

Can Intermittent Theta Burst Stimulation as Add-On to Psychotherapy Improve Nicotine Abstinence? Results from a Pilot Study

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Key Words

Nicotine · Abstinence · Craving · Repetitive transcranial magnetic stimulation · Intermittent theta burst stimulation · Cognitive-behavioral therapy

Abstract

Smoking is among the leading causes of mortality worldwide. Discontinuing smoking can increase life expectancy to the presmoking level. Unaided attempts are often ineffective, strengthening the necessity of cognitive-behavioral therapy (CBT), nicotine replacement or pharmacotherapy. Still, relapse rates are high. Recently, a modulation of nicotine craving, which predicts relapse, through transcranial magnetic stimulation to the prefrontal cortex was shown. In a pilot study, we investigated whether 4 sessions of intermittent theta burst stimulation (iTBS) as add-on treatment to CBT reduces nicotine craving and improves long-term abstinence (at 3, 6 and 12 months). Smokers were randomly assigned to a treatment (n = 38) or a sham group (n = 36). Although we did not find reduced craving, we could show higher abstinence rates in the treatment group at 3 months. At 6 and 12 months abstinence rates did not differ significantly. Results at 12 months, however, have to be interpreted cautiously due to significant differences in the dropout rates between the two groups at this time point. We provide

first evidence for a beneficial effect of additional iTBS on intermediate nicotine abstinence; however, the low number of iTBS sessions might have prevented longer effects. More lasting effects might be achieved by iTBS maintenance sessions in analogy to the treatment of depression.

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Introduction

Smoking is one of the main risk factors for developing cardiovascular problems, cancer and lung diseases [1–3], which are among the leading causes of mortality worldwide [1, 4]. Prevalence of smoking is at about 30% in the US and Europe [4, 5], morbidity increases with the number of cigarettes smoked as well as with the number of years of smoking [2, 6]. Importantly, life expectancy has been shown to increase up to presmoking levels when quitting smoking permanently [2]. Yet, only a small proportion of smokers succeed in quitting unaided and about 90% relapse within 1 year [7, 8].

Cognitive-behavioral therapy (CBT), nicotine replacement therapy, and pharmacotherapy (e.g. bupropion, varenicline) improve the 1-year success rate up to 35% [9].

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Drugs, however, are frequently accompanied by side effects, such as nausea, sickness and insomnia [9]. New approaches in the field of brain stimulation techniques have been investigated as to whether they can improve success rates. Pogarell et al. [10] have shown that repetitive transcranial magnetic stimulation (rTMS) to the prefrontal cortex (PFC) effectively stimulates dopamine release in the mesolimbic dopaminergic system structures, including the ventral tegmentum, the nucleus accumbens and parts of the PFC, which are involved in the perception of reward and craving [11–13]. For a detailed description of the molecular and neural processes involved in nicotine addiction, withdrawal symptoms and craving, the reader is referred to the available literature [e.g. 14–19]. More specifically, studies indicate a positive modulation of addiction-related behaviors, such as decreased craving or consumption following rTMS of the right or left PFC [cocaine: 20, alcohol: 21, nicotine: 22, 23] or transcranial direct current stimulation (tDCS) of the bilateral PFC [alcohol: 24, nicotine: 25]. A summary of the current literature is provided by Barr et al. [26] and Jansen et al. [27].

Intermittent theta burst stimulation (iTBS) is an rTMS protocol that is administered at lower intensities and shorter intervals, improving its tolerability and safety in comparison to conventional rTMS protocols [28]. It has been shown to produce longer-lasting effects than rTMS [i.e. up to 60 min after a single session: 29]. Given the promising findings of rTMS studies concerning addictive behavior, iTBS offers another more tolerable option to approach nicotine addiction.

In the present pilot study, we therefore investigated whether we could replicate and extend previous TMS/tDCS findings of improved immediate abstinence rates and/or reduced self-reported craving by administering 4 sessions of iTBS to the right dorsolateral PFC (dlPFC), accompanying a well-established CBT. As craving might represent the crucial mediating factor in nicotine addiction, we opted for right dlPFC stimulation as this area has been found to be associated with a reduction of craving. Furthermore, we investigated the longevity of this effect by following participants up until 12 months after treatment cessation.

