, ABM training did not reduce attentional bias as measured by a pictorial probe detection task, nor did it affect responding on a Simulated Drug-Choice Task that has been linked with addiction severity (Moeller et al., 2009). These findings do not support the use of the current ABM method for facilitating treatment response in MA users.

The reason that ABM training was not beneficial in MA users is unclear. However, the data are consistent with a recent meta-analysis which showed that, across different drugs of abuse, cognitive bias modification strategies did not significantly improve post-test measures of addiction or craving (Cristea, Kok, & Cuijpers, 2016). This meta-analysis showed a moderate effect of cognitive bias modification on measures of attentional bias and a small effect on follow-up measures of drug use ($g = 0.18$), but follow-up measures were collected in fewer than half of the studies evaluated. Further consideration of the meta-analysis has also suggested that study type (experimental laboratory study or randomized clinical trial) and effectiveness in reducing attentional bias may influence clinical outcome (Cristea, Kok, & Cuijpers, 2018; Wiers, Boffo, & Field, 2018).

To the extent that attentional bias must be reduced to improve clinical outcome (Wiers et al., 2018), current results are discouraging as it relates to the measurement of attentional bias. Specifically, the pictorial probe detection task exhibited very poor split half reliability, such that different halves of the tests were often uncorrelated with one another (ps > 0.05). Further, attentional bias indices from the task were uncorrelated with baseline measures of craving and simulated drug use (see Table 2). This raises doubts regarding the utility of the measure as it relates to the clinical outcomes of interest. Although it is possible that the specific pictures used in the task contributed to poor reliability (e.g., MA pictures were selected based on how “interesting” they were to two MA users, which may not have been the optimum means to elicit bias), it is noteworthy that several other studies have documented poor reliability of probe detection tasks(Ataya et al., 2012; Field & Christiansen, 2012; Kappenman, Farrens, Luck, & Proudfit, 2014; Waechter, Nelson, Wright, Hyatt, & Oakman, 2014). This suggests that other measures of attentional bias are needed to effectively measure the construct. It is also possible that attentional bias changes on a moment-moment basis depending upon an individual’s motivational state, potentially complicating the measurement of attentional bias as a trait-like phenomenon (Field et al., 2014).

Current results showed that attentional bias on a traditional measure (MacLeod & Mathews, 1988) increased in both the ABM and Control groups over time. Given that spontaneous and cue-induced craving showed concomitant reductions over time, it does not appear that the increase in attentional bias was associated with other indications of poor treatment outcome. Although the increase in attentional bias may be a spurious finding given task unreliability, another study also showed an increase in attentional bias after ABM training (Field et al., 2007). As we did, investigators in that study used novel pictures to assess attentional bias after training (instead of the same stimuli used for training), and the authors proposed that novelty may have influenced bias. Other studies have likewise shown that reduced attentional bias on a training task does not generalize to attentional bias as measured by different stimuli (Field, Duka, et al., 2009; T. Schoenmakers et al., 2007; T. M. Schoenmakers et al., 2010). While this collectively casts doubt on the effectiveness of ABM

training to change attentional bias, additional research is needed to evaluate factors that may contribute to these findings, including construct measurement and specific methodological factors such as training implemented, participants evaluated and research setting of interest (e.g., treatment setting or preventive intervention).

MA users in the current study did not exhibit attentional bias toward MA stimuli at baseline (on average, their reaction times to probes in the location of MA pictures were slower than that for neutral pictures). Similar results were obtained in a study of individuals with cocaine use disorder (Mayer et al., 2016). It has been hypothesized that individuals with substance use disorders who are in treatment may consider drug-related stimuli aversive given the motivation to quit using drugs, potentially resulting in attentional bias *away* from drugs (Field et al., 2016). With the aforementioned reliability issues it is unclear whether or not this was the case for the current data, but it raises issues that should be considered for the measurement of attentional bias in treatment settings.

Given the ineffectiveness of ABM training on the outcomes assessed, it should be noted that all participants in our study received fairly comprehensive behavioral treatment (e.g., individual and group therapy, motivational interviewing) in a residential setting. It is therefore possible that no effect was observed for ABM training because effect sizes for this manipulation were minimal relative to that produced by the totality of the other treatment received. This would also help to explain why spontaneous and cue-induced craving reduced over time, independent of effects on attentional bias. It therefore remains to be seen whether ABM could affect positive change in the absence of other treatment.

