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

Supplementary Materials

1.1 Supplementary Methods

1.2 Subjects

1.2.1 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.

1.2.2 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.

1.3 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]

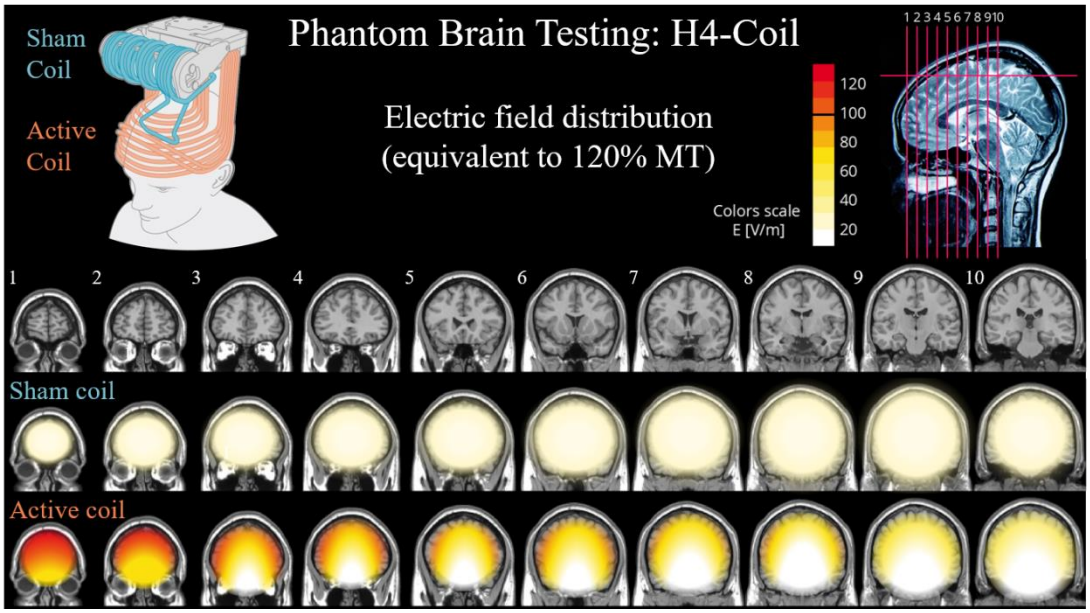

Figure S1. Distribution of electric fields induced by the active and sham coils. The electric field distribution was measured in a model of the human head (15 x 13 x 18 cm), filled with physiologic saline solution. The colored field maps for the active H4 and sham coils indicate the electrical field 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.

1.4 Statistical analysis

1.4.1.1 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.

1.4.1.2 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).

1.4.1.3 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.

1.4.2 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.

1.5 Supplementary Results

Enrollment and Randomization of Patients.

