# Repetitive transcranial magnetic stimulation for smoking cessation: A pivotal multicenter double-blind randomized controlled trial

# Supplementary Materials

## Supplementary Methods

## Subjects

### Inclusion Criteria

* Male or female subjects, 22-70 years old.
* Current, chronic (> ten cigarettes/day) smokers, who have smoked for more than one year, with no period of abstinence greater than three months during the past year.
* Subjects who are motivated to quit smoking (with responses “very likely,” or “somewhat likely” to the motivation questionnaire).
* Satisfactory answers on safety screening questionnaire for transcranial magnetic stimulation.
* Gave informed consent for participation in the study.

### Exclusion Criteria

* Currently on Nicotine Replacement Therapy (NRT) or smoking cessation drugs (e.g., Zyban, Chantix, etc.) or undergoing behavioral smoking cessation interventions.
* Cognitive or functional disability, diagnosed according to DSM-5 criteria.
* Active psychiatric disorder according to DSM-5 (Axis I and Axis II) criteria within the last year, other than Tobacco Use Disorder (TUD).
* Current alcohol or other substance abuse or dependence.
* Alcohol or other substance use disorder during the last 12 months before recruitment.
* Subject is smoking any other form of tobacco or other substances.
* Subject is taking psychotropic medications on a regular basis.
* Subjects with a high risk for severe violence or suicidality as assessed during the screening interview.
* Subjects who suffer from an unstable physical disease such as high blood pressure (>150 mmHg systolic / diastolic > 110 mmHg) or acute, unstable cardiac disease.
* History of epilepsy or seizure (EXCEPT those therapeutically induced by ECT).
* Increased risk of seizure for any reason, including prior diagnosis of increased intracranial pressure (such as after large infarctions or trauma), or history of significant head injury or trauma with loss of consciousness for > five minutes.
* History of any metal in the head (outside the mouth).
* Metallic particles in the eye, implanted cardiac pacemaker or any intracardiac lines, implanted neurostimulators, intracranial implant (e.g., aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or implanted medical pumps.
* Individuals with a significant neurological disorder or insult including, but not limited to:
  + Any condition likely to be associated with increased intracranial pressure
  + Space occupying brain lesion
  + History of cerebrovascular accident
  + Transient ischemic attack within two years
  + Cerebral aneurysm
  + Dementia
  + Mini Mental State Exam score of less than or equal to 24
  + Parkinson’s disease
  + Huntington’s chorea
  + Multiple sclerosis
* Subjects suffering from frequent and severe migraine headaches.
* Subjects suffering from significant hearing loss.
* Subjects taking pro-convulsant medications (e.g., antidepressants or antipsychotic medications).
* Previous treatment with TMS.
* Subjects who cannot communicate reliably with the investigator or who are not likely to cope with the requirements of the experiment.
* Participation in a clinical trial within the last 30 days before the beginning of this clinical trial or similar participation in another clinical trial.
* Known or suspected pregnancy or lactation.
* Women of childbearing potential and not using a medically accepted form of contraception when engaging in sexual intercourse.

## Electric field distribution of the active and sham coils

The H4 coil has been shown to bilaterally stimulate neuronal pathways in the lPFC and insula with an intensity above the neuronal threshold for activation.1,2



**Figure S1.** 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 H4 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 H4-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. The field produced by the sham coil at any point in the brain is far below the threshold for neuronal activation. MT, motor threshold.

## Statistical analysis

#### Sample size and power analysis

The weighted average of our pilot study and studies of Bupropion, Varenicline, and NRT, resulted in abstinence rates of 38.6% and 18.4% for the treatment and control groups, respectively.1,3-7 Thus, assuming a difference of 20% between groups and 80% power with a two-sided level of significance of 5%, a total number of 164 (82 per group) participants were required. By allowing for a potential 40% drop-out, 270 participants were required, and by monitoring dropout rate, the total number of participants enrolled could be adapted accordingly.

#### Study analysis sets

For safety and efficacy analyses, the intent-to-treat (ITT) analysis set, which consisted of all participants randomized, was used. In accordance with the ITT principle, all participants randomized who received at least one treatment (active or sham) and had at least one post-baseline assessment available for analysis were kept in their originally assigned treatment group and used for the ITT efficacy (ITT-E) analysis. Completer (CO) analysis set consisted of all participants from the ITT analysis set who completed the rTMS treatment phase and the Short-FU phase (i.e., had at least four weeks of assessments related to the primary endpoint following the grace period).

#### Analysis

CQR was compared between the study groups with a chi-squared test. In addition, the CQR was modeled with logistic regression, with baseline daily number of cigarettes smoked, sex and center used as covariates. Prognostic factors (age, gender, treatment question, age of smoking onset, duration of smoking at baseline) and sensitivity analysis for the CQR at Short-FU and Long-FU were performed in the following manner: adjustment for other covariates such as demographics or other baseline characteristics (e.g., sex, age, race and history of smoking) were performed by adding these variables to the above described logistic model. Weekly point prevalence abstinence rates were analyzed in the same manner. The number of cigarettes smoked presented over time and analyzed with a repeated measures analysis of covariance model. Baseline daily number of cigarettes smoked, sex and center were used as covariates. FTND scores were compared between the treatment groups with chi-squared tests. MNWS scores, TCQ scores, and Nicotine craving scale scores were presented over time and analyzed with a repeated measures analysis of covariance model. Baseline daily number of cigarettes smoked, sex and center (recruiting site) were used as covariates. Group differences in the (pre-session) VAS craving scores during the treatment phase were analyzed using repeated measures ANOVA with group as a between-subject factor and treatment day as within-subject factor. Post-hoc analysis was conducted using the Bonferroni test.

All statistical tests were two-sided. Where confidence limits were appropriate, the confidence level was 95%. For comparison of means (continuous variables), the two-sample t-test or the Wilcoxon rank sum test were used, as appropriate. For comparison of proportions (discrete data), the Chi-squared test or Fisher’s exact test were used as appropriate.

### Missing data

If a participant missed an assessment visit but had been abstinent (i.e., a negative confirmatory test) at the visits prior to and following the missing visit, and claimed complete abstinence throughout, that participant was classified as abstinent. Dropouts and participants lost to follow-up were classified as non-abstinent.

