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Original Research Article

PREDICTORS OF RESPONSE TO REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR SMOKING CESSATION: A PROSPECTIVE STUDY

Vamsi Krishna Inakollu[1], S Md Shahid Basha[2], M. Suresh Kumar[3]

[1]*Associate Professor, Department of Psychiatry, Institute of mental Health, Kadapa, Dr. NTR University of Health Sciences, Vijayawada, Andhra Pradesh, India.*
[2]*Assistant Professor, Department of Psychiatry, Institute of mental Health, Kadapa, Dr. NTR University of Health Sciences, Vijayawada, Andhra Pradesh, India.*
[3]*Assistant Professor, Department of Psychiatry, Institute of mental Health, Kadapa, Dr. NTR University of Health Sciences, Vijayawada, Andhra Pradesh, India.*

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Corresponding Author:
Dr. Vamsi Krishna Inakollu,
Associate Professor, Department of Psychiatry, Institute of mental Health, Kadapa, Dr. NTR University of Health Sciences, Vijayawada, Andhra Pradesh, India.
Email: ivk.vamsi@gmail.com

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ABSTRACT

Background: Nicotine dependence remains a significant public health challenge in India. Repetitive transcranial magnetic stimulation (rTMS) is a promising neuromodulatory treatment, but interindividual variability in response necessitates identification of predictive factors. **Aim:** To identify clinical and sociodemographic predictors of rTMS efficacy in smoking cessation among Indian adults

Materials and Methods: Fifty nicotine-dependent adults received high-frequency (10 Hz) rTMS over the left DLPFC, 5 days/week for 3 weeks. The primary outcome was a reduction in daily tobacco use. FTND scores were assessed at baseline, 3 weeks, and 6 weeks. Regression analysis identified predictors of treatment response.

Results: Participants showed significant reductions in cigarette consumption and FTND scores ($p<0.001$). Predictors of better response included age < 40yrs, FTND score< 6, tobacco use < 10 years, no comorbid alcohol use, and absence of medical comorbidity.

Conclusion: Sociodemographic and clinical characteristics predict rTMS outcomes. Personalized treatment selection can enhance smoking cessation success.

Keywords: Repetitive Transcranial Magnetic Stimulation (rTMS), nicotine dependence, predictors, India, smoking cessation.

INTRODUCTION

Tobacco use is a leading cause of preventable morbidity and mortality in India. Tobacco kills more than Eight million people each year. In the year 2020, 22.3% of the global population used tobacco. Nicotine contained in tobacco is highly addictive and tobacco use is a major risk factor for cardiovascular and respiratory diseases, over 20 different types of cancer, and many other debilitating health conditions.[1]

The Global Adult Tobacco Survey (GATS-2) reported a high prevalence of tobacco use among Indian adults. According to the Global Adult Tobacco Survey (GATS) conducted in 2016–17, the overall prevalence of smoking tobacco use is 10.38% and smokeless tobacco use is 21.38% in India.[2] Nicotine dependence is a disorder of regulation of nicotine use arising from repeated or continuous use of nicotine. Smoking cessation is one of the most important preventive health measures to reduce the risk of mortality and morbidity.[3] Current smoking cessation methods have limited efficacy, with high relapse rates. Conventional cessation methods often yield suboptimal long-term outcomes.[4] Traditional smoking cessation treatments, including nicotine replacement therapy (NRT), bupropion, varenicline, and behavioral interventions, have yielded modest quit rates, especially in populations with high levels

of nicotine dependence or psychiatric comorbidities.[5] Furthermore, pharmacological treatments may be poorly tolerated or contraindicated in certain individuals, leading to suboptimal outcomes. This underscores the need for non-pharmacological, neurobiologically informed approaches to augment current cessation strategies.[6,7,8]

Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive neuromodulation technique that delivers magnetic pulses to specific brain regions involved in craving, reward, and executive control—particularly the dorsolateral prefrontal cortex (DLPFC). The left DLPFC has been implicated in inhibitory control and decision-making, and high-frequency (10 Hz) rTMS over this region has shown promise in reducing cravings of substance addiction in several clinical trials.[9,10,11]Repetitive transcranial magnetic stimulation (rTMS) has shown promise for reducing cravings and promoting smoking cessation.[12,13,14] Repetitive transcranial magnetic stimulation (rTMS) has demonstrated promise in modulating craving-related neural circuits, yet approximately 40-60% of patients fail to achieve sustained abstinence.[15,16] It is important for the clinician to be able to assess the response potential of a given patient to rTMS, and this among other things requires relevant predictive factors to be available. Identifying reliable predictors of treatment response could enhance clinical outcomes and resource allocation. This review of the literature aims to determine and analyse reported predictive factors for therapeutic response to rTMS treatment for smoking cessation.

A recent large multicenter RCT confirmed rTMS's effectiveness in promoting abstinence, showing significantly higher quit rates compared to sham (19.4% vs. 8.7%) using deep rTMS targeting lateral prefrontal and insular cortices (Tang et al., 2024).[17] However, a secondary analysis of that trial found no robust clinical or demographic predictors of who benefits most. Although trends suggested younger age and higher baseline craving might predict better outcomes, these did not reach statistical significance after multiple testing correction (Tang et al., 2024).[17] Studies by West et al.,[18] Hymowitch et al.,[19] Li et al.[12] and Dinur-Klein et al.[13] demonstrated that rTMS significantly reduced craving intensity and cigarette consumption among treatment-seeking smokers, with effect sizes comparable to or exceeding those seen with pharmacotherapies. This highlights the need for research in diverse settings to explore potential predictors, including socio-demographic factors, dependence severity, comorbidities, and treatment history, to better tailor rTMS interventions for smoking cessation. Previous research has suggested potential neurobiological, genetic, and clinical predictors of rTMS response, but these have not been systematically evaluated in Indian populations. Recent research efforts have focused on identifying predictors of treatment response to rTMS. Variables such as age, baseline nicotine dependence (e.g., Fagerström Test scores), duration of smoking history, and even neuroimaging-derived cortical thickness have been investigated.[20-23] However, very limited data exist from low- and middle-income countries like India, where social, cultural, and genetic factors may modulate treatment outcomes differently.[24,25] Therefore, this study aims to fill this gap by identifying clinical and demographic predictors of rTMS efficacy in an Indian cohort of nicotine-dependent individuals, to inform the development of tailored intervention strategies for smoking cessation.

Objectives

1. To identify clinical predictors of rTMS efficacy in smoking cessation.
2. To assess the influence of demographic variables such as age, gender, and smoking history.

MATERIALS AND METHODS

This prospective observational interventional cohort study was conducted at Deaddiction Unit, Institute of Mental Health, Kadapa, Andhra Pradesh from December 2024 to June 2025 after obtaining approval from the Institutional Ethics Committee (IEC No: 16/GMC/KDP/2024 dated 16-12-2024). Written informed consent was obtained from participants.

Participants

A total of 50 outpatients diagnosed with DSM 5 criteria for nicotine dependence were recruited. The inclusion criteria for the study comprised age group of 18-65 years with daily smoking ≥10 cigarettes per day, FTND score ≥4 and who provided informed written consent for participation. Exclusion criteria included contraindications to rTMS like epilepsy, metal implants etc, co-morbid Psychiatric disorders or co-occurring other substance dependence and ongoing use of pharmacological smoking cessation aids.

Intervention Protocol

Medistim model of MS 50 type rTMS machine from Medicaid Systems brand available in department of psychiatry at IMH Kadapa was used for study. Participants were received High-frequency rTMS targetted over left DLPFC (F3 location) with parameters of 10Hz, 120% Resting Motor Threshold, 3000 pulses/session. A total of 15 sessions given over 3 weeks with 20 minutes per session and 5 days per week.