It is also possible that the control condition implemented had a positive effect on clinical outcomes. In the control condition, participants still underwent attentional control training (they needed to focus and train attention over time), even if their attention was not always modified away from MA stimuli (50% of the time). Training in attentional control in general, irrespective of MA stimuli, may have contributed to positive effects observed on craving without group differences (see Wiers, Gladwin, Hofmann, Salemink, & Ridderinkhof, 2013).

In fMRI scanning of a subset of participants (n = 17), we observed activation in regions that would be expected for a cue-induced craving paradigm, including regions within the ventromedial prefrontal cortex, striatum, and lateral parietal cortex. Post-hoc analyses revealed that only a subset of these regions, mainly the ventromedial prefrontal cortex, showed a reduction in cue-induced activation over time in a smaller sample of N=12 that received both pre- and post-treatment scans. Nevertheless, these results are suggestive of reductions in craving with treatment occurring along with reductions in VMPFC activation. Due to small sample size, power to detect an interaction between group and time was likely limited; however, given the weak behavioral effects observed, there is little evidence to suggest that a neural effect of ABM would be found even with larger samples.

Limitations of this research should be noted. Poor reliability of the probe detection task leaves open the question of whether or not ABM training changed attentional bias. Also, because most participants remained in residential treatment well after the conclusion of the

study, the effect of ABM training on MA and other drug use could not be measured; these data are needed to appropriately assess clinical benefit. Nonetheless, results do not suggest promise in the use of ABM training, as currently implemented, to improve outcomes for MA users in treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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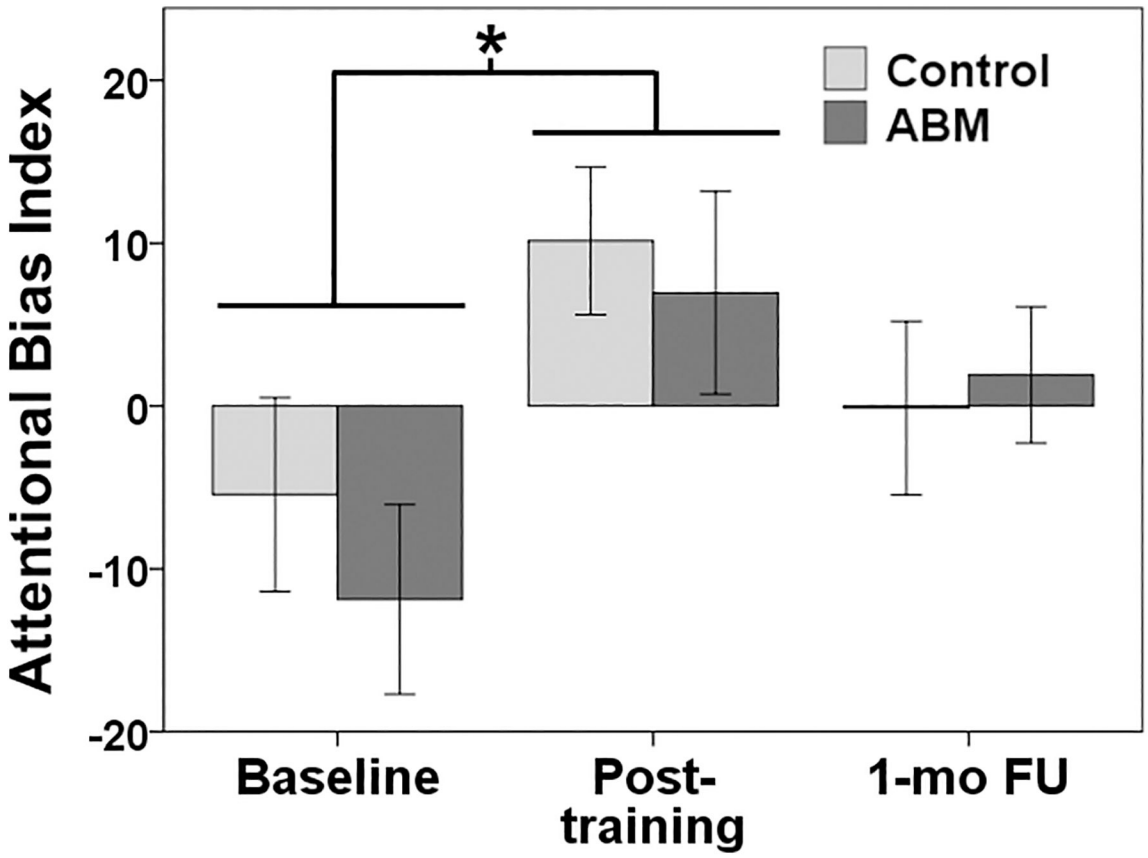