## Supplementary Results

### Supplementary Tables

Table S1. Demographic Characteristics (ITT analysis set)

|  | | | **Active** | **Sham** | **p-value** |
| --- | --- | --- | --- | --- | --- |
| **Age (years)** |  | **N** | 123 | 139 | 0.9456(\*) |
| **Mean (SD)** | 45.0 (13.00) | 44.8 (13.40) |
| **Median [Range]** | 46.5 [21.5;67.8] | 45.8 [22.9;67.4] |
| **Height (cm)** |  | **N** | 123 | 139 | 0.6774(\*) |
| **Mean (SD)** | 171.7 (9.78) | 172.2 (10.68) |
| **Median [Range]** | 172.0 [150.0;205.0] | 171.0 [132.0;203.0] |
| **Weight (kg)** |  | **N** | 122 | 137 | 0.4716(\*) |
| **Mean (SD)** | 83.7 (20.41) | 81.9 (21.80) |
| **Median [Range]** | 80.8 [50.0;151.0] | 79.9 [45.4;225.0] |
| **BMI (kg/m2)** |  | **N** | 122 | 137 | 0.4023(\*) |
| **Mean (SD)** | 28.4 (6.24) | 27.6 (7.54) |
| **Median [Range]** | 27.3 [18.2;51.7] | 26.2 [16.5;76.1] |
| **Gender** | **Male** | **% (n/N)** | 51.2% (63/123) | 52.5% (73/139) | 0.8337(#) |
| **Female** | **% (n/N)** | 48.8% (60/123) | 47.5% (66/139) |
| **Marital Status** | **Married** | **% (n/N)** | 23.6% (29/123) | 28.8% (40/139) | 0.0908(#) |
| **Single** | **% (n/N)** | 54.5% (67/123) | 39.6% (55/139) |
| **Divorced** | **% (n/N)** | 17.1% (21/123) | 26.6% (37/139) |
| **Widower** | **% (n/N)** | 4.9% (6/123) | 5.0% (7/139) |
| **Race** | **Caucasian** | **% (n/N)** | 68.3% (84/123) | 66.9% (93/139) | 0.8110(#) |
| **Afro-American** | **% (n/N)** | 25.2% (31/123) | 25.9% (36/139) | 0.8975(#) |
| **Hispanic** | **% (n/N)** | 4.1% (5/123) | 3.6% (5/139) | 1.0000($) |
| **Other** | **% (n/N)** | 2.4% (3/123) | 4.3% (6/139) | 0.5077($) |
| **Years of Education** | **< 9 years of education** | **% (n/N)** | - | 1.4% (2/139) | 0.0743($) |
| **9 to 12 years of education** | **% (n/N)** | 33.3% (41/123) | 23.0% (32/139) |
| **> 12 years of education** | **% (n/N)** | 66.7% (82/123) | 75.5% (105/139) |

(\*) t-test;(#) chi-square test; ($) Fisher's exact test

Table S2. Medical History (ITT analysis set)

|  | **Active** | | **Sham** | | **Chi-Square p-value** |
| --- | --- | --- | --- | --- | --- |
| **Normal** | **Abnormal** | **Normal** | **Abnormal** |
| **Body System H/E/E/N/T** | 86.2% (106/123) | 13.8% (17/123) | 89.9% (125/139) | 10.1% (14/139) | 0.3484 |
| **Respiratory** | 84.6% (104/123) | 15.4% (19/123) | 84.2% (117/139) | 15.8% (22/139) | 0.9326 |
| **Cardiovascular** | 84.6% (104/123) | 15.4% (19/123) | 78.4% (109/139) | 21.6% (30/139) | 0.2037 |
| **Gastrointestinal** | 83.7% (103/123) | 16.3% (20/123) | 81.3% (113/139) | 18.7% (26/139) | 0.6037 |
| **Musculoskeletal** | 69.9% (86/123) | 30.1% (37/123) | 70.5% (98/139) | 29.5% (41/139) | 0.9177 |
| **Dermatology** | 91.9% (113/123) | 8.1% (10/123) | 92.8% (129/139) | 7.2% (10/139) | 0.7759 |
| **Hematopoietic / Lymph** | 99.2% (122/123) | 0.8% (1/123) | 98.6% (137/139) | 1.4% (2/139) | 0.6347 |
| **Endocrine/Metabolic** | 89.4% (110/123) | 10.6% (13/123) | 92.1% (128/139) | 7.9% (11/139) | 0.4571 |
| **Genitourinary** | 83.7% (103/123) | 16.3% (20/123) | 80.6% (112/139) | 19.4% (27/139) | 0.5053 |
| **Chest** | 93.5% (115/123) | 6.5% (8/123) | 95.7% (133/139) | 4.3% (6/139) | 0.4320 |
| **Neurologic** | 91.1% (112/123) | 8.9% (11/123) | 95.0% (132/139) | 5.0% (7/139) | 0.2121 |
| **Allergy/Drug Sensitivity** | 80.5% (99/123) | 19.5% (24/123) | 75.5% (105/139) | 24.5% (34/139) | 0.3357 |
| **Other** | 78.9% (97/123) | 21.1% (26/123) | 84.2% (117/139) | 15.8% (22/139) | 0.2674 |

Table S3. Smoking History (ITT analysis set)