Outcome Measures

- **Primary Outcome:** Change in daily cigarette/bidi consumption
- **Secondary Outcomes:** FTND scores at baseline, 3 weeks, and 6 weeks

Data Collection

Demographic and clinical data were collected using a semi-structured proforma. FTND assessments were administered at three time points.

Ethical Considerations: Ethical clearance was obtained. Written informed consent was secured from

all participants. Data confidentiality and anonymity were maintained.

Statistical Analysis

SPSS Version 26 was used. Descriptive statistics summarized socio demographic data. Paired t-tests compared pre-post intervention outcomes. Logistic and linear regression models identified predictors of abstinence and smoking reduction. Statistical significance was determined with a threshold p vale of less than 0.05.

RESULTS

A total of 50 participants were enrolled in the study. The mean age of all participants was 34.8 ± 8.1 years, and all were male (100%). Most were married (72%) and had completed at least high school education (68%). A majority were employed in skilled or semiskilled occupations (54%).

Participants reported an average tobacco use duration of 11.3 ± 5.7 years, with a mean of 17.4 ± 4.8 cigarettes/bidis per day. The average Fagerstrom Test for Nicotine Dependence (FTND) score at baseline was 6.2 ± 1.1, indicating moderate to high dependence. Other relevant baseline variables include Monthly tobacco expenditure of ₹1250 ± 480, History of prior quit attempts (lasting ≥1 month) in 42%, family history of tobacco use: 56%. 36% reported Alcohol use not mounting to dependence and 28 %reported medical comorbidities like hypertension, diabetes.(Table 1)

Table 2 depicts the effect of rTMS on Smoking Behavior. All participants underwent 15 sessions of high-frequency (10 Hz) rTMS over the left dorsolateral prefrontal cortex (DLPFC). Statistically significant reductions were observed in both daily tobacco consumption and FTND scores from baseline to post-intervention. At 3 weeks, mean cigarettes/day reduced to 8.1 ± 3.6, and FTND to 3.7 ± 1.3. At 6 weeks, further reductions to 5.6 ± 3.1 cigarettes/day and FTND score 2.8 ± 1.4. Predictors of abstinence or ≥50% reduction at 6 weeks were analyzed via logistic regression as depicted in Figure 1. Significant predictors of positive response included age group - younger patients more likely to have low dependence who have shown better response to rTMS, baseline lower dependence with FTND score <6 have better response to rTMS, less number of years of tobacco use have good response, higher abstinence noted in alcohol non-drinkers, higher success in those without comorbidities and better response noted among smokers who had previous quit attempts.

Table 1: Baseline Characteristics of Participants (n = 50)

Variable	Value
Age (mean ± SD)	34.8 ± 8.1 years
Gender (% male)	100%
Married (%)	72%
Education ≥ High School	68%
Employment (Skilled/Semiskilled)	54%
Daily Cigarettes/Bidis (mean ± SD)	17.4 ± 4.8
FTND Score (mean ± SD)	6.2 ± 1.1
Duration of Tobacco Use (mean ± SD)	11.3 ± 5.7 years
Tobacco Expense/Month (mean ± SD)	₹1250 ± 480
Alcohol Use Present (%)	36%
Medical Comorbidity Present (%)	28%
Previous Quit Attempts (≥1)	42%
Family History of Tobacco Use (%)	56%

Table 2: Smoking Behavior Pre- and Post-rTMS

Time Point	Cigarettes/day (Mean ± SD)	FTND Score (Mean ± SD)
Baseline	17.4 ± 4.8	6.2 ± 1.1
3 Weeks	8.1 ± 3.6	3.7 ± 1.3
6 Weeks	5.6 ± 3.1	2.8 ± 1.4

Statistical significance: Paired t-tests revealed a highly significant reduction ($p < 0.001$) in both parameters at 3 and 6 weeks compared to baseline.

