**Smoking Cessation Induced by Deep Repetitive Transcranial Magnetic Stimulation of the Prefrontal and Insular Cortices: A Prospective, Randomized Controlled Trial**

*Supplemental Information*

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**Passed phone screening – attended screening visit (n = 140)**

**Excluded (n = 25)**
- Not meeting inclusion criteria (n = 10)
- Refused to participate (n = 13)
- Other reasons (n = 2)

**Randomized (n = 115)**

**Sham stimulation (n = 41)**

**1Hz stimulation (n = 24)***

**10Hz stimulation (n = 50)**

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**Allocation; ITT Analysis**

**Dropout during Treatment**

**Discontinued intervention (n = 10, 24%)**

**Discontinued intervention (n = 10, 42%)**

**Discontinued intervention (n = 18, 36%)**

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**End of Treatment; PP Analysis**

**Analyzed (n = 31)**

**Analyzed (n = 14)**

**Analyzed (n = 32)**

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**Dropout during Follow-up**

**Loss to follow-up (n = 4) 13%**

**Loss to follow-up (n = 2) 14%**

**Loss to follow-up (n = 3) 9%**

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**Follow-up Analysis**

**Analyzed (n = 23)**

**Excluded from analysis (n = 4)**

**Analyzed (n = 12)**

**Excluded from analysis (n = 1)**

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**Figure S1.** CONSORT flowchart. The number of subjects screened and recruited for the study as well as the numbers of subjects that dropped out are presented. *recruitment to the low frequency groups was discontinued following interim analysis results, and as a result only 24 subjects were allocated to low frequency treatment. ITT, intent-to-treat; PP, per-protocol.*
Figure S2. Distribution of electric fields induced by the active and sham coils. The electric field distribution was measured in a model of the human head (15 x 13 x 18 cm), filled with physiologic saline solution. The colored field maps for the active HADD and sham coils indicate the electrical field absolute magnitude in each pixel, for 10 coronal slices, 1 cm apart, along with the appropriate MRI coronal images. The HADD-coil was placed over the theoretical frontal cortex of the head model and the field in each pixel was measured using a ‘pick-up’ dipole probe, attached to an oscilloscope. The red colors indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m based on the average threshold for motor activation of the hand. The field maps are adjusted for stimulator power output of 60%, which is the average level required to obtain 120% of the threshold (120 V/m), at a depth of 1.5 cm. It can be seen that the field produced by the sham coil at any point in the brain is far below the threshold for neuronal activation. MT, motor threshold.

Coil Parameters and Localization of Stimulation Point

The coil was equipped with both a positioning and cooling system. The positioning system included a helmet that comprises the coils, an adjustable pantograph arm connected to the helmet, and a device enabling rotation of the helmet around three orthogonal rotation axes. The positioning device enabled accurate and comfortable displacement and positioning.
of the coil over the patient's head. The cooling system was designed to maintain ambient temperature in the coils during repetitive operation.

On each repetitive transcranial magnetic stimulation (rTMS) session, the optimal spot on the scalp for stimulation of the right abductor pollicis brevis (APB) muscle was localized. This was achieved by exploration relative to its typical location, with single-pulse TMS applied at a low rate (<0.2 Hz). We first found a location that consistently gave rise to a motor-evoked potential in APB, and then determined the lowest stimulation intensity that gave rise to this activation during rest. After defining the resting motor threshold (RMT), the coil was then moved forward 6 cm anterior to the motor spot and aligned symmetrically (over the lateral prefrontal cortex location) and trains of pulses were delivered at 120% of the measured RMT.

**Presentation of Smoking-Related Cue**

In the cue condition, each daily rTMS session was preceded by a presentation of a smoking cue. The cue consisted of a person lighting up a cigarette and taking one puff, a meter away from the subject. Cue effectiveness was measured at baseline using a simplified visual analog scale (VAS) ranking the relative position of the participant’s response to the question “How much do you want to smoke right now?” on a linear scale between two possible choices: “not at all” (score = zero) and “more than ever” (score = ten). A significant effect of cue presentation was observed. The mean VAS score was elevated following the cue, from a mean score of 4.7 ± 0.481 to 5.95 ± 0.489. A paired t-test revealed a significant VAS score difference ($t = 4.1, p = 0.0002$), suggesting that the smoking cue efficiently induced a desire for smoking.