|  | | | **Active** | **Sham** | **p-value** |
| --- | --- | --- | --- | --- | --- |
| **Age Started Smoking (years)** |  | **N** | 123 | 139 | 0.3905(\*) |
| **Mean (SD)** | 16.9 (3.96) | 17.4 (5.35) |
| **Median [Range]** | 17.0 [8;40] | 16.0 [8;41] |
| **Total Years Smoking** |  | **N** | 123 | 139 | 0.5966(\*) |
| **Mean (SD)** | 27.1 (13.05) | 26.2 (13.73) |
| **Median [Range]** | 27.0 [4;50] | 25.0 [3;62] |
| **Spouse Smoke** |  | **% (n/N)** | 25.6% (30/117) | 27.1% (35/129) | 0.7911(#) |
| **Father Smoked** |  | **% (n/N)** | 64.2% (77/120) | 65.9% (89/135) | 0.7686(#) |
| **Mother Smoked** |  | **% (n/N)** | 46.7% (57/122) | 50.7% (70/138) | 0.5193(#) |
| **Cigarettes / Day** |  | **N** | 123 | 139 | 0.8738(\*) |
| **Mean (SD)** | 18.3 (7.68) | 18.2 (7.21) |
| **Median [Range]** | 16.0 [10;60] | 18.0 [10;50] |
| **Cigarettes / Day During Heaviest Smoking Period** |  | **N** | 123 | 139 | 0.6741(\*) |
| **Mean (SD)** | 27.8 (10.61) | 27.2 (10.48) |
| **Median [Range]** | 25.0 [10;60] | 25.0 [10;60] |
| **Time to First Morning Cigarette (min.)** |  | **N** | 122 | 139 | 0.4412(\*) |
| **Mean (SD)** | 23.2 (39.26) | 27.4 (48.84) |
| **Median [Range]** | 10.0 [0;360] | 10.0 [1;480] |
| **No. Quit attempts** | **1** | **% (n/N)** | 14.3% (17/119) | 21.9% (30/137) | 0.2832(#) |
| **2** | **% (n/N)** | 10.9% (13/119) | 16.1% (22/137) |
| **3** | **% (n/N)** | 23.5% (28/119) | 18.2% (25/137) |
| **4** | **% (n/N)** | 11.8% (14/119) | 9.5% (13/137) |
| **5** | **% (n/N)** | 12.6% (15/119) | 7.3% (10/137) |
| **>5** | **% (n/N)** | 26.9% (32/119) | 27.0% (37/137) |
| **Longest Period of abstinence** | **1 week or less** | **% (n/N)** | 26.7% (32/120) | 26.1% (36/138) | 0.7283(#) |
| **1 week - 1 month** | **% (n/N)** | 19.2% (23/120) | 13.8% (19/138) |
| **>1 month - 6 months** | **% (n/N)** | 25.0% (30/120) | 26.1% (36/138) |
| **>6 months - 1 year** | **% (n/N)** | 12.5% (15/120) | 12.3% (17/138) |
| **longer than 1 year** | **% (n/N)** | 16.7% (20/120) | 21.7% (30/138) |
| **Previous Quitting Methods** | **Bupropion** | **% (n/N)** | 12.4% (15/121) | 10.1% (14/138) | 0.5664(#) |
| **Varenicline** | **% (n/N)** | 24.0% (29/121) | 25.4% (35/138) | 0.7951(#) |
| **Nicotine Patch** | **% (n/N)** | 33.9% (41/121) | 35.5% (49/138) | 0.7843(#) |
| **Nicotine Gum** | **% (n/N)** | 27.3% (33/121) | 26.8% (37/138) | 0.9336(#) |
| **Nicotine Lozenge** | **% (n/N)** | 9.1% (11/121) | 10.1% (14/138) | 0.7744(#) |
| **Nicotine Oral Inhaler** | **% (n/N)** | 5.8% (7/121) | 4.3% (6/138) | 0.5971(#) |
| **Cold Turkey** | **% (n/N)** | 73.6% (89/121) | 76.8% (106/138) | 0.5442(#) |
| **CBT or therapy** | **% (n/N)** | 3.3% (4/121) | 2.9% (4/138) | 1.0000($) |
| **Hypnosis** | **% (n/N)** | 10.7% (13/121) | 5.8% (8/138) | 0.1456 (#) |
| **Other** | **% (n/N)** | 21.5% (26/121) | 18.1% (25/138) | 0.4960 (#) |

(\*) t-test,(#) chi-square test, ($) Fisher's exact test

Table S4. Nicotine Withdrawal and Craving Assessment Scales at Baseline (ITT)

|  | | | **Active** | | **Sham** | | **p-value** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **FTND** | | **N** | 123 | | 139 | | 0.2682(\*) |
| **Mean (SD)** | 5.5 (1.98) | | 5.3 (2.04) | |
| **Median [Range]** | 6.0 [0;10] | | 5.0 [1;10] | |
| **MNWS (self-reported)** | | **N** | 123 | | 139 | | 0.4502(\*) |
| **Mean (SD)** | 7.6 (5.42) | | 8.1 (6.12) | |
| **Median [Range]** | 6.0 [0;28] | | 7.0 [0;29] | |
| **MNWS (observer reported)** | | **N** | | 123 | | 139 | 0.0049(\*) |
| **Mean (SD)** | | 0.8 (1.39) | | 1.4 (1.92) |
| **Median [Range]** | | 0.0 [0;8] | | 1.0 [0;12] |
| **TCQ (Total Score)** | | **N** | 123 | | 139 | | 0.2913(\*) |
| **Mean (SD)** | 44.9 (15.77) | | 42.7 (18.10) | |
| **Median [Range]** | 43.0 [14;84] | | 43.0 [0;84] | |
|  | **TCQ – Emotion** | **N** | 123 | | 139 | | 0.8819(\*) |
| **Mean (SD)** | 7.7 (5.43) | | 7.6 (5.74) | |
| **Median [Range]** | 7.0 [0;21] | | 7.0 [0;21] | |
|  | **TCQ - Expectancy** | **N** | 123 | | 139 | | 0.4784(\*) |
| **Mean (SD)** | 15.0 (4.52) | | 14.6 (5.81) | |
| **Median [Range]** | 15.0 [4;21] | | 16.0 [0;21] | |
|  | **TCQ - Compulsivity** | **N** | 123 | | 139 | | 0.2101(\*) |
| **Mean (SD)** | 8.7 (5.37) | | 7.9 (5.49) | |
| **Median [Range]** | 8.0 [0;21] | | 7.0 [0;21] | |
|  | **TCQ - Purposefulness** | **N** | 123 | | 139 | | 0.1321(\*) |
| **Mean (SD)** | 13.5 (4.09) | | 12.6 (4.72) | |
| **Median [Range]** | 14.0 [4;21] | | 13.0 [0;21] | |

The Fagerstrom test of nicotine dependence (FTND); Minnesota nicotine withdrawal scale (MNWS); Tobacco craving questionnaire (TCQ); (\*) t-test

