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Transcranial Magnetic Stimulation Combined With Nicotine Replacement Therapy for Smoking Cessation: A Randomized Controlled Trial

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ABSTRACT

Background: Further evidence suggests that repetitive Transcranial Magnetic Stimulation (rTMS) is an effective method to reduce tobacco craving among smokers.
Hypothesis: As relapse is common within a few days after smoking cessation, we hypothesized that combining the anti-craving effects of rTMS with Nicotine replacement therapy (NRT) to attenuate withdrawal symptoms could increase abstinence rates in smokers with severe nicotine dependence who quit smoking.
Methods: Thirty-seven smokers who failed to quit with the usual treatments were randomly assigned to two treatment groups to receive either active ($n = 18$) or sham ($n = 19$) 1-Hz rTMS of the right dorsolateral prefrontal cortex. The day after quitting smoking, each patient combined NRT (21-mg patch) with active or sham rTMS (10 sessions) for 2 weeks. Cessation support was then continued with NRT alone using lower-dose patches. Abstinence rates and self-report craving scales were used to assess the therapeutic results during the combined treatment and for up to 12 weeks after quitting.
Results: At the end of the combined treatment, there were significantly more abstinent participants in the active rTMS group ($n = 16$) than in the sham rTMS group ($n = 9$) ($P = 0.027$). The craving scales analysis revealed that active rTMS ($P = 0.011$) but not sham rTMS ($P = 0.116$) led to a significant decrease in the compulsive factor. However, no lasting rTMS effect was found.
Conclusions: 1-Hz rTMS combined with NRT improved the success rate of abstinence in smokers during tobacco cessation. The stimulation-induced reduction in compulsivity may explain this result.

Introduction

Tobacco Use Disorder (TUD) is major health issue. It is a well-known risk factor for many diseases and the first cause of preventable death in the world today. There are 1.3 billion smokers worldwide, half of whom will die from diseases caused by smoking [1,2]. Smoking causes 5 million deaths per year, and if current smoking patterns persist, 10 million smokers per year will be dying by 2025 [1].

Smoking cessation is difficult as only 3% of those quitting without treatment succeed at 6 months [3]. Even though pharmacological treatments or electronic cigarettes can increase quit rates, smoking remains a chronic addictive disease and carries a high rate of relapse [4–6]. A recent trial with 657 smokers showed low rates of cessation at 6 months with nicotine patches (21-mg patch, one daily), nicotine e-cigarettes or placebo e-cigarettes: verified abstinence was respectively 5.8%, 7.3% and 4.3% [7]. In this study, most participants relapsed within 50 days and the median time to relapse in the nicotine patch group was 14 days, indicating that relapse occurs especially during detoxification [7]. Thus, there is a

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need to find new therapeutic approaches to help smokers who wish to quit, especially during the first few days of abstinence as it is a critical period for relapse [8]. An ideal treatment would lead to reductions in both cigarette craving (strong subjective desire or irresistible urges with obsessive thoughts) and nicotine withdrawal symptoms (irritability, frustration or anger, anxiety, dysphoric or depressed mood, restlessness, difficulty concentrating, insomnia, decreased heart rate, and increased appetite) [1–9].

Over the last five years, a growing number of clinical and behavioral studies have indicated that repetitive Transcranial Magnetic Stimulation (rTMS), a non-invasive brain stimulation technique, is a promising way to treat Substance Use Disorders (SUD). Further evidence suggests that tobacco craving can be effectively reduced by modulating cortical excitability in the Dorso-Lateral Prefrontal Cortex (DLPFC) using rTMS [10–15]. Brain stimulation seems to have direct effects on both general craving and cue-induced craving. These data have been consolidated by a recent meta-analysis of the effects of modulating activity in the DLPFC by non-invasive neurostimulation techniques including rTMS. The study provided evidence that stimulation can decrease craving levels in various addictive behaviors [16].

We hypothesized that combining rTMS, to inhibit neuronal firing in areas critically involved in processing craving for cigarettes, with NRT, to attenuate nicotine withdrawal symptoms, may help smokers to quit.

