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Tolerability and feasibility of accelerated repetitive transcranial stimulation for reduction of nicotine craving

Dear Editor,

Tobacco smoking remains the leading cause of preventable death in the world, leading to approximately 6 million deaths a year. A recent review estimated offering smokers a combination of individual counseling and pharmacotherapy resulted in only an 11–16% cessation rate at 6 months [1]. Craving is associated with smoking relapse [2], and has been a frequent target of treatment interventions including nicotine replacement therapy, bupropion, and varenicline [3]. Several recent investigations reported that repetitive transcranial magnetic stimulation (rTMS) applied to the dorsolateral prefrontal cortex (DLPFC) reduced craving [4], and cigarette consumption [5,6]. Though promising, the work to date has been limited by the current treatment paradigm of rTMS where treatments are delivered each day for several weeks. In prior rTMS smoking cessation trials, study retention has only ranged from approximately 50%–67% [5,6]. Subsequently finding a way to condense treatment courses may increase the feasibility of delivering this promising intervention to smokers. Recently several studies have explored the feasibility and efficacy of delivering "accelerated" courses of rTMS for depression, delivering several treatments each day [7,8]. We wanted to determine if an accelerated course of treatment could be feasibly delivered to cigarette smokers. These feasibility data might spur the development of accelerated rTMS for smoking cessation paradigms.

In order to determine if an accelerated course of rTMS could be feasibly delivered to cigarette smokers, we completed a preliminary, parallel-designed, randomized, double-blind, sham-controlled, pilot trial delivering five-treatments of either active, or sham rTMS in a single day to non-treatment seeking nicotine-dependent cigarette smokers. Additionally, cigarette craving was assessed after each treatment session. Prior to beginning enrollment, this trial was approved by the institutional review board of the Medical University of South Carolina, and pre-registered with clinicaltrials.gov (NCT03352609). Cigarette smoking participants were recruited via fliers and online advertisements, and underwent a telephone screen prior to attending a single visit. Participants were included if they were current daily smokers (>10 cigarettes/day) who were not currently making a quit attempt. Participants were excluded if they met DSM-5 criteria for any other substance use disorder, met criteria for any other major psychiatric illness, were currently taking any psychotropic medication or nicotine replacement, had any unstable medical condition, were pregnant, had any implanted metal in their head, or were at elevated risk of seizure. Prior to undergoing study procedures, informed consent was obtained. The MINI international neuropsychiatric interview, review of current medications, medical history, urine pregnancy test and confirmation of smoking status by exhaled CO reading of >10 ppm, were all used to confirm participants met study inclusion/exclusion criteria. Current level of nicotine dependence was evaluated by the Fagerstrom Test for Nicotine Dependence (FTND) and two-week time line-follow back. Smoking was permitted up to the start of the visit, which was approximately an hour prior to beginning craving assessments and participants abstained for the remainder of visit.

Participants meeting all inclusion/exclusion criteria were randomized to active or sham rTMS. Active rTMS was delivered via a MagPro double blinded rTMS Research System (Magventure, Denmark) with a Cool-B65 Butterfly combined active and sham coil. For sham stimulation, a validated system was utilized which used transcutaneous electrical nerve stimulation [9]. Treatment was delivered to the left dorsolateral prefrontal cortex using the Beam-F3 method [10] at 110% of resting motor threshold. Each rTMS session consisted of a total of 3000 pulses of 10hz stimulation (5s on-10s off). During the initial session, the dose was slowly increased to a maximum of 110% of rMT over several minutes to improve comfort. During the visit participants received 5-sessions of rTMS, each separated by 30 minutes, for a total of 15,000 pulses. The primary outcome measure was the percent of participants who tolerated the intervention and completed the five-session course at 110% rMT. Cigarette craving was evaluated using a modified Questionnaire on Smoking Urges-Brief (QSU-B) scale with computerized

Table 1
Participant craving and reported adverse effects.

Participant	Active/Sham	Average Cigarettes	FTND	%rMT	Change in craving	Subjective
1	Active	19	8	100	+0.7%	Mild scalp discomfort with dose titration
2	Sham	21	8	110	−21.3%	Denied adverse effect
3	Sham	47	7	110	−10%	Denied adverse effect
4	Sham	15	6	110	+3.3%	Mild transient nausea at start of first treatment, immediately resolved
5	Active	13	6	110	−14%	Denied adverse effect

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analog ratings between 0 and 100. After completion of 5-sessions, patients were asked if they thought they received active or sham treatment and were evaluated for adverse events (AE's).