Figure 1. Attentional bias on the pictorial probe detection task as measured by MacLeod & Mathews (1988).

Higher scores reflect faster reaction times to detect the probe when replacing an MA-related versus a neutral picture, respectively (i.e., more bias). N = 21 per group for the baseline and post-training assessments. At one-month follow-up, ABM N = 16; Control N = 16. ***** = significant main effect of time ($p < 0.05$).

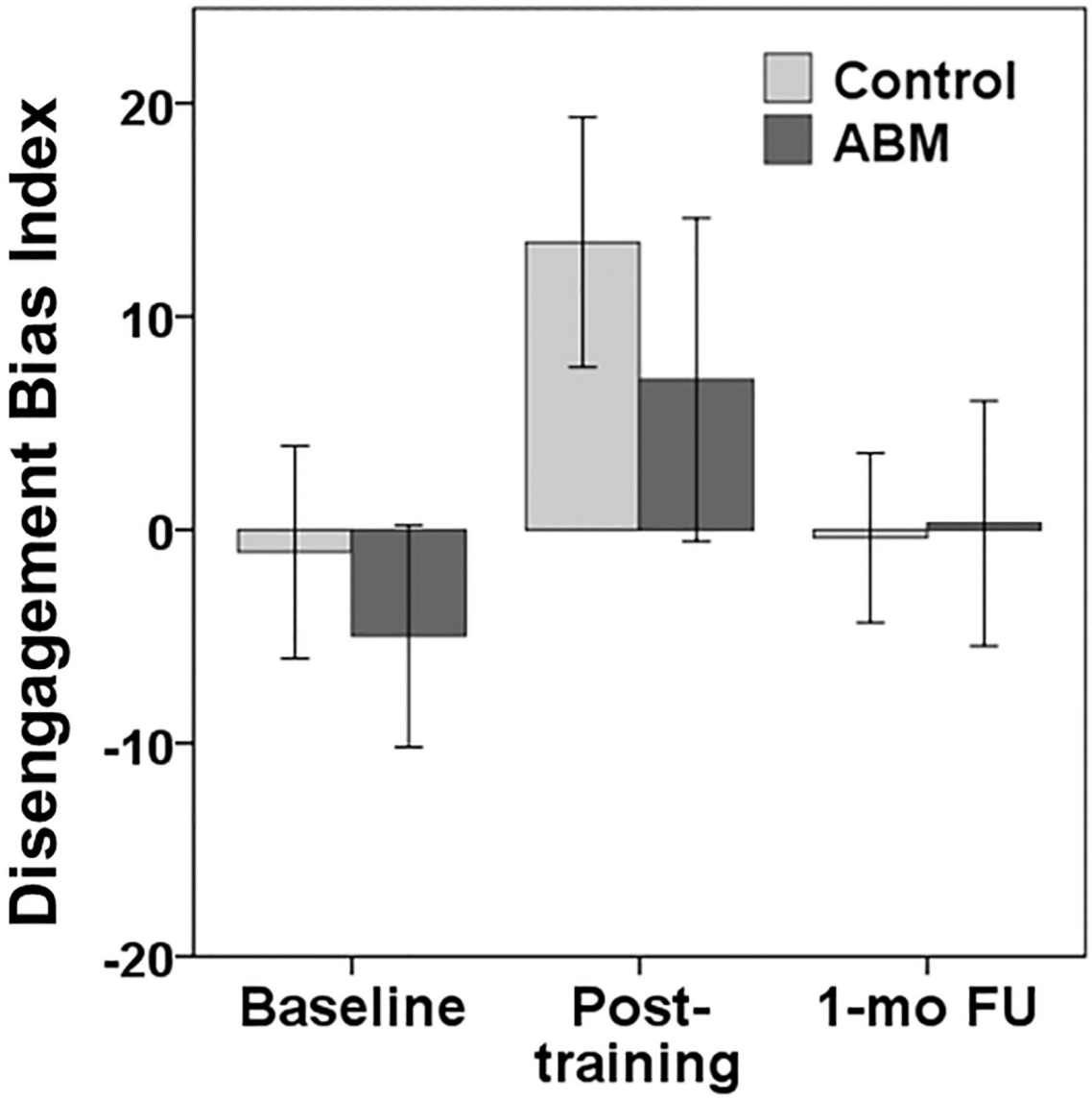

Figure 2. Disengagement bias on the pictorial probe detection task.

Higher scores reflect slower reaction times to detect the probe when replacing a neutral picture in an MA-related/neutral pair versus when replacing a neutral picture in a neutral/neutral pair, respectively (i.e., more difficulty disengaging from the MA stimulus). N = 21 per group for the baseline and post-training assessments. At one-month follow-up, ABM N = 16; Control N = 16. No significant differences were observered (ps > 0.05).