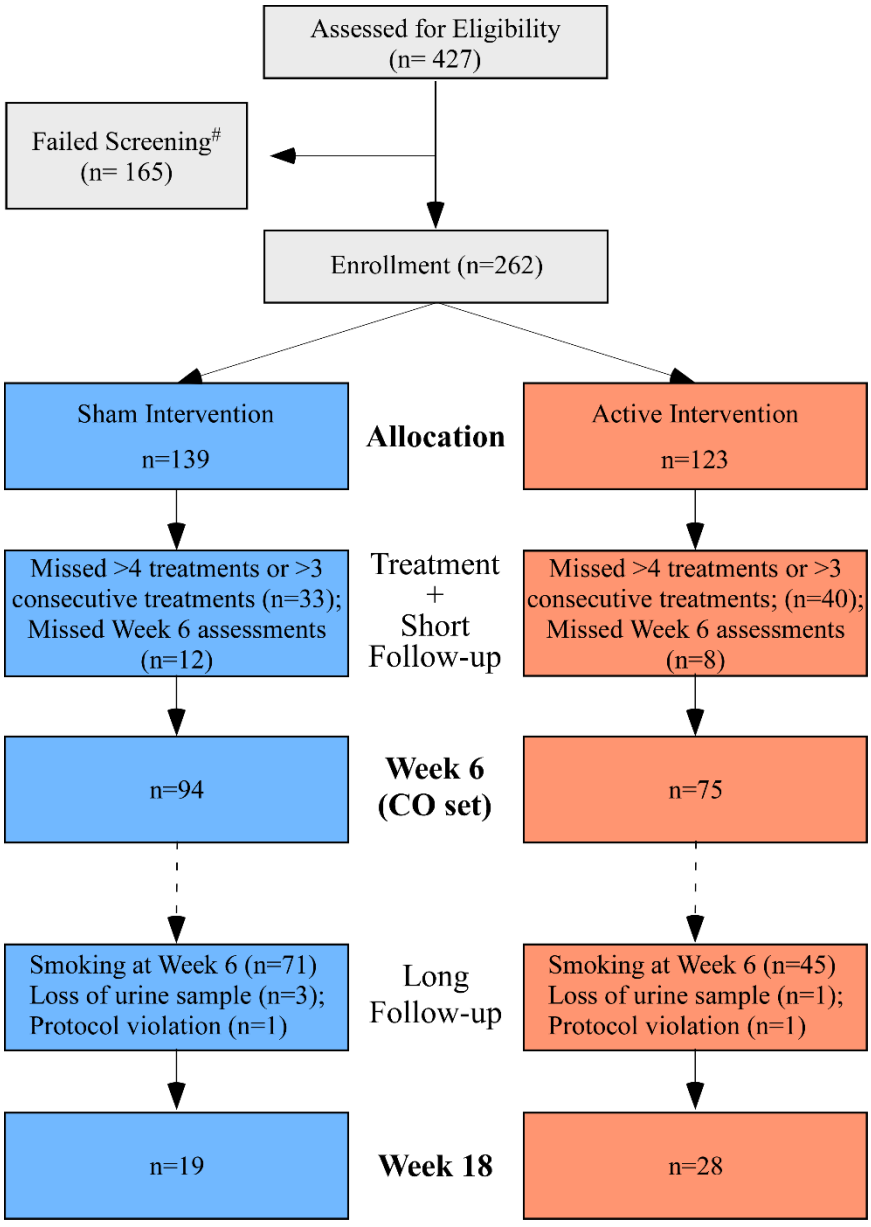

Figure S2. Dropouts and participants lost to follow-up were classified as non-abstinent. *Did not meet inclusion/exclusion criteria or refused participation. Completers (CO) were subjects who completed both the rTMS treatment phase and the week 6 assessments relevant to the 4-week CQR determination. The ITT-Safety (ITT-S) cohort included all 262 randomized participants. The ITT-Efficacy (ITT-E) cohort included all randomized participants who had at least one post-baseline assessment. Twenty seven subjects were excluded from the ITT-S (n = 262) cohort to form the ITT-E (n = 235) cohort, of which twenty four dropped out of the study after only one or two treatment visits due to inability to commit to the study schedule.

1.5.1 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/m^2)		**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)	

			Active	Sham	p-value
	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)	
	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)	0.7283(#)
	>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	
	Mean (SD)	5.5 (1.98)	5.3 (2.04)	0.2682(*)
	Median [Range]	6.0 [0;10]	5.0 [1;10]	
MNWS (self-reported)	**N**	123	139	
	Mean (SD)	7.6 (5.42)	8.1 (6.12)	0.4502(*)
	Median [Range]	6.0 [0;28]	7.0 [0;29]	
MNWS (observer reported)	**N**	123	139	
	Mean (SD)	0.8 (1.39)	1.4 (1.92)	0.0049(*)
	Median [Range]	0.0 [0;8]	1.0 [0;12]	
TCQ (Total Score)	**N**	123	139	
	Mean (SD)	44.9 (15.77)	42.7 (18.10)	0.2913(*)
	Median [Range]	43.0 [14;84]	43.0 [0;84]	
TCQ – Emotion	**N**	123	139	
	Mean (SD)	7.7 (5.43)	7.6 (5.74)	0.8819(*)
	Median [Range]	7.0 [0;21]	7.0 [0;21]	
TCQ - Expectancy	**N**	123	139	
	Mean (SD)	15.0 (4.52)	14.6 (5.81)	0.4784(*)
	Median [Range]	15.0 [4;21]	16.0 [0;21]	
TCQ - Compulsivity	**N**	123	139	
	Mean (SD)	8.7 (5.37)	7.9 (5.49)	0.2101(*)

		Active	Sham	p-value
	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 (rather than the 4-week CQR primary outcome measure) **until week 18 is 12/75 (16%) and 3/94 (3.2%) in the Active and Sham groups, respectively (χ^2 = 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	$F_{1, 159} = 4.504$, $p = 0.0353$	$F_{14, 2226} = 16.794$, $p < 0.0001$	$F_{14, 2226} = 1.791$, $p = 0.0345$
2	$F_{1, 159} = 4.659$, $p = 0.0323$	$F_{14, 2226} = 22.548$, $p < 0.0001$	$F_{14, 2226} = 1.795$, $p = 0.0339$
3	*$F_{1, 157} = 3.689$, $p = 0.0565$*	$F_{14, 2198} = 17.034$, $p < 0.0001$	*$F_{14, 2198} = 0.566$, $p = 0.8928$*
2-1 (Diff)[a]	*$F_{1, 159} = 0.122$, $p = 0.7272$*	$F_{14, 2226} = 2.831$, $p = 0.0003$	*$F_{14, 2226} = 0.273$, $p = 0.9963$*
3-1 (Diff)[b]	*$F_{1, 157} = 0.068$, $p = 0.7933$*	$F_{14, 2198} = 3.216$, $p < 0.0001$	*$F_{14, 2198} = 1.164$, $p = 0.295$*

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%

		Active		Sham	
		N	%	N	%
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 ($p = 0.65$).

1.6 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; $\chi 2 = 8.2744$, $p = 0.0040$), 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.

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