Table S5. 4 week CQR until week 6

|  | **Active** | **Sham** | **Chi-Square** | **Chi-Square p-value** | **Logistic Regression p-value** |
| --- | --- | --- | --- | --- | --- |
| **ITT** | 17.6% (19/108) | 4.8% (6/126) | 10.0328 | 0.0015 | 0.0024 |
| **CO** | 25.3% (19/75) | 6.4% (6/94) | 12.1669 | 0.0005 | 0.0010 |

Table S6. 4 week CQR until week 18

|  | **Active** | **Sham** | **Chi-Square** | **Chi-Square p-value** | **Logistic Regression p-value** |
| --- | --- | --- | --- | --- | --- |
| **ITT** | 19.4% (21/108) | 8.7% (11/126) | 5.655 | 0.0174 | 0.0196 |
| **CO** | 28.0% (21/75) | 11.7% (11/94) | 7.4675 | 0.0063 | 0.0073 |

Table S7. Relapse Rates during the long follow up phase among quitters at week 6.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Active** | **Sham** | **Fisher’s exact test p-value** |
| **ITT - Remained quitter during week 18** | | | |
| **No** | 36.84% (7/19) | 50.00 % (3/6) | 1.000 |
| **Yes** | 63.16% (12/19) | 50.00% (3/6) | 1.000 |
| **CO - Remained quitter during week 18** | | | |
| **No** | 36.84% (7/19) | 50.00 % (3/6) | 1.000 |
| **Yes** | 63.16% (12/19) | 50.00% (3/6) | 1.000 |

Continuous abstinence rate until week 18is 12/75 and 3/94 in the Active and Sham groups, respectively (χ2 = 8.46, p = 0.003)

Table S8. Number of Cigarettes Smoked

|  | | **Active** | | **Sham** | | **Diff. (Active - Sham)** | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Adj. Means** | **95% CI** | **Adj. Means** | **95% CI** | **Adj. Means** | **95% CI** | **p-value** |
|  | **Week** |  |  |  |  |  |  |  |
| **ITT** | **1** | 90.53 | [81.07;99.98] | 98.81 | [90.34;107.28] | -8.28 | [ -19.45;2.88] | 0.1457 |
| **2** | 60.87 | [51.29;70.45] | 77.51 | [69.04;85.97] | -16.64 | [ -27.91;-5.37] | 0.0039 |
| **3** | 38.31 | [28.24;48.39] | 57.45 | [48.60;66.30] | -19.14 | [ -31.14;-7.14] | 0.0018 |
| **4** | 42.05 | [31.88;52.23] | 60.07 | [51.07;69.08] | -18.02 | [ -30.22;-5.82] | 0.0038 |
| **5** | 42.22 | [31.87;52.56] | 61.09 | [52.01;70.17] | -18.87 | [ -31.27;-6.48] | 0.0029 |
| **6** | 31.38 | [20.92;41.83] | 47.52 | [38.24;56.80] | -16.14 | [ -28.79;-3.48] | 0.0125 |
| **CO** | **1** | 90.61 | [80.32;100.90] | 99.64 | [90.44;108.83] | -9.03 | [ -21.43;3.38] | 0.1536 |
| **2** | 60.17 | [49.88;70.46] | 80.52 | [71.36;89.68] | -20.35 | [ -32.73;-7.98] | 0.0013 |
| **3** | 39.15 | [28.80;49.50] | 58.32 | [49.09;67.55] | -19.18 | [ -31.66;-6.69] | 0.0027 |
| **4** | 43.24 | [32.89;53.59] | 59.80 | [50.53;69.07] | -16.56 | [ -29.08;-4.05] | 0.0096 |
| **5** | 42.99 | [32.58;53.39] | 61.54 | [52.23;70.85] | -18.55 | [ -31.15;-5.95] | 0.0040 |
| **6** | 32.07 | [21.55;42.60] | 47.09 | [37.60;56.57] | -15.01 | [ -27.85;-2.17] | 0.0220 |