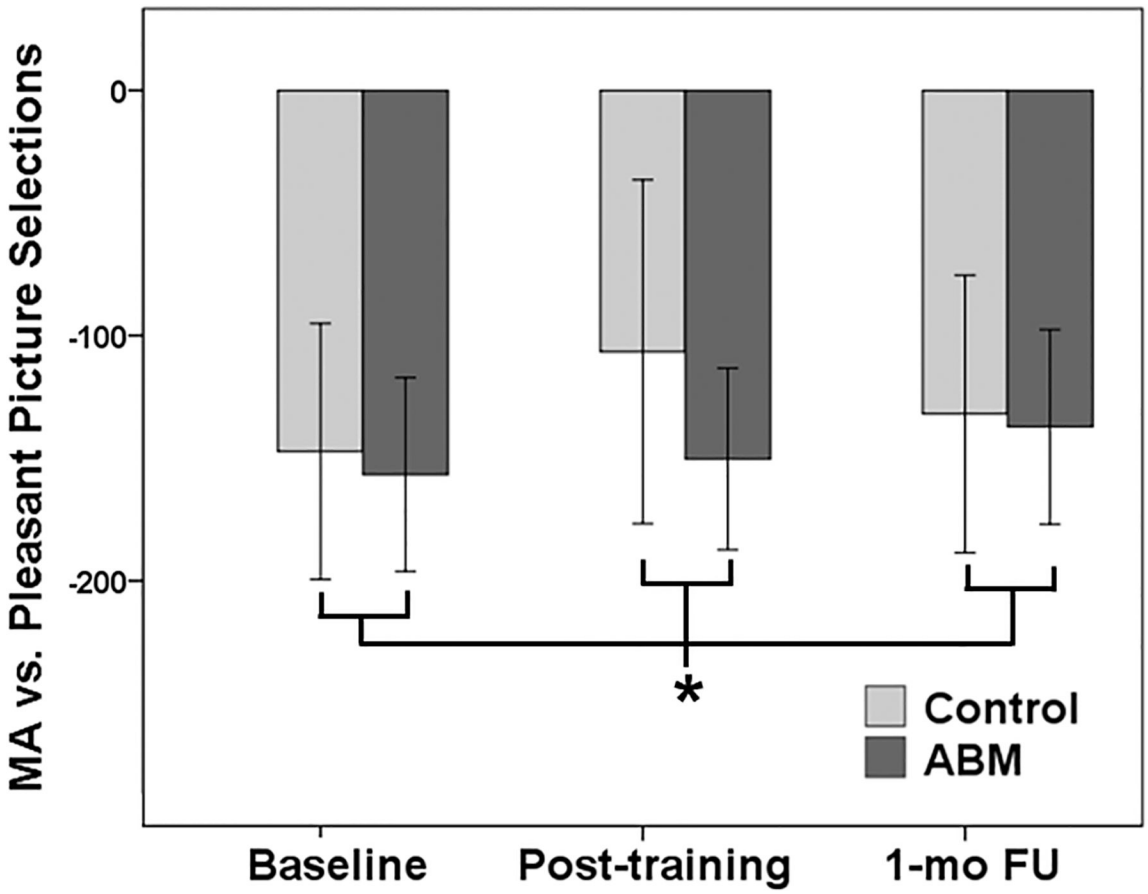

Figure 3. Simulated drug choice task.

Participants freely chose to view MA, neutral and pleasant pictures by pressing a key on a computer. Scores shown consist of the contrast between selection of MA pictures vs. pleasant pictures (overall, participants chose pleasant pictures more frequently than MA pictures so scores are negative). N = 21 per group for baseline. At post-training ABM N = 21, Control N = 20. At one-month follow-up, ABM N = 18; Control N = 15. In GLMM analysis, a significant main effect was obsevered for group ($p < 0.05$) independent of time.