We chose to use the low frequency (LF) range of 1 Hz on the right DLPFC rather than High Frequency (HF) (5–20 Hz) as the stimulation parameter for several reasons:

- First, some studies had reported that abstinence-induced craving to smoke was predicted by increased cerebral blood flow in the right DLPFC, which reflects increased neuronal activity in this cortical region [17],
- Second, some studies had reported a decrease in cortical excitability in the target area after long-train LF rTMS [18–21],
- Third, both LF right-sided DLPFC and HF left-sided DLPFC stimulation seem to have equivalent anti-craving effects [16].

Thus, in smokers with severe nicotine dependence who failed to quit with the usual treatments, we evaluated the clinical benefits of the combination of LF-rTMS with NRT in a randomized controlled study.

Material and methods

Participants

The study was conducted at the University Hospital of Dijon (France) with active enrollment extending from August 2011 through October 2014. Thirty-seven male and female smokers participated in the study. To qualify for enrollment, subjects had to meet the following criteria: 1) 18–65 years of age; 2) desire to quit smoking; 3) a score $\geq$7 in the Fagerström Test for Nicotine Dependence (FTND) indicating high levels of nicotine dependence [22]; 4) a history of at least two unsuccessful attempts to quit. Failure to quit including all of the methods useful to help smokers to quit (nicotine, varenicline, bupropion, acupuncture, e-cigarette, etc.). The following exclusion criteria were used: 1) smoking abstinence during the 3 months preceding the screening visit; 2) current NRT or other smoking cessation aids; 3) pregnancy or breastfeeding; 4) current or previous neurological (including seizures), psychiatric, cardiac or internal diseases; 5) current intake of any psychiatric medication; 6) current drug (other than nicotine) or alcohol abuse; 7) a history of any SUD (other than nicotine) during the year preceding the screening visit; 8) hospital staff working in our department. At screening, participants reported their personal characteristics (e.g. age, education …) and baseline smoking behavior (e.g. number of cigarettes/day, previous attempts to quit), as well as nicotine dependence via the FTND, the most widely used nicotine dependence test [22].

The study was approved by the Committee for the Protection of Persons (CPP) number II of Eastern France (registration number: 2010-A01207-32). After providing participants with a complete description of the study, written informed consent was obtained.

Experimental design

The study was a prospective, placebo-controlled, randomized (1:1) clinical trial, with blind assessments. The study had three phases (Fig. 1):

1) The first phase was a 2-week period of combined rTMS and NRT. It was decided to use the combination therapy during the first 2 weeks of abstinence because craving and withdrawal symptoms are at their peak and relapse is most likely in this period [3]. The combined treatment was always planned to begin on Monday in order to have the 5 rTMS daily sessions from Monday till Friday during 2 consecutive weeks. The participants were asked to stop smoking the night before. As they were not allowed to smoke from the first day of the combined treatment, they were asked to start NRT using 21-mg/24-h transdermal patches immediately when they got up (i.e. on Monday morning). The first rTMS session was started a few moments later in the same morning. The rTMS sessions, which were active or placebo according to randomization, lasted for 2 weeks in combination with the 21 mg/24 h transdermal patches.
2) The second phase was a 4-week period during which participants received NRT alone with a gradual reduction of the dosage: 14-mg/24-h transdermal patches for 2 weeks, and then 7-mg/24-h patches during the following 2 weeks before ending the treatment.
3) The third phase was a 6-week follow-up phase without any treatment, which ended with the blind being lifted.

The randomization was done with the help of the Clinical Research Unit's Methodology Assistance Network of the University Hospital of Dijon (URC-ResAM: Unité de Recherche Clinique – Réseau d'Aide Méthodologique du CHU de Dijon) as follows: envelopes numbered from 1 to 37 containing the inclusion arm (rTMS or Placebo) were chronologically allocated to participants at inclusion (block size of 4).

Stimulation parameters

rTMS was provided using a MagPro X100 (MagVenture A/S, Denmark) with 75 mm figure-of-8 coils (MCF-B65). The coil was held tangentially to the scalp with the handle pointing back and away from the midline at 45°. Sham rTMS was performed using a similar 75 mm figure-of-8 coils (MCF-P-B65 placebo coil) in which a shield provides a field reduction of approximately 80% according the manufacturer. During the stimulation, the placebo coil thus produced a light sensation on the scalp with a negligible electric field in the brain. The Resting Motor Threshold (RMT) was measured using standard visual methods [23]. For participants included in the sham conditions, the RMT was fictitiously determined using the placebo coil: we used the same method as that used to determine the real RMT by progressively increasing the