Table S9. Change from Baseline in Total TCQ and Subscale Scores

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Active** | | | **Sham** | | | **Diff** | | |
| **ITT** | **Week/ Visit** | **Adj. Means** | **95%CI** | **p-value** | **Adj. Means** | **95%CI** | **p-value** | **Adj. Means** | **95%CI** | **p-value** |
| **Total**  **TCQ** | **2** | -10.16 | [0.00;-6.13] | <.0001 | -6.23 | [0.00;-2.64] | 0.0007 | -3.94 | [-8.63;0.76] | 0.1005 |
| **3** | -19.07 | [0.00;-14.83] | <.0001 | -11.90 | [0.00;-8.13] | <.0001 | -7.17 | [-12.16;-2.18] | 0.0049 |
| **4** | -20.59 | [0.00;-16.26] | <.0001 | -14.15 | [0.00;-10.38] | <.0001 | -6.44 | [-11.52;-1.35] | 0.0132 |
| **5** | -21.30 | [0.00;-16.93] | <.0001 | -16.47 | [0.00;-12.63] | <.0001 | -4.83 | [-9.99;0.33] | 0.0667 |
| **6** | -24.44 | [0.00;-20.10] | <.0001 | -18.89 | [0.00;-15.05] | <.0001 | -5.56 | [-10.70;-0.42] | 0.0341 |
| **18** | -31.12 | [0.00;-24.49] | <.0001 | -29.40 | [0.00;-21.53] | <.0001 | -1.72 | [-11.51;8.08] | 0.7308 |
| **Emotion** | **2** | -1.57 | [0.00;-0.56] | 0.0024 | -0.64 | [0.00;0.26] | 0.1632 | -0.93 | [-2.10;0.25] | 0.1221 |
| **3** | -3.61 | [0.00;-2.55] | <.0001 | -1.87 | [0.00;-0.93] | 0.0001 | -1.74 | [-2.99;-0.49] | 0.0064 |
| **4** | -3.82 | [0.00;-2.74] | <.0001 | -2.55 | [0.00;-1.60] | <.0001 | -1.27 | [-2.55;-0.00] | 0.0497 |
| **5** | -4.03 | [0.00;-2.94] | <.0001 | -3.08 | [0.00;-2.12] | <.0001 | -0.95 | [-2.24;0.34] | 0.1503 |
| **6** | -4.56 | [0.00;-3.47] | <.0001 | -3.52 | [0.00;-2.56] | <.0001 | -1.04 | [-2.33;0.25] | 0.1127 |
| **18** | -5.33 | [0.00;-3.67] | <.0001 | -5.37 | [0.00;-3.40] | <.0001 | 0.04 | [-2.41;2.49] | 0.9746 |
| **Expectancy** | **2** | -3.14 | [0.00;-1.79] | <.0001 | -1.96 | [0.00;-0.76] | 0.0014 | -1.18 | [-2.75;0.39] | 0.1393 |
| **3** | -5.95 | [0.00;-4.53] | <.0001 | -3.96 | [0.00;-2.70] | <.0001 | -1.99 | [-3.65;-0.32] | 0.0193 |
| **4** | -6.18 | [0.00;-4.74] | <.0001 | -4.39 | [0.00;-3.13] | <.0001 | -1.79 | [-3.49;-0.10] | 0.0384 |
| **5** | -6.54 | [0.00;-5.08] | <.0001 | -5.19 | [0.00;-3.91] | <.0001 | -1.35 | [-3.07;0.37] | 0.1248 |
| **6** | -7.81 | [0.00;-6.36] | <.0001 | -6.05 | [0.00;-4.77] | <.0001 | -1.76 | [-3.47;-0.04] | 0.0446 |
| **18** | -10.01 | [0.00;-7.80] | <.0001 | -9.65 | [0.00;-7.02] | <.0001 | -0.36 | [-3.63;2.92] | 0.8306 |
| **Compulsivity** | **2** | -1.91 | [0.00;-0.90] | 0.0002 | -1.31 | [0.00;-0.41] | 0.0043 | -0.60 | [-1.77;0.58] | 0.3209 |
| **3** | -3.79 | [0.00;-2.73] | <.0001 | -2.07 | [0.00;-1.12] | <.0001 | -1.72 | [-2.97;-0.47] | 0.0069 |
| **4** | -4.28 | [0.00;-3.20] | <.0001 | -2.68 | [0.00;-1.73] | <.0001 | -1.60 | [-2.87;-0.33] | 0.0139 |
| **5** | -4.22 | [0.00;-3.13] | <.0001 | -3.06 | [0.00;-2.10] | <.0001 | -1.16 | [-2.45;0.13] | 0.0789 |
| **6** | -4.95 | [0.00;-3.86] | <.0001 | -3.46 | [0.00;-2.50] | <.0001 | -1.49 | [-2.77;-0.20] | 0.0236 |
| **18** | -6.22 | [0.00;-4.57] | <.0001 | -6.01 | [0.00;-4.04] | <.0001 | -0.22 | [-2.67;2.23] | 0.8611 |
| **Purpose Fullness** | **2** | -3.54 | [0.00;-2.39] | <.0001 | -2.31 | [0.00;-1.28] | <.0001 | -1.24 | [-2.57;0.10] | 0.0705 |
| **3** | -5.71 | [0.00;-4.50] | <.0001 | -3.97 | [0.00;-2.90] | <.0001 | -1.73 | [-3.16;-0.31] | 0.0168 |
| **4** | -6.29 | [0.00;-5.06] | <.0001 | -4.48 | [0.00;-3.41] | <.0001 | -1.81 | [-3.26;-0.36] | 0.0145 |
| **5** | -6.49 | [0.00;-5.25] | <.0001 | -5.09 | [0.00;-3.99] | <.0001 | -1.40 | [-2.88;0.07] | 0.0611 |
| **6** | -7.12 | [0.00;-5.89] | <.0001 | -5.81 | [0.00;-4.72] | <.0001 | -1.31 | [-2.77;0.16] | 0.0797 |
| **18** | -9.49 | [0.00;-7.60] | <.0001 | -8.28 | [0.00;-6.03] | <.0001 | -1.21 | [-4.01;1.58] | 0.3938 |
|  |  | **Active** | | | **Sham** | | | **Diff** | | |
| **CO** | **Week/ Visit** | **Adj. Means** | **95%CI** | **p-value** | **Adj. Means** | **95%CI** | **p-value** | **Adj. Means** | **95%CI** | **p-value** |
| **Total**  **TCQ** | **2** | -11.78 | [0.00;-7.52] | <.0001 | -6.28 | [0.00;-2.51] | 0.0011 | -5.50 | [-10.56;-0.43] | 0.0334 |
| **3** | -19.17 | [0.00;-14.91] | <.0001 | -11.47 | [0.00;-7.65] | <.0001 | -7.69 | [-12.78;-2.61] | 0.0031 |
| **4** | -20.05 | [0.00;-15.79] | <.0001 | -14.08 | [0.00;-10.29] | <.0001 | -5.97 | [-11.04;-0.89] | 0.0212 |
| **5** | -21.62 | [0.00;-17.34] | <.0001 | -16.01 | [0.00;-12.18] | <.0001 | -5.61 | [-10.71;-0.50] | 0.0315 |
| **6** | -24.31 | [0.00;-20.04] | <.0001 | -18.60 | [0.00;-14.79] | <.0001 | -5.71 | [-10.81;-0.62] | 0.0281 |
| **18** | -30.49 | [0.00;-24.07] | <.0001 | -29.17 | [0.00;-21.55] | <.0001 | -1.32 | [-10.80;8.16] | 0.7845 |
| **Emotion** | **2** | -2.07 | [0.00;-1.04] | <.0001 | -0.92 | [0.00;0.00] | 0.0502 | -1.16 | [-2.39;0.07] | 0.0653 |
| **3** | -3.79 | [0.00;-2.76] | <.0001 | -1.90 | [0.00;-0.97] | <.0001 | -1.89 | [-3.12;-0.65] | 0.0028 |
| **4** | -3.89 | [0.00;-2.85] | <.0001 | -2.74 | [0.00;-1.82] | <.0001 | -1.15 | [-2.38;0.09] | 0.0685 |
| **5** | -4.20 | [0.00;-3.16] | <.0001 | -3.14 | [0.00;-2.21] | <.0001 | -1.06 | [-2.30;0.19] | 0.0952 |
| **6** | -4.56 | [0.00;-3.52] | <.0001 | -3.56 | [0.00;-2.63] | <.0001 | -1.00 | [-2.24;0.24] | 0.1133 |
| **18** | -5.26 | [0.00;-3.70] | <.0001 | -5.39 | [0.00;-3.54] | <.0001 | 0.13 | [-2.17;2.43] | 0.9118 |
| **Expectancy** | **2** | -3.08 | [0.00;-1.64] | <.0001 | -1.63 | [0.00;-0.35] | 0.0126 | -1.45 | [-3.17;0.26] | 0.0958 |
| **3** | -5.70 | [0.00;-4.26] | <.0001 | -3.56 | [0.00;-2.27] | <.0001 | -2.14 | [-3.86;-0.42] | 0.0147 |
| **4** | -5.86 | [0.00;-4.42] | <.0001 | -4.11 | [0.00;-2.83] | <.0001 | -1.75 | [-3.47;-0.03] | 0.0457 |
| **5** | -6.54 | [0.00;-5.09] | <.0001 | -4.85 | [0.00;-3.55] | <.0001 | -1.69 | [-3.42;0.04] | 0.0549 |
| **6** | -7.65 | [0.00;-6.20] | <.0001 | -5.86 | [0.00;-4.57] | <.0001 | -1.79 | [-3.51;-0.06] | 0.0422 |
| **18** | -9.73 | [0.00;-7.56] | <.0001 | -9.49 | [0.00;-6.91] | <.0001 | -0.24 | [-3.45;2.97] | 0.8823 |
| **Compulsivity** | **2** | -2.51 | [0.00;-1.43] | <.0001 | -1.42 | [0.00;-0.46] | 0.0037 | -1.09 | [-2.38;0.19] | 0.0941 |
| **3** | -3.86 | [0.00;-2.78] | <.0001 | -2.06 | [0.00;-1.09] | <.0001 | -1.80 | [-3.09;-0.52] | 0.0061 |
| **4** | -4.13 | [0.00;-3.05] | <.0001 | -2.63 | [0.00;-1.67] | <.0001 | -1.50 | [-2.79;-0.22] | 0.0219 |
| **5** | -4.21 | [0.00;-3.13] | <.0001 | -2.94 | [0.00;-1.97] | <.0001 | -1.27 | [-2.56;0.03] | 0.0552 |
| **6** | -4.87 | [0.00;-3.78] | <.0001 | -3.39 | [0.00;-2.43] | <.0001 | -1.47 | [-2.76;-0.18] | 0.0252 |
| **18** | -6.05 | [0.00;-4.43] | <.0001 | -5.91 | [0.00;-3.99] | <.0001 | -0.14 | [-2.53;2.26] | 0.9110 |
| **Purpose Fullness** | **2** | -4.14 | [0.00;-2.91] | <.0001 | -2.27 | [0.00;-1.18] | <.0001 | -1.87 | [-3.33;-0.41] | 0.0121 |
| **3** | -5.84 | [0.00;-4.61] | <.0001 | -3.90 | [0.00;-2.80] | <.0001 | -1.94 | [-3.40;-0.47] | 0.0096 |
| **4** | -6.19 | [0.00;-4.96] | <.0001 | -4.54 | [0.00;-3.45] | <.0001 | -1.65 | [-3.11;-0.18] | 0.0274 |
| **5** | -6.69 | [0.00;-5.46] | <.0001 | -5.03 | [0.00;-3.92] | <.0001 | -1.66 | [-3.14;-0.19] | 0.0268 |
| **6** | -7.27 | [0.00;-6.03] | <.0001 | -5.74 | [0.00;-4.64] | <.0001 | -1.53 | [-3.00;-0.06] | 0.0418 |
| **18** | -9.43 | [0.00;-7.58] | <.0001 | -8.22 | [0.00;-6.02] | <.0001 | -1.22 | [-3.95;1.51] | 0.3821 |

