

Neural and Behavioral Effects of Cognitive Bias Modification (CBM)
NCT04430543
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Study Protocol and Analytic Plan-

Participants and recruitment- Forty heavy/at-risk drinkers (ages 18-34) who report an interest in changing their drinking behavior will be recruited for this proposed project. “Interest” will be operationalized as an affirmative answer on an item adapted (for past-month) from the CAGE questionnaire: “In the past month, have you felt you should cut down or stop drinking?” (Mayfield, McLeod, & Hall, 1974). Heavy/at-risk drinking will be defined in terms of consumption (7+/14+ drinks per week and/or 3+/4+ drinks on one occasion over the past week for women and men, respectively; USDHHS, 2005) and score on the Alcohol Use Disorders Identification Test (AUDIT score of 8-19; Babor, Higgins-Biddle, Saunders, & Monteiro, 2001). A score between 8-19 on the AUDIT is indicative of heavy use while scores 20 and above are indicative of a more severe alcohol use disorder (i.e., “dependence”, DSM-IV; APA, 2013; APA, 2000). Participants will be recruited through online advertisements on Craigslist, social media websites, and “Quickie Job Board” listings on student websites as well as via flyers in community and student health centers.

Procedures- If eligible based on online screener, participants will be further informed about study procedures and, if interested, will discuss availability and schedule their baseline appointment. At this time participants will be told they must refrain from using alcohol for at least 12 hours prior to their appointment. Participants will then be informed of the risks and benefits of the study. The researcher will obtain study consent. Baseline assessments will be administered, including self-report assessments about alcohol use, drug use, consequences, and alcohol craving. Participants will complete the baseline fMRI scan, which involves administration of two versions of an alcohol cue reactivity (CR) task, each described below. Following this baseline scan, participants will complete a brief web-based intervention for alcohol use and will subsequently be randomized to either cognitive bias modification (CBM) or sham training. They will complete the first session of either CBM or sham training after randomization as well as an additional 4 CBM/sham sessions at home (via web) over one week following baseline (schedule: CBM training on days 1, 2, 4, and 6 following baseline). To maximize completion rates, participants will be financially compensated for each training session completed as instructed. Participants will return to the

lab one-week following their baseline appointment. At follow-up assessment, participants will complete all baseline assessment measures in addition to a second fMRI session consisting of the same CR tasks. Finally, participants will be emailed a link to a web-based survey at 1- and 6-months following baseline to assess drinking behavior.

Baseline and Follow-up Measures- The *AUDIT* (Babor et al., 2001) will measure alcohol use and consequences at all 4 time points. The Desire for Alcohol Questionnaire (DAQ; Love, James, & Willner, 1998) will assess alcohol craving. Both CR tasks administered in the scanner will consist of a block design. The first alcohol CR task consists of two types of blocks—1) alcohol and 2) neutral beverage (i.e., soft drinks, juice, water). The second task, the cued-CR task, involves 3 blocks utilizing the same images as the alcohol-CR task. Subjects will receive instructions regarding their reaction to the photos.

CBM training tasks- Participants will undergo a total of 5 CBM or sham training sessions (*1 baseline; 4 web*) of about 15 minutes each (400 trials). Training tasks will be similar to an alcohol approach avoidance task (AAT) in that they will involve moving their mouse forward to simulate an avoidance/push response and backward to simulate an approach/pull response in response to alcohol and neutral stimuli depending on *photograph* orientation.

Neuroimaging Procedures- Scanning will take place using a research-dedicated Siemens 3T MRI scanner at Boston University's Rajen Kilachand Center for Integrated Life Sciences and Engineering (CILSE), using a 32-channel head coil. For each MRI session we will acquire: 1] a T1-weighted 3D anatomical of the entire brain (1 mm isotropic), 2] a T2-weighted structural in-plane for EPI alignment, 3] fMRI runs to measure BOLD activity during the experimental task. BOLD activity will be measured using single-shot, T2*-weighted echo-planar imaging. Acquisition will be whole-brain, with a voxel size of 2 mm³ (TR 2 s, TE 27 ms; flip angle 80°; FOV 192 x 192 mm). Behavioral responses will be made using a MR-compatible button box.

