Supplementary Online Content

Manning V, Garfield JBB, Staiger PK, et al. Effect of cognitive bias modification on early relapse among adults undergoing inpatient alcohol withdrawal treatment: a randomized clinical trial. *JAMA Psychiatry*. Published online November 4, 2020. doi:10.1001/jamapsychiatry.2020.3446

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Detailed methods:

Measures

Demographic and clinical questionnaire: A baseline questionnaire collected participants' date of birth, self-identified gender, country of birth, Australian Aboriginal and/or Torres Strait Islander status, number of years of completed formal education, employment status, housing status, age of first alcoholic drink, age at which they felt alcohol use became problematic, number of previous withdrawal treatment episodes, other drugs of concern (if any), history of substance use disorders in first-degree relatives, and self-reported history of formally-diagnosed psychiatric disorders.

Approach bias: In the Alcohol Approach/Avoidance Task (AAT), used to measure approach bias, we used 20 images (10 of alcoholic beverages and 10 of non-alcoholic beverages), representing beverage types and brands most commonly consumed by participants in a previous pilot study[1]. We used an "irrelevant-feature" version of this task, in which participants were required to react to images using a joystick based on the orientation of a rectangular "frame" that surrounded each image, rather than reacting based on the image content. Specifically, they were instructed to push the joystick away from themselves if the frame was in landscape orientation, and pull the joystick towards themselves if the frame was in portrait orientation. Image size increased or decreased in response to pull and push movements, respectively, to simulate the picture expanding towards the participant, or receding into the distance. Each image was repeated twice (for a total of 40 trials). Half of alcohol pictures and half of non-alcohol pictures each appeared in a landscape frame and the other half appeared in a portrait frame. Trials were considered valid if the initial response was correct and the reaction time (RT) was 300-3000 ms. Median RT of valid trials were calculated separately for each of the 4 picture-response categories (i.e., alcohol-push, alcohol-pull, non-alcohol-push, non-alcohol pull), if at least 70% of trials (ie, at least 7 of the 10 trials for any picture-response category) were valid. If less than 70% of trials were valid, the median for that picture-response category was considered missing. For each picture type (alcohol; non-alcohol), the median RT for pull responses was subtracted from the median RT for push responses to quantify approach bias.

Single-item craving ratings: Immediately before and after each session, participants were asked to rate "How strong is your craving for alcohol right now?" on a visual analogue scale (VAS) anchored with "not at all" and "extremely" at the left and right ends, respectively. VAS markings were converted to 0-100 scores.

Subjective task ratings: Following the final session, participants were asked to rate the training task in response to 3 items: "I found the task improved my attention", "I found the task decreased my craving for alcohol" and "I found the task interesting". Ratings options were "strongly disagree", "disagree", "unsure", "agree", and "strongly agree".

Intervention

Images used in the CBM task were representative of beverage types consumed by participants in previous pilot studies, and differed from those used in the assessment-AAT. Incorrect responses caused a red 'X' to be displayed, and participants were required to repeat the trial.

Statistical analysis

To calculate internal consistency of the AAT, we separately calculated Cronbach's alpha for the alcohol approach bias items and non-alcohol approach bias items, following the method reported by Kersbergen, Woud, and Field[2]. Thus, we calculated difference scores between each nth "push alcohol" trial and each nth "pull alcohol" trial, deriving 10 difference scores for alcohol images. The same process was used to derive 10 difference scores for non-alcohol images. Bootstrapping was used to calculate 95% confidence intervals for both Cronbach's alpha values.

Craving VAS scores were analysed using a linear mixed model which tested the effects of timing (pre-session vs. post-session), session (1-4), and group, as well as all 2-way and 3-way interactions between these variables. Examination of residuals plots of craving VAS ratings suggested that the assumption of homogeneity of variance was violated, so these scores were subject to a logit transformation [$\log((x + 0.5)/(100 - x + 0.5))$]

before analysis (although we display raw scores in eTable 2 for ease of interpretation). Logistic regression was used for preliminary tests of whether post-training craving ratings mediated the effect of CBM on abstinence at follow-up.

Subjective task ratings were converted to numerical values ("strongly disagree" = 1; "disagree" = 2; "unsure" = 3; "agree" = 4; "strongly agree" = 5) and compared between groups with t-tests. We conducted exploratory analyses examining whether gender, age, and Severity of Alcohol Dependence Questionnaire (SADQ) score moderated the effect of CBM, as well as a site-stratified analysis to test whether treatment site moderated this effect. For these analyses, we conducted logistic regressions with treatment condition, the moderator variable, and the condition x moderator interaction term included as predictors of abstinence.

eResults. Detailed Results

Recruitment: A breakdown of the number of participants randomized to each group at each recruitment site is shown in eTable 1.

eTable 1. Number of participants recruited at each site.

