Drug and Alcohol Dependence 182 (2018) 8–18

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Preventing relapse to smoking with transcranial magnetic stimulation: Feasibility and potential efficacy

Christine E. Sheffer[a,b,*], Warren K. Bickel[c], Thomas H. Brandon[d], Christopher T. Franck[e], Darwin Deen[a], Luana Panissidi[a], Syed Amir Abdali[a], Jami C. Pittman[a], Sara E. Lunden[a], Neelam Prashad[a], Ria Malhotra[a], Antonio Mantovani[a]

[a] City University of New York School of Medicine, City College of New York, Harris Hall, 160 Convent Ave, New York, NY 10031, USA
[b] Roswell Park Cancer Institute, Carlton House, Room 402, Buffalo, NY 14263, USA, USA
[c] Advanced Recovery Research Center, Virginia Tech Carilion Research Institute, 2 Riverside Circle, R-3113, Roanoke, VA 24016, USA
[d] Moffitt Cancer Center, Tobacco Research and Intervention Program,4115 East Fowler Avenue Tampa, FL 33617, USA
[e] Department of Statistics, Virginia Tech, 403-E Hutcheson Hall (MC 0439), 250 Drillfield Drive Blacksburg, VA 24061, USA

ARTICLE INFO

Keywords:
Smoking cessation
Transcranial magnetic stimulation
Relapse prevention
Feasibility

ABSTRACT

Many smokers attempt to quit every year, but 90% relapse within 12 months. Converging evidence suggests relapse is associated with insufficient activation of the prefrontal cortex. Delay discounting rate reflects relative activity in brain regions associated with relapse. High-frequency repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex (LDLPFC) increases cortical excitability and reduces delay discounting rates, but little is known about feasibility, tolerability, and potential efficacy for smoking cessation. We hypothesized that 8 sessions of 20 Hz rTMS of the LDLPFC combined with an evidence-based self-help intervention will demonstrate feasibility, tolerability, and potential efficacy in a limited double-blind randomized control trial. Smokers (n = 29), abstinent for 24 h, motivated to quit, and not using cessation medications, were randomized to active 20 Hz rTMS at 110% of Motor Threshold or sham stimulation that replicated the look and sound of active stimulation. Stimulation site was located using the 6 cm rule and neuro-navigation. Multiple clinical, feasibility, tolerability, and efficacy measures were examined. Active rTMS decreased delay discounting of $100 ($F(1, 25.3694) = 4.14$, $p = .05$) and $1000 ($F(1, 25.169) = 8.42$, $p < .01$), reduced the relative risk of relapse 3-fold (RR 0.29, CI 0.10–0.76, Likelihood ratio $\chi 2$ with 1 df = 6.40, $p = .01$), increased abstinence rates (active 50% vs. sham 15.4%, X^2 (df = 1) = 3.80, $p = .05$), and increased uptake of the self-help intervention. Clinical, feasibility, and tolerability assessments were favorable. Combining 20 Hz rTMS of the LDLPFC with an evidence-based self-help intervention is feasible, well-tolerated, and demonstrates potential efficacy.

1. Introduction

Despite extraordinary successes in tobacco control, tobacco kills nearly 6 million people annually worldwide ((WHO, 2011). In the US, most cigarette smokers want to quit, over half quit every year, but over 90% reverse this decision within 1 year, choosing the immediate reward of smoking over long-term benefits of quitting (Babb et al., 2017; Fiore et al., 2008; Heyman, 2009; Hughes, 2007a; Malarcher et al., 2011). Delay discounting is the degree to which one "de-values" rewards as a function of time to their receipt (Ainslie, 1975; Kirby, 1997; Logue, 1988; Mazur, 1987). Smokers demonstrate higher discounting rates than non-smokers (Baker et al., 2003; Bickel and Madden, 1999; Bickel et al., 2008; Mitchell, 1999; Odum et al., 2002; Reynolds, 2004). Higher discounting rates are associated with relapse and decrease with effective addictions treatment (Bickel et al., 2014; Krishnan-Sarin et al., 2007; Mackillop and Kahler, 2009; Sheffer et al., 2014; Sheffer et al., 2012; Stanger et al., 2012; Yoon et al., 2007). Consequently, delay discounting is a promising new therapeutic target in the treatment of tobacco dependence (Bickel et al., 2014; Koffarnus et al., 2013).