Table S10. Logistic regression for prediction of quitting at week 6 based on change in craving (VAS3-VAS2) in the first treatment session.

|  | **ITT** | | | **CO** | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Odds Ratio** | **Wald** | **p-value** | **Odds Ratio** | **Wald** | **p-value** |
| **Active** | 0.63 | 8.26 | 0.004 | 0.55 | 9.61 | 0.001 |
| **Sham** | 1.17 | 0.53 | 0.464 | 1.19 | 0.72 | 0.396 |

The change in craving during the first session (VAS3-VAS2) significantly predicts quitting in the Active but not the Sham group in both analysis sets. The odds ratio is 0.63 for the Active ITT cohort and 0.55 for the Active CO cohort. Therefore a *decrease* of 1 point in the VAS3-VAS2 index predicts an increase of 1/0.634 = 1.57 in the probability to quit in the ITT cohort and 1/0.55 = 1.82 in the CO cohort. For example, given that the probability to quit in the Active ITT cohort at week 6 as measured in the present study is 17.5% and the average VAS3-VAS2 is -1.22 (ITT), the probability for quitting in a group of subjects with an average VAS3-VAS2 index of -2.22 would be 17.5\*1.57 = 27.5%. Similarly, given that the probability to quit in the CO cohort is 25.3% and the average VAS3-VAS2 is -1.11 (CO), the probability for quitting in a group of subjects with an average VAS3-VAS2 index of -2.11 would be 25.3\*1.82 = 46.0%.

Table S11. Statistical summary of changes in VAS craving scores during the treatment phase (15 sessions over 3 weeks).

