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NEUROMODULATION TECHNIQUES FOR THE TREATMENT OF NICOTINE ADDICTION

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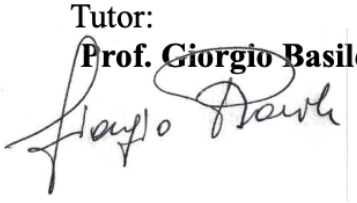

ACCADEMIC YEAR 2024-2025

Summary

Introduction

Nicotine addiction

Tobacco is the second most used psychoactive substance worldwide, with more than one billion consumers (Reitsma et al., 2021). Despite its decline in developed countries (Dai et al., 2022; Jha, 2020; Jha and Peto, 2014; Reitsma et al., 2021), tobacco smoking remains the primary cause of early deaths occurring before the age of 70 in Europe and the United States. The health and financial burdens imposed by tobacco use have prioritized its control as a vital public health need. Over the past three decades, cigarette smoking has caused more than 200 million deaths and it still remains a leading contributor to global premature mortality and illness. It is a major driver of cardiovascular disease, chronic obstructive pulmonary disease (COPD), lung cancer, and various other health conditions (Bade and Dela Cruz, 2020; Duffy and Criner, 2019; Rezk-Hanna and Benowitz, 2019).

Smoking prevalence is significantly higher among individuals with lower education and income levels (Palipudi et al., 2012), as well as those with mental health conditions, who exhibit rates three times higher than the general population (Evans-Polce et al., 2020; Smith and Wrobel, 2014). In countries with high tobacco consumption, smokers without tobacco-related illnesses often show less motivation to quit (Jha, 2018). This resistance to cessation is likely influenced by both neurological adaptations caused by long-term nicotine exposure and psychological mechanisms developed during past quit attempts.

Tobacco smoking, recognized as the most prevalent substance-use disorder, is marked by craving, withdrawal symptoms, and compulsive use despite harmful consequences (Potvin et al., 2015). Research underscores the addictive nature of smoking, driven by

the impact of nicotine on brain reward systems: its rewarding effects, which encourage use, involve dopamine projections from the ventral tegmental area to the *nucleus accumbens*, while its aversive effects, which counterbalance intake and alleviate withdrawal, engage the medial habenula-interpeduncular nucleus pathway. Other brain regions, including the prefrontal cortex, ventral striatum, ventral pallidum, nucleus tractus solitarius, and insula, also play roles in nicotine dependence (Goldstein and Volkow, 2011), (see figure 1).

These interconnected brain regions form a topographically organized cortico-striatal circuit integral to goal-directed behavior and stimulus-value attribution; this network is believed to be crucial in regulating drug-seeking and drug-taking behaviors (Basile et al., 2021).

Like other addictive substances, abruptly discontinuing tobacco leads to withdrawal symptoms such as irritability, anxiety, low mood, difficulty concentrating, changes in sleep patterns, and increased appetite, making quitting a significant challenge (Fagerstrom, 2012; West, 2009, 2017). Many adults continue smoking as they use nicotine consumption as a coping strategy towards feelings of emptiness or apathy associated with boredom (Missen et al., 2013; Thrasher and Bentley, 2006), whereas adolescents often initiate smoking driven by curiosity, peer influence, and media exposure (Mejia et al., 2023). These mechanisms contribute to high relapse rates, with most individuals struggling to quit due to craving and withdrawal symptoms; only 3–10% of quit attempts are successful after one year.

Current treatments, including behavioral support, varenicline, bupropion, and nicotine replacement therapy (NRT), increase the likelihood of success, yet their long-term

efficacy remains limited. This underscores the urgent need to explore new, effective, and safe alternatives to address cigarette smoking addiction (Pipe et al., 2022).

Neuromodulation techniques

Neuromodulation can be defined as the alteration of neuronal activity through targeted delivery of a stimulus, either electrical or magnetic, to specific areas of the nervous system. It aims to modulate brain or neural circuit function to achieve therapeutic effects, especially in conditions where traditional treatments may be insufficient (Alipour et al., 2025).

In the context of neuromodulation, Non-Invasive Brain Stimulation techniques (NIBS techniques), such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), are a family of techniques used to modulate brain activity without surgery or implants. In the context of nicotine addiction**,** NIBS methods have entered into the recognized and recommended guidelines therapies, due to the advantages related to safety, tolerability, cost-effectiveness, and compatibility with other possible treatments.

TMS exploits a high-intensity magnetic field, generated by a light electric current in a coil, which, when applied to the scalp, allows it to interfere with normal neural activity, modulating excitability and neuronal communication. rTMS is essentially TMS delivered in *repetitive trains of pulses*, usually at a specific frequency (e.g., 1 Hz, 10 Hz, 20 Hz). This repetition is what allows it to *modulate cortical excitability over time*, producing longer-lasting neuroplastic effects.

The possibility of examining changes in cortical excitability after prolonged exposure to substances has given considerable impetus to the study of this technique in the field of

addiction, proposing it as a therapy also in nicotine addiction. In this field, TMS is a non- invasive therapeutic practice which appears to be effective in reducing nicotine craving (Rachid, 2016).

According to two reviews of literature about the evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation, high-frequency (HF) rTMS of the dorsolateral prefrontal cortex (DLPFC) seems to attenuate nicotine consumption and craving (Lefaucheur et al., 2014, 2020). However, studies showed a significant heterogeneity in terms of methods and patients' profiles, and they did not show an increase in long-term abstinence rates, especially in patients with comorbid psychiatric conditions (Mahoney et al., 2020). To this day, only a Level C recommendation has been proposed for the possible efficacy of HF rTMS of the left DLPFC in reducing cigarette consumption.