Nicotine addiction affects multiple brain regions and functions, but most remarkably the structures connected by the medial forebrain bundle reward system (Koob and Le Moal, 2008a,b). The acute positive

* Corresponding author at: Department of Health Behavior, Roswell Park Cancer Institute Carlton House, Room 402, Buffalo, NY 14263, USA.
E-mail addresses: Christine.sheffer@roswellpark.org (C.E. Sheffer), wkbickel@vtc.vt.edu (W.K. Bickel), thomas.brandon@moffitt.org (T.H. Brandon), chfranck@vt.edu (C.T. Franck), ddeen@med.cuny.edu (D. Deen), Lpanissidi87@gmail.com (L. Panissidi), saabdali@med.cuny.edu (S.A. Abdali), Jami.c.pitt@gmail.com (J.C. Pittman), saralunden@gmail.com (S.E. Lunden), Prashad.neelam@gmail.com (N. Prashad), rmalhot000@citymail.cuny.edu (R. Malhotra), amantovani@med.cuny.edu (A. Mantovani).

http://dx.doi.org/10.1016/j.drugalcdep.2017.09.037
Received 8 May 2017; Received in revised form 25 September 2017; Accepted 26 September 2017
Available online 04 November 2017

reinforcing effects of nicotine are mediated by excessive neurochemical activity in this system, particularly the ventral tegmental area (VTA), nucleus accumbuns (NA), and amygdala. Through conditioning, previously neutral stimuli are linked with nicotine administration, becoming powerful cues that trigger strong incentive salience (i.e., motivation to smoke). Smoking cessation is associated with dysregulation of this system within the ventral striatum, extended amygdala, and frontal cortex along with increased incentive salience and decreased sensitivity to natural rewards (e.g., food, water, sex, nurturing). Located in the prefrontal cortex (PFC), executive control over incentive salience is key to preventing relapse (Edwards and Koob, 2010). The dorsolateral prefrontal cortex (DLPFC), a functional node in the frontal-striatal network, has a significant role in executive control (Bechara, 2005; Ernst and Paulus, 2005; Evans, 2008; Fecteau et al., 2010; Krain et al., 2006). Dysregulation of the PFC, marked by decreased brain activity in this region, parallels deficits in executive function and increases in impulsiveness (Koob et al., 2014).

Delay discounting rates are associated with relative activity levels in two frontal-striatal neural circuits: 1) The executive function network, primarily located in the PFC, and 2) the impulsive network, primarily located in limbic/paralimbic regions (Alexander et al., 1986; Bickel et al., 2014; Hanlon et al., 2015; Mackillop and Kahler, 2009; Mcclure et al., 2004). Higher discounting rates are associated with decreased activity in the PFC relative to limbic/paralimbic activity (Mackillop et al., 2012; Mcclure et al., 2004). Delay discounting rate is now considered a viable biologic marker for the relative functioning of these networks consistent with the Competing Neurobehavioral Decisions Systems (CNDS) model (Bickel et al., 2012; Bickel et al., 2014; Bickel et al., 2007; Koffarnus et al., 2013). Smoking cessation involves repeatedly choosing between the immediate reward of smoking and other options in the context of fluctuating neurobiological, environmental, and cognitive influences. We propose that relapse might reflect a situation where the DLPFC is insufficiently activated to exert effective control on the urge to smoke (Hanlon et al., 2015).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that selectively modulates neuronal activity (Di Lazzaro et al., 2005; Fitzgerald et al., 2006; George et al., 2002; Hoogendam et al., 2010; Thickbroom, 2007). High frequency (HF) rTMS (>1 Hz) increases regional cerebral blood flow, cortical excitability, and improves cognitive function, attention, learning, and memory when applied to the PFC (Guse et al., 2010; Li et al., 2017; Pascual-Leone et al., 1998; Siebner and Rothwell, 2003; Speer et al., 2000; Wu et al., 2000). HF rTMS of the left DLPFC decreases delay discounting rates (Sheffer et al., 2013a,b), but has shown mixed potential for reducing craving and cigarette consumption (Amiaz et al., 2009; Eichhammer et al., 2003; Johann et al., 2003; Li et al., 2013; Sheffer et al., 2013a,b; Wing et al., 2012). These mixed findings might be associated with variability in intensity (range 10–20 Hz), amount of stimulation (range 1–10 sessions) and the lack of a behavioral treatment component. When applied to the motor cortex, 20 Hz demonstrates the largest impact and lowest inter-subject variability (Maeda et al., 2000), but is sometimes not well tolerated. When applied to the left DLPFC, 20 Hz demonstrates a significantly larger effect on delay discounting rates than 10 Hz (Sheffer et al., 2013a,b). In the treatment of depression, the efficacy of rTMS is positively associated with the number of stimulation sessions (Teng et al., 2017). In the treatment of tobacco dependence, adding behavioral interventions to medications significantly improves outcomes with the greatest effects from ≥ 8 sessions (pg. 100–103) (Fiore et al., 2008). We propose that combining 8 sessions of 20 Hz rTMS of the left DLPFC with an evidence-based cognitive-behavioral intervention will decrease discounting rates, support abstinence, and given the effects on cognitive function, improve the uptake of the behavioral intervention; however, little is known about feasibility, tolerability, and potential efficacy.