Site	Sham	CBM	Total
1	69	69	138
2	34	30	64
3	21	18	39
4	29	30	59

Sites 1, 2, and 4 were withdrawal units connected to public hospital services. Site 3 was a withdrawal unit run by an addiction treatment non-government organization that receives public funding.

AAT internal consistency: For alcohol approach bias, Cronbach's alpha was .35 (95% CI: .19-.50). For non-alcohol approach bias, alpha was .34 (95% CI: .20-.49).

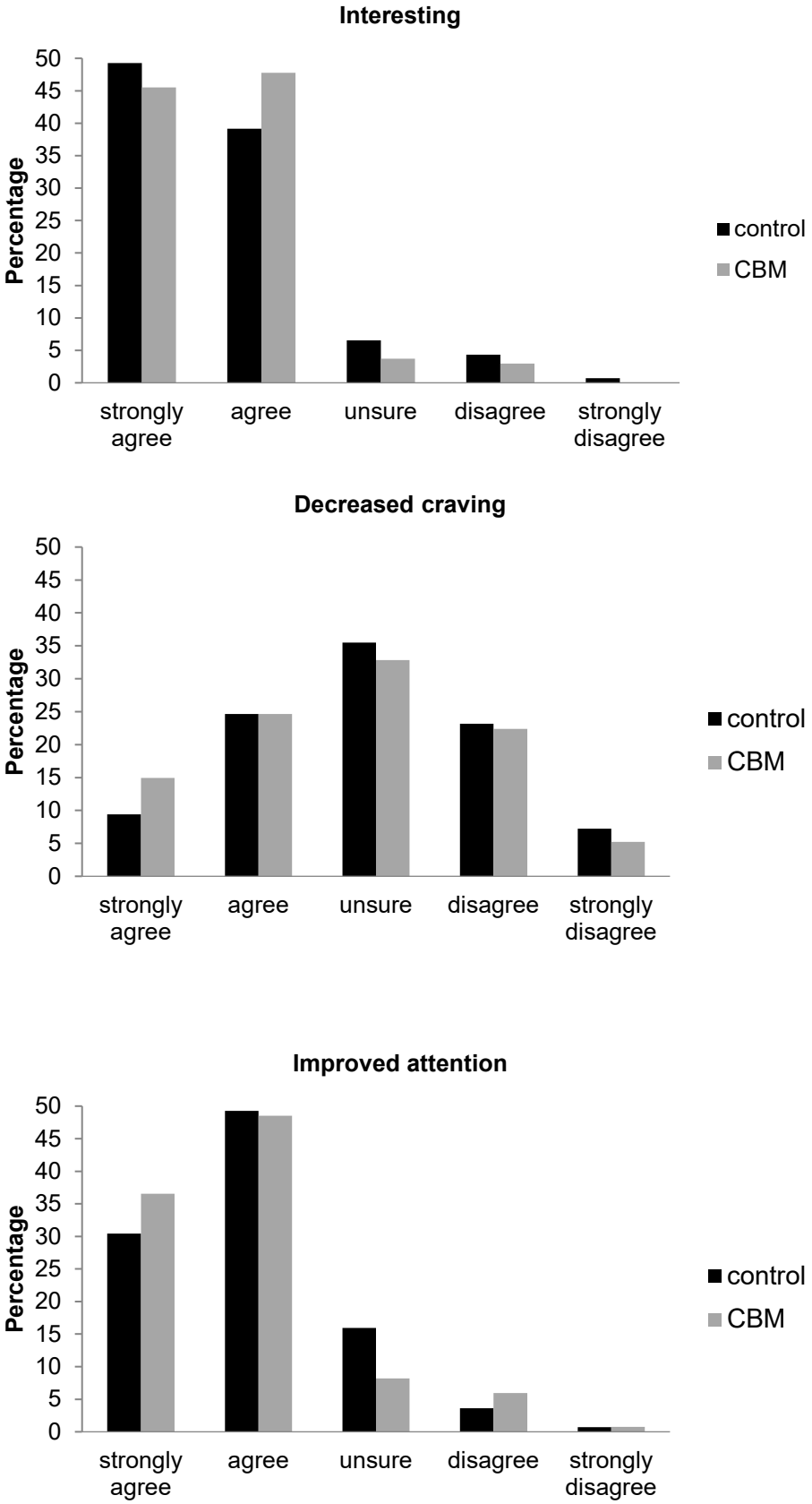
Craving VAS ratings: Raw (untransformed) ratings of craving intensity before and after each session are shown in eTable 2. Analyses of logit-transformed ratings found no significant main effects of group ($F(1, 294)=0.08$, $p=.78$) or timing ($F(1, 1084)=0.04$, $p=.84$), but there was a main effect of session ($F(3, 800)=34.11$, $p<.001$), showing a decrease in craving across sessions. All pairwise comparisons between session scores (averaged across timing and group) were significant (all $p<.003$), suggesting that there was a significant decline in craving between each day of training. This change between sessions did not interact with group ($F(3, 800)=0.87$, $p=.46$) or timing ($F(3, 1085)=0.44$, $p=.73$). Nevertheless, there was a significant group x timing interaction ($F(1, 1084)=4.78$, $p=.03$). Averaged across sessions, there was a non-significant tendency for logit-transformed craving ratings to increase in controls between the pre- and post-session rating ($p=.09$), but decrease significantly in the CBM group ($p=.049$). This finding allays concerns that exposing alcohol withdrawal patients to alcohol stimuli in CBM sessions may be unsafe, in terms of triggering cravings. The 3-way interaction between group, timing, and session, was non-significant ($F(3, 1085)=0.84$, $p=.47$).