Transcranial direct current stimulation (tDCS) is a neurostimulation technique based on the passage of a weak current (1–2mA) across the cortex using at least two electrodes (Chase et al., 2020). Studies show that anodal stimulation, which can depolarize the neurons, can reduce craving originated in response to environmental/external stimuli, increasing the cortical excitability of the left DLPFC. The effects of tDCS are due to the modification of the conductivity of sodium and calcium channels and to the shifting of electrical gradients that affect the ion balance inside and outside the neuronal membrane, modulating its activation threshold. According to a recent study, tDCS applied to the DLPFC is a possible treatment for smoking addiction because of its effectiveness in reducing craving (Perri and Perrotta, 2021).

Aims of the study

This research project starts from the assumption that tobacco smoking is the most common substance use disorder due to nicotine addiction, and it represents a public health priority. Available treatments for nicotine addiction, such as bupropion, varenicline, and nicotine replacement therapy, have shown relatively poor long-term outcomes (Pipe et al., 2022). For this reason, it could be useful to identify new, effective, and safe alternatives to treat cigarette smoking addiction. In this field, Non-Invasive Brain Stimulation techniques (NIBS), as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), have entered into the recognized and recommended guidelines therapies.

Based on this background, the present research was aimed at evaluating whether an experimental protocol consisting of combined NIBS techniques administered in succession to the patient (tDCS + rTMS) was more effective and lasting than conventional rTMS protocol generally used for treating nicotine addiction.

The distinctive feature of this protocol lies both in the markedly shorter treatment duration and in the sequential application of combined tDCS and rTMS, designed to maximize the neuromodulatory impact. rTMS is known to induce synaptic plasticity in a frequency-dependent manner, generating effects comparable to long-term potentiation (LTP) or long-term depression (LTD). In parallel, tDCS modulates the baseline excitability of neurons, enhancing it through anodal stimulation or reducing it with cathodal stimulation, thereby increasing the responsiveness of neural circuits to subsequent interventions (Lang et al., 2004; Romero Lauro et al., 2014; Varoli et al., 2018) . In this framework, tDCS acts as a cortical *priming* technique, creating a more favorable state for TMS to induce stronger and more targeted neuroplastic modifications (see Figure 2).

Material and methods

Sample

A total sample of 72 subjects was enrolled among the general population.

The inclusion criteria for recruitment were:

a) Age between 18 and 65 years.

b) Ability to read and sign the informed consent.

c) Addiction and craving for cigarette smoking (nicotine addiction).

The exclusion criteria were:

a) Concomitant severe, unstable, active neurological or physical disease.

b) Patients with schizophrenia.

c) Patients with intellectual disability.

d) Patients with substance related disorders other than tobacco/nicotine.

e) Patients with previous episodes of epilepsy or unexplained seizures.

f) Patients who have implanted electronic devices and/or cochlear implants and/or vagus nerve stimulators.

g) Patients with cardiac pacemakers.

h) Patients with non-removable metal objects near the coil.

Study design

Participants were randomly assigned in a 1:1 ratio to one of two treatment groups, each consisting of 36 subjects.

- **Group A** received a conventional repetitive transcranial magnetic stimulation rTMS protocol (Conventional protocol) as described by Prikryl et al. (2014). The stimulation was delivered at a frequency of 10 Hz, with 50 pulses per train across 20 trains, for a total of 2000 pulses per session. Inter-train intervals lasted

30 seconds. Treatment was administered once daily over 21 days. Stimulation targeted the left dorsolateral prefrontal cortex (DLPFC) at 110% of the individual's motor threshold, defined as the minimum intensity required to induce motor evoked potentials (MEPs).

- **Group B** underwent a short, intensive neuromodulation protocol using a "double session" format (Combined protocol). This involved the sequential application of transcranial direct current stimulation (tDCS) followed by rTMS, delivered twice daily for 5 consecutive days, resulting in a total of 10 tDCS and 10 rTMS sessions.

The specifics of each component are as follows:

- **tDCS protocol:** adapted from Alghamdi et al., 2019. Round PiSTIM electrodes (12 mm diameter; surface area approximately 3.14 cm^2) were used. Anodal stimulation was applied to the left DLPFC, and cathodal stimulation to the homologous area on the right. A highly conductive saline gel was used to ensure optimal contact. Stimulation was delivered at 1500 μA for a duration of 20 minutes.
- **rTMS protocol:** Adapted from Scarpino et al., 2019. Stimulation was administered at a frequency of 15 Hz, with 50 pulses per train across 48 trains, for a total of 2400 pulses per session. Inter-train intervals were set at 15 seconds, resulting in a total session duration of 880 seconds. Stimulation targeted the left DLPFC at 100% of the motor threshold.

