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Review Articles

Brain Stimulation Methods to Treat Tobacco Addiction

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ABSTRACT

Background: Tobacco smoking is the leading cause of preventable deaths worldwide, but many smokers are simply unable to quit. Psychosocial and pharmaceutical treatments have shown modest results on smoking cessation rates, but there is an urgent need to develop treatments with greater efficacy. Brain stimulation methods are gaining increasing interest as possible addiction therapeutics.
Objectives: The purpose of this paper is to review the studies that have evaluated brain stimulation techniques on tobacco addiction, and discuss future directions for research in this novel area of addiction interventions.
Methods: Electronic and manual literature searches identified fifteen studies that administered repetitive transcranial magnetic stimulation (rTMS), cranial electrostimulation (CES), transcranial direct current stimulation (tDCS) or deep brain stimulation (DBS).
Results: rTMS was found to be the most well studied method with respect to tobacco addiction. Results indicate that rTMS and tDCS targeted to the dorsolateral prefrontal cortex (DLPFC) were the most efficacious in reducing tobacco cravings, an effect that may be mediated through the brain reward system involved in tobacco addiction. While rTMS was shown to reduce consumption of cigarettes, as yet no brain stimulation technique has been shown to significantly increase abstinence rates. It is possible that the therapeutic effects of rTMS and tDCS may be improved by optimization of stimulation parameters and increasing the duration of treatment.
Conclusion: Although further studies are needed to confirm the ability of brain stimulation methods to treat tobacco addiction, this review indicates that rTMS and tDCS both represent potentially novel treatment modalities.

Introduction

Although tobacco smoking rates have decreased in Western nations over the past decade [1], tobacco is still the leading cause of mortality in the USA [2] and third most frequent cause of preventable mortality in industrialized countries [3]. Various treatments have been shown to increase the odds for successfully quitting (up to 2–3 times compared to placebo), including counseling [4–6] and pharmaceutical aids such as nicotine replacement therapy (e.g., nicotine patch, gum and inhaler), bupropion (Zyban®) and varenicline (Chantix®) [7–12]. Nevertheless, the majority of those attempting to quit will relapse [13–17].

Nicotine is the main psychoactive ingredient in tobacco smoke and is believed to result in its addictive properties. Nicotine binds to ubiquitously distributed nicotinic acetylcholine receptors (nAChRs) [18] to influence the release of neurotransmitters including

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dopamine (DA), noradrenaline, serotonin, endogenous opioids, γ-aminobutyric acid (GABA) and glutamate [19]. Nicotine's ability to induce the release of DA in the nucleus accumbens (NAc) underlies its reinforcing effects, which are thought to initiate the process of addiction [20]. Neuroadaptations following chronic nicotine exposure are thought to underlie the compulsive drug seeking, tolerance, withdrawal and craving seen in tobacco addiction [21,22].

In the past decade, progress has been made in developing neurobiologically-based interventions for smoking. The interest in brain stimulation as a potential treatment rests on its ability to induce changes in brain function. The purpose of this article is to review the literature on brain stimulation as a treatment for tobacco dependence, and provide a discussion on future directions for research in this novel area of addiction interventions. All relevant studies were identified through NCBI Pubmed (http://www.ncbi.nlm.nih.gov) and manual searches. Search terms included 'repetitive transcranial magnetic stimulation,' 'rTMS,' 'transcranial direct current stimulation,' 'tDCS,' 'deep brain stimulation,' 'DBS,' with adjoining terms, 'tobacco,' 'nicotine,' 'smoking,' and 'addiction.' Due to the paucity of literature in this area, $N = 15$ studies were identified and included in this review ($n = 12$ journal articles; $n = 3$ conference abstracts).

Repetitive transcranial magnetic stimulation (rTMS)

rTMS is a non-invasive brain stimulation technique that has shown positive results in the treatment of depression [23,24], schizophrenia [25], and more recently addiction [26–32] (for further reviews see [33,34]). rTMS uses alternating magnetic fields to induce electric currents in the cortical tissue [35]. Low-frequency (LF; ≤1 Hz) rTMS is believed to inhibit neuronal firing in a localized area and is used to induce virtual brain lesions. High-frequency (HF; >3 Hz) rTMS is believed to be excitatory in nature and can result in neuronal depolarization under the stimulating coil [36]. However, the effects of rTMS are not limited to the site of stimulation and can induce changes in distant interconnected sites of the brain, and consequently may influence subcortical regions [35,37–40].

