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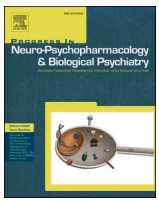

Does deep TMS really works for smoking cessation? A prospective, double blind, randomized, sham controlled study

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ABSTRACT

Introduction: A substantial proportion of smokers wishing to quit do not stop smoking when using current therapies to aid cessation. Magnetic pulses to specific brain areas designated as transcranial magnetic stimulation may modulate brain activity and thereby change chemical dependencies. Deep transcranial magnetic stimulation (dTMS) with the H4 coil stimulates neuronal pathways in the lateral prefrontal cortex and insula bilaterally, areas involved in tobacco addiction. Objective: To evaluate the efficacy and safety of dTMS with T4 coil in smoking cessation. Methods: In a double blind, controlled clinical trial, adult smokers of at least 10 cigarettes/day were randomized to active ($n = 50$) versus sham dTMS ($n = 50$). The protocol involved up to 21 sessions administered over up to 12 weeks. Tobacco use was monitored by self-report and confirmed by expired air monoximetry (at each dTMS visit) and blood cotinine (at the screening visit and at the end of sessions). Participants completed abstinence, mood and cognition scales at determined timepoints during follow-up. Results: In the intention to-treat-analysis, the cessation rate of the intervention and control groups was 14.0%. The reported side effects were as expected for this procedure. Although there were no serious adverse events, three participants were withdrawn according to safety criteria. Conclusion: Active treatment with dTMS H4 coil was safe but not effective for smoking cessation.

1. Introduction

About 1.3 billion people use tobacco worldwide. >80% live in low- and middle-income countries, where the burden of tobacco-related disease and death is heavier (World Health Organization (WHO), 2022). Cigarette smoking kills >8 million people a year (World Health Organization (WHO), 2022). Standard treatment of tobacco addiction consists of pharmacotherapy and behavioral support. However, given that a substantial proportion of smokers who receive standard treatment do not quit cigarettes even for a brief period, novel approaches to aid cessation are needed.

Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive neuromodulation method capable of inhibiting or activating brain areas through the oscillation of magnetic pulses, based on Faraday's principle of electromagnetic induction (Faraday, 1832). Since the publication of first studies in the 1990s, showing safety and efficacy in the use of rTMS for treatment of depression (McClintock et al., 2018), interest in applying this technique to other psychiatric and neurological disorders, including chemical dependences, has grown, and includes treatment of tobacco addiction (Rachid, 2016).

Tseng et al. (Tseng et al., 2022) (2022) conducted a systematic review and meta-analysis to identify randomized controlled trials that investigated the efficacy of non-invasive brain stimulation method for smoking cessation. In their conclusion, prefrontal target interventions appear to reduce the number of cigarettes smoked with good acceptability; furthermore, standard rTMS activating this brain region was associated with the largest improvement.

In 2005, a coil modification on standard TMS method made it

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possible to achieve directly deeper targets. Named deep Transcranial Magnetic Stimulation (dTMS), this procedure activates brain structures at up to 5.5 cm from the scalp, compared to 2 cm with the standard coil rTMS (Zangen et al., 2005). This method of cerebral neuromodulation has been shown to be safe and well tolerated and FDA (Food Drug Administration, USA) approved its clinical use for treating depression (Perera et al., 2016) and obsessive-compulsive disorder (Rapinesi et al., 2019).

One of the brain areas that modulates tobacco addiction is the insula, a brain structure which appears to be targeted by dTMS. The insula may act as a critical neuro-substrate for maintenance of addiction, in part by controlling drug desirability, but also by its potential role in regulating withdrawal symptoms during abstinence (Naqvi et al., 2007; Moran et al., 2018; Ibrahim et al., 2019).

To test the effect of dTMS on smoking rates, a pilot study (Dinur-Klein et al., 2014) randomized 115 participants to active dTMS with 1 Hz or 10 Hz, or sham dTMS, with the application of 13 sessions during five weeks of follow-up Dinur-Klein et al). Results indicated a significant reduction in urinary cotinine levels in the 10 Hz treatment group as well as an abstinence rate of 44%. Based on these findings, a multicenter study (Zangen et al., 2021) was conducted as a double-blind, randomized, sham-controlled clinical trial by Zangen et al. Eligible persons were randomized to active ($n = 108$) or sham ($n = 126$) dTMS applied during 18 sessions over 6 weeks. Our center should have participated in this multicenter protocol conducted by Zangen et al., but due to delays in the regulatory process, we carry out the same protocol in a single center.