Assessment

The evaluation of smoking behavior, nicotine dependence, and expectations related to abstinence was carried out using the following validated psychometric tools:

- **Cigarettes Per Day (CPD):** This measure reflects the individual's current smoking status. A reduction in CPD by 50% or more is generally considered clinically significant, as such a decrease has been linked to lower risks of cancer and cardiovascular disease (Rostron et al., 2020).
- **Fagerström Test for Nicotine Dependence (FTND):** This instrument (Meneses-Gaya et al., 2009) includes six items and allows for the classification of nicotine dependence into five categories: very low (0–2 points), low (3–4), moderate (5), high (6–7), and very high (8–10).
- **Smoking Abstinence Expectancies Questionnaire (SAEQ):** Developed by Abrams et al., 2011, the SAEQ is a brief and reliable self-report tool assessing short-term expectations associated with nicotine withdrawal. It comprises 28 items rated on a 7-point Likert scale, covering four subscales: negative mood, somatic symptoms, harmful consequences, and positive consequences. Higher total scores indicate more negative expectations regarding abstinence. While no standardized cutoff exists, a score of 98 - representing half of the maximum score - has been suggested as indicative of high negative expectancies about undesirable outcomes.
- **Addictive Behavior Questionnaire (ABQ):** This self-administered instrument assesses various forms of addictive behavior throughout the stages of intervention. It includes two components: the Severity Index (SI) and the Seven

Domains Addiction Scale (7DAS) (Caretti et al., 2018). In the present study it was administered to exclude the presence of other concurrent addictions.

Assessment using CPD, FTND, and SAEQ was conducted at three time points: baseline (T0), end of treatment (T1), and six months post-treatment (T2).

After each treatment session, adverse effects, whether observed or spontaneously reported, were documented and categorized by onset, duration, severity, action taken, and outcome.

Statistical analysis

An a priori sample size estimate was performed (G*Power 3.1.9.2.): given the assumption of an effect size of 0.8, a significance level of 0.05 with a power of 0.85, a minimum sample size of 60 with 30 subjects per group was determined. Given a dropout of about 20 percent, a final sample size of 36 subjects was selected for each group._The data collected from the study underwent verification and quality assurance procedures, followed by descriptive statistical evaluation. The distribution of the data was examined by examining skewness and kurtosis: as some variables did not conform to the assumption of normality, statistical analyses were conducted using non-parametric tests. To mitigate potential bias arising from participant dropout, an intention-to-treat (ITT) analysis was conducted employing the Last Observation Carried Forward (LOCF) method. Continuous variables were summarized as median and interquartile range (IQR), and between-group comparisons at baseline and post-intervention were performed using the Mann–Whitney U test for independent samples; the Wilcoxon signed-rank test was conducted to examine intra-group differences within the Conventional Protocol group across the time points (T0 vs T1, T0 vs T2).

The magnitude of the treatment effect was quantified using Cohen's *d*, with values <0.50 considered small, 0.50–0.79 as moderate, and ≥0.80 as large. Noncontinuous data were expressed as percentages, and the comparison between the two groups was performed by using the Chi-Square test.

Statistical significance was set at $\alpha = 0.05$. All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Out of the 72 subjects enrolled, 63 completed the study (87.5% completion rate). There were nine premature dropouts, seven in the Conventional treatment group (discontinuation rates = 19.4%), and two in the Combined treatment group (discontinuation rates = 5.5%). In the Conventional group, all seven participants withdrew due to concerns about the length of the protocol; in the Combined group, the two dropouts were due to the onset of influenza symptoms.

The sociodemographic and clinical characteristics of the participants are reported in Table 1. No significant differences were found between the two groups except for the number of previous quit attempts: the group treated with the Conventional protocol reported a significantly higher number of attempts compared to the group treated with Combined one ($p = 0.03$).

After confirming the comparability of the two groups at baseline, between-group differences in smoking-related outcomes (CPD, Fagerström scores, and SAEQ total and subscale scores) were examined across time points. At baseline, no significant differences were observed between the Conventional and Combined protocol groups across any of the assessed variables.

For cigarettes per day (CPD), participants receiving the Combined protocol reported a significantly greater reduction compared to the Conventional protocol group at both T1 ($p = .002$, Cohen's $d = 0.57$) and T2 ($p = .016$, $d = 0.46$).

Regarding nicotine dependence (Fagerström Test), no baseline differences were found; however, at T1 the Combined protocol showed significantly lower scores compared to the Conventional protocol ($p = .022$, $d = 0.56$), whereas no significant difference was observed at T2 ($p = .103$, $d = 0.47$).

For the Smoking Abstinence Expectancies Questionnaire (SAEQ) total score, as well as the subscales Somatic Symptoms (SS), Harmful Consequences (HC), and Positive Consequences (PC), no significant differences emerged between groups at any time point ($p > 0.05$, effect sizes small). Conversely, the Negative Mood (NM) subscale showed a significant advantage for the combined protocol at T1 ($p = .029$, $d = 0.45$), which did not persist at T2 ($p = .200$, $d = 0.21$).

The Wilcoxon signed-rank test was applied only to assess intra-group changes within the Combined Protocol group. The analysis revealed significant reductions in the number of cigarettes smoked per day (CPD) both from T0 to T1 ($Z = –4.794$, $p < .0001$) and from T0 to T2 ($Z = –4.822$, $p < .0001$). Similarly, a significant decrease in nicotine dependence, as measured by the Fagerström Test, was observed at both T1 ($Z = –4.617$, $p < .0001$) and T2 ($Z = –4.117$, $p < .0001$). Regarding smoking expectancy (SAEQ), a significant reduction emerged in the Total score only at T2 ($Z = –2.695$, $p = .007$), while the Negative Mood subscale (SAEQ-NM) showed significant decreases at both T1 ($Z = –2.620$, $p = .009$) and T2 ($Z = –3.137$, $p = .002$). No statistically significant changes were found in the Somatic Symptoms (SAEQ-SS), Harmful Consequences (SAEQ-HC), or Positive Consequences (SAEQ-PC) subscales across the two time points.

