Supplemental Information

SUPPLEMENTAL METHODS

Inclusion/Exclusion Criteria

All individuals were screened with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; [1]), as the SCID for DSM-V was not yet available at the initiation of these experiments.

For Experiment 1, inclusion criteria required that participants 1) meet DSM-IV criteria for Cocaine Dependence; 2) be aged 21-55 years; 3) not currently taking any psychoactive medications; and 4) have a negative medical history for seizures. Exclusion criteria included 1) current use of prescription or illicit psychoactive drugs other than cocaine and marijuana; 2) DSM-IV current or past substance dependence other than cocaine; 3) smoking >1 pack of cigarettes per day; 4) current breath alcohol concentration >0.002 on any experimental visit; 5) a lifetime history of head injury; 6) a history of seizures or migraine headaches (as TMS may exacerbate these conditions); 7) ferromagnetic implants and other contraindications to the high-field MRI environment (e.g. claustrophobia); and 8) pregnancy (determined through urinalysis). Inclusion criteria for Experiment 2 was similar to Experiment 1 except required that individuals meet DSM-IV criteria for Alcohol Dependence, not Cocaine Dependence. Exclusion criteria were also similar to Experiment 1 except included current use of prescription or illicit psychoactive drugs other than marijuana, and any DSM-IV current or past substance dependence criteria other than alcohol.
Neuroimaging Preprocessing

MRI data were preprocessed using SPM12 (Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB 7.14 (MathWorks, Inc., Natick, MA). MR Images were first converted from DICOM format to 4D NIfTI files and motion corrected (Realign: 6 parameter rigid-body realignment to first image in each timeseries using a least-squares approach). Normalization parameters, bias correction and anatomical tissue maps were determined simultaneously, using the Segment toolbox. Individual anatomical images were stripped of their skulls by masking the bias-corrected image with the combined tissue masks of grey matter, white matter, and CSF. The functional images derived from realignment were coregistered, through the mean image, to the skull-stripped anatomical image (Coregister: Estimate, using normalized mutual information). Coregistered images were then normalized (Normalize: Write) to MNI template space with the nonlinear warps derived from the Segment tool. Finally, functional images were masked (to remove the skull) and smoothed (8mm FWHM Gaussian kernel) to facilitate subsequent between-subject analysis. Data analyses were conducted on a total of 49 participants [30 males; mean(SD) age = 34(11) years; range 21-54 years; see Table 1 for detailed demographics].

Active Sham Continuous Theta Burst Stimulation (cTBS)

The Magventure MagPro system includes an integrated active sham. When the coil was oriented in the treatment position, real cTBS was administered and the scalp electrodes placed on the left frontalis muscle under the coil were unplugged from the machine and, thus, not active. When the coil was flipped 180 degrees, the active side of the coil faced away from the
scalp and the electrodes were plugged into the machine. In this configuration, the sound and pressure of the coil remained constant and the scalp electrodes were active, thus, mimicking the multi-sensory experience of real cTBS without the CNS stimulation. Previous studies in our lab have demonstrated that participants are unable to differentiate real from sham stimulation, with participants exhibiting ~48% accuracy (i.e. approximately chance) in identifying whether they received real or sham cTBS in a given session [2]. However, for continued assurance, participants were surveyed after each session to routinely assess the integrity of the study blind.

**Generalized Psychophysiological Interaction (gPPI) Analysis**

* **gPPI Region-of-interest (ROI) Definition and Timecourse Extraction.** Regions-of-interest (ROIs) comprising frontal-striatal and salience circuitry were selected from the standard Automated Anatomical Labeling (AAL) Atlas. These included the VMPFC (AAL: left and right Frontal_Med_Orb), left caudate (AAL: Caudate_L), right caudate (AAL: Caudate_R), left putamen (AAL: Putamen_L), right putamen (AAL: Putamen_R), left insula (AAL: Insula_L), right insula (AAL: Insula_R), and anterior cingulate cortex (AAL: left and right Cingulum_Ant). Masks of each ROI were created in Matlab using the WFU PickAtlas toolbox (Wellcome Trust Centre for Neuroimaging, London, UK). In addition, because the AAL Atlas does not include the ventral striatum, a ventral striatum ROI was derived from the Oxford-GSK-Imanova connectivity atlas provided in FSL [3]. The ROI mask was limited to the bilateral ventral striatum as defined by the probabilistic connectivity atlas with 3 parcellations defined at a 50% threshold. The nine (9) ROI
masks were then used in AFNI’s ‘3dmaskave’ function to extract ROI timecourses from the fMRI data for subsequent gPPI computation.

**gPPI Computation.** The gPPI analysis was conducted as described by McLaren et al. [4]. First, the observed BOLD data for VMPFC was deconvolved into estimates of neural activity using a neural deconvolution algorithm [5]. Second, ON times for conditions Drug, Neutral, Blur, and Rate were separately convolved with the hemodynamic response function (HRF) for each condition to form a set of task regressors. Third, to define the PPI interaction terms, the deconvolved neural estimates were separately multiplied by each task condition (i.e. Drug, Neutral, Blur, and Rate) and then convolved with the HRF. Each of these interaction regressors was then included in a general linear model (GLM), such that the observed BOLD timecourse for each ROI was regressed simultaneously onto 1) the convolved task predictors (i.e., main effect of task), 2) the BOLD data from VMPFC (i.e., main effect of VMPFC), and 3) each of the separate convolved PPI (task condition × neural estimate) regressors. The difference in magnitude of the β coefficients for the separate PPI interaction regressors (i.e. Drug/Alcohol vs. Neutral contrast) provided an estimate of task-modulated FC between VMPFC and that ROI.