We performed a randomized control study using the same H4 coil and the same protocol of stimulation as suggested by Dinur-Klein et al., and followed by Zangen et al., to validate the efficacy of this protocol on smoking cessation.

2. Methods

2.1. Study design

The trial was placebo-controlled (sham), randomized, double-blind, unicentric clinical trial. Conducted in Sao Paulo, Brazil, with active enrollment from July 2017 to December 2021. Candidates were recruited from the general population. The study was approved in the submission process by the Institutional Ethical Committee (CAAE 35068014.4.0000.0068) of the University of São Paulo (Heart Institute record number 052/16/021) and registered at clinicaltrial.gov (NCT03264313). All participants completed the Free and Informed Consent Form before starting any study activities.

2.2. Eligibility criteria

Men and women aged between 22 and 70 years who were chronic smokers (for more than one year) with cigarette consumption >10 cigarettes/day and no period of abstinence for >3 months during the past year were eligible, if they were willing and motivated to quit smoking.

2.3. Exclusion criteria

Presence of dTMS contraindications according to a standard safety questionnaire (Keel and Smith, 2001); current use of other smoking cessation intervention; psychiatric disorder Axis I, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (American Psychiatry Association, 2013) (DSM-5) with the exception of depressive and anxiety disorders, provided they were stable (maintenance of medication for the last 3 months and without planned changes until the end of follow-up); substance or drug abuse or dependence at present or in the last year prior to selection; use of any other tobacco or nicotine sources (nicotine replacement therapy, electronic cigarettes, chewed tobacco, etc); subjects at high risk of violence or suicide assessed during the selection interview; presence of any unstable physical illness; significant neurological disorder; personal history of epilepsy, known family cases of epilepsy or increased personal risk of seizure of any origin; frequent and/or severe headaches; significant hearing loss and/or tinnitus; previous rTMS treatment; participation in other clinical research during the 30 days before study start and pregnancy/lactation.

Use of medications for general medical conditions was allowed as was use of the following:

- Zolpidem up to 10 mg/day orally or zolpidem CR (6.25 or 12.5 mg/day orally).
- Benzodiazepines in a dose equivalent to 3.0 mg of lorazepam or less.
- Antidepressants (except bupropion).

All participants underwent neuropsychological evaluation before being considered eligible. The evaluation consisted of Structured Clinical Interview for DSM-5 (SCID – 5) (First et al., 2016), Hamilton Depression Rating Scale (Ham—D) (Haminton, 1960), Hamilton Anxiety Rating Scale (Ham-A) (Hamilton, 1959) and Mini-Mental State Examination (MMSE) (Folstein and McHugh, 1975).

2.4. Randomization and blinding

Eligible participants were randomly allocated in consecutive order into one of two treatment groups, active or sham (1:1 randomization) based on the numerical sequence of previously prepared electronic cards. The cards were delivered by the device company (Brainsway®) and were indistinguishable except for the identification number, assigning active or sham treatment. Once a card was designated to a participant, the same card (active or sham) was used for that participant throughout the study. Before start of the session, the individual electronic card was inserted into the device, and it controlled the stimulus to be delivered whether active or sham. The sham and active coils were placed inside the same procedure helmet, and during the session, the device produced the same sounds and superficial artifacts whether an active or sham procedure was conducted. All participants, operators and other staff involved in the study were blinded to the session condition.

A person who was not connected to the clinical team held the identifying card list. For emergency cases, the list could be accessed at once.

2.5. Intervention design

The initial treatment protocol specified the administration of 18 dTMS sessions over 6 weeks, as did the previously reported multicenter dTMS study (Zangen et al., 2021).The protocol schedule was composed of 3 following weeks with daily weekday sessions for a total of 15 sessions, plus 3 weeks with 1 session per week.

However, after 30% of participants completed treatment, the steering committee considered the interim analysis of smoking rates and adjusted the period of treatment by extending the treatment period to 12 weeks, as well as increasing the number of dTMS sessions to 21 with the addition of 3 sessions with biweekly frequency during the additional six weeks. This amendment thus allowed the length of treatment to be compared to the usual length of pharmacological treatment for smoking cessation (Anthenelli et al., 2016). The University ethical committee approved this amendment.