**Dropout Report**

Dropout rates did not significantly differ between the groups ($p = 0.3$) and the baseline characteristics of dropout participants were comparable to those of completers (Table S1), suggesting that dropouts were not inherently different from completers. The reasons provided by subjects for dropping-out are shown in Table S2. Notably, the most prevalent reason stated was lack of time to complete treatment. Nevertheless, the somewhat higher dropout rates in the groups receiving active treatments (1 Hz or 10 Hz) may suggest an unreported discomfort associated with the active stimulation.
Table S1. Comparison of the characteristics of dropouts versus completers

<table>
<thead>
<tr>
<th>Measure*</th>
<th>Dropouts</th>
<th>Completers</th>
<th>Statistic†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (male/female)</td>
<td>38 (21/17)</td>
<td>77 (48/29)</td>
<td>$X^2_1 = 0.5, p = 0.46$</td>
</tr>
<tr>
<td>Age</td>
<td>48.0 ± 12.6</td>
<td>50.2 ± 9.9</td>
<td>$t_{113} = -0.81, p = 0.42$</td>
</tr>
<tr>
<td>Cigarettes/ Day</td>
<td>29.7 ± 10.0</td>
<td>28.3 ± 8.5</td>
<td>$t_{113} = 0.78, p = 0.43$</td>
</tr>
<tr>
<td>Pack Years</td>
<td>45.7 ± 27.5</td>
<td>41.6 ± 17.8</td>
<td>$t_{113} = 0.84, p = 0.4$</td>
</tr>
<tr>
<td>BMI</td>
<td>26.9 ± 6.1</td>
<td>27.1 ± 5.3</td>
<td>$t_{112} = -0.16, p = 0.8$</td>
</tr>
<tr>
<td>Education*</td>
<td>1/26/11</td>
<td>4/46/27</td>
<td>$X^2_2 = 0.98, p = 0.6$</td>
</tr>
<tr>
<td>Family Status*</td>
<td>11/27</td>
<td>21/56</td>
<td>$X^2_1 = 0.03, p = 0.85$</td>
</tr>
<tr>
<td>Previous Trials*</td>
<td>3</td>
<td>3.5</td>
<td>$X^2_1 = 0.18, p = 0.67$</td>
</tr>
<tr>
<td>Previous Successes*</td>
<td>0</td>
<td>1</td>
<td>$X^2_1 = 0.3, p = 0.58$</td>
</tr>
<tr>
<td>Motivation to Quit*</td>
<td>100</td>
<td>100</td>
<td>$p = 0.62$</td>
</tr>
</tbody>
</table>

BMI, body mass index.
*See Table 2 in the main text for details.
†Chi-Square/ Wilcoxon Rank-Sum Test/ t-test.

Table S2. Main dropout justification as mentioned by subjects

<table>
<thead>
<tr>
<th>Reason for dropping-out</th>
<th>Sham (24%)*</th>
<th>1 Hz (42%)*</th>
<th>10 Hz (36%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of time</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Personal reasons unrelated to treatment</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Adverse treatment effects (headache, nausea)</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Discomfort with treatment</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Unspecified</td>
<td>4</td>
<td>5</td>
<td>9</td>
</tr>
</tbody>
</table>

*See Figure S1 (consort diagram) for details.

Detailed Statistical Analysis

Continuous variables were compared using $t$-test, analysis of variance (ANOVA) or non-parametric equivalents. Dependent continuous variables included: cotinine levels, self-reported number of cigarettes smoked, Fagerström Test for Nicotine Dependence score, short
Tobacco Questionnaire (sTCQ) score, age, body mass index and pack years. The study hypothesis of no difference between the study groups in the above described dependent variables were tested with analysis of covariance (ANCOVA) for change in each parameter as a function of Treatment and Cue, using baseline measurement as covariates. Effect sizes are presented as difference between means ± standard error. In tests with several time points, repeated measures ANCOVA were performed.

Categorical variables were compared with a logistic regression, chi-square test or Fisher’s exact test where relevant. The categorical variables were: gender, education, marital status, number of previous trials to quit, number of previous successes to quit (abstinent of more than one month), and motivation to quit. We also construed two important binary variables of clinical relevance. The first was named treatment responsiveness (responsive/non-responsive). We defined response as a reduction of at least 50% in self-reported number of cigarettes smoked on the last session relative to screening. The second binary variable referred to smoking cessation (yes/no).

Significance for pairwise comparisons on all secondary outcomes, continuous or categorical, was established by the Binjamini-Hochberg method (false discovery rate = 0.05) to correct for multiple comparisons.

Data analysis was performed using SAS v9.2 (SAS Institute, Cary NC, USA). All tests were two tailed. Using the Pocock correction resulting from one interim analysis, significance level was set at alpha = 0.025.