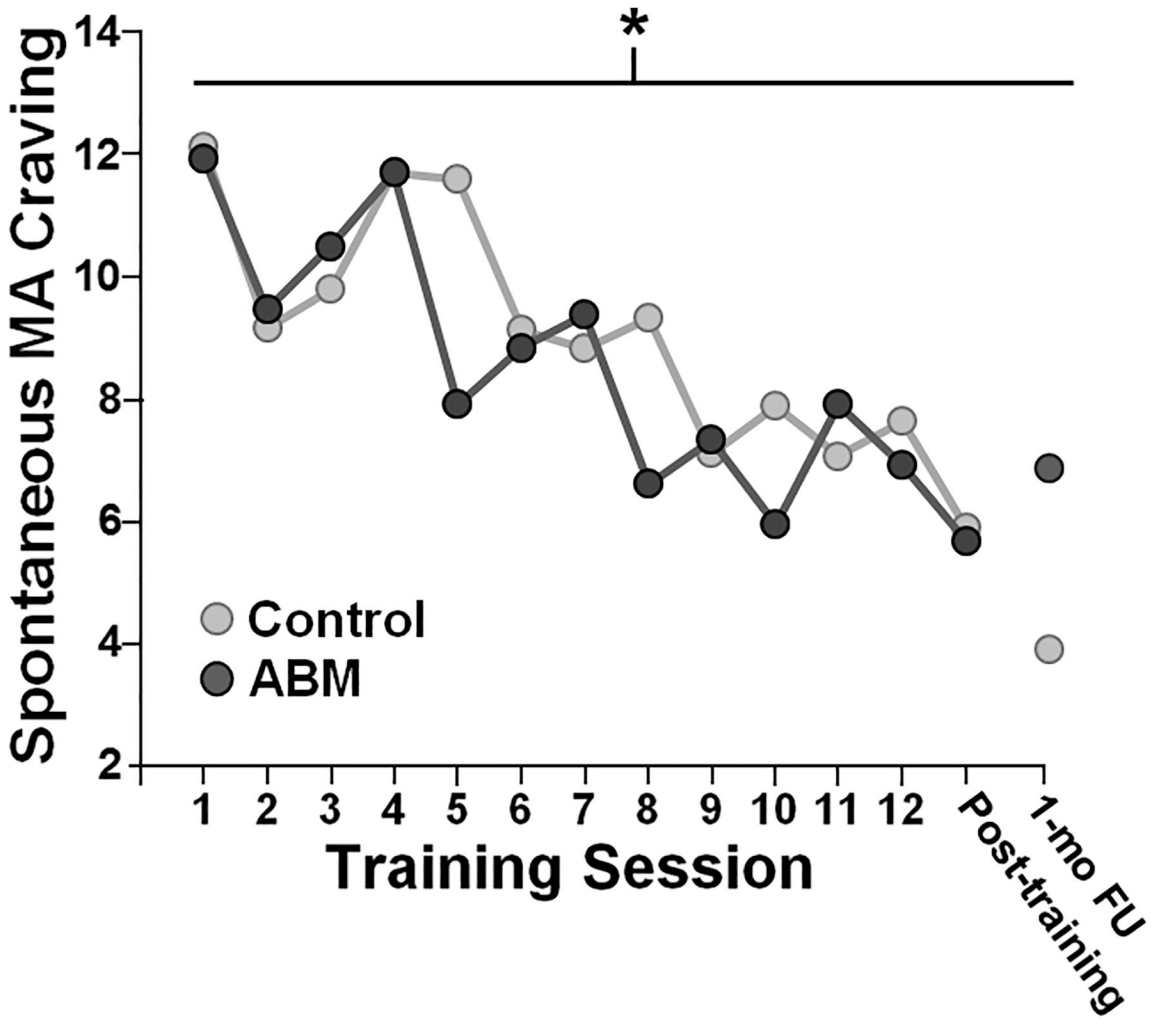

Figure 4. Self-reported spontaneous MA craving across study visits.

Craving was measured with an MA-adapted version of the Brief Cocaine Craving Questionnaire (Sussner et al., 2006). N = 21 per group for the baseline, session and post-training assessments. At one-month follow-up, ABM N = 18; Control N = 15. ***** = significant main effect of time ($p < 0.05$).