For participants who reported no cigarettes between 10 and 12 weeks, further follow-up was offered that consisted of 3 additional visits, once a month for 3 months, providing a total of 24 weeks of follow-up. At each of these visits, one active dTMS or sham session was performed according to the initial randomization, and CO monoximetry was administered to confirm abstinence. The initial treatment (active or sham) remained blinded at these visits.

2.6. Procedures

Participants were instructed to remain smoke-free for 2 h prior to each visit. Measurement of vital signs (heart rate, blood pressure, temperature) was taken before and at the end of each session and body weight recorded weekly. The motor threshold (MT) was measured at the beginning of the procedure by stimulating the primary motor cortex in the hand region, before administration of dTMS at each session. MT was defined as the lowest stimulation intensity needed to induce visible motor activation of the fingers, preferably thumb movement (corresponding to the abductor pollicis brevis muscle). The individual treatment intensity was calculated as a function of this value (120% of the MT).

Immediately prior to the start of dTMS intervention, the participant was exposed to "smoking provocations." The objective of this procedure was to stimulate areas linked with smoking desire. The Visual Numerical Scale (VNS) quantified the desire to smoke at that moment on a scale between 0 and 10. The provocation procedure consisted of 3 steps and lasted approximately 5 min. Smoking desire was quantified with VNS before starting the provocation (VNS1), immediately after provocation (VNS2) and after the dTMS session (active or sham) (VNS3).

The degree of nicotine dependence was measured using the Fagerström test (Fagerstrom et al., 1990) and the score developed by Issa et al. (Issa, 2012) Withdrawal symptoms were measured with the Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes and Hatsukami, 1986) and the Tobacco Craving Questionnaire (TCQ) (Heishman et al., 2003). MNWS and TCQ were administered before starting sessions (T-1), at the end of the 2nd and 3rd weeks, and then in each further session visit: 4th, 5th, 6th, 8th, 10th and 12thweeks (Fig. 1).

Symptoms of depression and anxiety were evaluated, respectively, by the Ham-D and Ham-A scales. These assessments were applied before the sessions began (T-1), at week 6 and at week 12 (Fig. 1).

Cognitive assessments included Digits (Wechsler, 1997)' Rey's Auditory-Verbal Learning Test (RAVLT) (Malloy-Diniz et al., 2007) and the Trail Making Test (Montiel and Seabra, 2012). The cognitive assessments were administered at the same timepoints as the Hamilton's scales: T-1,week 6, week 12 (Fig. 1).

Cigarette consumption was monitored through self-report (daily diary) and confirmed by carbon monoxide (CO) concentration in exhaled air (CO monoximetry) at all visits and by blood cotinine concentrations, measured in the first session (week 1) and at the end of protocol.

Participants were encouraged, at the first session, to reduce cigarette consumption and asked to try to quit smoking at the end of the first week. If they were still smoking in the beginning of the second week, they were instructed to smoke following the Cue Restricted Smoking (Scholz et al., 2021) behavioral technique. This technique, developed by our group, aims to lessen stimuli associated with smoking by asking the smoker to smoke only alone, while standing and facing a wall, without any accompanying drink, food, or accessories (e.g., books, cell phones, and such).

2.7. Technical specifications of dTMS

dTMS was delivered using a Magstim Rapid2 TMS stimulator (Magstim, UK) equipped with the H4-coil (Braisnway, Israel). The H4 coil stimulates neuronal pathways in the lateral prefrontal cortex and insula bilaterally. All participants wore earplugs throughout all sessions. One session consisted of 10 Hz frequency, delivering 60 cycles of repeated pulses (trains) approximately over 20 min. A total of 1800 pulses were delivered per session. Each cycle consisted of trains lasting 3 s on and 15 s intervals between trains (time off).

2.8. Statistical analysis

Sample size was calculated based on 80% power an 5% alpha error. Expected abstinence rate of 40% versus 10%, respectively in the active and sham group, was based on the pilot dTMS study by Dinur-Klein et al. (Dinur-Klein et al., 2014) The sample number was 80 participants, 40 in each arm. We took into consideration an expected loss of 20%, so inclusion of 100 participants was planned.