A positive treatment outcome was considered as a reduction of more than 50% in CPD, in line with previous findings (Rostron et al., 2020). Table 3 presents the percentage decrease in CPD observed in the two intervention groups at timepoints T1 and T2. At T1, 27.8% of individuals in the Conventional Protocol group reported a reduction of more than 50% in cigarette use, whereas 63.9% of those in the Combined Protocol group reached this level of reduction. The Chi-square test demonstrated a statistically significant distinction between the two groups at this time point ($p = .001$). At T2, 41.7% of participants in the Conventional Protocol group lowered their cigarette consumption by over 50%, while 63.9% in the Combined Protocol group showed the same decrease. The Chi-square test reflected a statistically significant difference between the groups ($p = .033$), though less pronounced than at T1.

Regarding subjects who have achieved smoking cessation at T1, 2 members of the Conventional Protocol group successfully quitted smoking, compared with 7 in the Combined Protocol group. The Chi-square test (χ^2) indicated that this difference reached statistical significance ($p = 0.020$). At T2, 3 individuals in the Conventional Protocol group had stopped smoking, compared to 8 in the Combined Protocol group: the Chi-square test (χ^2) outcome showed that this difference did not reach the threshold for statistical significance at this time point ($p = 0.058$).

Finally, the analysis of motor threshold values at T0 and T1 indicated an overall statistically significant global decrease, as assessed with the Mann–Whitney U test. This reduction was observed across both treatment groups. Specifically, in the Conventional Protocol group, motor threshold values decreased from a median of 62 at T0 to 56 at T1 ($Z = –3.387$, $p = .001$). Similarly, in the Combined Protocol group, the median motor threshold decreased from 58 at T0 to 55 at T1 ($Z = –3.387$, $p = .001$). These findings

suggest a global, statistically significant reduction in cortical excitability thresholds across both treatment protocols, with no differences between the two groups ($z = -.107$; $p = .915$).

Mild and transient adverse effects were observed across both intervention protocols. In the Conventional Protocol group, six subjects reported headache. In the Combined Protocol group, four subjects experienced mild scalp burning sensations and four reported headache. These effects were mild, self-limiting, and did not necessitate treatment discontinuation, typically resolving within the first few days of stimulation.

Discussions

The overall completion rate of the study was high (87.5%), indicating that both neuromodulation protocols were generally well tolerated and acceptable to participants. Dropout rates were disproportionately higher in the Conventional group (19.4%) compared with the Combined protocol (5.5%). The main reason for dropout in the Conventional group was the perceived excessive length of the protocol, whereas discontinuation in the Combined group was unrelated to the intervention itself (i.e. influenza symptoms). This pattern suggests that the shorter, more intensive combined protocol may offer advantages in feasibility and adherence.

When compared with trials in smokers from the general population, our observed retention rates are favourable. Meta-analytic data from behavioural randomized cessation studies report mean retention rates around 80.5% (IQR ~68.5–89.5%) at key follow-up points (Bricca et al., 2022). In many clinic-based or community

behavioural/pharmacotherapy programs, ~20-30% dropout rates over the active intervention phase are common (Jumbe et al., 2022; Silva et al., 2024).

In this context, the 19.4% dropout in our Conventional protocol is at the higher bound of typical attrition, but not abnormal. More striking is the very low attrition in the Combined arm (5.5%), which is significantly lower than what is commonly observed. This suggests that the Combined protocol not only might enhance efficacy but also offers superior feasibility and acceptability in a sample of smokers from the general population.

The two groups were largely comparable according their sociodemographic and clinical characteristics at baseline. The only variable that significantly differed was the number of previous quit attempts, with participants in the Conventional group reporting a higher history of unsuccessful cessation efforts compared with those in the Combined group ($p = 0.03$). This imbalance may reflect a greater degree of treatment resistance or motivational fluctuations in the Conventional arm, and it could represent a potentially confounding factor when interpreting treatment outcomes. Nevertheless, no baseline differences emerged in key smoking-related measures, including CPD, Fagerström Test for Nicotine Dependence scores, and Smoking Abstinence Expectancy Questionnaire (SAEQ) scores, which strengthen the validity of longitudinal comparisons. Overall, the general comparability of the groups provides a sound foundation for evaluating treatment-related effects, whereas the difference in quit attempt history underscores the importance of considering prior cessation trajectories as a potential moderator of neuromodulation efficacy.

Analysis of cigarette consumption revealed that participants undergoing the Combined protocol achieved significantly greater reductions in CPD compared with those

receiving the Conventional protocol, both at the post-treatment assessment (T1: p = .002, d = 0.57) and at follow-up (T2: p = .016, d = 0.46). The effect sizes, ranging from moderate to small-to-moderate, suggest that the Combined intervention not only facilitated an acute reduction in cigarette use, but also conferred benefits that persisted beyond the active stimulation phase. From a mechanistic perspective, the enhanced efficacy of the Combined protocol is consistent with the concept of *priming-induced plasticity*, whereby preconditioning with anodal tDCS may increase cortical excitability and responsiveness to subsequent TMS pulses, amplifying their capacity to modulate fronto-striatal circuits implicated in craving regulation and inhibitory control (Alkhasli et al., 2022; Pisoni et al., 2018).

