Journal of Rare Cardiovascular Diseases
ISSN: 2299-3711 (Print) | e-ISSN: 2300-5505 (Online)
www.jrcd.eu
RESEARCH ARTICLE

Cutting-Edge RTMS vs. Sham Stimulation for Tobacco Dependence: A Randomized Controlled Trial on Craving Reduction and Smoking Cessation

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Article History
Received: 08.08.2025
Revised: 15.09.2025
Accepted: 24.10.2025
Published: 05.11.2025

Abstract: ***Background:*** Tobacco dependence remains one of the most pressing global health issues, contributing significantly to the burden of non-communicable diseases. Despite the availability of pharmacological treatments and behavioral therapies, long-term abstinence rates remain suboptimal, often due to persistent cravings and high relapse risk. Craving, a core symptom of tobacco dependence, is closely linked to neural dysfunction in the prefrontal cortex and mesolimbic reward system. Repetitive Transcranial Magnetic Stimulation (rTMS), a non-invasive neuromodulation technique, targets cortical regions such as the dorsolateral prefrontal cortex (DLPFC) to alter activity in neural circuits involved in craving, impulse control, and addiction-related behaviors. Preliminary studies have indicated that high-frequency rTMS can reduce cue-induced craving and support smoking cessation. However, existing trials are limited by small sample sizes, brief follow-up durations, and inconsistent protocols. There remains a need for well-designed randomized controlled trials to establish its clinical effectiveness in nicotine addiction. ***Objectives*** 1. To compare the efficacy of rTMS versus sham stimulation in reducing nicotine cravings. 2. To evaluate smoking cessation rates following rTMS treatment. ***Methods:*** A randomized, double-blind, sham-controlled trial was conducted among 120 adult smokers aged 21–55 years, meeting DSM-5 criteria for Tobacco Use Disorder and motivated to quit. Participants were randomized to two groups: • Active rTMS group (n = 60): Received 10 daily sessions of high-frequency (10 Hz) rTMS over the left DLPFC for 2 consecutive weeks. • Sham group (n = 60): Received identical procedures using a sham coil without active stimulation. Baseline assessments included demographic data, smoking patterns, Fagerström Test for Nicotine Dependence (FTND), and craving ratings using a Visual Analog Scale (VAS). Follow-up assessments were conducted at 2, 4, and 6 weeks post-intervention. Primary outcomes were changes in craving scores and self-reported smoking status. Secondary outcomes included reduction in daily cigarette consumption and FTND scores. ***Results*** At 6 weeks, the active rTMS group demonstrated a significantly greater reduction in craving scores (mean VAS reduction: -5.8 ± 1.4) compared to the sham group (-2.6 ± 1.7; $p < 0.001$). Self-reported 7-day point prevalence abstinence was observed in 40% of the rTMS group versus 17% in the sham group ($p = 0.004$). Mean daily cigarette consumption reduced from 15.2 ± 3.6 to 4.3 ± 2.2 in the rTMS group versus 14.9 ± 3.5 to 9.6 ± 3.1 in the sham group. FTND scores also decreased significantly in the active group. No serious adverse events were reported. ***Conclusion*** High-frequency rTMS is a promising, well-tolerated intervention for reducing nicotine craving and promoting short-term smoking abstinence. Compared to sham stimulation, rTMS significantly reduced craving intensity and daily cigarette use, highlighting its potential as an adjunctive therapy for tobacco dependence.

Keywords: RTMS, Tobacco Use Disorder, Smoking Cessation, Craving, Fagerström Test, Randomized Controlled Trial, Neuromodulation

INTRODUCTION

Tobacco use continues to be a major global health burden, contributing to approximately 8 million deaths each year due to its association with cancer, cardiovascular disease, and chronic respiratory conditions (WHO, 2023). Despite the availability of first-line pharmacotherapies such as nicotine replacement therapy (NRT) and non-nicotine replacement therapy (bupropion, varenicline), smoking cessation remains elusive for many, with relapse rates often exceeding 70% within the first year of quitting attempts. This highlights an urgent need for novel and effective therapeutic strategies to complement existing interventions.

In recent years, Repetitive Transcranial Magnetic Stimulation (rTMS) has emerged as a promising tool in the treatment of substance use disorders (SUDs), including tobacco dependence. rTMS is a non-invasive procedure that uses magnetic pulses to modulate neural activity in targeted brain regions most notably, the dorsolateral prefrontal cortex (DLPFC), which involves executive control, decision-making, and inhibitory regulation of craving-related impulses. Through this mechanism, rTMS may help restore top-down control

over maladaptive reward-seeking behaviors observed in addiction (1,2).

