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Transcranial Magnetic Stimulation Efficacy for Smoking Cessation

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Abstract

Smoking is considered the leading cause of preventable death and chronic disease worldwide. Despite significant funding towards understanding the neurobiology of addiction and options for smoking cessation treatment, tobacco kills more than 8 million people each year. Extensive research and neuroimaging studies have helped identify the pathway and mechanisms of dependency, craving, and withdrawal, which allows for targeted treatment options. Current guidelines recommend a combination of pharmacological treatment with behavioural counselling for optimal success. However, research continues for innovative interventions. One option being pioneered for addiction treatment is use of transcranial magnetic stimulation (TMS) therapy. When targeting appropriate brain structures, TMS has been shown to neuromodulate the brain pathway associated with addiction. This review of recent literature and studies assesses the ability of TMS to reduce cravings, cigarette consumption, and abstinence.

Introduction

Nicotine addiction is a complex and multifaceted disease process involving a variety of neurotransmitters and several regions of the brain. The release of dopamine, norepinephrine, glutamate, serotonin, GABA and other neurotransmitters from the nicotinic acetylcholine receptor (nAChRs) is implicated in the pleasure, stimulation and mood modulation, and ultimate addiction potential with nicotine. The release of dopamine from the ventral tegmental area (VTA) into mesolimbic, prefrontal cortex (PFC), and nucleus accumbens (NAc), or reward center of the brain, is highly associated with addiction [1-4]. Repeated exposure to nicotine causes neuroadaptations that increase the number of nAChRs; this positively reinforces the effects of nicotine, is associated with craving levels, and leads to increased symptoms with withdrawal in the absence of nicotine [3-6] (Figure 1). The goal of smoking cessation treatments is to modulate a part of this reward system.

Transcranial magnetic stimulation (TMS) is a non-invasive treatment modality that utilizes magnetic energy to create electrical currents within an area of the brain. A coil device is placed on the patient's head and 1.5 to 3.0 Tesla of magnetic pulses are rapidly alternated into the targeted tissue. This energy penetrates the extracerebral structures and depolarizes neurons within the cortex [7]. Varied coil designs, frequencies, and depths are used to stimulate specifically identified brain regions. The repetitive delivery, or pulse, of this magnetic energy excites the target region and over time, induce neuroplasticity. While protocols vary, patients typically receive several hundred to a thousand pulses in a 20 to 30-minute treatment, three to five days per week, for several weeks. The most common side effects are headache, application site discomfort, and back pain, with a small risk of seizure, estimated at 1 per 60,000 sessions [8]. TMS treatment is considered generally well-tolerated by patients (Figure 2).

The ability to target brain regions non-invasively makes TMS treatment seemingly ideal for smoking cessation. Neuroimaging, through fMRI studies and PET scan, has identified the dorsolateral prefrontal cortex (DLPFC), medial orbitofrontal cortex (mOFC), and insula as critical sites that control the dopamine pathway and nicotine craving [9-11]. TMS has been successful used for treatment-resistant major depressive disorder since 2008, and in August 2020, the FDA approved the first TMS system for smoking cessation [12]. This review aims to examine the most recent studies evaluating TMS as a treatment option for smoking cessation.

Review and Analysis

In their application for the above FDA approval, Brainsway TMS system provided evidence from a randomized, double blind, controlled study of 262 participants receiving deep TMS versus placebo sham TMS [13,14]. Males or females, age 22-70, who smoke at least 10 cigarettes daily over the previous year, with no more than 3 months of abstinence, were included in the study. Treatment protocol was high-frequency treatment 5-days per week, for 3 weeks, following by 3 once-a-week treatments. The TMS arm showed statistically significantly higher continuous quit rates (CQR) than placebo at four week (27.3% vs 11.3%) and six weeks (15.4% vs 4.3%), as well as self-reported cigarettes smoked per day. The most common adverse effect in both arms was headache (24% vs 18%), application site discomfort (11% vs 2%), and back pain (6.5% vs 2%), but no reports of discontinuation due to side effects. As Brainsway was the sponsor of this study, there is a high risk of bias that should be fully evaluated once all results are posted.