In rodents, rTMS has been shown to increase DA in the dorsal hippocampus [41] and NAc [41,42], and modulate GABA synthesis [43]. In humans, rTMS can induce changes in cortical inhibition. HF frequency rTMS (up to 25 Hz) applied to the motor cortex has been shown to both enhance [44] and reduce [45] neurophysiological indices of $GABA_B$ receptor-mediated inhibitory neurotransmission in different studies. HF rTMS also affects indexes of $GABA_A$ receptor-mediated inhibitory neurotransmission [46,47]. Positron Emission Tomography (PET) studies have demonstrated that 10 Hz rTMS over the dorsolateral prefrontal cortex (DLPFC) increases extracellular levels of DA in cortical and subcortical brain regions [48,49]. Regional cerebral blood flow (rCBF) studies have shown that HF and LF rTMS to the left DLPFC are respectively associated with increases and decreases in rCBF across a range of cortical and subcortical regions in depressed patients [50]. In contrast, LF rTMS to the right DLPFC in control subjects has been shown to be associated with increased rCBF at the stimulation site and in the ventrolateral prefrontal cortex [51]. These studies demonstrate that rTMS has the potential to treat tobacco addiction by altering cortical excitability through the modulation of neurotransmitters (e.g., DA and GABA). Ultimately, the effects of rTMS on cortical excitability will be influenced by the basic excitability niveau of the person being treated, which may explain why similar stimulation conditions have sometimes led to different neurobiological effects.

Treatment of tobacco addiction with rTMS

Our search identified 6 randomized double-blind sham-controlled studies on rTMS and tobacco addiction (Table 1). Five studies applied HF rTMS to the DLPFC [26,27,52–54]. In a cross-over study, Johann et al. (2003) administered one active and sham session of 20 Hz rTMS delivered to left DLPFC to treatment-seeking smokers under 12 h abstinent conditions [26]. rTMS significantly reduced the level of craving reported after treatment. The same research group investigated the effects of two sessions of active and sham rTMS at the same parameters [27]. Cravings were not significantly reduced, but the number of cigarettes smoked in the 6 h following treatment was. Recently, Amiaz et al. (2009) assessed the effects of 10 days of treatment with either active or sham 10 Hz rTMS treatment applied to the left DLPFC. To test whether induction of tobacco craving before treatment would result in a more specific disruption of circuitries associated with craving, subjects were presented with either smoking or neutral cues immediately before rTMS treatment. rTMS, independent of exposure to smoking pictures, reduced subjective and objective measures of cigarette consumption and nicotine dependence [28]. It also reduced cue-induced craving and blocked the development of general craving induced by repeated presentation of smoking-related pictures. Interestingly, there was a trend for lower cigarette consumption in the active rTMS-smoking picture group at 6 month follow-up. Our research group has recently completed a preliminary parallel-groups sham-controlled trial of rTMS in combination with the nicotine patch to treat tobacco addiction in heavily-dependent patients with schizophrenia [52]. rTMS did not increase abstinence rates, but did significantly reduce tobacco cravings induced by short-term (30–60 min) abstinence which was assessed before application of the nicotine patch. Together, these studies indicated that rTMS of the DLPFC has the potential to reduce tobacco cravings and cigarette consumption in smokers, including those with schizophrenia.

Rose et al. (2011) implemented a within-subject design to examine the effects of rTMS to the Superior Frontal Gyrus (SFG). Compared to 1 Hz rTMS to the SFG or motor cortex, 10 Hz to the SFG resulted in increased cue-induced craving but lower craving during presentation of neutral cues [53]. These findings highlight the excitatory and inhibitory influence of SFG on tobacco cravings but do not provide evidence for the utility of rTMS of the SFG for the treatment of tobacco addiction.

In addition to studies focusing on treatment-related outcomes, researchers have begun to examine the mechanisms underlying rTMS's effects. The effects of 1 Hz rTMS applied to the left DLPFC on neural responses to smoking cues were reported in an abstract. Connectivity analysis revealed that the stimulated region became less responsive to input from the contralateral DLPFC and medial temporal regions which may have resulted in the trend for reduced craving following active rTMS [54]. It is clear that further studies are needed to fully understand the complex effects of rTMS on tobacco addiction.

Cranial electrostimulation (CES)

Similar to rTMS, CES (also known as transcranial electrostimulation therapy or neuroelectric therapy) uses a low intensity alternating current commonly applied through two electrodes attached to the earlobes or mastoid [55,56]. CES was originally developed in the 1950s for anxiety and depression treatment, and was later used to treat pain [57]. The evaluation of CES to treat addictive disorders began in the 1980s with some positive findings [58]. However, optimal frequency and duration of stimulation parameters still need to be determined. The exact mechanism of CES is still largely unknown but the modulation via direct action upon the hypothalamus, limbic system and/or the reticular