Transcranial Magnetic Stimulation (TMS) and Sham TMS Methods

**Figure S1.** Transcranial magnetic stimulation (TMS) method. (A and B) Repetitive TMS (rTMS) was delivered using the Neuronetics model 2100 therapy system investigational device and figure-eight, solid-core coil (Neuronetics Inc, Malvern, Pennsylvania) demonstrated on one of us (M.O). The novel active sham condition consisted of the sham coil and electrical pads inserted under the coil on the patient’s head (left panel). Three magnetic coils with a metal insert blocked the field, identical in weight and external appearance and with similar acoustic properties when actively pulsed. One coil, coil A, was unblended and was used to determine motor thresholds. The remaining 2 coils were distinguishable only by external labels as coil B or C, with one being active and the other sham.

**Blind and Control Methods**

Patients, clinical raters and other study personnel, except one investigator (X.L.) were masked to coil functionality. The same investigator applied rTMS to all subjects. This investigator was also involved in data analysis with SPSS. Because participants’ craving response to nicotine cues was completed on a computer, the investigators’ only communication with participants during assessment of cravings was to set up the program. Participants completed their craving ratings without any verbal communication. Furthermore, integrity of the blind was assessed immediately at the end of each visit. Patients made a “best guess” whether he/she had completed the active or sham rTMS. As a group, participants were successfully blind to rTMS treatment condition. Participants successfully identified 6 out of 14 (43%) sham treatments and 8 out of 14 (57%) real treatments [χ² (1) = 0.57, p = 0.45, not significant].
Thus, this study was not double-blind in the sense of ‘no one who knew the status of the patient ever came in contact with the subject or touched the data.’ It is double blind in that the patients were truly blind and could not guess, and all ratings were done by blinded raters or in a fashion (computerized visual analog) that did not allow any interaction. Moreover, the only unblinded investigator made it a point to set the study up and then sit quietly in the room and not interact with subjects.

The Scalp Discomfort of Real rTMS Matches to Sham Electrical Stimulation

In runup work to the OPT-TMS study (1), we assessed the amount of electrical stimulation that is needed to best mimic 10 Hz, 120% TMS. In that study we set the TENS unit to 5. This study used a slightly lower intensity stimulation (100% TMS) and we thus set the TENS unit for all subjects to 3 as initial intensity. The electrical current of the sham system using a sham rTMS coil was titrated to a level matching participants’ ratings of real rTMS. We did not record adverse events unless subjects dropped out of the study. Generally speaking, some subjects felt discomfort on the stimulation site at the start and became used to it after a few minutes. Unfortunately, we did not collect the information on adverse events and it is unknown whether scalp discomfort was greater in response to the active or sham TMS (2, 3).

The Sounds of the Sham and Active TMS Pulses

The sounds of the sham and active TMS pulses were slightly dissimilar. However, someone listening in the room could likely not detect any difference in noise. However, there may be a difference in what the patient perceives, in terms of the percussive effects of TMS and bone conduction transmission. This difference is thought to be negligible however and in this study was not enough to allow patients to guess (2, 3).

The Effect of Order of Active TMS Presentation

Participants randomly received active TMS or sham TMS on the first visit, then the other on the second visit, and counterbalanced across participants. This design should overcome the order effect. Including the order of active TMS, factor analysis results showed that no significant order effect of TMS presentation was found ($F = 0.129$, $p = 0.721$).

Baseline Comparison

We did compare pre-procedure (baseline) craving between block #1 (scenic) and block #3 (scenic). A repeated measure analysis result did not show any change of baseline (block #1
$= 56.14 \pm 4.81 \text{ vs. block } #3 = 56.19 \pm 4.67; F_{1, 13} = 0.002, p = 0.965)$. We also compared two visits (TMS vs. Sham) pre-experiment data (pre-sham-block #4 = 63.0 ± 4.7 (SE) vs. pre-active TMS-block #4 = 64.1 ± 5.9 (SE); pre-sham-block #2 = 56.2 ± 4.9 (SE) vs. pre-active TMS-block #2 = 57.6 ± 5.5 (SE); pre-sham-block #1 = 57.4 ± 5.7 (SE) vs. pre-active TMS-block #1 = 57.1 ± 4.9 (SE); pre-sham-block #3 = 55.5 ± 4.8 (SE) vs. pre-active TMS-block #3 = 57.9 ± 5.2 (SE).

All comparisons are no significant differences. Correlation analysis showed that pre-sham measurement did significantly correlate with pre-active TMS measurement ($p < 0.01$). Taken together, the current cue presentation paradigm is valid and reliable.

**Other Comparisons - Smoking Cues vs. Scenic Images and Neutral Cues vs. Scenic Images**

**Table S1.** Comparisons between smoking cues, neutral cues and scenic images

<table>
<thead>
<tr>
<th>The time of measures</th>
<th>Treatment</th>
<th>Cue presentation (means ± SE)</th>
<th>$t$</th>
<th>df</th>
<th>$p$</th>
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<tr>
<td></td>
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The Correlation between the Lifetime Years of Smoking and rTMS Response

The correlation between the lifetime years of smoking and rTMS response is not significant ($r = 0.013, p = 0.96$).

Subject Characteristic Appeared to be Associated with rTMS Response

Classification of dependence on Fagerström Test for Nicotine Dependence (FTND) score: 0-2 very low, 3-4 low, 5 moderate, 6-7 high, 8-10 very high. According to the classification, we divided the 14 participants into two groups - group 1-low dependence group: FTND score <5; group 2-moderate and high dependence group: FTND score ≥5. Comparing rTMS response between the two groups, we found that rTMS produced more effect in the moderate and high dependence group than the low dependence group (8.6 ± 7.5 vs. 40.8 ± 10.9, $t = 2.25$, $df = 12$, $p = 0.44$).

rTMS has been widely used in depression. However, treatment-related factors influencing antidepressant response with TMS include stimulation intensity, frequency, number of pulses administered, and duration of the treatment course (4, 5). Increasing the distance from the coil to the target cortex decreases the intensity of the stimulation reaching the brain, which is negatively correlated with antidepressant response and with the degree of stimulation-induced brain activation (6, 7). The impact of atrophy on coil-to-cortex distance has been posited to contribute to reduced efficacy in the elderly (8, 9). Adjusting dose to overcome atrophy may result in better effects in the elderly (10). Other treatment factors related to neurophysiological responses to TMS include coil and stimulator type, waveform shape and polarity, coil position, and orientation relative to target cortex (11). Even when these factors are held constant, considerable variability in neurophysiological responses to TMS has been described (12). Very few TMS studies have been completed on nicotine dependence treatment and it is likely that many factors may influence the rTMS effect of nicotine craving. As such, it is not surprising that we had one subject who showed an increase in craving following rTMS and two subjects that did not show any effect of rTMS on craving.

On the other hand, one fMRI study completed by our group showed that large individual variability may provide insight into the inconsistent outcomes of previous research using TMS for smoking cue-induced craving (13). In other words, the subject who showed a >20% increase in craving and the other subjects who showed no change may have a different ‘hot spot’ for TMS treatment. This may suggest that we should choose to stimulate the primary site of craving directly in the future study.