Two data sets were used for comparison in the statistical analysis. The intention to treat analysis (ITT) included all randomized participants who received at least one treatment to compare smoking cessation rates in the active and sham groups and the per treatment analysis (PTT) was composed of participants who completed a minimum of 75% of the sessions, for secondary analyses.

Initially, the data were analyzed descriptively. For categorical variables, absolute and relative frequencies were presented, and for numerical variables, summary measures (mean and standard deviation) were calculated.

The presence of associations between two categorical variables was assessed using Chi-Square test, or alternatively, in cases of small samples, Fisher's exact-test. The comparison of paired sample distributions was performed via McNemar's test. Mean comparisons between the two groups were performed using Student's t-test. Normality in data

		Base Line	Treatment								
		T-1	week 1	week 2	week 3	week4	week5	week6	Week8	week10	week12
Neuropsychological Assessment	SCID-5	•									•
	MMSE	•									
	Fargeström	•						•			•
Smoking history		•									
Ham-D and Ham-A		•						•			•
Cognitive assessments		•						•			•
MNWS/TCQ		•		•	•	•	•	•	•	•	•
Physical exam		•									
Pregnancy test		•									
dTMS/Sham sessions			1 a 5	6 a 10	11 a 15	16	17	18	19	20	21
Adverse Events Questionnaire			•••••	•••••	•••••	•	•	•	•	•	•
Provocation (NVS)			•••••	•••••	•••••	•	•	•	•	•	•
Blood Cotinine			•								•
Monoximetry of expired air			•••••	•••••	•••••	•	•	•	•	•	•
Daily cigarette consumption			------	----------	----------	----------	----------	----------	----------	----------	----------
Stop Smoking Orientation			•••••	•••••	•••••	•	•	•	•	•	•
Cue restricted smoking				•••••	•••••	•	•	•	•	•	•

Fig. 1. Timeline for treatment and assessments.
Notes: SCID-5 – Structured Clinical Interview for DSM 5 (Diagnostic and Statistical Manual of Mental Disorders 5th edition), MMSE – Mini *Mental* State Examination, HAM-D - Hamilton scale for depression, HAM-A - Hamilton scale for anxiety, MNWS – Minnesota Nicotine Withdraw Scale, dTMS – deep Transcranial Magnetic Stimulation, NVS- Numeric Visual Scale.

distribution was verified using the Kolmogorov-Smirnov test. In case of violation of this assumption, the non-parametric Mann-Whitney test was used.

Univariate and multivariate logistic regression models were used to assess the effects of treatment, number of sessions and mental disorder on smoking cessation. The adequacy of fit of the multivariate model was evaluated using Hosmer and Lemeshow test.

Linear, logistic and tobit regression models with random effects (Skrondal and Rabe-Hesketh, 2004) were used to evaluate the effects of time and intervention on each of the dependent variables, respectively of numerical, categorical (dichotomous) and numerical nature with censorship limitation (cotinine).

Analyses of cognitive scores were performed using relative differences ((Final Measurement – Initial Measurement)/Initial Measurement x 100%).

For all statistical tests, a significance level of 5% was used. Analyses were performed using the SPSS 20.0 and STATA 17 statistical packages.

2.9. Outcome measures

The primary outcome measure was the two-week continuous abstinence until week 12 in the intent-to-treat efficacy set, as determined by daily smoking diaries confirmed through CO of exhaled air $\leq$3 ppm and also by blood cotinine collected at pretreatment and in the end of active treatment (Cropsey et al., 2014; Issa et al., 2010). The blood cotinine values to prove cessation was <25 ng/ml.

The secondary objectives were 1) to examine whether extension of the treatment period from 6 to 12 weeks affected cigarette consumption and biomarkers (CO and cotinine blood levels); 2) to compare the active and control groups in regard to withdrawal symptoms, cognition and mood (scales/questionnaires assessments) and adverse events and safety; 3) follow-up the abstinence rate at 24 weeks between the participants that quitted smoking at week 12.

3. Results

Among 254 consecutive candidates who presented to the study, the first 100 that were found to meet eligibility criteria were included. They were randomized to active (n = 50) or sham (n = 50) treatment. Participant flow is illustrated by the chart (Fig. 2).

The two groups were similar regarding demographic and clinical variables (Table 1).

3.1. Efficacy analysis – primary endpoint

In analyses using the ITT data set, the abstinence rate in both groups was 14.0% (p = 1.00; 95%CI 5.8%–26.7%). Seven participants stopped smoking in each group, showing no statistical difference between active and sham groups (Table 2).