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Main effect** | |  |
| **VAS** | **Group**  **(Active vs. Sham)** | **Time**  **(Reduction over 3 weeks)** | **Interaction**  **(Group x Time)** |
| **1** | F1, 159 = 4.504,  p = 0.0353 | F14, 2226 = 16.794,  p < 0.0001 | F14, 2226 = 1.791,  p = 0.0345 |
| **2** | F1, 159 = 4.659,  p = 0.0323 | F14, 2226 = 22.548,  p < 0.0001 | F14, 2226 = 1.795,  p = 0.0339 |
| **3** | *F1, 157 = 3.689,*  *p = 0.0565* | F14, 2198 = 17.034,  p < 0.0001 | *F14,* 2198 *= 0.566,*  *p = 0.8928* |
| **2-1 (Diff)a** | *F1, 159 = 0.122,*  *p = 0.7272* | F14, 2226 = 2.831,  p = 0.0003 | *F14,* 2226 *= 0.273,*  *p = 0.9963* |
| **3-1 (Diff)b** | *F1, 157 = 0.068,*  *p = 0.7933* | F14, 2198 = 3.216,  p < 0.0001 | *F14,* 2198 *= 1.164,*  *p = 0.295* |

*Italic font* – No significant difference; **a** The effect of provocation; **b** The effect of acute treatment

Table S12. Change from Baseline in FTND

|  | | **Active** | | **Sham** | | **Diff** | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Adj. Means** | **95% CI** | **Adj. Means** | **95% CI** | **Adj. Means** | **95% CI** | **p-value** |
| **ITT** | **Week 6** | -2.21 | [0.00;-1.49] | -1.65 | [0.00;-1.00] | -0.55 | [-1.18;0.07] | 0.0815 |
| **Week 18** | -3.32 | [0.00;-2.34] | -3.27 | [0.00;-2.18] | -0.05 | [-1.22;1.13] | 0.9389 |
| **CO** | **Week 6** | -2.21 | [0.00;-1.48] | -1.65 | [0.00;-0.99] | -0.56 | [-1.21;0.08] | 0.0856 |
| **Week 18** | -3.32 | [0.00;-2.33] | -3.29 | [0.00;-2.19] | -0.03 | [-1.21;1.16] | 0.9639 |

Table S13. Change from Baseline in MNWS - Participant Self-Reported

|  | | **Active** | | **Sham** | | **Diff** | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Adj. Means** | **95% CI** | **Adj. Means** | **95% CI** | **Adj. Means** | **95% CI** | **p-value** |
| **ITT** | **2 weeks** | 1.76 | [0.48;3.03] | 2.85 | [1.72;3.99] | -1.10 | [-2.58;0.39] | 0.1474 |
| **3 weeks** | -0.19 | [0.00;1.15] | 1.11 | [0.00;2.30] | -1.30 | [-2.87;0.28] | 0.1067 |
| **4 weeks** | -0.60 | [0.00;0.77] | 0.24 | [0.00;1.44] | -0.84 | [-2.45;0.77] | 0.3057 |
| **5 weeks** | -1.42 | [0.00;-0.03] | -0.77 | [0.00;0.44] | -0.64 | [-2.27;0.99] | 0.4401 |
| **Week 6** | -1.51 | [0.00;-0.14] | -1.79 | [0.00;-0.57] | 0.28 | [-1.35;1.90] | 0.7386 |
| **Week 18** | -2.89 | [0.00;-0.79] | -2.99 | [0.00;-0.51] | 0.11 | [ -2.99;3.20] | 0.9456 |
| **CO** | **2 weeks** | 1.31 | [0.00;2.67] | 2.33 | [1.13;3.53] | -1.02 | [-2.63;0.59] | 0.2128 |
| **3 weeks** | -0.42 | [0.00;0.94] | 0.97 | [0.00;2.19] | -1.39 | [-3.01;0.22] | 0.0911 |
| **4 weeks** | -0.73 | [0.00;0.63] | -0.09 | [0.00;1.11] | -0.64 | [-2.25;0.98] | 0.4388 |
| **5 weeks** | -1.57 | [0.00;-0.21] | -1.07 | [0.00;0.15] | -0.50 | [-2.13;1.12] | 0.5445 |
| **Week 6** | -1.79 | [0.00;-0.43] | -2.11 | [0.00;-0.90] | 0.32 | [-1.30;1.94] | 0.6971 |
| **Week 18** | -2.95 | [0.00;-0.91] | -3.13 | [0.00;-0.71] | 0.18 | [-2.83;3.19] | 0.9074 |

Table S14. Change from Baseline in MNWS - Observer Reported

|  | | **Active** | | | **Sham** | | | **Diff** | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Adj. Means** | **95% CI** | **p-value** | **Adj. Means** | **95% CI** | **p-value** | **Adj. Means** | **95% CI** | **p-value** |
| **ITT** | **2 weeks** | 0.36 | [0.00;0.77] | 0.0814 | 0.77 | [0.41;1.14] | <.0001 | -0.41 | [-0.89;0.06] | 0.0873 |
| **3 weeks** | 0.29 | [0.00;0.72] | 0.1772 | 0.29 | [0.00;0.67] | 0.1367 | 0.00 | [-0.50;0.51] | 0.9903 |
| **4 weeks** | 0.20 | [0.00;0.63] | 0.3703 | 0.37 | [0.00;0.76] | 0.0569 | -0.17 | [-0.69;0.34] | 0.5038 |
| **5 weeks** | -0.03 | [0.00;0.41] | 0.8823 | 0.11 | [0.00;0.50] | 0.5841 | -0.14 | [-0.66;0.38] | 0.5920 |
| **Week 6** | -0.36 | [0.00;0.08] | 0.1047 | -0.01 | [0.00;0.38] | 0.9737 | -0.36 | [-0.87;0.16] | 0.1786 |
| **Week 18** | -0.37 | [0.00;0.30] | 0.2746 | -0.48 | [0.00;0.31] | 0.2335 | 0.11 | [-0.87;1.10] | 0.8250 |
| **CO** | **2 weeks** | 0.33 | [0.00;0.78] | 0.1481 | 0.67 | [0.27;1.07] | 0.0012 | -0.34 | [-0.87;0.20] | 0.2153 |
| **3 weeks** | 0.21 | [0.00;0.66] | 0.3609 | 0.22 | [0.00;0.63] | 0.2858 | -0.01 | [-0.55;0.52] | 0.9626 |
| **4 weeks** | 0.18 | [0.00;0.63] | 0.4265 | 0.31 | [0.00;0.71] | 0.1320 | -0.13 | [-0.66;0.41] | 0.6385 |
| **5 weeks** | -0.09 | [0.00;0.36] | 0.6865 | 0.02 | [0.00;0.42] | 0.9375 | -0.11 | [-0.65;0.43] | 0.6921 |
| **Week 6** | -0.37 | [0.00;0.08] | 0.1101 | -0.08 | [0.00;0.32] | 0.6940 | -0.29 | [-0.82;0.25] | 0.2980 |
| **Week 18** | -0.42 | [0.00;0.26] | 0.2235 | -0.55 | [0.00;0.25] | 0.1778 | 0.13 | [-0.86;1.13] | 0.7929 |