This pilot study examined the effects of 8 sessions of 20 Hz rTMS combined with the 8 Forever Free® (FF) evidence-based self-help relapse prevention booklets (Brandon et al., 2000; Brandon et al., 2004) in a limited double-blind randomized control trial with multiple feasibility, tolerability, and efficacy outcomes. For practical purposes, 8 sessions within 2 weeks appeared likely to produce a detectable effect and could be delivered to a relevant sample in a conservative timeframe. We hypothesized that there would be no significant differences between the sham and the active conditions across time among multiple feasibility and tolerability measures and that active stimulation would decrease delay discounting, and increase latency to relapse, proportional abstinence rates, and FF content uptake.

2. Materials and methods

2.1. Participants

Recruited with newspaper advertising, eligible participants were English-speaking, right-handed adults aged 21–65 years old, who smoked 5–20 cigarettes daily (i.e., to ensure a moderate level of nicotine dependence), were motivated to quit, submitted negative urine screens for drugs of abuse, were able to undergo a magnetic resonance image (MRI) of the head, and passed the Transcranial Magnetic Stimulation Adult Safety and Screening Questionnaire (Rossi et al., 2011; Rossi et al., 2009). Exclusion criteria included medications that lower seizure threshold or for smoking cessation, pregnancy, brain abnormalities that increase participant risk, and inability to achieve ≥ 24 h of abstinence from smoking immediately prior to the first stimulation session.

2.2. Equipment and materials

The Brainsight neuro-navigation system (Rouge Research, Inc. Montreal, Canada) was used for precise placement of rTMS coils. This system links the stimulation coil with an MRI-derived 3D reconstruction of the participant's brain and participant's real head geometry. Stimulation was delivered with the Magstim Rapid2 stimulator (Magstim Company, Ltd., Whitland, UK) and 70-mm figure-8 double air film active and sham coils. Participants received the 8 FF relapse prevention booklets in a take-home binder which included materials for tracking content exposure (Brandon et al., 2000; Brandon et al., 2004).

2.3. Procedure

This study was conducted on the City College of New York campus from January 2015 to June 2016 and approved by the City University of New York Institutional Review Board. All participants provided informed consent. Baseline assessment was followed by a structural MRI of the brain (3 T, no contrast). Simple randomization was applied by the study coordinator. The numbers 1 through 30 were printed on index cards and place in a large manila envelope. Once final eligibility was determined, an index card was drawn, recorded, and replaced. Odd numbers were assigned to the active condition, even numbers to sham. Participants were required to achieve biochemically confirmed 24-h abstinence prior to the first stimulation sessions. Participants received 8 active or sham rTMS sessions, maximum 4 per week, over the course of 2 weeks. Participants read the 8 FF booklets, in order, during the stimulation sessions and were encouraged to continue to read the material in the lab and/or at home. In-person outcome assessments were conducted 4, 8, and 12 weeks after the quit date. Daily cigarette use was assessed weekly by telephone. Participants were compensated $10 for each visit, received a $20 bonus if they completed 8 stimulation visits in two weeks, and a $25 bonus if they attended all 3 outcome assessment visits.

Resting motor threshold (MT), assessed prior to the 1st and 5th sessions, was defined as the minimum stimulation intensity required to elicit a motor evoked potential (MEP) of 50 μV from the abductor pollicis brevis (APB) muscle in 3 of 6 trials. The target stimulation site