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Transcranial Magnetic Stimulation for Nicotine Dependence: A Brief Review with Focus on Emerging Non-Tobacco Products

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Abstract

Transcranial Magnetic Stimulation (TMS) is a noninvasive treatment that has shown promise in reducing nicotine cravings and the risk of relapse. While TMS has been effective for treating tobacco use disorder, its application to newer modes of nicotine delivery, such as vaping and nicotine pouches, is understudied. This article highlights the need for updated TMS protocols that are responsive to current trends in nicotine use, especially in younger populations. Expanded research including a wide range of nicotine products will increase the generalizability and clinical relevance of TMS for the treatment of nicotine dependence**.**

Keywords: Transcranial Magnetic Stimulation, Nicotine Dependence, Non-Tobacco Nicotine Products, Immunomodulation

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1. Introduction

Transcranial Magnetic Stimulation (TMS) is a promising non-invasive neuromodulation technique for treating substance use disorders (SUDs) (1). Recent studies and clinical trials have demonstrated TMS as a method to reduce cravings in individuals with SUDs. Through regulating cortical and dopaminergic activity, TMS may assist in lowering the risk of relapse while breaking the learned behavioral patterns that lead to compulsions (2). TMS is thought to exert its effects by modulating activity in the mesocorticolimbic system, which serves a crucial role in the maintenance of addictive behaviors (3). Among the various substance disorders studied through TMS protocols, nicotine dependence, specifically tobacco use disorder, has emerged as one of the most extensively investigated.

In SUDs, the dorsolateral prefrontal cortex (DLPFC) is widely implicated in generating craving-related responses and exerting inhibitory control over them (4). The DLPFC manages stress responses by regulating the production and release of dopamine (4) and dysfunction in this pathway may reduce stress resilience and increase susceptibility to relapse. The left DLPFC is a frequent target in TMS protocols because its stimulation elicits dopamine release in the striatum. This response is believed to lead to the reductions in cue-induced craving (4).

2. Discussion

Between 2003 and 2018, at least nine randomized controlled trials (RCTs) reported significant reductions in tobacco cravings and consumption following active repetitive transcranial magnetic stimulation (rTMS) compared with sham high frequency rTMS stimulation (5). The outcomes of these nine randomized controlled trials are summarized in Table 1.

However, these studies had relatively small sample sizes, ranging from 14 to 77 participants. A more robust investigation by Zangen and colleagues, published in 2021, demonstrated a significantly higher four-week continuous quit rate (CQR) in individuals receiving active rTMS compared to those in the sham group ($p = 0.006$) (6). This study enrolled 262 participants and employed a treatment protocol involving daily rTMS to the lateral prefrontal and insular cortices for three weeks, followed by once-weekly sessions for an additional three weeks. Notably, the positive outcomes from this trial contributed to the U.S. Food and Drug Administration's approval of rTMS for smoking cessation. Despite these encouraging results, the authors emphasized that comparable large-scale studies are still lacking. It should be noted that the results from current studies can be difficult to compare due to methodological differences as well as differences in the physiology of each participant (6).

One variable that remains largely unexplored is the application of TMS for non-tobacco forms of nicotine, such as vaping and nicotine pouches. A 2019 systematic review of TMS studies for smoking revealed that each of the studies analyzed specifically dealt with smoking (7). This gap is notable given the rapid shift in nicotine use patterns among younger populations, for whom tobacco smoking is no longer the predominant mode of nicotine consumption. Preclinical data suggests that adolescence is a critical period of vulnerability to nicotine exposure; the adolescent brain exhibits increased neuroplasticity, and nicotine's rewarding effects may strengthen dependence risk (8).

The heightened vulnerability in adolescent populations underscores the need to monitor the diverse nicotine consumption methods used by young adults. Cigarette smoking among 18 to 24-year-olds dropped from 29.1% to 5.4% from 1997 to 2020. In addition, it was found that thirty-day nicotine vaping rates increased to 25.5% in adolescents by 2019 (9). Previous attempts to quantify the nicotine content in electronic cigarettes have been challenging since nicotine levels vary between brands. Despite the increasing prevalence of electronic cigarettes, no current TMS trials include participants who use electronic cigarettes as their primary nicotine source.

Another emerging trend is the increasing use of nicotine pouches, which presents new opportunities and considerations for TMS research. Recent data suggest that nicotine pouches can produce nicotine plasma levels comparable to cigarettes (10). Like electronic cigarettes, there are currently no neuromodulation studies involving nicotine pouch users, highlighting the need to incorporate these product categories into future research.

3. Conclusion

To assess possible TMS efficacy in nicotine dependence in all age groups, it is necessary to draft protocols for studies with all types of nicotine

consumption included. The rise of non-tobacco nicotine products, especially in youth populations, presents the opportunity and challenge in aiming for future TMS protocol development. Future

research should prioritize larger and more diverse sample sizes, broader age ranges, and inclusion of various nicotine delivery methods. Future studies should also adopt cue reactivity tasks to better reflect non-tobacco nicotine products, which lack the consistent sensory cues of traditional smoking, such as lighting or smoke. Because most TMS protocols rely on cue-based craving assessments, identifying cues for vaping and pouch use is essential (6, 7). The variety of these newer products makes cue-related responses more variable and harder to measure. Thus, incorporating these variables will enhance the generalizability and potential efficacy of rTMS protocols across the spectrum of nicotine dependence.

Conflict of Interest: The author declares no conflict of interest.

Table 1. Randomized Controlled Trials of TMS for nicotine dependence

Study (Author and Year)	Sample Size and Population	TMS Targetand Protocol	Duration /Sessions	Primary Outcomes	Key Findings
Eichham mer et al.,2003	n = 14 smokers	Left DLPFC; 10 Hz, high frequency rTMS	5 days	Cigarette consumpti on	Active rTMS significantly reduced daily cigaretteuse vs sham.
al., 2009	smokers	DLPFC; 10Hz, 20 min/sessio n	sessions (2 weeks)	craving & consumpti on	craving and cigarette use compared with sham.
Wing et al., 2012	n = 15 patients with schizophre nia	Left DLPFC; 20Hz rTMS	3 days	Tobacco craving	Significantly decreased craving in activegroupvs sham.
Dieler et al., 2014	n = 20 nicotine-dependent adults	Left DLPFC; intermitten t theta-burst stimulation (iTBS) adjunct to psychother apy	10 sessions	Nicotine abstinence	Higher abstinence maintenancein iTBS + psychotherapy group; pilot feasibility.
Pripfl et al., 2014	n = 14 smokers	Left DLPFC; single-session 10 Hz rTMS	1 session	Cue-induced craving& EEG delta power	Reduced craving and decreasedEEG deltapowervs sham.
Kleinet al., 2014	smokers	prefrontal +insular cortices; deeprTMS	sessions (over 3 weeks)	cessation rate	quit rate significantly higher in active group (44%)vs sham (28%).
al., 2015	smokers receiving NRT	DLPFC; 1 Hz rTMS + nicotine replaceme nt	sessions eachday for two weeks	& craving	rTMS + NRT improved abstinenceand craving reduction vs NRTalone.
etal., 2018	smokers abstinent for 24 hours	DLPFC; 20 Hz rTMS	sessions	prevention	preliminary evidence of lower relapse riskvssham.
al., 2018	smokers with schizophre nia, 14 controls)	DLPFC; 20 Hz rTMS	sessions per treatmen t week	behavior& cognition	smoking behavior; cognitive effects varied bygroup,acute administration insufficient for treatment

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