Logistic regression analysis showed no difference in abstinence rates

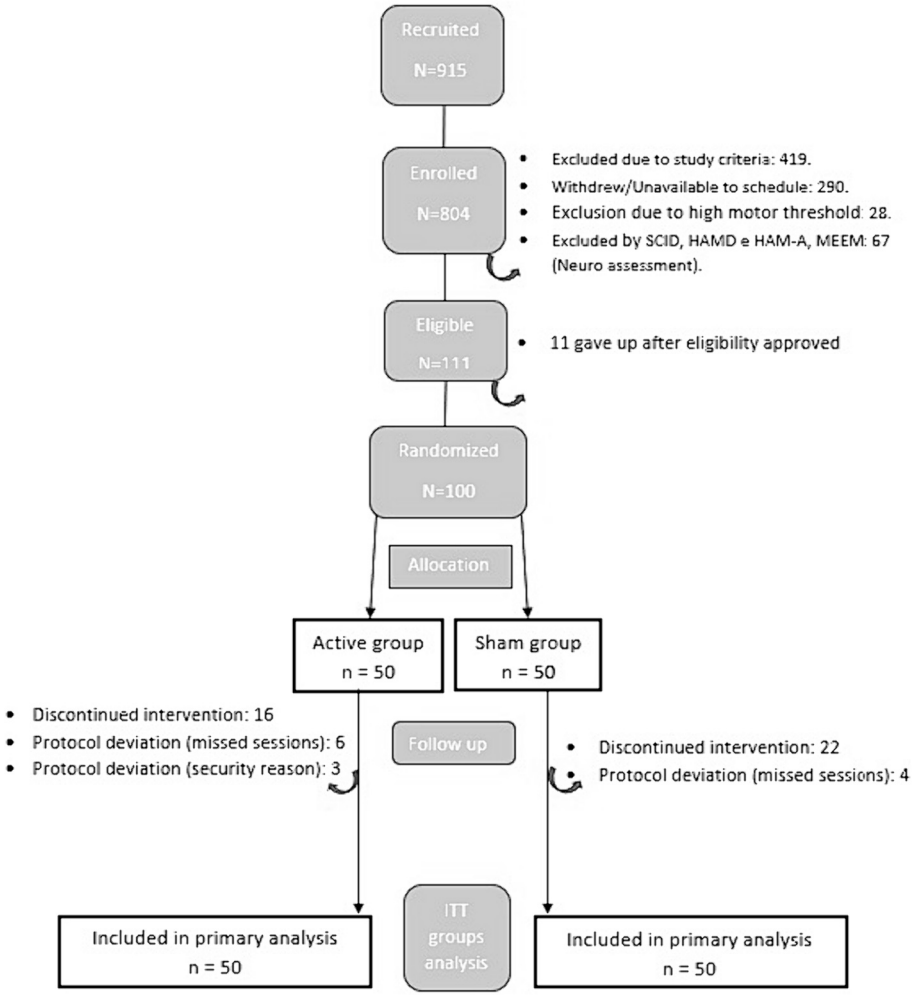

Fig. 2. Flowchart.
Notes: SCID – Structured Clinical Interview for DSM 5 (Diagnostic and Statistical Manual of Mental Disorders 5th edition), MMSE – Mini *Mental* State Examination, HAM-D - Hamilton scale for depression, HAM-A - Hamilton scale for anxiety.

Table 1
Demographic and clinical features of participants.

