Supplemental Material

Screens and Assessments:

Screens: A multidrug urine panel (Quikvue 5-panel urine drug screen, Quidel, San Diego, CA) and a human chorionic gonadotropin (HCG) test for pregnancy (females only).

Assessments: Mini International Neuropsychiatric Interview (Sheehan et al., 1998), Cocaine Craving Questionnaire (Sussner et al., 2006; Tiffany, Singleton, Haertzen, & Henningfield, 1993), Addiction Severity Index (McLellan, Luborsky, Woody, & O'Brien, 1980) Beck Depression Inventory-II (Beck, Steer, & Brown, 1996), Fagerstrom Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) and the State-Trait Anxiety Inventory (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983)

Exclusion Criteria: Cocaine users were excluded on the basis of: a current use of prescription or illicit psychoactive drugs (other than cocaine and marijuana), DSM-IV current or past substance dependence criteria other than cocaine, smoking more than 1 pack of cigarettes per day, current breath alcohol concentration greater than 0.002, a lifetime history of head injury, a history of seizures or migraine headaches and violation of other MRI and TMS safety measures.

Interleaved TMS/Functional MRI protocol:

Coil Positioning**:** Participants were positioned supine on the scanner bed and the TMS coil (Magstim SuperRapid stimulator) was mounted in the MR head coil in a custom TMS coil holder with 6 degrees of freedom (Bohning et al., 1999). The standardized international 10–20 EEG system was used as the basis for positioning the TMS coil as it accounts for variability in participant skull size and is consistently used in clinical TMS applications. The coil was centered over FP1 (Elevation from nasion: 10% of the distance from the nasion to inion, Leftward rotation from the nasion: 5% circumference), a location approximating the left frontal pole as this area corresponds with the left medial prefrontal cortex/frontal pole (Okomoto et al., 2004). Although this choice shifted TMS stimulation to the left ventral medial cortex, stimulation at Fz (midline) would likely have been heavily attenuated by the high amounts of cerebrospinal fluid, as well as being positioned too dorsal to affect limbic circuitry.

TMS/BOLD Resting Motor Threshold Determination: For the TMS/BOLD portion of the experiment the resting motor threshold (RMT) was acquired using the coil and amplifier that would be used for stimulation while the participant was in the MRI scanner. This necessitated

that RMT was determined in the MRI scanner room and thus participants were instructed to sit on the retracted bed of the MRI scanner. The basics of TMS were explained to each patient and then we began the process to find the RMT. RMT was determined by visual inspection of movement in the abductor pollicis muscle. Amplifier output is set to a level that initiates a motor evoked potential in the contralateral muscle for half of the pulses. This is a standard procedure that normalizes the amplifier output (TMS dose) to individual neurological response.

Image acquisition: This study was performed on a Siemens 3T TIM Trio scanner (Siemens, Erlangen, Germany). Following high resolution anatomical image acquisition (TR = 1900 ms, TE = 4 ms, voxel dimensions 1.0 x 1.0 x 1.0 mm, 160 slices, 32 Channel head coil [Siemens, Erlangen, Germany]), participants received 2 interleaved TMS-BOLD imaging runs with the coil on FP1 (10 pulses per run). Extensive pilot work and prior studies in our laboratory were used to determine that TMS-induced artifacts in the EPI data were minimized using a sparse acquisition technique in which the biphasic TMS pulse (250μs) is applied during a 100ms gap between 2 volumes. Accordingly, each participant received 20 TMS pulses (110% resting motor threshold), with an interpulse interval of 10.18s, applied during a 100ms gap between EPI image acquisition (flip = 90degrees, TR = 2.5 s, TE = 0.023 s, FOV = 192 mm, voxel size= 3x3x3, 12-channel RAPID Biomedical coil [Rimpar, Germany]). Though this conservative number of pulses lowers the signal to noise ratio, the cautious design is based on prior work (Hanlon et al., 2013) and the limited knowledge related to the subjective effects of MPFC stimulation within the scanner. This protocol was applied immediately before and after cTBS.

Continuous Theta Burst protocol:

Following the first TMS-BOLD acquisition, the participants walked to an adjacent room for the cTBS procedure. Two trains of either real or sham LTD-like cTBS were applied over the left frontal pole (FP1) in a counterbalanced manner (1 train: 120 sec, 3 pulse bursts presented at 5Hz, 15 pulses/sec, 1800 pulses/train, 60 sec intertrain interval; 110% RMT, MagPro) using a figure-of- 8 coil (Coil Cool-B65 A/P). During the real and sham cTBS treatment sessions the amplifier output was escalated (over 30 seconds) from 80% to 110% RMT to enhance tolerability. The coil was left in position during the 60 second intertrain interval. The MagVenture MagPro system has an integrated active sham which passes current through two surface electrodes placed on the scalp. The electrodes were placed on the left frontalis muscle under the coil for both the real and sham stimulation sessions, though they were only active during

sham stimulation. Real and sham stimulation were well tolerated. Subjective reports indicated that the painfulness of the treatment subsided after the first 15-30 sec, consistent with prior studies showing an endogenous opiate effect of prefrontal rTMS (Taylor et al., 2012; Taylor et al., 2013). At the conclusion of each visit the participants filled out a form indicating their confidence (scale 1-10) on whether they received sham or real treatment. Participants guessed that it was the real TMS condition for nearly all visits. There were only 2 individuals that guessed that it was the sham condition on either visit. Only one of them was correct. Pooled accuracy was 47.6% suggesting that individuals were not aware of the treatment being received.

