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Manipulation of Cigarette Craving with Transcranial Magnetic Stimulation

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The health risks and societal costs of cigarette smoking are well documented, but the prevalence of smoking among American adults remains high at approximately 20%. Most smokers endorse a desire to quit, but very few (only about 4–7%) will actually do so in a given year without treatment. Current commonly used treatments for tobacco dependence include nicotine replacement therapy (e.g., patch, gum, and lozenge), varenicline HCl (Chantix), bupropion HCl (Zyban), and group and/or individual psychotherapy. These treatments result in roughly 20–25% abstinence rates in smokers at 6 months or more after treatment initiation and are therefore considerably better than attempting abstinence without treatment. However, there continues to be a vital need to improve treatments for cigarette smokers wanting to quit because such a high percentage of smokers who initiate treatment will relapse within the first year. A potential new treatment option for tobacco dependence that is currently being evaluated is transcranial magnetic stimulation (TMS).

TMS has proven to be a useful tool for both studying brain circuits that support behavioral and cognitive processing and some therapeutic uses. The magnetic fields of TMS systems induce small currents in cerebral tissue, leading to depolarization in the brain region adjacent to the stimulation coil (the target) and in other neurons transsynaptically (1). These fields can be characterized along many parameters, such as field strength and frequency of stimulation. For repetitive TMS (rTMS), conventional terminology refers to the pulsed fields as having slow (low frequency, ≤ 1 Hz) or fast (high frequency, >1 Hz) repetition frequencies, with slow stimulation frequencies leading to decreases in cortical activity and fast stimulation leading to increases.

With repeated treatment sessions, these changes persist when stimulation is not occurring, presumably through neuroadaptation mechanisms. Depending on pulse parameters and neuroanatomic target, neuronal circuits can be manipulated to enhance or reduce their functional activity, with the choice related to the desired clinical effect(s). Evidence supporting the efficacy and safety of fast rTMS for the treatment of major depression led to Food and Drug Administration clearance of a system for that indication (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm265269.htm), and a recent meta-analysis concluded that rTMS should be viewed as a useful clinical treatment method for depression (2).

In the field of addiction, several reviews of the emerging use of rTMS have recently been published (3–5). When delivered to the prefrontal cortex, rTMS has been found to reduce craving for cigarettes, alcohol, cocaine, and food (5) and (in some studies) has been found to

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transiently reduce intake (3,4) (although not all studies have demonstrated these same effects (4,5)).

It has been postulated that rTMS delivered to the dorsolateral prefrontal cortex affects craving/addiction through its influence on decision making (5) and inhibitory control (3) because risky decision making and difficulty with inhibitory control are traits common to people who suffer from addiction.

In addition, a possible mechanism for the effects in addiction of rTMS to frontal brain regions is that this method enhances dopamine release in mesocorticolimbic brain circuitry (3), which could alleviate substance use urges by mimicking the dopamine release associated with substance use and withdrawal, thereby diminishing the need to take additional substances. Furthermore, given the ability of brain stimulation to modulate cortical excitability, it has been hypothesized that these stimulations result in neuroadaptations and changes in synaptic plasticity in the brain reward system (5), which could be relevant for the treatment of addiction.

In this month's issue of *Biological Psychiatry*, Rose *et al.* (6) describe their innovative study in which subjective craving responses to cigarette (and neutral) cues and cigarette smoke presentation were modulated by high-frequency (10 Hz) rTMS directed at the superior frontal gyrus (SFG). Stimulation at this frequency and location increased craving in response to cigarette cues and diminished craving in response to neutral cues compared with other rTMS administrations (low frequency [1 Hz] delivered to the SFG and low frequency [1 Hz] directed at the motor cortex). High-frequency rTMS delivered to the SFG also strengthened craving alleviation in response to cigarette smoke presentation (when this smoke was delivered in a manner that simulated the participant's own smoking pattern).

Taken together, these results indicate that high-frequency rTMS directed at the SFG accentuates natural responses to cigarette-related (and neutral) cues and also to cigarette smoking itself. These results show great promise for the possibility of manipulating smoking-related symptoms and smoking behavior and could possibly guide future treatment trials of rTMS for tobacco dependence.

Whereas the study by Rose *et al.* (6) focused on SFG function based on studies by their group, smoking-related symptoms have also been linked to SFG activity in other recent studies as well. In one such study (7), a subgroup of smokers (based on genotype) was found to have a correlation between cigarette cue-induced SFG activation and severity of nicotine dependence. In another set of studies, cigarette cue exposure delivered through a virtual reality environment was associated with increased SFG activity, and this activation was diminished from before to after cue exposure treatment of smokers (8). Additionally, in a brain-imaging study of SFG function, part of this gyrus was found to mediate the detection of unfavorable outcomes, response errors, response conflict, and decision uncertainty (9), which are functions potentially associated with addiction. Thus, the SFG has been repeatedly linked to smoking-related symptoms, may mediate certain types of smoking cessation treatment response, and holds promise as a target for TMS modulation of smoking-related symptoms.

In addition to the SFG, other brain regions have been frequently linked to smoking-related symptoms (10), and future research using brain stimulation in smokers could focus on these regions as well. As for cortical structures that should be considered as potential targets for manipulation by neuromodulation, the dorsolateral prefrontal, anterior cingulate, orbitofrontal, and insular cortices all have been implicated in tobacco dependence and have demonstrated functions that could be related to addictive behavior. These regions are associated with such functions as decision making, behavioral inhibition, attention, and

repetitive behavior and are therefore logical targets for neuromodulation in addiction, as has been done in the initial studies referred to in the abovementioned text. Although it would be ideal to be able to explore the potential therapeutic benefit of stimulation at each of these sites, some regions are more accessible than others, which may explain why specific surface regions (e.g., dorsolateral prefrontal cortex) have been more extensively studied than deeper regions (e.g., anterior cingulate and insular cortices).

Subcortical structures that could be targets of neuromodulation treatments include the thalamus, ventral striatum (brain reward area), and brainstem. These regions have high densities of nicotinic acetylcholine (nicotine) receptors, with the thalamus being of particular interest in tobacco dependence because it has the highest density of nicotinic acetylcholine receptors in the brain and has been reported to be a relay station for cortical drive. These factors strongly implicate the thalamus as mediating at least some symptoms of tobacco dependence. The brainstem and ventral striatum are also strongly implicated in smoking behavior because the brainstem contains neurons in the ventral tegmental area that project to the ventral striatum and release dopamine in response to nicotine administration.

Taken together, the research by Rose *et al.* (6), along with related studies, may encourage additional research focused on manipulating smoking-related symptoms and smoking behavior, with the overall goal of improving abstinence rates in smokers seeking treatment.

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