	Treatment		Total	*p*
	dTMS (*n* = 50)	Sham (*n* = 50)		
Gender, *n* (%)				0.205
Female	20 (40.0)	14 (28.0)	34 (34.0)	
Male	30 (60.0)	36 (72.0)	66 (66.0)	
Age (years)				0.535[b]
Mean ± SD	49.1 ± 12.0	47.6 ± 11.5	48.4 ± 11,7	
Marital status, *n* (%)				0.777[a]
Single	18 (36.0)	23 (46.0)	41 (41.0)	
Married	22 (44.0)	20 (40.0)	42 (42.0)	
Divorced	9 (18.0)	6 (12.0)	15 (15.0)	
Widowed	1 (2.0)	1 (2.0)	2 (2.0)	
Education, *n* (%)				0.380[a]
Basic	0 (0.0)	1 (2.0)	1 (1.0)	
Medium	12 (24.0)	7 (14.0)	19 (19.0)	
Technic	0 (0.0)	1 (2.0)	12 (12.0)	
Incomplete superior	6 (12.0)	6 (12.0)	60 (60.0)	
Complete superior	27 (54.0)	33 (66.0)	7 (7.0)	
Pos-Graduation	5 (10.0)	2 (4.0)	1 (1.0)	
Clinical Comorbidity, *n* (%)				0.509
No	34 (68.0)	37 (74.0)	71 (71.0)	
Yes	16 (32.0)	13 (26.0)	29 (29.0)	
Body mass index (BMI)(kg/m^2)				0.820[b]
Mean ± SD	26.5 ± 4.4	26.3 ± 4.4	26.4 ± 4.4	
Past mental disorder, *n* (%)				0,790
Yes	9 (18.0)	8 (16.0)	17 (17.0)	
Current mental disorder, *n* (%)				0,491[b]
Yes	8 (16.0)	2 (4.0)	10 (10.0)	
Age started smoking (years)				0.709[c]
Mean ± SD	16.6 ± 4.5	17.1 ± 4.6	16.8 ± 4.5	
Total years smoking (years)				0.491[b]
Mean ± SD	31.9 ± 12.3	30.3 ± 10.7	31.1 ± 11.5	
Number cigarettes/day (T0)				0.548[c]
Mean ± SD	20.0 ± 8.6	18.8 ± 7.2	19.4 ± 7.9	
Fagerström score				0.605[b]
Mean ± SD	5.4 ± 2.1	5.1 ± 2.1	5.3 ± 2.1	
Issa score				0.089[c]
Mean ± SD	3.1 ± 0.9	2.7 ± 0.9	2.9 ± 0.9	
Initial Cotinine - classification, *n* (%)				0.672
Between 25 e 200	12 (25.0)	13 (28.9)	25 (26.9)	
Higher than 200	36 (75.0)	32 (71.1)	68 (73.1)	

p – descriptive level of Qui-square test, Fisher Test([a]), t of Student ([b]) or Mann-Whitney Test([c]).

Table 2
Abstinence rate in ITT analysis.

	Active	Sham	*p* Value
Smoking Cessation (*n*100)	14% (7/50)	14% (7/50)	1.00

between the active and sham groups when the treatment period of 6 versus 12 weeks were compared ($p = 1.00$; 95% CI 0.32%–3.09%). Likewise, comparison of the number of treatment sessions did not show differences in abstinence rates between active and sham groups ($p = 0.96$; 95% CI 0.30%–3.61%). Current mental disorder was also not significantly associated with the primary outcome ($p = 0.57$; 95% CI 0.31%–8.58%) (Supplementary material).

3.2. Per -protocol data set (PT)

We have 74 participants, 37 in each arm that complete at least 75% of the sessions. We performed secondary analysis is this subgroup related to cigarettes consumption, scales assessments of abstinence, mood, anxiety, cognitive tests.

It is important to observe that there was reduction in the daily consumption of cigarettes, confirmed through CO in exhaled air and in cotinine plasma levels between the beginning of protocol to the end. Nevertheless, the reduction was observed in both arms (active and sham) (Table 3).

3.3. Assessments of abstinence, mood, anxiety, and VNS

Withdrawal symptoms score (MNWS), controlled by group, time and interaction, showed no statistical difference between groups (Supplementary material).

There was a reduction in the mean of TCQ scores between the first and the last sessions, with statistical significance in time; however, no difference between the groups was seen (Supplementary material).

A comparison of Ham-D and Ham-A scores showed similar score evolution in both groups over time, with no statistical difference between active and control groups (Supplementary material). Mean values remained within the normal range. Likewise, analysis of VNS scores showed no interactions or time and treatment effects (Supplementary material).

3.4. Cognitive assessments

In the active group, mean increases in two sub-items of the RAVLT test were observed: Delayed Evocation ($p = 0.025$; Mean ± SD: 19.36 ± 41.25) and Median Recognition ($p = 0.034$; Mean ± SD: 4. 90 ± 12.44). Mean increases in the active group were also found in the Digits test, subitem Reverse Order ($p = 0.001$; Mean ± SD: 28.97 ± 44.67).