Table 3: Logistic Regression Predictors of 6-week Abstinence

Predictor Variable	Adjusted OR (95% CI)	p-value
Age < 40 years	2.14 (1.03–4.67)	0.04
FTND Score < 6	2.68 (1.22–5.91)	0.01
<10 Years of Tobacco Use	1.91 (1.03–3.53)	0.03
No Alcohol Use	1.82 (1.00–3.31)	0.05
No Medical Comorbidity	2.11 (1.12–4.72)	0.03
≥1 Previous Quit Attempt	1.67 (0.92–3.40)	0.07

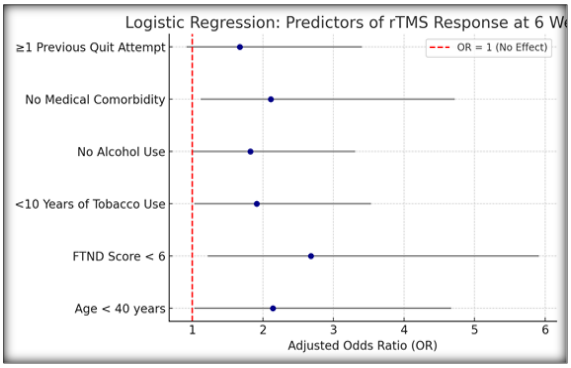

Figure 1: Logistic Regression Plot: Displays Adjusted Odds Ratios (OR) with 95% Confidence Intervals for predictors of response to rTMS at 6 weeks

Significant predictors show OR > 1, indicating higher likelihood of treatment response.

DISCUSSION

The results of our study reinforce the therapeutic value of high-frequency rTMS in smoking cessation, as evidenced by significant reductions in both daily cigarette consumption and FTND scores at 3 and 6 weeks post-intervention. These findings are in line with previous international studies that have established rTMS as an effective neuromodulatory tool in the context of nicotine dependence. Dinur-Klein et al,[13] in a double-blind randomized controlled trial, observed that 13 sessions of high-frequency rTMS over the left DLPFC led to significant reductions in craving and tobacco use, with abstinence rates of approximately 44% at follow-up. Similarly, Li et al,[12] reported decreased craving and cigarette consumption following rTMS, with neuroimaging data suggesting enhanced functional connectivity in the frontostriatal circuits, a network known to mediate impulse control and craving regulation.

Our findings further suggest that certain clinical and demographic variables significantly predict response to rTMS. Specifically, younger age (<40 years), lower baseline FTND score (<6), and shorter duration of tobacco use (<10 years) were associated with higher likelihood of abstinence at 6 weeks. Importantly, a recent large multicenter RCT in smoking cessation demonstrated rTMS's efficacy but could not identify reliable clinical predictors of response in its secondary analysis (Tang et al., 2024).[17] Their modeling suggested only weak, non-significant trends for younger age and craving intensity as potential moderators. This underscores the complexity of predicting neuromodulation outcomes in addiction and highlights the importance of examining context-specific factors, such as cultural, socio-economic, and clinical variables relevant to Indian settings. Our study contributes to this gap by identifying practical clinical and demographic features that may help personalize rTMS treatment in resource-constrained settings.

These observations are consistent with studies by Zangen et al.,[15] Gersner et al,[16] and West et al,[18] which demonstrated that individuals with less entrenched smoking patterns and lower dependence scores showed better neurocognitive and behavioral responses to rTMS. In a community-based Indian studies by Sharma et al,[23] and Reddy et al,[24] younger age and fewer years of tobacco use were associated with higher quit rates using standard therapy, underscoring the general importance of early intervention. Age-related neuroplasticity may partially explain the greater responsiveness in younger participants. Structural and functional studies indicate that the prefrontal cortex, the primary target of rTMS in smoking cessation, exhibits reduced plasticity and responsiveness to stimulation with advancing age. Additionally, smokers with lower dependence may have more preserved executive functioning and greater capacity for behavioral change when supported by neuromodulatory interventions.

