High-Frequency Repetitive Transcranial Magnetic Stimulation Decreases Cigarette Smoking

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Background: The mesolimbic dopaminergic reward system seems to play a crucial role in reinforcing effects of nicotine. Recently, acute high-frequency repetitive transcranial magnetic stimulation (rTMS) of frontal brain regions has been shown to efficiently modulate the mesostriatal and mesolimbic dopaminergic system in both animals and humans. For this reason, we investigated whether high-frequency rTMS would be able to influence nicotine-related behavior by studying rTMS effects on craving and cigarette smoking.

Method: Fourteen treatment-seeking smokers were included in a double-blind crossover trial, conducted in 2002, comparing single days of active versus sham stimulation. Outcome measures were rTMS effects on number of cigarettes smoked during an ad libitum smoking period and effects on craving after a period of acute abstinence.

Results: High-frequency (20-Hz) rTMS of left dorsolateral prefrontal cortex reduced cigarette smoking significantly (p < .01) in an active stimulation compared with sham stimulation. Levels of craving did not change significantly.

Conclusion: High-frequency rTMS may be useful for treatment in smoking cessation. (J Clin Psychiatry 2003;64:951–953)
Subjects were regular cigarette smokers (12 female, 2 male) aged 23 to 55 years. Smoking characteristics (Table 1) were comparable to those reported in other studies investigating therapeutics for nicotine addiction. All candidates received a structured clinical interview combined with a short physical examination and completed several questionnaires, including the Fagerström Test of Nicotine Dependence (FTND) as well as a drug and health history questionnaire. Standard cut-off thresholds were used to eliminate those persons with significant current or past alcohol, drug, or psychiatric symptomatology. Subjects were also excluded for positive urine toxicology (cocaine, opiates, amphetamines, benzodiazepines). All candidates abstained from smoking 12 hours before each rTMS session and gave written informed consent to take part in the study, which was approved by the local ethics committee.

**Study Design**

Within a crossover design, each subject received 2 trials of active and 2 trials of sham stimulation in a randomized order on 4 consecutive days. Patients and clinical staff were unaware of stimulation condition. On each study day, sessions started in the early afternoon (1 p.m.). The participants received 20 trains of rTMS at a rate of 20 Hz for 2.5 seconds over 14 minutes (1000 pulses/session; intertrain interval: 42.5 seconds) by means of a repetitive magnetic stimulator (Magstim Co., Whitland, Dyfed, U.K.). Stimulation site was the left dorsolateral prefrontal cortex, defined as 5 cm anterior and in a parasagittal plane from the point of maximum stimulation of the abductor pollicis muscle. Stimulation intensity was at 90% of motor threshold. Sham stimulation was given at the same location and frequency by using a sham-coil system (Magstim, U.K.). The stimulation paradigm was identical with stimulation conditions leading to a marked dopamine release in mesolimbic structures such as the nucleus accumbens.

**Ratings**

Two outcome measures were used. Craving was measured with a 10-cm–long, 100-point visual analogue scale administered at baseline and 30 minutes after rTMS treatment. Using this scale, the subjective state “desire to smoke” was assessed, as it has been done earlier in a study on naltrexone alteration of acute smoking response. “Desire to smoke” ratings have been shown to be sensitive to assess self-reported levels of craving. Number of cigarettes smoked was noted during an ad libitum smoking phase (6-hour period) after rTMS treatment. The subjects were instructed to smoke freely using their own chosen brand of cigarettes. Data were obtained under natural conditions in the subjects’ normal living or working environment, not under laboratory conditions, since environmental and other contextual factors have been shown to decisively influence individual smoking behavior. For this reason, subjects had to keep a daily diary 3 weeks before entering the study in order to check compliance and accurate assessment of numbers of cigarettes smoked.

**Statistical Analysis**

Each subject participated in several trials, so we expected a repeated-measures covariance structure of the data. Instead of the more traditional repeated-measures analysis of variance, we used a linear mixed-effects model for data analysis. This class of statistical models allows for more flexibility in model construction and selection. In this context, using this linear mixed-effects model enabled us to judge whether an order effect of stimulation conditions (active stimulation/sham stimulation) should be included in the model, on the basis of objective statistical criteria. The threshold for significance was set at p < .05.

**RESULTS**

Using a linear mixed-effects model for data analysis, group membership (active vs. sham stimulation) was the
fixed-effect covariate and subject ID was included as a random-effect covariate.

The fixed group effect was found to be significant (p < .01) for “number of cigarettes smoked” (95% CI = 1.301 to 5.109) but not for “craving.” The direction of the effect indicated that the number of cigarettes smoked was significantly smaller under active stimulation conditions compared with sham stimulation conditions (Figure 1).

Other than complaints of mild headache in 2 cases after active stimulation, patients tolerated rTMS without difficulty.

**DISCUSSION**

The present study implies that high-frequency rTMS may reduce cigarette smoking. In contrast, levels of craving did not change significantly. The failure to find rTMS effects on craving should not be misinterpreted as having shown that rTMS does not alter craving. It might be due to methodological issues such as the assessment of craving, focusing on subject’s desire to smoke, the rating scale being less sensitive than the cigarette count, or the actual sample size being too small to show statistically significant effects.

The mechanism of action of high-frequency rTMS in cigarette smokers is an object of speculation but may be similar to that of some drugs used to treat smokers. Bupropion is supposed to act by mimicking nicotine’s actions on brain reward systems by blocking neuronal uptake of dopamine. An identical mechanism might account for the action of high-frequency rTMS, since selective dopamine release in subcortical structures could be demonstrated after rTMS both in animals and humans. Especially, immediate marked release of dopamine after prefrontal high-frequency rTMS, as indicated by raclopride positron emission tomography, may closely resemble pronounced catecholamine-releasing effects preferentially resulting from fast forms of nicotine delivery such as cigarette smoking. Moreover, high-frequency rTMS has been shown to influence an array of neurotransmitters and biogenic amines including arginine vasopressin and serotonin (5-HT), which are also altered by nicotine. In particular, tobacco smoking is associated with reductions in hippocampal serotonin, which may be corrected by rTMS-induced increase in hippocampal 5-HT concentrations. These biological qualities of high-frequency rTMS may explain why even daily sessions of active rTMS were able to reduce cigarette smoking, whereas acute doses of bupropion failed to reduce smoking.

Our data obtained in a small number of cigarette smokers need to be confirmed, but the results of this pilot study support further investigation of high-frequency rTMS for treatment in smoking cessation.

**Drug names:** bupropion (Zyban and others), naltrexone (ReVia and others).

**REFERENCES**