**Interim Results**

After 7-8 participants in each group completed the entire study (44 completers overall), an interim analysis was conducted. Two measurements were assessed in this analysis: daily cigarette consumption evaluated through self-reports and cotinine levels in urine samples calculated as the cotinine-to-creatinine ratio (Cot/Cre; see Materials and Methods). A two-way ANCOVA was conducted to compare between the six groups, with Treatment and Cue as main effects and baseline measurement as covariates. Results are shown in Table S3 and are briefly discussed below.
Table S3. Interim Results. Data shows means ± SEM (n = 44) of the daily cigarette consumption (self-report) and of urine cotinine levels (cotinine/creatinine ratio) after the last treatment, normalized to baseline levels. Negative values represent decrease from baseline.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0+</th>
<th>0-</th>
<th>1+</th>
<th>1-</th>
<th>10+</th>
<th>10-</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily cigarettes</td>
<td>-7.2 ± 3.5</td>
<td>-10.5 ± 3.9</td>
<td>-7.5 ± 3.8</td>
<td>-12.5 ± 3.7</td>
<td>-21.1 ± 3.7</td>
<td>-14.1 ± 3.5</td>
<td>0.04/0.88/0.22</td>
</tr>
<tr>
<td>Urine cotinine</td>
<td>-2.1 ± 11.7</td>
<td>-0.9 ± 11.7</td>
<td>-23.0 ± 11.7</td>
<td>-3.4+11.7</td>
<td>-47.6 ± 11.6</td>
<td>-10.4 ± 11.0</td>
<td>0.07/0.05/0.3</td>
</tr>
</tbody>
</table>

*p value (Treatment/ Cue/ Treatment*Cue interaction) is extracted from a two-way ANCOVA with baseline levels (obtained prior to first treatment) as covariates.

**Subjective Evaluation of Nicotine Consumption**

Analysis of the change in self-reported daily cigarette consumption revealed a significant effect of Treatment ($F_{2,43} = 3.4$, $p = 0.04$), and pairwise comparisons revealed a greater reduction in the 10 Hz group compared with the Sham ($p = 0.019$) and 1 Hz groups ($p = 0.05$). No significant difference was found between the 1 Hz and Sham groups ($p = 0.756$) and no significant effects were found for cue or for the treatment by cue interaction. Further pairwise analyses revealed a significantly greater reduction in daily cigarette consumption for the 10+ group compared with the 0-, 0+ and 1+ groups ($p = 0.05$, $p = 0.01$ and $p = 0.016$, respectively). All other pairwise comparisons were not statistically significant ($p > 0.05$).

**Objective Evaluation of Nicotine Consumption**

Analysis of the Cot/Cre levels revealed a marginally significant effect of treatment ($F_{2,36} = 2.91$, $p = 0.07$), wherein post hoc comparisons tests revealed a greater Cot/Cre reduction in the 10 Hz group ($p = 0.022$), but not in the 1 Hz group ($p = 0.32$), compared with the Sham group. No significant difference was found between the 10 Hz and 1 Hz groups ($p = 0.183$). A marginally significant effect was found for cue ($F_{1,36} = 4.12$, $p = 0.051$), wherein groups in which the cue was presented showed a greater reduction in the Cot/Cre ratio. However, no significant treatment X cue interaction was found ($F_{2,36} = 1.24$, $p = 0.3$). Pre-planned pairwise comparisons revealed a significant reduction in cotinine levels in the 10+ group compared with the 0-, 0+ and 10- groups ($p = 0.008$, $p = 0.0097$, $p = 0.011$ and $p = 0.027$, respectively). All other pairwise comparisons were not statistically significant ($p > 0.05$).
Taken together, the interim results demonstrated superiority of the 10+ group compared with all other groups. The effect of the cue itself, however, was not consistent between groups and measurements. We therefore decided to stop the recruitment of new participants to the 1 Hz groups and focus on the 10 Hz and Sham groups, both with and without cue presentation.

**Predictive Values for Treatment Success**

To investigate possible predictive values for rTMS treatment success, associations were first tested (using t-test, ANOVA and Pearson correlation) for all treatment groups and for each treatment group separately, between the changes in the objective measurements of cigarette consumption (Cot/Cre ratio) to all baseline demographic parameters. Of these, a significant association was found only for education ($F = 3.5, p = 0.04$). Associations were also tested specifically for the best treatment group (10+), however no associations were found with any of the tested variables.