Twenty-two individuals were screened by phone, of which six were invited for a visit, and five met with study staff, all of whom enrolled. All participants were male with an average age of 37 ± 13.8. They reported smoking an average of 22.9 ± 13.9 cigarettes a day with an average FTND score of 7.0 ± 1.0 indicating a high level of dependence. Two participants were randomized to active rTMS, both of whom completed the study procedure. One such participant achieved the goal dose of 110% rMT without reported side effects, reported a 14% reduction in average craving, and felt he had received active treatment due to having a decreased urge to smoke. The other participant receiving active stimulation requested treatment not be escalated above 100% rMT due to scalp discomfort, and reported a negligible change in his craving before and after treatment, with a 0.7% increase in craving. Three participants received sham treatment, all of whom completed the study protocol at 110% rMT, and all believed they had received active stimulation. One participant receiving sham stimulation reported transient nausea, and neither of the other participants reported AE's. Among participants receiving sham treatment, one reported a 3% increase in average craving and two reported decreases of 21.3% and 10% in average craving respectively. (See Table 1)

In this pilot investigation, we found that it was feasible to deliver 5-sessions of 10hz LDLPFC rTMS for a total of 15,000 pulses to nicotine-dependent cigarette smoking individuals in a single day. Further, treatment using this paradigm was well tolerated with four of five participants achieving 110% of rMT, and all five completing the visit. These data suggest that the accelerated delivery of rTMS to non-treatment seeking nicotine-dependent smoking participants likely can be performed. Future larger investigations will be needed to determine whether a course of accelerated rTMS (delivering 15 or more total sessions of treatment), is well tolerated, and efficacious in reducing craving, or cigarette smoking.

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References

[1] Lancaster T, Stead LF. Individual behavioural counselling for smoking cessation. Cochrane Database Syst Rev 2017;(3).
[2] Killen JD, Fortmann SP. Craving is associated with smoking relapse: findings from three prospective studies. Exp Clin Psychopharmacol 1997;5(2):137–42.
[3] Cahill K, Stevens S, Lancaster T. Pharmacological treatments for smoking cessation. J Am Med Assoc 2014;311(2):193–4.
[4] Li X, Hartwell KJ, Owens M, Lematty T, Borckardt JJ, Hanlon CA, et al. Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex reduces nicotine cue craving. Biol Psychiatry 2013;73(8):714–20.
[5] Amiaz R, Levy D, Vainiger D, Grunhaus L, Zangen A. Repeated high-frequency transcranial magnetic stimulation over the dorsolateral prefrontal cortex reduces cigarette craving and consumption. Addiction 2009;104(4):653–60.
[6] Dinur-Klein L, Dannon P, Hadar A, Rosenberg O, Roth Y, Kotler M, et al. Smoking cessation induced by deep repetitive transcranial magnetic stimulation of the prefrontal and insular cortices: a prospective, randomized controlled trial. Biol Psychiatry 2014;76(9):742–9.
[7] Williams NR, Sudheimer KD, Bentzley BS, Pannu J, Stimpson KH, Duvio D, et al. High-dose spaced theta-burst TMS as a rapid-acting antidepressant in highly refractory depression. Brain 2018;141(3):e18.
[8] George MS, Raman R, Benedek DM, Pelic CG, Grammer GG, Stokes KT, et al. A two-site pilot randomized 3 day trial of high dose left prefrontal repetitive transcranial magnetic stimulation (rTMS) for suicidal inpatients. Brain Stimul 2014;7(3):421–31.
[9] Arana AB, Borckardt JJ, Ricci R, Anderson B, Li X, Linder KJ, et al. Focal electrical stimulation as a sham control for repetitive transcranial magnetic stimulation: does it truly mimic the cutaneous sensation and pain of active prefrontal repetitive transcranial magnetic stimulation? Brain Stimul 2008;1(1):44–51.
[10] Beam W, Borckardt JJ, Reeves ST, George MS. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. Brain Stimul 2009;2(1):50–4.

David Friedrich*, Xingbao Li
Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA

Karen J. Hartwell
Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA

Ralph H. Johnson Veterans Administration Medical Center, Charleston, SC, USA

E. Baron Short, Gregory L. Sahlem
Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA

Mark S. George
Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA

Ralph H. Johnson Veterans Administration Medical Center, Charleston, SC, USA

* Corresponding author. Department of Psychiatry, 67 President St., Charleston, SC 29425.
E-mail address: friedric@musc.edu (D. Friedrich).

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