Power Analyses and Sample Size- In this initial phase of research, 40 heavy/at-risk drinkers will be recruited. This sample size will provide power to identify statistically significant differences in neurocognitive responses only if large effects are observed. However, this initial study will provide

preliminary data to enable effect size estimates to form the basis of a larger scale project (i.e., at the postdoctoral level). Previous studies evaluating changes in BOLD CR (Wiers et al., 2015a; Wiers et al., 2015b; Vollstädt-Klein et al., 2011) have used similar sample sizes. These studies also recognize that future research utilizing larger sample sizes would be necessary to confirm findings.

Missing Data- Testing the primary hypotheses will involve data collected at baseline and the one-week follow-up while testing secondary hypotheses will involve data collected at up to 3 time points. Attrition rates will be minimized by the compensation schedule detailed above. Previous studies have shown motivation to change is negatively associated with attrition in web-based intervention studies of heavy drinkers (Postel et al., 2011). The fact that participants are reportedly interested in changing their drinking behavior as well as the short duration between baseline and follow-up testing (1 week) are likely to enhance follow-up rates. Finally, multiple studies with young adult hazardous drinkers that have established effective follow-up procedures have been conducted in the primary researcher's lab. It is recognized that there is the potential for some individual data to be lost given complications with scanning (e.g., excessive movement). *All efforts will be made to minimize the risk of participant data being lost due to such complications. However, should data be compromised, additional participants will not be recruited.* Behavioral outcome data will be analyzed with an intent to treat method in line with the aims of the overall study design.

Analyses- Preliminary analyses will be conducted to ensure no outliers exist for any of the measures and to ensure there are no significant differences between groups on baseline variables. In the event that significant outliers or baseline differences are discovered, separate analyses will be conducted—individuals will be stratified based on the variables in which outliers/baseline differences occur.

Preprocessing and modeling of the fMRI data will be carried out using SPM12. Whole brain analysis will be conducted at a voxel-wise $p < .01$, using the cluster size method to correct for multiple comparisons at $p < .01$. Data analysis will also employ region of interest (ROI) analysis. Predefined ROIs include the bilateral amygdala, nucleus accumbens (NAcc), and dorsolateral and medial prefrontal cortex (dlPFC and mPFC). Anatomical ROIs will be generated using the Wake Forest University (WFU) Pickatlas automatic

anatomical labeling tool (Maldjian, Laurienti, Kraft, & Burdette, 2003) available for SPM. The analytic plan for testing study hypotheses are as follows: Primary Aim 1—For the alcohol CR task, two within subject contrasts will be calculated—1] alcohol CR > neutral CR pre-CBM/sham and 2] (alcohol CR > neutral CR) pre-CBM/sham – (alcohol CR > neutral CR) post-CBM/sham—in pre-defined ROIs. Primary Aim 2—as with the alcohol CR task, the within subject contrasts will be 1] INDULGE CR > INHIBIT CR pre-CBM/sham and 2] (INDULGE CR > INHIBIT CR) pre-CBM/sham – (INDULGE CR > INHIBIT CR) post-CBM/sham. Similar within subject contrasts will be explored for INHIBIT CR and INHIBIT NEUTRAL CR as a control. T-tests will be used to compare within subject contrasts for each task as well as to compare between-group contrasts (i.e., alcohol CR and INHIBIT CR pre-and post- CBM/sham). Secondary Aim: Correlations will be run to determine whether BL BOLD activity in each ROI significantly correlate with behavioral measures for both BL and 1-week follow-up. For significant correlations, pre- and post-CBM/sham difference scores will be calculated for behavioral measures and then correlated with significant BOLD contrasts representing change in neural activity.