Although encouraging, the magnitude of the observed effects must be considered in light of potentially moderating variables, such as the higher number of previous quit attempts in the Conventional group, which may partly account for differential responsiveness. Nevertheless, the consistency of the benefit across time points highlights the promise of dual-modality protocols in enhancing the clinical utility of non-invasive neuromodulation for tobacco dependence.

With respect to nicotine dependence severity, no baseline differences were observed between groups, yet participants in the Combined protocol demonstrated significantly lower Fagerström scores at T1 compared with those in the Conventional protocol (p = .022, d = 0.56). This finding suggests that the Combined approach may acutely reduce dependence-related features, potentially through modulation of craving and withdrawal circuits. However, the absence of a significant between-group difference at T2 (p = .103, d = 0.47) indicates that these benefits may diminish once active stimulation ceases, highlighting the need for strategies to sustain treatment effects over time, such

as implementation with cognitive-behavioral therapy (Perrotta and Perri, 2022) or neuromodulatory booster treatments.

In terms of self-efficacy, no significant between-group differences emerged for the SAEQ total score or for the Somatic Symptoms, Harmful Consequences, and Positive Consequence subscales, suggesting that both protocols exerted comparable effects on broader self-regulatory confidence. Notably, the Combined protocol conferred a short-term advantage on the Negative Mood subscale at T1 ($p = .029$, $d = 0.45$), consistent with the hypothesized role of neuromodulation in enhancing prefrontal regulation of affective states. Yet, this effect did not persist at T2, implying that while neuromodulation may temporarily buffer negative affects, sustained improvements may require booster sessions or adjunctive psychosocial support. Together, these results indicate that the Combined protocol yields modest but meaningful short-term benefits in both dependence severity and affective self-efficacy, though the permanence of these effects remains uncertain.

Intra-group analyses within the Combined protocol revealed robust and sustained improvements in multiple smoking-related outcomes. Participants demonstrated significant reductions in CPD from baseline to post-treatment (T1: $Z = –4.794$, $p < .0001$) and follow-up (T2: $Z = –4.822$, $p < .0001$), as well as significant decreases in nicotine dependence as measured by the Fagerström Test at both T1 ($Z = –4.617$, $p < .0001$) and T2 ($Z = –4.117$, $p < .0001$). These findings are consistent with previous studies in smokers from general population, where active tDCS and rTMS interventions have been shown to reduce cigarette consumption and dependence (Falcone et al., 2016; Ghorbani Behnam et al., 2019; Mousa et al., 2025), supporting the efficacy of neuromodulation in tobacco use cessation beyond clinical populations.

Regarding smoking expectancy, the Combined protocol produced significant reductions in the SAEQ Total score at T2 ($Z = –2.695$, $p = .007$), and in the Negative Mood subscale (SAEQ-NM) at both T1 ($Z = –2.620$, $p = .009$) and T2 ($Z = –3.137$, $p = .002$), whereas no significant changes occurred in SAEQ-SS, SAEQ-HC), or SAEQ-PC subscales. The sustained improvement in negative mood-related expectancies may reflect enhanced prefrontal regulation of affective states, a plausible mechanism by which tDCS priming amplifies the efficacy of subsequent rTMS. These findings are consistent with previous evidence that neuromodulation targeting the dorsolateral prefrontal cortex enhances prefrontal control over craving-related affective states and reduces smoking motivation under stress or negative mood (Boggio et al., 2009; Fregni et al., 2008). The absence of significant changes in other expectancy subscales (e.g., somatic symptoms, harmful consequences, or positive consequences) may reflect the selectivity of neuromodulation effects on affective and craving-related processes following DLPFC-targeted stimulation (Li et al., 2013).

Clinically meaningful reductions in smoking, defined as a ≥50% decrease in CPD, were significantly more frequent in participants receiving the Combined protocol than in those receiving Conventional TMS. At post-treatment (T1), 63.9% of Combined protocol participants achieved this threshold, compared with 27.8% in the Conventional group ($p = .001$). At follow-up (T2), the Combined protocol maintained a rate of 63.9% responders, while the Conventional protocol reached 41.7% ($p = .033$). These results indicate that the Combined protocol not only produces larger mean reductions in smoking, but also increases the likelihood of clinically significant change.

These findings are in line with previous results observed in smokers from general population. Interestingly, Abdelrahman et al. (2021) reported that high-frequency rTMS

over the left dorsolateral prefrontal cortex significantly reduced CPD and nicotine dependence, with effects persisting up to three months. Similarly, Li et al. (2020) observed that 10 sessions of rTMS produced a 62.9% reduction in CPD compared with 39.4% in the sham group, and fMRI data linked these changes to prefrontal and reward-related circuitry modulation. Perri and Perrotta (2021) found that tDCS over the prefrontal cortex reduced cigarette craving by ~50%, accompanied by decreases in cigarette consumption. Finally, a systematic review and meta-analysis by Petit et al (2022) confirmed that non-invasive brain stimulation interventions, including tDCS and rTMS, significantly improved smoking abstinence rates at 3–6 months post-treatment in general population samples.

Beyond consumption, intra-group analyses within the combined protocol revealed significant reductions in CPD and nicotine dependence at both post-treatment (T1) and follow-up (T2), as well as selective improvements in negative mood expectancies and overall smoking expectancy at T2. This pattern is consistent with previous literature showing that neuromodulation selectively impacts affective and craving-related cognitions, potentially through enhanced prefrontal regulation of reward and inhibitory control circuits (Amiaz et al., 2009; Xu et al., 2013).