A previous smaller double-blind randomized controlled study (n=115) demonstrated similar findings. Patients, all who smoked over 20 cigarettes per day and had failed previous treatment attempts, received 13 high-frequency dTMS sessions over a 3-week period [15]. They self-reported their cravings using the Tobacco Craving Questionnaire (sTCQ), dependence using the Fagerstrom Test for Nicotine Dependence (FTND), and their amount of use, which was confirmed with urine cotinine levels. Results demonstrated a statistically significantly reduction in cigarette consumption and nicotine dependence in the group treated with high-frequency (10Hz) deep TMS versus sham TMS and low frequency (1 Hz) TMS. At 6 months post-treatment, patients in the high-frequency TMS treatment arm self-reported higher rates of abstinence than in the placebo group (28% vs 5%). The study was only completed by 77 patients, 67% of the initial participants. There was no significant statistical difference

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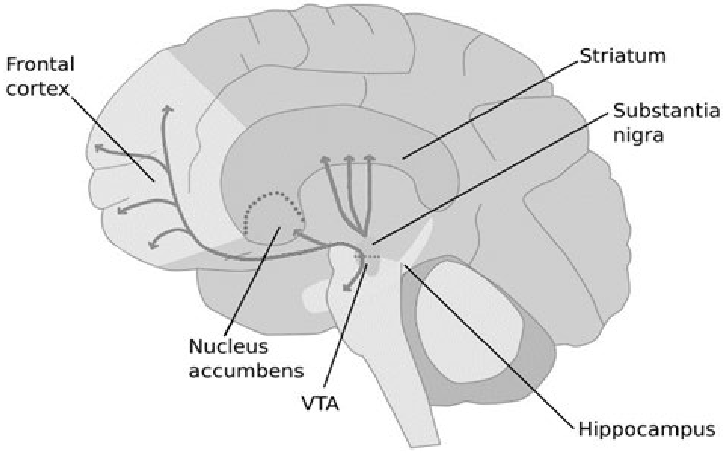

Figure 1: The brain reward center pathway.

Source: Brain rewards pathway. The Bryant Lab Addiction Genetics. Botson University

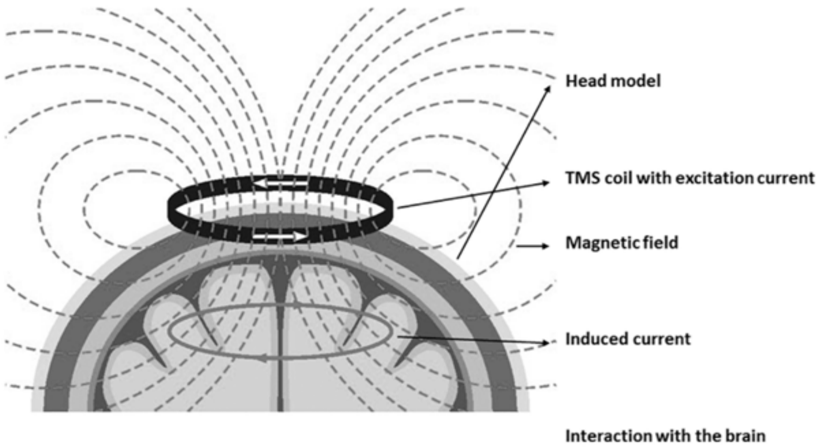

Figure 2: TMS coil.

Source: Principles of Transcranial Magnetic Stimulation (TMS) where the coil and its magnetic field induces current in the brain.

in drop-out rates between groups so contributing factors include low adherence to smoking cessation treatment as well as adverse side effects. This study was also supported by Brainsway.

A pilot study of 14 active smokers utilized fMRI to evaluate neurophysiology changes following 10 TMS treatments [16]. Patients were given localized high-frequency 20 Hz TMS to the DLPFC and superior medial frontal cortex (SMFC) for 10 treatments (T10) in two weeks, with additional follow-up 25 days after treatment (F25). Of the 10 participants who completed the study, 9 had remained abstinent at F25, based upon monitored carbon monoxide (CO) levels and self-reporting. Withdrawal symptoms, using the Minnesota Nicotine Withdrawal Scale (MNWS) and craving scales were performed at baseline, T10 and F25; both were significantly decreased at T10 and F25 compared to baseline, without a significant difference between T10 and F25. Additionally, fMRI was performed at baseline and T10 to evaluate cerebral blood flow (CBF) and brain activity irregularity (BAI) as previous studies had linked increased CBF and BAI to nicotine dependence [17,18]. Here, researchers found a significant decreased in CBF in areas of the brain attributed to cravings, withdrawal, and impulsivity including the thalamus, ventral striatum, anterior cingulate cortex (ACC), and the prefrontal cortex, and decreased BAI in the right anterior insula, dorsal striatum and ACC. While a small study with an early end-point and no long term follow up, researchers were able to demonstrate initial brain changes and concurrent patterns of craving and use due to TMS treatment and smoking cessation.

In another imaging study, patients (n=10) received fMRI before and after a single true TMS treatment and a sham TMS treatment [19]. After TMS treatment, but not sham, imaging showed a decrease in brain activity within the subjects insula and thalamus, and decreased connectivity between the left DLPFC and the medial orbitofrontal cortex (mOFC); these areas have been previously implicated in the neural circuitry of nicotine addiction [20].