In a logistic regression analysis including both group and logit-transformed post-session 4 craving ratings as predictors, both variables significantly predicted abstinence. Lower cravings predicted higher odds of abstinence (odds ratio=0.85, 95% CI: 0.74-0.98, $p=.03$), while CBM again predicted abstinence (odds ratio=1.80, 95% CI: 1.07-3.01, $p=.03$). However, in a separate analysis, group did not predict session 4 post-session craving ($F(1,241)=0.23$, $p=.64$), suggesting that this craving rating could not have mediated the effect of CBM on abstinence. Thus we did not proceed to path analyses to further examine mediation.

eTable 2. Mean (and SD) visual analogue scale ratings of craving before and after each training session.

	Pre-training		Post-training	
Session	control	CBM	control	CBM
1	33.02 (27.63)	31.49 (26.61)	35.59 (30.58)	29.86 (27.83)
2	27.04 (25.47)	26.38 (23.01)	30.18 (27.59)	26.20 (24.77)
3	25.45 (27.56)	22.70 (23.47)	25.54 (27.63)	22.75 (24.38)
4	21.20 (26.64)	19.50 (23.18)	21.04 (25.87)	20.02 (25.24)

Task ratings: Participants' subjective ratings of the task are shown in eFigure 1. Task ratings were completed by 272 participants (138 sham, 134 CBM). As shown, a large majority of participants either "agreed" or "strongly agreed" that the task was interesting and that it improved their attention, while opinions on whether it reduced their craving were more evenly distributed across response options. There were no significant differences between groups on any of these ratings ("interesting" $t(270)=-0.42$, $p=.674$; "craving" ($t(270)=-1.20$, $p=.233$; "attention": $t(270)=0.89$, $p=.373$).



eFigure. Proportion of participants endorsing each rating option: "I found the task interesting" (top), "the task decreased my craving for alcohol (middle), and "the task improved my attention" (bottom).

Moderation of CBM's clinical effect: In a logistic regression analysis of the primary outcome which was stratified by site, we found no evidence for any main effect of site on abstinence rates (p=.92) or any site x group interaction (p=.47). A significant main effect of group was again detected (p=.04). Thus, there was no evidence that the efficacy of CBM was moderated by differences between sites (e.g., in terms of the therapeutic programme/services they provided or the "types" of clients they admitted).

To test whether gender moderated the effect of CBM, we conducted 2 sets of analyses, since one participant reported non-binary gender. The first set of analyses analysed males vs. other (i.e., female and non-binary) and found no main effect of gender (odds ratio=1.02, 95% CI: 0.53-1.99, p=.94) or interaction between condition and gender (p=.84). The second set of analyses analysed females vs. other (i.e., male and non-binary) and again found no main effect of gender (odds ratio=0.96, 95% CI: 0.49-1.87, p=.90) or interaction between condition and gender (p=.95). For age, we also found no significant main effect (odds ratio=0.99, 95% CI: 0.96-1.02, p=.69) or interaction with condition (p=.97). Severity of Alcohol Dependence Questionnaire (SADQ) scores also did not significantly predict abstinence (odds ratio=0.98, 95% CI: 0.95-1.01, p=.16) or interact with condition (p=.14).

eReferences

1. Manning V, Staiger PK, Hall K, Garfield JBB, Flaks G, Leung D, Hughes LK, Lum JAG, Lubman DI, Verdejo-Garcia A. Cognitive Bias Modification Training During Inpatient Alcohol Detoxification Reduces Early Relapse: A Randomized Controlled Trial. *Alcohol Clin Exp Res.* 2016;40(9):2011-2019.

2. Kersbergen I, Woud ML, Field M. The validity of different measures of automatic alcohol action tendencies. *Psychol Addict Behav.* 2015;29(1):225-230.