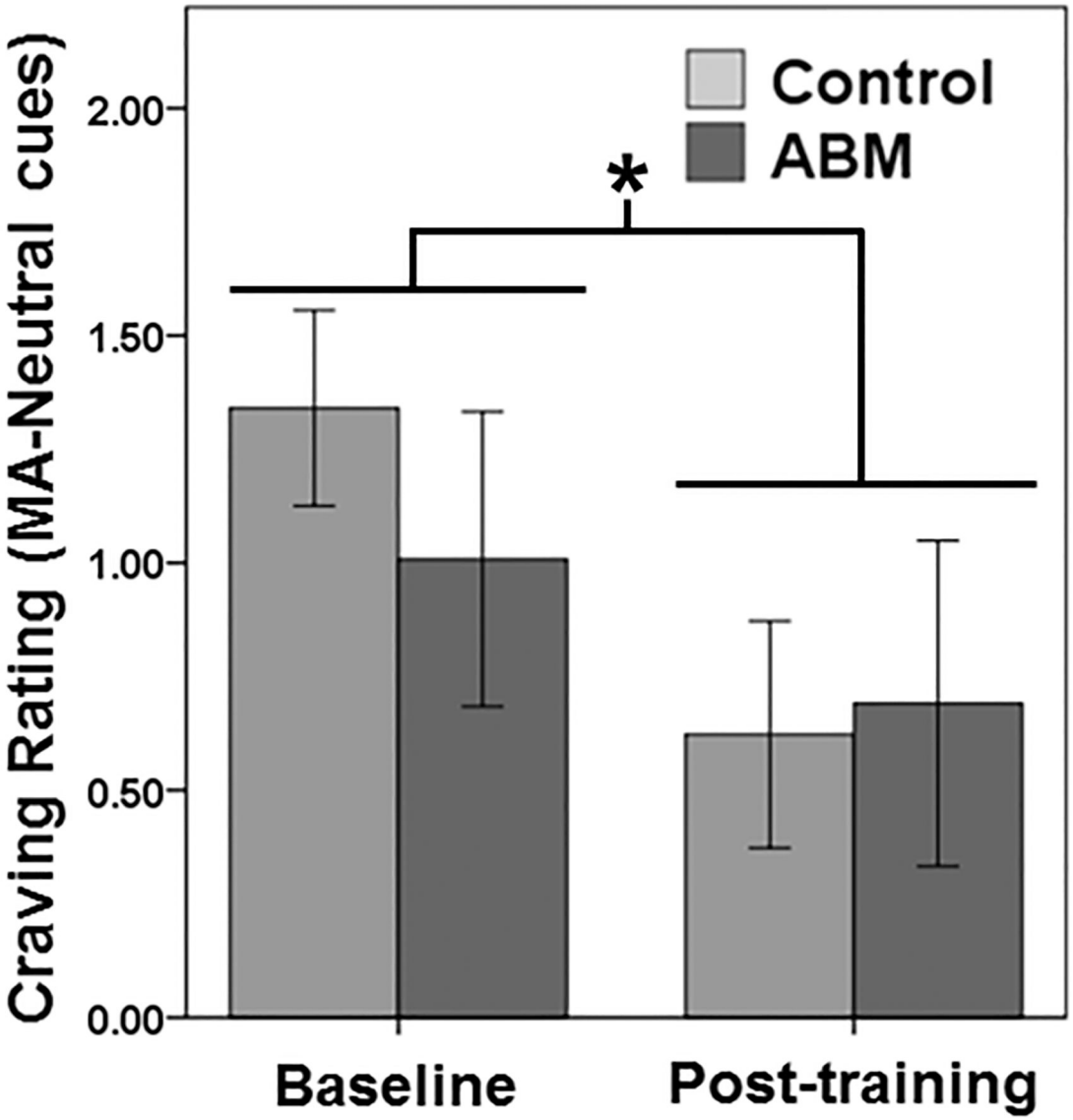

Figure 5. Cue-induced MA craving ratings.

Participants were shown MA-related and neutral pictures while undergoing fMRI and rated how much they felt "like using meth right now" on a 4-point Likert scale. Craving ratings on the Y axis reflect the subjects' average craving rating after viewing MA