Several studies have provided preliminary support for the utility of rTMS in tobacco use disorder. Systematic reviews and meta-analyses report that high-frequency stimulation of the DLPFC reduces cue-induced craving and may increase short-term abstinence rates among treatment-seeking smokers (1,3,5). For example, Wing et al. (2013) and Barr et al. (2011) showed that repeated rTMS sessions significantly attenuated craving intensity and cigarette consumption, particularly when combined with behavioral support (3,4). Moreover, newer trials such as those by Ibrahim et al. (2023) and Li et al. (2022) have explored both conventional and deep rTMS protocols with encouraging outcomes for smoking cessation (7,8).

Despite these promising findings, the evidence base remains limited by small sample sizes, short treatment durations, heterogeneous stimulation parameters, and limited follow-up periods. Furthermore, while several trials have evaluated rTMS as a monotherapy or adjunct, rigorous comparisons against well-controlled sham conditions are still needed to isolate its true clinical efficacy (6). A comprehensive review by Mehta et al. (2024) emphasized the need for high-quality, randomized trials to validate neuromodulation-based approaches and define their role in addiction treatment frameworks (1).

In this context, the current study aims to assess the efficacy of rTMS with high frequency compared to sham stimulation in reducing nicotine cravings and promoting smoking cessation. By focusing on a motivated population of smokers diagnosed with tobacco use disorder, and employing serial assessments of craving and cigarette use, this randomized controlled trial seeks to strengthen the clinical evidence for rTMS as a neuromodulatory intervention for tobacco dependence.

MATERIALS AND METHODS

1. Study Design

A double-blind, sham-controlled randomised trial was conducted to assess the efficacy of high-frequency repetitive transcranial magnetic stimulation (rTMS) versus sham stimulation for reducing nicotine cravings and promoting smoking cessation among adults with tobacco use disorder.

2. Study Setting and Duration

The study was conducted at Saveetha Medical College and Hospital for a period of 6 weeks.

3. Study Population

The study included 120 adult smokers aged 21 to 55 years, who met DSM-5 criteria for Tobacco Use Disorder and expressed motivation to quit smoking.

4. Sample Size and Sampling

120 participants were enrolled using purposive sampling and were randomized equally into two groups:

- rTMS Group (n = 60)
- Sham Stimulation Group (n = 60)

5. Inclusion Criteria

- Age between 21 and 55 years
- DSM-5 diagnosis of Tobacco Use Disorder
- Smoked ≥10 cigarettes/day for at least the past year
- Motivated to quit smoking
- Provided written informed consent

6. Exclusion Criteria

- Current psychiatric or neurological illness (e.g., epilepsy, bipolar disorder, psychosis)
- Use of other tobacco cessation treatments during the study
- History of seizure or contraindications to TMS (e.g., metal implants in the head)

7. Randomization and Blinding

Participants were randomized into two groups using a computer-generated random number sequence. Allocation concealment was ensured. Participants and outcome assessors were blinded to group assignment.

8. Intervention Protocol

Group A – Active rTMS (n = 60):

- rTMS with high frequency (10 Hz) was delivered over the left dorsolateral prefrontal cortex (DLPFC) using a figure-of-eight coil.
- Each session consisted of 3,000 pulses per day, delivered in 75 trains of 40 pulses with 25-second inter-train intervals.
- Sessions were conducted daily (Monday to Friday) for 2 weeks (10 sessions total).

Group B – Sham rTMS (n = 60):

- Sham stimulation was administered using a **sham coil** that mimicked the sound and sensation of real rTMS without delivering active stimulation, under identical parameters and time frames.

9. Outcome Measures

Outcome	**Instrument**	**Assessment**
Craving Intensity	Visual Analog Scale (VAS: 0–10)	Baseline, 2, 4, and 6 weeks
Nicotine Dependence	Fagerström Test for Nicotine Dependence (FTND)	Baseline, 2, 4, and 6 weeks
Smoking Pattern	Self-reported daily cigarette use	Baseline, 2, 4, and 6 weeks
Smoking Abstinence	7-day point prevalence abstinence (self-report)	6 weeks

10. Procedure

After eligibility screening and informed consent, participants underwent baseline assessments including demographic details, smoking history, Fagerström Test for Nicotine Dependence (FTND), and Visual Analog Scale (VAS) for craving. Participants were then randomized to the active rTMS or sham stimulation group. Interventions were administered by a psychiatry postgraduate under the supervision of a qualified psychiatrist. Assessments were conducted during the 6-week study period at weeks 2, 4, and 6. SPSS version 23 was used to analyse data.

11. Ethical Considerations

The study was approved by the Institutional Ethics Committee. All participants provided **written informed consent**, and confidentiality was maintained throughout the trial. No major adverse effects were reported during the study period.

