How to Assess the Role of Transcranial Magnetic Stimulation in Nicotine Addiction

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Substance use disorders (SUD) in general and nicotine dependence in particular account for significant mortality, morbidity, and socioeconomic burdens. This is a global issue that affects various societies as established by numerous health organizations including the World Health Organization, the Centers for Disease Control, and the National Institute on Drug Abuse. Researchers now believe that whereas positive reward from nicotine initiates smoking, it is mainly the relief from withdrawal symptoms and negative affect associated with it that contribute to the persistence of smoking and relapse (1). Nicotine directly stimulates *N*-acetylcholine receptors (nAChRs) in the ventral tegmental area and increases dopamine (DA) levels in mesolimbic brain structures that initiate and perpetuate addictive behaviors. Activation of nAChRs on glutaminergic and gamma-aminobutyric acid (GABA)ergic terminals also modulate DA release in the nucleus accumbens and frontal cortex. Nicotine also increases release of norepinephrine in the amygdala and hippocampus, regions known as "incubators of craving phenomenon" that are activated on exposure to substance-related cues. Conversely, withdrawal from nicotine and cravings are associated with lower DA levels. Less than 5% of smokers who stop smoking on their own achieve 6- to 12-month abstinence (2).

Definitive treatments for prolonged and sustained smoking cessation have not been dramatically effective. Evidence-based treatment improves successful abstinence rates by a factor of 5 (3), yet 75% of persons resume smoking within 6 months. A combination approach of psychological and behavioral therapies with pharmacology are clinically the most effective.

Over the last two decades, neuromodulation tools have emerged as adjunctive or alternative therapies for various neuropsychiatric disorders. With an urgent need for improved outcomes in SUD, it was an expected development for neuromodulation to enter the field. The effects of transcranial magnetic stimulation (TMS) have been shown to be positive in reducing cravings, responsiveness to cues, and consumption of addictive substances in a number of studies including cocaine, alcohol, opiates, and in several nicotine studies, including the recent study by Li *et al.* (4,5). Unfortunately, none have yet shown significant improvement in long-term abstinence.

These investigations have focused primarily on the dorsolateral prefrontal cortex area, given its strong connection to the deeper mesolimbic brain structures and its role in decision-making and impulsivity. Keep in mind that current technology (excluding deep TMS and H-coil) precludes direct stimulation of subcortical areas.

Although the exact mechanisms of action are to be elucidated, the effects of prefrontal TMS on nicotine addiction neural pathways probably are multifactorial. Local and transynaptic modulation of mesolimbic regions are well established with imaging studies (6). The postulated mechanisms of action include changes in dopamine levels, direct modulation of glutaminergic and GABAergic activity, and presumably effects on monoamines. In fact, intracerebral microdialysis in animals has shown that TMS can stimulate DA release in the hippocampus and nucleus accumbens. TMS applied to the human prefrontal cortex has been shown to increase DA release in the mesolimbic system (7) and to modulate $GABA_B$ (8). Dorsolateral prefrontal cortex stimulation has also been shown to reduce impulsivity, a major problem in SUD.

In the recent study by Li *et al.* (4), the authors elegantly demonstrated that repetitive TMS (rTMS) administered with parameters similar to those used in the clinical treatment of mood disorders (10 Hz, 120% of motor threshold and 3000 pulses for 1 session) (9) was effective in significantly reducing response to craving when presented with smoking cues. Additionally, this was the first study to show a positive correlation between degree of response to rTMS and severity of nicotine addiction determined by the number of cigarettes consumed, a measure related to the risk of relapse after smoking cessation. This study controlled effectively for sham and real rTMS, and the technique used for sham TMS is described at length in the article.

There is a need for larger and long-term studies because the majority of studies involving nicotine had relatively small numbers of participants and lacked long-term follow-up. The cue-exposure paradigm used by Li *et al.* attends to the environmental role in eliciting craving and its contribution to relapse. Behavioral extinction therapies have failed to reduce cue-induced craving, possibly because there are so many environmental cues associated with smoking. This adds to the significance of this work and certainly supports follow-up studies with repeated sessions. However, for this line of research to develop, equal attention should be made to internal cues of negative affect because they, too, have been linked to craving and relapse. Considering the comorbidity of nicotine dependence and psychiatric disorders and shared substrates that mediate nicotine dependence and depression-like symptoms (10), a greater synergy can be made between the recent development in parameter optimization for TMS as a clinical antidepressant treatment and future anti-smoking trials. Factors such as age and sex are also important to consider in future research because they also affect success rates in smoking cessation trials.

Finally, although TMS studies to date do not support immediate application in the smoking session treatment arsenal, they offer a unique perspective on the pathophysiology of nicotine addiction. TMS and other neuromodulation tools will inform the development of more effective treatment to complement the existing therapeutic modalities.

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