Active sham stimulation. We used the integrated active sham system present on the MagVenture MagPro Device. This allows active sham to be delivered with the same pattern, sound, and pressure as the real magnetic stimulation. When the TMS coil is oriented in one direction real TMS is applied while the scalp electrodes remain inactive. For sham stimulation the coil is flipped 180 degrees, placing the active face away from the scalp and the scalp electrodes are active. In this configuration the inactive face is making contact (maintaining pressure) and the TMS coil still fires (sound is equivalent) with each pulse. The output of the sham system is proportional to the individual's motor threshold. For this experiment the gain on the sham system was set to 9 as that was indistinguishable from real TMS in pilot work in our laboratory.

Timing between cTBS and imaging. A timer was started after the final cTBS pulse and the participants were led back to the scanner to begin the second TMS/BOLD procedure (which included a new low resolution T1 image for localization). There were no significant between condition differences between the conclusion of cTBS and initiation of TMS/BOLD (sham: 6:17±1:03 (range: 4:50 – 8:31), real cTBS: 7:00±1:23 (range 4:50 – 7:56), p = 0.23).

Functional MRI Image Analysis.

Preprocessing and functional imaging analysis was performed using standard parametric mapping techniques (SPM8, London, UK) in Matlab R2012a (MathWorks, Natick, MA).

Preprocessing: Images in each session were first converted from .dicom to .nii. The functional volumes from each session (pre separated from post) were then *realigned* to the mean with a two pass procedure (realigned to the first image and then realigned to the resulting mean) using a 6 parameter rigid body transformation (sampled using 4th Degree B-Spline interpolation) that minimizes the squared error between images (least squares approach).

The resulting mean images from realignment, as well as subject anatomical images, were then *segmented* using the New Segment Toolbox. This segments the tissues based both on intensities as well as tissue probability maps. In each case the grey matter, white matter and csf maps are imported into Image Calculator with the bias corrected images to mask out the skull, resulting in images from which the skull has been stripped.

Next, the skull stripped mean functional images were *coregistered* using a normalized mutual information algorithm to the skull stripped individual anatomical image, with all other functional images kept in register. The skull stripped anatomical image was then warped into template space using the Normalise: Estimate function of SPM8. A custom, skull stripped anatomical image (found at http://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152NLin2009 [ICBM 2009c Nonlinear Asymmetric template], included masks used to remove skull) was used for normalization. The resulting warps were then applied to all coregistered images. Finally, the normalized images were *smoothed* using an 8x8x8 mm FWHM Gaussian kernel.

Statistical analysis: The TMS/BOLD data were modeled as an event-related design with TMS pulses as instantaneous events and subsequently convolved with the canonical hemodynamic response function. To test the hypothesis that cTBS over the frontal pole (e.g. MPFC) induced an LTD-like effect specifically on limbic circuitry involved in craving, the evoked BOLD signal after real and sham TBS was compared to the evoked signal before real and sham TBS using paired t-tests. Statistical maps were created for both the within treatment (real or sham) and between treatment contrasts. The primary contrast of interest was [Real TMS (posttreatment-pretreatment) – Sham TMS (posttreatment-pretreatment)]. A Monte Carlo simulation ($p<0.01$, 3dClustSim) was employed for all statistical contrasts to generate a Family Wise Error correction equivalent to alpha < 0.05. Anatomical locations were determined by interrogation of the Harvard-Oxford Brain Atlas in FSL View.

3dClustSim – Family Wise Error Correction

3dClustSim, a program (http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html) included with AFNI [1] was used to correct for multiple comparisons and generate contrast maps with an effective 2-sided alpha < 0.05. The program requires that the FWHM Gaussian smoothing of the data (in x, y and z dimensions) is included. This was determined using the REST toolbox[2] in SPM8. In each case the spmT_* maps for the contrast of interest and the SPM generated implicit mask were used to determine the smoothness present in the contrast of interest.

These smoothness values and the corresponding mask images were used in 3dClustSim (2000 iterations [-iter 2000], clusters determined by face, edge or vertex contact [-NN 3]) to determine cluster volumes that produce a 2-sided alpha of <0.05 for varying values of voxel thresholding. We chose p <0.01 as our initial threshold resulting in the following k values: Treatment Condition = 96, Sham condition = 93, Treatment vs Sham condition = 95, pre cTBS real or sham = 116, pre cTBS real and sham = 156.

1 Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research, an International Journal*, *29*(3), 162–73.

2 Song, X.-W., Dong, Z.-Y., Long, X.-Y., Li, S.-F., Zuo, X.-N., Zhu, C.-Z., … Zang, Y.-F. (2011). REST: a toolkit for resting-state functional magnetic resonance imaging data processing. *PloS One*, *6*(9), e25031.