RESULTS

The two study groups were comparable across all baseline demographic and clinical variables, indicating successful randomization. There were no significant differences in age, education level, or baseline cigarette use (all $p > 0.05$). As per the study design, all participants were male, ensuring homogeneity in the sample and supporting the internal validity of the outcome comparisons.

Table 1: Socio-Demographic Characteristics of Participants

Variable	**rTMS Group (n = 60)**	**Sham Group (n = 60)**	**p-value**
Age (years)	38.2 ± 8.4	37.5 ± 7.9	0.64
Gender– Male (%)	60 (100%)	60 (100%)	1
Education – Uneducated (%)	3 (5%)	2 (3%)	0.77
Education – Primary (%)	8 (13%)	9 (15%)	
Education – Secondary (%)	24 (40%)	22 (37%)	
Education – Graduate (%)	25 (42%)	27 (45%)	
Mean Daily Cigarette Use	15.2 ± 3.6	14.9 ± 3.5	0.56

At the end of 6 weeks, participants in the rTMS group showed significantly better improvements in all primary and secondary outcome measures compared to the sham group.

- VAS craving scores significantly decreased from 7.8 ± 1.1 to 2.1 ± 1.4 in the rTMS group ($p < 0.001$), while the sham group showed a smaller reduction from 7.6 ± 1.3 to 5.2 ± 1.7 ($p = 0.02$). There was statistically significant ($p < 0.001$) difference between groups.
- FTND scores, reflecting nicotine dependence, dropped significantly in the rTMS group from 6.9 ± 1.0 to 2.8 ± 1.2($p < 0.001$), compared to a modest reduction in the sham group from 6.8 ± 0.9 to 5.1 ± 1.3 ($p = 0.04$). The between-group comparison also favored rTMS ($p < 0.001$).
- Mean daily cigarette use declined markedly in the rTMS group, from 15.2 ± 3.6 to 4.3 ± 2.2 ($p < 0.001$), while the sham group showed a smaller reduction from 14.9 ± 3.5 to 9.6 ± 3.1 ($p = 0.03$). There was a statistically significant ($p < 0.001$) difference.
- For 7-day point prevalence abstinence at 6 weeks, 40% of participants in the rTMS group reported abstinence compared to 17% in the sham group, which was statistically significant ($p = 0.004$).

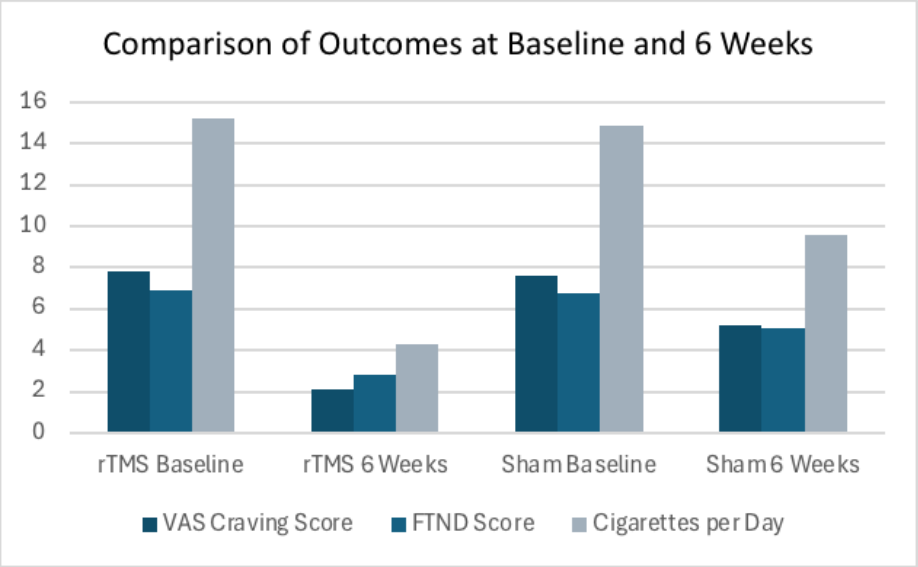
These findings demonstrate that high-frequency rTMS significantly outperformed sham stimulation in reducing cravings, dependence severity, cigarette consumption, and promoting short-term smoking abstinence.