Logistic regression analysis revealed that younger age, lower dependence levels, shorter tobacco use history, absence of alcohol use, and no comorbid medical illness significantly predicted better cessation outcomes.These findings are consistent with global literature (Li et al., 2013,[12] ; Tang et al., 2024),[17] and Indian studies (Sharma et al., 2021; Reddy et al., 2021).[23,24] These results mirror international reports, such as Gersner et al. (2022),[23] which found age < 40 and ≤ 10 years of smoking predicted higher quit rates. The use of a structured proforma allowed for comprehensive baseline profiling. Items such as prior quit attempts, family history, and tobacco expenditure provided insight into behavioral and social determinants of cessation outcomes. Our results suggest that rTMS can be most effective when targeted at motivated individuals with lower clinical complexity. The inclusion of socio-demographic, behavioral, and medical comorbidity data enhances treatment personalization and supports resource optimization in addiction psychiatry. Sociodemographic and clinical characteristics collected through a semi-structured proforma were found to significantly influence treatment outcomes. Notably, participants with no comorbid medical conditions, lower tobacco expenditure, and absence of concurrent alcohol use had better cessation outcomes. These findings reinforce the multifactorial nature of nicotine dependence and support personalized intervention strategies.

Our study also revealed that prior quit attempts, though not independently significant, trended toward better rTMS response, possibly indicating greater motivation. These insights suggest that baseline profiling using structured tools can help clinicians identify ideal candidates for rTMS and predict likelihood of cessation success. A study by Zangen et al,[15] using deep TMS also found that treatment success was associated with fewer years of smoking, reinforcing the idea that earlier intervention may lead to better outcomes. Notably, our study adds to the

sparse Indian literature in this field, highlighting the relevance of these predictors in culturally and demographically distinct populations. Interestingly, our study also aligns with Indian findings that suggest socio-cultural factors, such as family support and readiness to quit, significantly impact cessation outcomes.[25] While these variables were not directly measured in our study, they likely interact with clinical predictors to influence rTMS response and merit inclusion in future research. Indian studies support these conclusions: Reddy et al,[24] observed greater benefit in those with lower dependence; Sharma et al,[23] found shorter duration correlated with better outcomes. Additionally, Indian population-based research in standard cessation programs confirms younger age and shorter smoking history as predictors of success. Though most Indian studies have focused on pharmacotherapy and behavioral interventions, our study aimed to formally analyze predictors of rTMS response in this context.

Despite promising results, the broader application of rTMS in India remains limited due to infrastructural and cost-related barriers. However, studies like ours provide a basis for developing evidence-based guidelines and identifying subgroups most likely to benefit, thereby ensuring efficient use of rTMS resources in public sector psychiatry settings. Our data also highlight the potential synergy of personalized neuromodulation approaches in India. By pre-identifying likely responders based on demographic and dependency profiles, clinicians can optimize treatment allocation and cost-effectiveness—particularly in resource-limited settings.

Limitations

Despite these strengths, our study is not without limitations. First, we relied on self-reported measures of cigarette use, which may be subject to recall or social desirability bias. Although FTND is a validated and widely used scale, the absence of biochemical validation (e.g., cotinine levels or CO monitoring) limits the objectivity of the outcome assessment. Secondly, the relatively short follow-up duration precludes conclusions about long-term abstinence maintenance. Small sample size prevented examination of socioeconomic predictors like education and support, as seen in international studies. Lastly, the single-center design and lack of sham control limits generalizability, though our findings provide a valuable foundation for larger multi-centric studies in India.

Future Directions

We recommend multi-center trials incorporating objective biomarkers, longer follow-ups, and broader sociodemographic variables (e.g., education, socioeconomic status, family support). Neuroimaging-based predictive models may further enhance treatment personalization.

CONCLUSION

Sociodemographic and clinical factors, as captured in a structured proforma, can help predict rTMS response in Indian smokers. A tailored intervention approach improves outcomes and clinical decision-making. This study demonstrates that younger age, lower dependence levels, shorter tobacco use history, absence of concurrent alcohol use and no co-morbid medical illness may help identify smokers most likely to benefit from rTMS therapy. A predictive model incorporating these factors showed good discriminate accuracy, suggesting potential clinical utility for treatment selection.

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