Table 3
Cigarettes consumption, carbon monoxide and cotinine plasma level in pre-treatment and at the end of treatment in active and sham groups, PT analysis.

Per treatment analysis (*n* 74)	Treatment group		*p* value		
	Active	Sham	Treatment	Time	Interaction between treatment and time
Number of cigarettes/days Mean (CI95%)			0.129	<0.001	0.659
Session 1	20.6 (18.0 to 23.2)	17.8 (15.2 to 20.4)			
Final Session	11.0 (8,4 to 13.6)	8.9 (6.3 to 11.5)			
Carbon monoxide ppm Mean (CI95%)			0.086	<0.001	0.937
Session 1	11.6 (9.9 to 13.3)	9.5 (7.8 to 11.2)			
Final Session	8.4 (6.8 to 10.1)	6.4 (4.8 to 8.1)			
Cotinine ng/ml Mean (CI95%)			0.511	0.001	0.828
Session 1	248.9 (204.5 to 293.4)	229.5 (186.4 to 272.6)			
Final Session	169.8 (125.2 to 214.4	142.2 (97.0 to 187.5)			

3.5. Followed- up until week 24

In the active treatment group, among seven participants who quit smoking at week 12, five completed continuous abstinence rate at 24a week of follow up. In the sham treatment group, six participants among seven who quit smoking attended the 24a week followed-up. All these participants maintained continue abstinence at week 24.

3.6. Safety and adverse events

No serious adverse events occurred during this study. Three participants in the active treatment group were withdrawn from the study in the first week because of forearm movements during the application of the pulse series. This recommendation was given by the device company, to avoid the occurrence of seizures. One participant in the sham group discontinued follow-up due to relapse of depression. All these withdrawals were included in ITT analysis.

Side effects during sessions or immediately after were reported by 38% in the active group versus 30% in the sham group.

The most common side effects reported in the active group were headache (10%), scalp pain or burning (10%) and mood change with mild irritability (6%); in the sham group, these corresponded to 8%, 6% and none, respectively. Effects such as: feeling of pressure in the eye, visual clouding, salivation, and dizziness were reported only by the sham group; these effects are technically not involved with the dTMS method.

4. Discussion

Our study is the third using the same coil (H4) and same parameters of stimulation in the field of treating nicotine dependence with dTMS. It is a double-blind, randomized, controlled clinical trial, and, unfortunately, we did not find effect of dTMS on smoking cessation in smokers who were motivated to quit. The continuous abstinence rates in week 12 were 14% in active and in sham groups. These findings contrast with previous initial and subsequent data from literature.

In the pilot study, conducted by Dinur-Klein et al. (Dinur-Klein et al., 2014), the highest cessation rate was observed in the 10 Hz active treatment group using the cigarette provocation suggestion before the session. This group had a cessation rate of 44%; however, the size of the group was small ($n = 16$).

The dTMS multicenter study, conducted by Zangen et al. (Zangen et al., 2021) showed smoking cessation rates in active group of 19.4%, and 8.7% in the sham group, which statistically significant difference ($p = 0.017$). However, despite this difference between the groups, the cessation rate was low, given the complexity and cost of the procedure, and considering the smoking cessation rates obtained with smoking cessation drugs (20).

It is very interesting to observe that in both studies, the multicenter conducted by Zangen and the unicenter conducted by our team, the cessation rates are substantially below the 44% rate observed in the pilot study (Dinur-Klein et al., 2014). These data support the low effectiveness of the dTMS method when used alone and with these parameters, including the use of coil H4. It is important to explain that the parameters and coil used in our study were like those conducted by Zangen et al. (Zangen et al., 2021), since our study would initially be included in a multicenter study, which did not materialize for bureaucratic reasons. The main differences between the studies, were that we extended the protocol to 12 weeks of treatment, exactly because the success rates were extremely lower than we expected, considering 44% of success rate obtained in pilot study. Unfortunately, this action did not affect the success rate, that kept low from 6 weeks until 12 weeks. Also, we incorporated carbon monoxide concentration in exhaled air to confirm tobacco consumption in each visit, and we used rigorous parameter of cotinine in plasma compatible with values that confirm cessation at the end of study.

The choice of how to verify smoking cessation is crucial to avoid biases or confounding factors regarding the reality of cessation rates. These tests, if misused, can cause false positive or false negative and distort the entire interpretation of results (Cropsey et al., 2014; Issa et al., 2010; Kim, 2016).