The Drug/Alcohol vs. Neutral contrast βs from the Pre- and Post-Real cTBS and Pre- and Post-Sham cTBS were entered into a three-way repeated-measures ANOVA and subsequent t-tests to determine the effect of treatment on changes in drug/alcohol cue-evoked FC.
Kearney-Ramos et al.

Supplement

L Caudate

d = -.50

R Caudate

d = -.35

L Putamen

d = -.48

R Putamen

d = -.37

L Insula

d = -.70

R Insula

d = -.12

ACC

d = -.23

Ventral Striatum

d = -.46
Supplemental Figure S1. Interaction plots across all regions of interest in cocaine users. For cocaine users (n=25), three-way repeated-measures ANOVA between treatment (real/sham) x time (pre/post) x ROI (8 ROIs) revealed a significant interaction between treatment x time (F_{1,768}=27.1, p<.00001), but not a main effect or interaction with ROI, indicating a general effect of treatment x time across all frontal-striatal and frontal-limbic ROIs. Post-hoc t-test of the interaction revealed that functional connectivity to drug vs. neutral cues was significantly attenuated following real vs. sham cTBS (t_{24}=-5.25, p<.00001). This significant difference was driven by significant attenuations following real cTBS (t_{24}=-4.74, p<.00001) as well as significant increases following sham cTBS (t_{24}=3.37, p<.001). Although there was no significant effect of ROI, the largest attenuating effects (for real vs. sham cTBS) were between the VMPFC and left caudate (effect size: Cohen's d=-.50) and left insula (d=-.70). There were also smaller decreases between the VMPFC and right caudate (d=-.35), left putamen (d=-.48), right putamen (d=-.37), ACC (d=-.23) and ventral striatum (d=-.46). This figure shows the treatment x time interaction plots for drug vs. neutral cue functional connectivity between the VMPFC and each given region. For each plot, the y-axis indicates marginal mean change from baseline (drug vs. neutral cue functional connectivity betas/parameter estimates). The blue lines indicate mean change from baseline for real cTBS. The orange lines indicate mean change from baseline for sham cTBS. In the top right of each panel, the effect size for the real vs. sham cTBS effects on drug vs. neutral cue functional connectivity for that region is displayed. In accordance with the generally-accepted system for interpreting effect sizes [6], small effect sizes were classified as those with Cohen's d≥.20, moderate effect sizes d≥.50, and large effect sizes d≥.80.
Functional connectivity change and clinical variables
*controlling for age and scalp-to-cortex distance

Relationship between functional connectivity change to cues after real vs. sham cTBS

**MPFC – L caudate**

**MPFC – L putamen**

**MPFC – L insula**

Functional connectivity change betas

Real cTBS (Post-Pre) – Sham (Post-Pre)

Years of Use

Baseline craving score

Trait anxiety score
Supplemental Figure S2. Relationship between functional connectivity change and clinical variables in cocaine users. For the cocaine users (n=25), VMPFC cTBS had the largest attenuating effects on frontal-striatal reactivity to cues among individuals with the shortest cocaine use histories (top panel; $r = 0.63$, $p<0.001^*$) and lowest baseline craving score (middle panel, $r = 0.58$, $p<.01^*$). Additionally, individuals with lower levels of trait anxiety received the largest attenuation of MPFC-insula connectivity ($r = 0.65$, $p<.001^*$) (*controlling for age and scalp-to-cortex distance).
Supplemental Figure S3. Interaction plots across all regions of interest in alcohol users. For alcohol users (n=25), three-way repeated-measures ANOVA between treatment (real/sham) x time (pre/post) x ROI (8 ROIs) revealed a significant interaction between treatment x time (F_{1,736}=24.6, p<.00001), but not a main effect or interaction with ROI, indicating a general effect of treatment x time across all frontal-striatal and frontal-limbic ROIs. Post-hoc t-test of the interaction revealed that FC to alcohol vs. neutral cues was significantly attenuated following real vs. sham cTBS (t_{23}=-5.91, FDR p<.00001). This significant difference was driven by significant attenuations following real cTBS (t_{23}=-4.70, FDR p<.00001) as well as significant increases following sham cTBS (t_{23}=2.81, FDR p<.01). Although there was no significant effect of ROI, the largest attenuating effects (for real vs. sham cTBS) were between the VMPFC and left caudate (effect size; Cohen’s d=-.50), right caudate (d=-.60), left putamen (d=-.65), left insula (d=-.51), ACC (d=-.51) and ventral striatum (d=-.54). There was also a smaller decrease between VMPFC and right putamen (d=-.29). This figure shows the treatment x time interaction plots for alcohol vs. neutral cue functional connectivity between the VMPFC and each given region. For each plot, the y-axis indicates marginal mean change from baseline (alcohol vs. neutral cue functional connectivity betas/parameter estimates). The blue lines indicate mean change from baseline for real cTBS. The orange lines indicate mean change from baseline for sham cTBS. In the top right of each panel, the effect size for the real vs. sham cTBS effects on alcohol vs. neutral cue functional connectivity for that region is displayed. In accordance with the generally-accepted system for interpreting effect sizes [6], small effect sizes were classified as those with Cohen’s d≥.20, moderate effect sizes d≥.50, and large effect sizes d≥.80.
Supplemental Figure S4. Relationship between functional connectivity change and clinical variables in alcohol users. For the alcohol users (n=24), VMPFC cTBS had the largest attenuating effects on frontal-striatal reactivity to cues among individuals with lower cTBS dose (all \( p < .05 \); *controlling for age and scalp-to-cortex distance).
SUPPLEMENTAL REFERENCES