Table S15. Adverse Events Compared to dTMS for the treatment of MDD and OCD

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **dTMS as an Aid in Smoking Cessation**  **(N=123 Participants)** | | **dTMS for treatment of MDD**  **(N=111 Participants)** | | **dTMS for treatment of OCD**  **(N=48 Participants)** | |
| **Anticipated Event** | **# of Participants** | **Incidence** | **# of Participants** | **Incidence** | **# of Participants** | **Incidence** |
| **Pain in Jaw** | 2 | 1.63% | 11 | 10.2% | 4 | 8.33% |
| **Application Site Discomfort** | 14 | 11.38% | 21 | 19.4% | 2 | 4.16% |
| **Application Site Pain** | 5 | 4.07% | 27 | 25.0% | 6 | 12.50% |
| **Headache** | 30 | 24.39% | 51 | 47.2% | 18 | 37.50% |
| **Muscle Twitching** | 6 | 4.88% | 7 | 6.5% | 1 | 2.08% |
| **Back Pain** | 8 | 6.50% | 5 | 4.6% | 2 | 4.17% |
| **Anxiety** | 0 | 0.00% | 6 | 5.6% | 6 | 12.50% |
| **Insomnia** | 1 | 0.81% | 8 | 7.4% | 1 | 2.08% |

Table S16. Blinding Assessment according to treatment Question (ITT)

|  | | **Active** | | **Sham** | |
| --- | --- | --- | --- | --- | --- |
| **N** | **%** | **N** | **%** |
| **ITT** | **Strong belief I received REAL** | 23 | 21.30% | 18 | 14.29% |
| **Low confidence or don’t know** | 82 | 75.93% | 102 | 80.95% |
| **Strong belief I received SHAM** | 3 | 2.78% | 6 | 4.76% |
| **Total** | 108 | 100.00% | 126 | 100.00% |
| **CO** | **Strong belief I received REAL** | 16 | 21.62% | 12 | 12.77% |
| **Low confidence or don’t know** | 55 | 74.32% | 77 | 81.91% |
| **Strong belief I received SHAM** | 3 | 4.05% | 5 | 5.32% |
| **Total** | 74 | 100.00% | 94 | 100.00% |

After the first treatment session, participants were asked which treatment (active or sham) they thought they received. The most frequent answer of participants in both the active (76%) and sham (81%) groups was that they had low confidence or did not know which treatment they received, with no significant difference between the groups (p = 0.65).

## Safety

No notable differences in vital signs, weight, or cognition (measured by the mini-mental state exam and the Buschke selective reminding test) were observed between the study groups at any time point. The adverse events reported in the study are typical side effects reported previously with the dTMS system (Table S15) and with other TMS devices, while efficacy was at least similar to medications with regard to relative improvement and effect sizes (active vs. placebo).8-11 The most frequent adverse event was headache (24.39% and 17.99% in the active and sham groups, respectively), with no statistically significant difference between the treatment groups. Most other forms of pain and discomfort (administration/application site pain/discomfort, pain in jaw, facial pain, muscle pain/spasm/twitching, neck pain, etc.) were reported as either mild or moderate and resolved after treatment. In most of the participants, the discomfort or pain disappeared once the participant became accustomed to the treatment. Finally, although a statistically significant difference was found between the percent of participants reporting any adverse event between the active and sham groups (53.66% and 35.97%, respectively; χ2 = 8.2744, p = 0.0040), there were no significant differences found between the treatment groups for any specific adverse event, except for application site discomfort (p = 0.0043).

There were four serious adverse events (SAE) reported in the study, of which three were assessed by the investigator as not related to the device treatment. These included a ruptured diverticulum, disturbance in social behavior, and an ectopic pregnancy. One SAE of tinnitus was reported as possibly related to the treatment. This participant reported feeling fullness in both ears, "like water in the ears" and indicated that the feeling developed as the treatments were ongoing. The participant did not complain of hearing loss or pain. The participant was terminated from the study after completing 12 active treatments, due to the investigator believing it is in the best interest of the participant, for safety reasons.

The dropout rate (until week 6) was 39% for the active group and 32% for the sham group, without significant difference between groups.

References

1 Dinur-Klein, L. *et al.* Smoking cessation induced by deep repetitive transcranial magnetic stimulation of the prefrontal and insular cortices: a prospective, randomized controlled trial. *Biol. Psychiatry* **76**, 742-749 (2014).

2 Fiocchi, S. *et al.* Deep transcranial magnetic stimulation for the addiction treatment: electric field distribution modeling. *IEEE Journal of Electromagnetics, RF and Microwaves in Medicine and Biology* **2**, 242-248 (2018).

3 Gonzales, D. *et al.* Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, versus placebo or sustained-release bupropion for smoking cessation: A randomized controlled trial. *JAMA* **296**, 56-63 (2006).

4 Hurt, R. D. *et al.* A comparison of sustained-release bupropion and placebo for smoking cessation. *N. Engl. J. Med.* **337**, 1195-1202 (1997).

5 Jorenby, D. E. *et al.* A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N. Engl. J. Med.* **340**, 685-691 (1999).

6 Tashkin, D. *et al.* Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *The Lancet* **357**, 1571-1575 (2001).

7 Watsky, E., Gong, J., Williams, K. & Reeves, K. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. Jama 296: 4755Gotti C, Zoli M, Clementi F (2006) Brain nicotinic acetylcholine receptors: native subtypes and their relevance. *Int. J. Obes. Relat. Metab. Disord.* **28**, 27881Grabowski (2006).

8 Ekhtiari, H. *et al.* Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine: A consensus paper on the present state of the science and the road ahead. *Neurosci. Biobehav. Rev.* (2019).

9 Lefaucheur, J.-P. *et al.* Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin. Neurophysiol.* **125**, 2150-2206 (2014).

10 Zibman, S., Pell, G. S., Barnea-Ygael, N., Roth, Y. & Zangen, A. Application of transcranial magnetic stimulation for major depression: Coil design and neuroanatomical variability considerations. *Eur. Neuropsychopharmacol.* (2019).

11 Food, U. (2019).