Collectively, these results suggest that a Combined approach can produce both statistically and clinically meaningful changes in smoking behaviour and dependence, with responder rates that compare favourably with existing neuromodulation studies in the general population. The sustained effect on CPD and nicotine dependence at follow-up underscores the potential of Combined protocols to enhance smoking cessation outcomes beyond Conventional single-technique interventions.

In addition to reductions in cigarette consumption, we examined the number of participants achieving complete smoking cessation. At post-treatment (T1), 7 participants in the Combined protocol had successfully quit smoking, compared with 2 in the Conventional group. This difference was statistically significant ($p = 0.020$), indicating that the Combined protocol increased the likelihood of achieving complete abstinence in the short term. At follow-up (T2), 8 participants in the Combined group remained abstinent, compared with 3 in the Conventional group, but this difference narrowly missed statistical significance ($p = 0.058$), suggesting a trend toward sustained benefit.

Additional studies support these effects: Ghorbani et al. (2019) showed a clinically good therapeutic effect in smokers treated with tDCS, Ibrahim et al. (2023) demonstrated benefits of insula-targeted rTMS for cessation, and Li et al. (2013) confirmed rTMS efficacy in treatment-seeking smokers. Systematic reviews and meta-analyses also indicate that non-invasive brain stimulation interventions (tDCS and rTMS) improve both smoking reduction and abstinence outcomes, with good acceptability in samples from general population (Mehta et al., 2024; Tseng et al., 2022).

Thus, the Combined protocol, when compared with the Conventional protocol. not only produces a significant reduction in cigarette consumption and nicotine dependence, but also increases the likelihood of clinically meaningful change, including complete abstinence. The findings underscore the promise of the Combined neuromodulation protocol in smokers from general population, highlighting both efficacy and feasibility advantages for smoking cessation interventions.

Analysis of resting motor threshold (MT) values revealed a significant global reduction from baseline (T0) to post-treatment (T1) across both intervention groups. In the

Conventional group, MT decreased from a median of 62 to 56 (Z = –3.387, p = .001), and in the Combined group MT decreased from 58 to 55 (Z = –3.387, p = .001). No significant between-group difference was observed (Z = –0.107, p = .915), suggesting that both neuromodulation protocols induced a comparable increase in cortical excitability.

These findings are consistent with previous studies indicating that both TMS and tDCS can modulate motor cortical excitability, often reflected as reductions in resting MT (Nitsche and Paulus, 2000; Rossini et al., 2015). The lack of a between-group difference suggests that while tDCS priming may enhance behavioral efficacy when combined with TMS, it does not necessarily further modulate global corticospinal excitability beyond the effects produced by TMS alone. These neurophysiological changes provide a plausible substrate supporting the behavioral improvements observed in CPD reduction, nicotine dependence, and smoking expectancy measures.

Overall, the MT findings indicate that both Conventional and Combined neuromodulation protocols are capable of inducing measurable neurophysiological effects, confirming the ability of non-invasive brain stimulation to modify cortical excitability even in general population smokers.

Both neuromodulation protocols were generally well tolerated, with only mild and transient side effects reported. The most common adverse event was headache, consistently with previous studies employing repetitive TMS for smoking cessation and other neuropsychiatric conditions (Amiaz et al., 2009; Dinur-Klein et al., 2014). In the Combined protocol, additional reports of mild scalp burning sensations were observed, which are typical sensory effects associated with tDCS stimulation and have been widely documented as benign and short-lasting (Brunoni et al., 2014; Matsumoto and

Ugawa, 2017). Importantly, none of these events required discontinuation, as they spontaneously resolved within a few days, confirming the overall safety and tolerability of both interventions.

These results reinforce the notion that combined neuromodulatory interventions may offer advantages in both clinical efficacy and treatment adherence, providing a strong rationale for their broader application in smokers from the general population. However, the durability of these benefits, optimization of stimulation parameters, and the underlying neurobiological mechanisms still remain incompletely understood. Future research should explore the integration of neuromodulation with personalized behavioral strategies, the use of neurophysiological biomarkers to predict treatment response, and the long-term sustainability of outcomes, paving the way for more targeted and effective smoking cessation interventions.

Limitations, Future perspectives, and conclusions

The results of the present research are promising and demonstrate that combining two neuromodulation techniques (tDCS and rTMS) can effectively reduce nicotine addiction.

Nevertheless, this study has some limitations. Firstly, the identification of the brain areas was not performed using MRI-guided neuronavigation, which may have slightly reduced the accuracy of the stimulation targeting. Secondly, the absence of a double-blind design and the participants' awareness that the protocol would last only a few days may have influenced their psychological expectations. Third, the lack of a one-year follow-up prevents us from extending conclusions about the duration of the treatment's effectiveness beyond the six months considered. Furthermore, the assessment of

efficacy relied on clinical observation tools and self-report measures, which may be insufficient in certain cases. Therefore, further studies are warranted to investigate the long-term durability of the clinical effects and assess the efficacy of the protocol in more severe cases.

Future randomized controlled trials (RCTs) should aim to evaluate the broader applicability and potential limitations of this combined neuromodulation approach, thus contributing to a more comprehensive understanding of its therapeutic potential.

The assessment of MT indicated the presence of cortical plasticity, although without providing specific information regarding its functional characteristics or behavioral implications. Emerging techniques combined with neuromodulation may serve as future biomarkers for evaluating treatment efficacy, thereby enabling more targeted approaches within personalized and precision medicine.