pictures following subtraction of their average craving ratings after viewing neutral pictures. ABM N = 7; Control N = 5. ***** = significant main effect of time ($p < 0.05$).

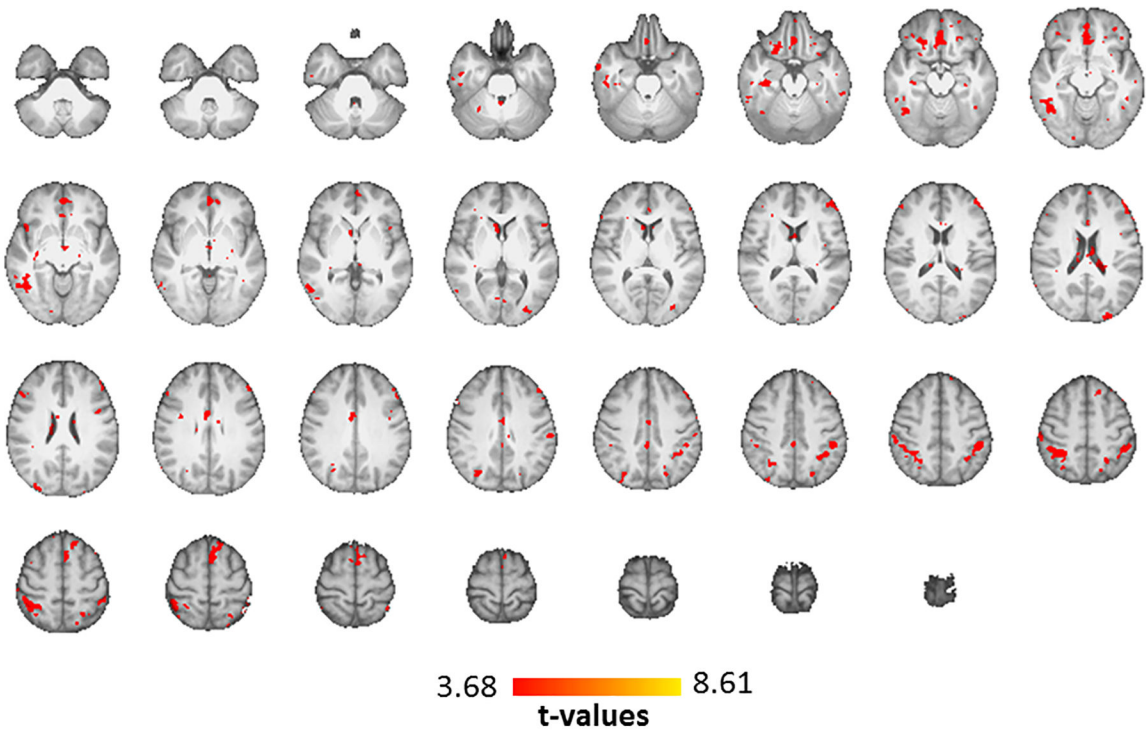

Figure 6. fMRI activation in response to MA vs. neutral cues during baseline testing across treatment groups (N=17).