In a randomized double-blind study of 29 patients, TMS combined with an evidence-based self-help booklet, were used to evaluate abstinence [21]. Patient received 8 high-frequency treatments or sham TMS treatments over 2 weeks where they read the "8 Forever Free" (FF) self-help relapse prevention booklet during treatment and

Study	*n*	Pulse Frequency	Site of Pulse	Treatments Provided	Results
George, et al. [13]	262	10 Hz vs placebo (0 Hz)	Insula, PFC	15 over 3 weeks, then 1 per week x 3 weeks (18 total)	- ↑ four-week CQR and ↓ number of cigarettes smoked per day
Dinur-Klein, et al. [15]	115	10 Hz, 1 Hz, placebo (0 Hz)	Insula, Lateral PFC	10 over 2 weeks, then 3 over 1 week (13 total)	- HF TMS ↓ cigarette consumption greater than placebo and LF TMS - HF TMS had ↑ rates of abstinence 6-mo post treatment
Chang, et al. [16]	14	20 Hz	DLPFC, SMFC	10 over 2 weeks	- 9 of 14 remained abstinent at F25 - ↓ craving and withdrawal score - ↓ BAI and CBF post treatment
Li, et al. [19]	10	10 Hz- 1 appt 0 Hz- 1 appt	Left DLPFC	1 active TMS, 1 sham TMS a week apart	- Single TMS session inhibits brain activity in thalamus and insula, and connectivity between the DLPFC and mOFC
Sheffer, et al. [21]	29	20 Hz vs placebo (0 Hz)	Left DLPFC	8 over 2 weeks	- 3 fold reduction in relative risk of relapse - ↑ rate of abstinence

Table 1: TMS Studies Reviewed.

recommended at home. Daily cigarette use was self-reported weekly over the phone, while in-person assessments were done at 4, 8, and 12 weeks after treatment. The mean and median time to relapse for TMS-treated patients was 45.2 and 33.5 days, versus 20.5 and 8 for sham TMS. Those receiving true TMS treatment were 3 times more likely to be abstinent at 12 weeks at 50% vs 15.4% for placebo sham. This study was novel in its approach to combining treatments though overall limited by its small size.

These studies demonstrate that TMS treatments at a frequency of 10 Hz or higher, can be an effective treatment option for smoking cessation. Four studies revealed a significant decrease in cigarette consumption and increase in abstinence rates [13,15,16,21]. One showed a decrease in standardized craving and withdrawal scores [16]. Two studies, using neuroimaging, were able to demonstrate localized decreases in cerebral blood flow and connectivity through the addiction pathway that was not seen in sham TMS [19,21]. No study reported a significant adverse event such as seizure. The most reported side effect was transient headache, and no study had a statistically higher dropout rate in the active TMS arm [21] (Table 1).

Discussion

These studies have demonstrated that TMS treatment to the DLPFC and nearby structures can significantly reduce cravings. This can be attributed to modulation of the neuropathway of the dopamine reward circuit of the brain. Despite positive results, the studies show significant heterogenosity of methods and have received a Level C recommendation for possible effectiveness of high frequency TMS of the left DLPFC on cigarette craving and consumption in the recently published evidence-based guidelines for therapeutic use of TMS [22,23]. More large, well-designed studies, with low risk of bias, are needed to support a higher recommendation.

While TMS has been on label and used for other conditions for over a decade, it's in its infancy for the treatment of addiction. To date, the FDA-approved coil and recommended treatment protocol has not been released commercially. However, a lack of standardization within the industry may plague companies. Each is tasked to engineer a proprietary coil and create a recommended treatment protocol. Current research is limited by access and cost of the treatment equipment, as well as access and cost for neuroimaging. As it becomes more available, there is an abundance of opportunity for additional research, as well as a need for comparative studies evaluating the efficacy of TMS treatment versus current pharmacology, behavioral support, and combined treatment regimens.

For patients and providers, TMS offers a solution that may be performed more quickly and lead to results sooner than pharmacotherapy. However, the patient must find a provider offering TMS, have a schedule that can accommodate daily appointments, and be aware that insurance coverage is variable. Self-pay is typically several hundred dollars per session, meaning a month of 20 sessions could run $4000-$10,000 out of pocket. For providers, the offering of TMS treatment can also be costly for equipment and training. Nevertheless, tobacco addiction is an epidemic with high mortality and morbidity rates that demands the attention of health care providers.

Conclusion

In 2017, an estimated 34.2 million Americans reported smoking cigarettes [24]. Of those, 55.1% reported making an attempt to quit in the last 12 months, with only 7.5% being able to successfully do so. Over 90% of those trying to quit are unsuccessful-a staggering number that demonstrates the highly addictive nature of nicotine. High frequency TMS treatment of these regions has been shown to successfully decrease cravings, cigarette consumption, and increase abstinence rates. This is supported by neuroimaging studies that demonstrate the mechanism of action for these findings. While more research is needed, there is opportunity to utilize this non-invasive treatment to address one of the largest medical concerns of our time.

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