Looking ahead, future perspectives in the field of non-invasive neuromodulation point toward the integration of advanced techniques that may allow a better personalization of treatment protocols. Among these, the combination of TMS with electroencephalography (TMS-EEG) represents a promising approach (Casarotto et al., 2010; Lioumis et al., 2009). By directly measuring the cortical response to magnetic stimulation with millisecond temporal resolution, TMS-EEG provides valuable information on individual patterns of cortical excitability, connectivity, and plasticity. Such neurophysiological markers may help to identify subject-specific responsiveness to different stimulation parameters, enabling the tailoring of neuromodulatory interventions according to the patient's unique cortical profile. In this way, TMS-EEG could serve as a biomarker-guided tool to optimize treatment efficacy, moving from

standardized protocols toward precision medicine approaches in the management of nicotine dependence.

Figures and tables

Figure 1. Schematic representation of neural circuits in nicotine addiction. The Ventral Tegmental Area (VTA) provides dopaminergic reinforcement to the Nucleus Accumbens (green). The amygdala and hippocampus project craving- and memory-related inputs (red), while the prefrontal cortex exerts top-down inhibitory control over reward processing (blue). The insula contributes to interoceptive and craving-related signals that influence prefrontal regulation (red). Together, these pathways illustrate the imbalance between enhanced reward/craving circuits and weakened executive control typical of addiction.

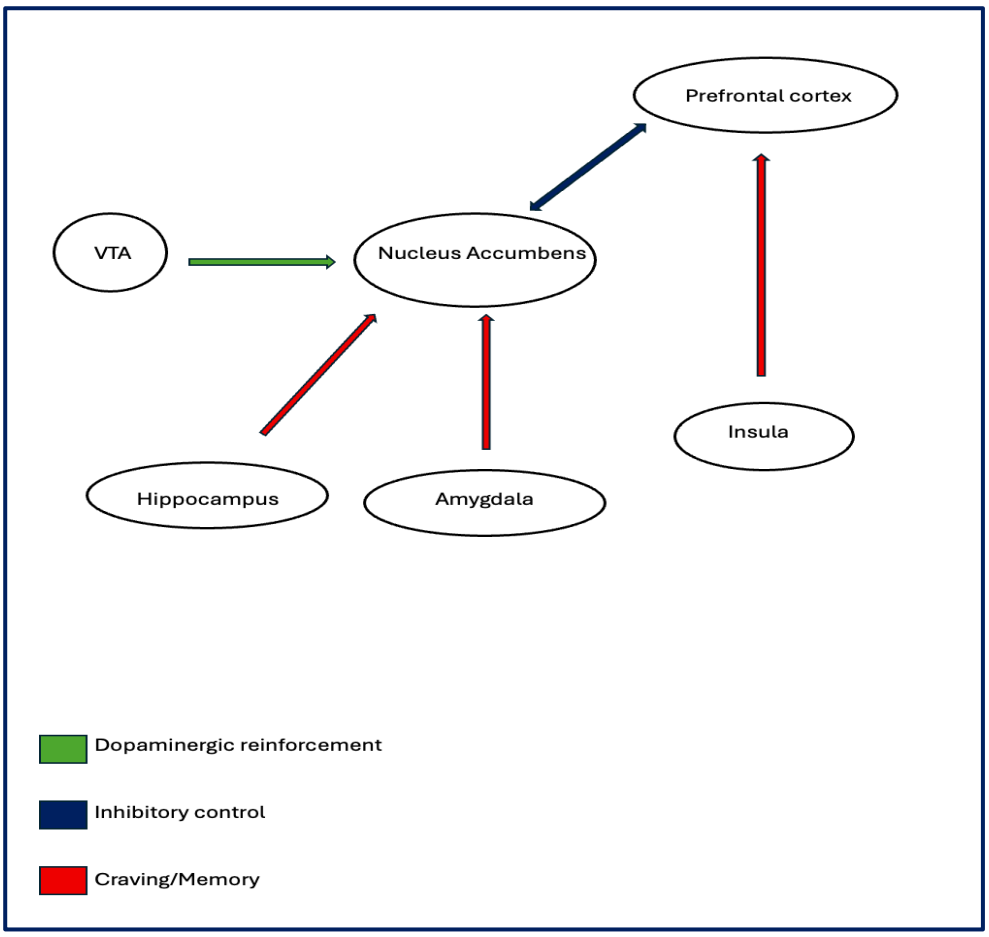

Figure 2. Priming mechanism of tDCS prior to TMS. Illustration of the sequential application of tDCS followed by TMS. Anodal or cathodal tDCS first modulates baseline cortical excitability, effectively "priming" the stimulated region. Subsequent TMS induces synaptic plasticity through LTP/LTD-like mechanisms. The combination of these effects leads to enhanced neuroplasticity, representing the theoretical basis of tDCS-TMS combined protocols.