Considering this scenario, it could impact on decision of FDA to keep the marketing clearance to a device using Transcranial Magnetic Stimulation (TMS) as an aid for short-term smoking cessation in adults; however, a recent study using transcranial magnetic stimulation was carried out, using another coil, H11, and other parameters, specifically focusing on stimulating the insula, conducted by Ibrahim et al. (Ibrahim et al., 2022) They applied dTMS or sham to participants using varenicline, stimulating only insula bilaterally with the H11 coil, with some parameter's changes, and adopting the primary end point at 12 weeks. They achieved a remission rate of 82.4% in the 12th week, statistically significant in relation to the sham group, 30.7% ($p = 0.013$). They used carbon monoxide concentrations and cotinine level in urine to confirm cessation. It was a small, randomized trial with 42 participants, and they tested if the dTMS in combination with varenicline, the most effective smoking cessation drug, could have an additional effect in smoking cessation.

So, the possibility of change the coil, specific for stimulate insula areas, keep the expectation of the Transcranial Magnetic Stimulation may be useful in smoking cessation, of course, considering that this result should be validated by randomized studies with larger samples.

The innovation of using H11 could have an important effect on the success rate, as mentioned by the authors, because the stimulation of several areas with the H4 coil does not allow defining which target had the best effect. With the use of the H11 coil, it was possible to observe improving in cessation until the 12th week. After that, the effect dropped until be equivalent to placebo, in the 26th week. Therefore, the question remains as to which are the best parameters and targets to be stimulated, and also, which dTMS scheme and for how long - in other words, which is the best dTMS protocol for smoking cessation alone or in association with smoking cessation drugs - needs to be extensively studied.

None of the previous mentioned studies applied tests related to cognition. In our study, a complete neuropsychological battery was applied before starting the sessions, halfway through the treatment and at the end, equally in both groups. The results of the cognitive tests indicated a trend of effect towards the active group. This cognitive effect was a secondary outcome, which was not related to smoking cessation. This finding, however, allows us to suggest some effects of dTMS on improving cognitive function, which is in line with what the literature shows. The tests that showed cognitive improvement cover memory, working memory, attention, and learning. The literature reinforces the effect of dTMS on these cognitive abilities (Laskov and Klírová, 2021; Kedzior et al., 2016). Overall, although there is some preliminary evidence suggesting that TMS may have the potential to improve cognition in certain populations, more well-designed studies are needed to confirm and better understand these effects before TMS can be widely used as an enhancement cognitive intervention.

Certainly, it's important to emphasize that these positive cognitive effects in the active treatment group reinforce that the device used in the present study worked appropriately. The higher occurrence of side effects in the active treatment group further supports this notion. Additionally, the fact that the study team was trained by personnel from the initial multicenter study minimizes the likelihood of technical difficulties being a contributing factor to any negative effect observed. Therefore, technical difficulties are unlikely to be the cause of negative effects.

The profile of reported side effects was typical of the method (Perera et al., 2016; Zangen et al., 2021).

4.1. Limitations

The unicentric nature of the study is a limitation, as it may restrict the generalizability of the results to broader populations or different contexts.

Another limiting aspect, the need to modify the study structure mid-course, can be viewed as a limitation in some respects. However, this adjustment ultimately provided the benefit of aligning the assessment of cessation at the 12-week mark with the standard protocol used in anti-smoking studies. This consistency enhances comparability with existing research in the field and facilitates a clearer interpretation of the results within the context of established methodologies. While the alteration may have introduced some complexity or disruption, its alignment with established standards ultimately strengthens the study's methodological rigor and interpretation of findings.

The complex nature of the protocol, particularly the requirement for daily visits over three weeks, posed significant practical limitations for participants. Factors such as the geographic characteristics of the city, including long distances to the hospital, heavy traffic, and employment responsibilities, compounded the challenges faced by participants, many of whom also had childcare obligations. These logistical hurdles likely contributed to a high dropout rate, which approached 50% in both groups.

5. Conclusion

In this double-blind, randomized, placebo-controlled clinical trial (sham), the use of rTMS, with the parameters used and the H4 coil, was not effective in treating smoking cessation.

The potential for cognitive improvements with dTMS is promising. However, it should be evaluated in more detail in future studies.

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Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2024.110997.

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