Displayed are slices from the t-statistic image from a one-sample non-parametric t-test across voxel, overlaid on the mean anatomical image (MPRAGE) across participants. Results were cluster-corrected at a cluster-determining threshold of $t>3.68$ (i.e., $P<0.001$). Suprathreshold clusters included those within ventromedial prefrontal cortex, superior frontal gyrus, right caudate, and bilateral posterior parietal cortex. Images are in MNI space displayed in radiological orientation (right=left).

Table 1

Characteristics of Research Participants

	Control Participants *N*= 21	ABM Participants *N*= 21
Age (yrs.)	34.9 ± 9.1	35.7 ± 7.7
Male/Female	12/9	15/6
Education (yrs.)	12.5 ± 1.7	12.9 ± 2.7
Estimated Full Scale IQ	102.7 ± 12.0	100.6 ± 13.1
Mother's Education (yrs.)	12.3 ± 2.5	11.9 ± 3.1
Race:		
Caucasian	10	10
African Am.	1	2
Multiracial	6	5
Other	4	4
Ethnicity:		
Hispanic or Latino	10	11
Not Hispanic or Latino	11	10
Comorbid Diagnoses:		
Alcohol Abuse/Dependence	10	11
Marijuana Abuse/Dependence	11	9
Cocaine Abuse/Dependence	5	3
Opiate Abuse/Dependence	7	4
Other Abuse/Dependence	7	9
Affective Disorder	4	4
HIV+ Serostatus	7	11
Beck Depression Inventory Score	10.8 ± 8.3	10.4 ± 6.8
Cigarette Smoker (yes/no)	15/6	15/6
Fagerström Score (smokers only)	3.3 ± 1.9	3.1 ± 2.2
Cigarettes per Day (smokers only)	8.8 ± 4.8	8.8 ± 6.1
Days Use Alcohol per Week	3.1 ± 2.7	3.2 ± 2.5
Alcoholic Drinks per Week	17.0 ± 28.9	19.8 ± 22.0
Days Use Marijuana per Week	4.1 ± 3.1	3.0 ± 3.3
Marijuana Use per Week (grams)	4.2 ± 5.4	7.02 ± 13.9
Days Use Cocaine per Week	1.2 ± 2.4	1.3 ± 2.4
Cocaine Use per Week (grams)	3.0 ± 6.8	2.8 ± 7.0
Days Use Opiates per Week	1.8 ± 3.0	1.2 ± 2.5
MA Usage:		
Age of Onset	20.9 ± 7.8	20.9 ± 8.7
Days Use MA per Week	6.6 ± 1.0	6.2 ± 1.7
MA Use per Day (grams)	2.4 ± 1.9	1.4 ± 1.5
Pre-treatment MA Use, Days of 30	21.9 ± 10.1	23.2 ± 9.3
Years of Heavy MA Use	7.0 ± 5.1	10.8 ± 7.9
Preferred Method of MA Use		

	Control Participants ***N*= 21**	**ABM Participants** ***N*= 21**
Smoke	12	9
Injection	5	8
Other	4	4

Note: Values reflect mean ± SD. MA = methamphetamine. Heavy MA use defined as using MA three times per week or binging twice weekly. Full Scale IQ estimated with the Wechsler Test of Adult Reading (Wechsler, 2001). None of the characteristics in the table differed significantly between the groups (ps > 0.05).

Table 2

Intercorrelation between dependent variables

	ABI	DI	SDC	SC	CIC
Attentional bias index (ABI)	---				
Disengagement index (DI)	0.37*	---			
Simulated drug choice (SDC)	0.07	0.30	---		
Spontaneous craving (SC)	0.16	−0.13	0.31*	---	
Cue-induced craving (CIC)	0.04	0.16	0.60*	0.20	---

Note: Dependent measures were assessed at baseline. Values reflect Pearson correlation coefficients (r).

* = $p < 0.05$.