Table 2: Outcomes at Baseline and 6 Weeks in rTMS vs. Sham Groups

Outcome	Group	Baseline	6 Weeks	p-value (within group)	p-value (between groups)
VAS Craving Score	rTMS	7.8 ± 1.1	2.1 ± 1.4	< 0.001	< 0.001
VAS Craving Score	Sham	7.6 ± 1.3	5.2 ± 1.7	0.02	
FTND Score	rTMS	6.9 ± 1.0	2.8 ± 1.2	< 0.001	< 0.001
FTND Score	Sham	6.8 ± 0.9	5.1 ± 1.3	0.04	
Daily Cigarette Use	rTMS	15.2 ± 3.6	4.3 ± 2.2	< 0.001	

Daily Cigarette Use	Sham	14.9 ± 3.5	9.6 ± 3.1	0.03	< 0.001
7-Day Point Prevalence Abst.	rTMS vs Sham	–	40% vs 17%	–	0.004

Figure 1: Comparison of outcomes at baseline and 6 weeks



DISCUSSION

This double-blind, sham-controlled randomised trial evaluated the efficacy of rTMS with high frequency over the left dorsolateral prefrontal cortex (DLPFC) in reducing craving and promoting smoking cessation among adult male smokers with tobacco use disorder. Our results demonstrated that active rTMS led to significant reductions in craving intensity, daily cigarette consumption, and nicotine dependence (as measured by FTND scores) compared to sham stimulation. Moreover, a notably higher proportion of participants in the rTMS group achieved 7-day point prevalence abstinence by week 6 (40% vs. 17%).

These findings align with a growing body of literature supporting the role of neuromodulation in addiction treatment. Mehta et al. (2024), in a comprehensive systematic review and meta-analysis, concluded that neuromodulation techniques, particularly rTMS, offer moderate to strong effects in reducing craving and consumption across several substance use disorders, including tobacco dependence (1). Similarly, Mahoney et al. (2020) noted that rTMS exerts its effects through modulation of prefrontal and mesolimbic circuitry regions implicated in executive control, reward processing, and compulsive drug-seeking behavior (2).

The significant reduction in VAS craving scores observed in our rTMS group supports the notion that high-frequency stimulation enhances top-down regulation over craving-related circuits. Wing et al. (2013) reported similar reductions in cue-induced craving and smoking frequency following repeated sessions of rTMS targeting the DLPFC (3). Additionally, Barr et al. (2011) emphasized the potential for rTMS to normalize disrupted prefrontal-striatal connectivity in chronic smokers, thereby restoring cognitive control over addictive impulses (4).

In our study, FTND scores and average daily cigarette use both declined significantly in the active stimulation group. This mirrors the findings of Gorelick et al. (2014), who described rTMS as a promising adjunct for reducing tobacco consumption and improving cessation rates, particularly when used with behavioral counseling or pharmacotherapy (5). Although we did not combine rTMS with pharmacologic agents, Ibrahim et al. (2023) demonstrated that deep rTMS targeting the insula, when combined with varenicline, yielded superior abstinence rates compared to varenicline alone (8). Our study contributes to this literature by showing that even standard DLPFC-targeted rTMS, when delivered independently, offers clinically meaningful benefits.

Importantly, our trial focused exclusively on male smokers, reflecting the real-world demographic of treatment-seeking tobacco users in India. This aligns with epidemiological trends and enhances the cultural

and clinical relevance of our findings. The absence of serious adverse effects, along with good tolerability, supports the safety profile of rTMS reported in previous reviews (6).

However, some limitations should be acknowledged. The short follow-up period (6 weeks) does not permit evaluation of long-term abstinence or relapse. Moreover, smoking abstinence was based on self-report, without biochemical verification (e.g., carbon monoxide breath analysis), which could introduce recall or reporting bias. Nevertheless, Li et al. (2022) observed meaningful craving reductions even within a 1-week treatment window in cancer patients, supporting the short-term effectiveness of rTMS (7).

CONCLUSION

This double-blind, sham-controlled randomised trial provides compelling evidence that rTMS with high frequency applied over the left dorsolateral prefrontal cortex significantly reduces nicotine cravings, daily cigarette consumption, and dependence severity in adult male smokers diagnosed with tobacco use disorder. Compared to sham stimulation, active rTMS led to greater craving relief and a higher proportion of self-reported short-term abstinence, with good tolerability and no serious adverse effects.

These findings reinforce the growing body of evidence suggesting that rTMS can effectively modulate the neurocircuitry underlying craving and executive dysfunction in addiction. While previous studies have demonstrated the promise of rTMS in substance use disorders broadly, this study adds valuable data from an Indian clinical setting.

Given the limitations of current pharmacological treatments and the burden of tobacco use, rTMS represents a promising adjunctive or alternative therapeutic strategy. However, future studies with longer follow-up periods, biochemical validation of smoking cessation, and exploration of individual predictors of treatment response are warranted to optimize and personalize rTMS protocols for tobacco dependence.

Incorporating rTMS into clinical tobacco cessation programs could offer a novel, neuroscience-informed approach to addressing nicotine addiction, particularly in cases where conventional interventions have proven ineffective or poorly tolerated.

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