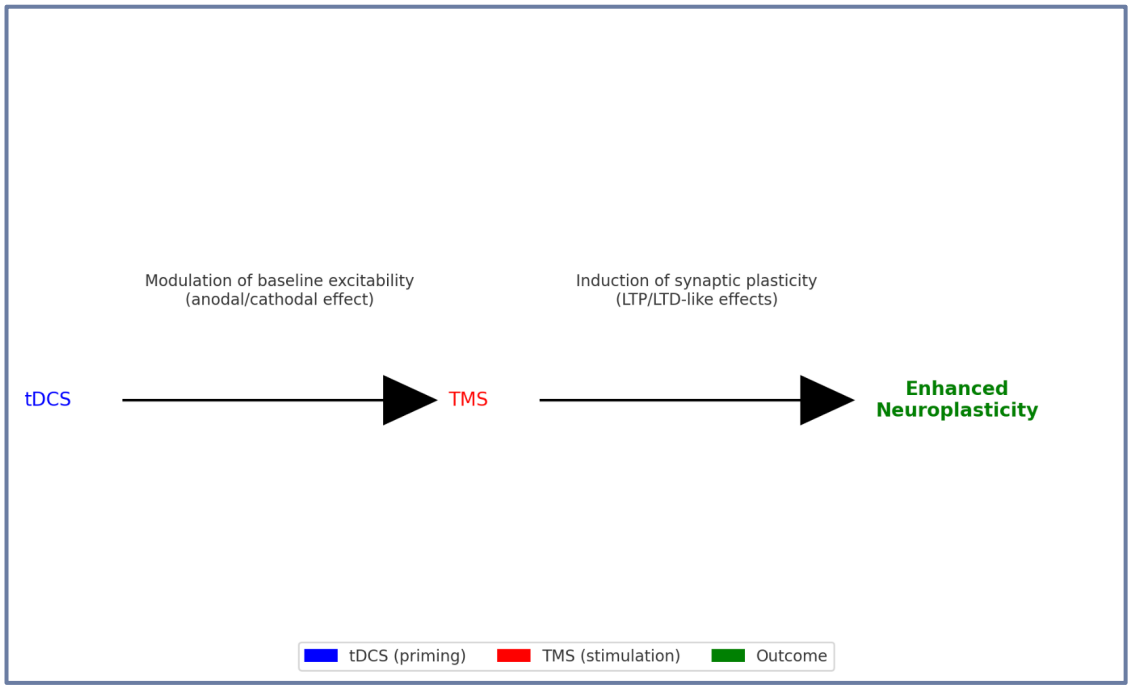

Table1. Descriptive characteristics of the sample and group-wise differences.

	Conventional protocol (n=36)		Combined protocol (n=36)		Mann-Whitney U-test
	Median	IQR	Median	IQR	*p*
Age	56	26	45.5	23	.129
Gender	2	1	1	1	.098
Educational level (years)	13	5	13	5	.637
Age of smoking onset (years)	15	5	15.5	5	.510
Number of attempts to quit	2	2	2	2	**.030**
CPD	21.5	14	20	14	.353

Table 2. Clinical changes in patients receiving conventional protocol versus combined protocol at baseline, end of treatment (T1) and week 24 (T2): Statistical differences and effect size (LOCF).

	Conventional protocol (n=36)			Combined protocol (n=36)			Mann-Whitney U-test			Cohen's d	
	Baseline Median (IQR)	T1 Median (IQR)	T2 Median (IQR)	Baseline Median (IQR)	T1 Median (IQR)	T2 Median (IQR)	Baseline (p)	T1 (p)	T2 (p)	Effect size T1	Effect size T2
CPD	21.50 (14)	15 (12)	15 (14)	20 (14)	5.50 (14)	8 (16)	.353	**.002**	**.016**	*0.57*	*0.46*
Fagerstrom	6.50 (2)	4 (3)	4 (3)	6 (4)	2.50 (6)	4 (5)	.624	**.022**	.103	*0.56*	*0.47*
SAEQ Total	62.50 (30)	53 (37)	56 (44)	53.50 (41)	46 (35)	39 (33)	.120	.267	.471	*0.14*	*0.15*
SAEQ SS	6.50 (14)	3 (12)	2 (9)	5 (7)	2 (7)	2 (7)	.457	.415	.660	0.08	*0.10*
SAEQ NM	23.50 (17)	16 (16)	10 (19)	15.50 (21)	7.50 (15)	6.5 (14)	.086	**.029**	.200	*0.45*	*0.21*
SAEQ HC	10 (14)	4 (10)	4 (9)	4 (12)	3 (8)	1.5 (9)	.126	.321	.265	0.06	*0.18*
SAEQ PC	25 (21)	24 (11)	20 (13)	26.50 (16)	27.5 (17)	21.5 (20)	.510	.183	.335	*0.22*	*0.26*

Table 3. Comparison of changes in cigarette consumption between the two treatment groups at T1 and T2 (LOCF)

	Conventional protocol (n=36)	Combined protocol (n=36)	χ^2
CPD Reduction >50% T1	10 (27.8%)	23 (63.9%)	**.001**
CPD Reduction >50% T2	15 (41.7%)	23 (63.9%)	**.033**
Quitting smoking T1	2 (5.6%)	7 (19.4%)	**.020**
Quitting smoking T2	3 (8.3%)	8 (22.2%)	.058

Table 4. Pre-post treatment comparison within the combined group (Wilcoxon test)

	Difference T0 vs T1		Difference T0 vs T2	
	Z	p	Z	p
CPD	-4.794[b]	**<.0001**	-4.822[b]	**<.0001**
Fagerstrom	-4.617[b]	**<.0001**	-4.117[b]	**<.0001**
SAEQ Total	-1.856[b]	.063	-2.695[b]	**.007**
SAEQ SS	-1.420[b]	.156	-1.541[b]	.123
SAEQ NM	-2.620[b]	**.009**	-3.137[b]	**.002**
SAEQ HC	-1.290[b]	.197	-1.539[b]	.124
SAEQ PC	-.359[c]	.719	-.941[b]	.347

b: based on positive ranks
c: based on negative ranks

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