Methods and Materials

Sample

Seventy-four smokers (34 female; age 45.46 ± 10.64 years) recruited via advertisements and screened in a telephone interview met the inclusion criteria: (1) a Fagerström Test for Nicotine Dependence score (FTND) ≥ 3 [30] and (2) a diagnosis of nicotine dependence according to ICD-10: F17.25 [31]. Other past or cur-

rent neurological or mental disorders were excluded via a short version of the SCID-I screening questionnaire [32]. Exclusion criteria followed the Wassermann protocol for a safe TMS application [33] and included previous TMS experience. The study was approved by the local ethics committee and all procedures were in accordance with the latest version of the Declaration of Helsinki. All participants gave written informed consent.

Study Protocol

All participants completed a 3-week group CBT (6 semiweekly meetings), i.e. the Würzburg Program for Ambulant Tobacco Dis-habituation. This program follows the guidelines for smoking cessation promoted by Raw et al. [34]. Between meetings 2 and 3, smoking cessation was scheduled. After that, CBT was accompanied by the iTBS treatment from meeting 3 to 6 (i.e. 4 iTBS sessions). Participants were randomly assigned to the treatment or the sham group. Thus, groups differed only with respect to iTBS treatment (CBT + iTBS treatment or CBT + sham iTBS). Following meeting 6, participants were contacted by phone after 3, 6 and 12 months to inquire about the abstinence rate (defined here as continuous abstinence, thus excluding any consumption of cigarettes since treatment).

Questionnaires

The FTND [30], a questionnaire determining the level of nicotine dependence, was administered before the treatment, all other questionnaires before (prior to meeting 1) and after treatment (after meeting 6). The Questionnaire on Smoking Urges (QSU) [35] identifies changes in the urge to smoke. The questionnaire of Self-Efficacy in Smokers (SER) [36] with its subscales confidence and temptation assesses the expectation to successfully quit smoking.

Intermittent Theta Burst Stimulation

Four sessions of iTBS (Medtronic MagPro X100, Medtronic MagPro, Düsseldorf, Germany) were administered over electrode position F4, which, according to the international 10–20 system [37, 38], is located over the right dlPFC [39]. The iTBS followed the protocols introduced by Huang et al. [29], i.e. three pulses of stimulation, repeated every 200 ms for 2 s, are given at 50 Hz. These TBS trains are repeated every 10 s, totaling 600 pulses (total duration: 190 s). Prior to stimulation, the individual motor threshold (MT) was determined over the left primary motor cortex, which did not differ between groups (treatment group: 33.27 ± 4.37 ; sham group: 34.46 ± 5.37). The treatment group was stimulated with a figure-of-eight coil (MC-B70, Medtronic MagPro, Düsseldorf, Germany) at 80% individual MT, while the sham group was stimulated at 60% individual MT, with the coil being tilted by 45° ¹. Stimulation was administered right before or after CBT meetings 3–6. Participants were blind with regard to iTBS stimulation, as were the respective CBT therapists who did not know the group assignment. None of the subjects reported any side effects after receiving iTBS.

¹ In a study systematically assessing this sham setup over the motor cortex, Loo et al. [40] could show negligible effects evoking motor-evoked potentials, reducing the measured stimulation level to $< 50\%$ at maximal machine output. Therefore, although effects cannot be excluded, choosing this kind of setup as well as reducing stimulation intensity to 60% MT is unlikely to result in effects at the cortical level.

Table 1. Summary of the group statistics of the investigated smoking-related variables

	iTBS treatment (n = 38)	Sham iTBS (n = 36)	Statistics
Age, years	46.74 ± 10.08	46.32 ± 9.48	n.s.
Male gender, n	16	24	n.s.
Age when started smoking, years	17.13 ± 3.59	17.94 ± 4.37	n.s.
Age at first cigarette, years	15.00 ± 2.85	15.47 ± 2.94	n.s.
Cigarettes/day, n	21.67 ± 5.14	22.89 ± 6.58	n.s.
Attempts to quit, n	2.13 ± 1.82	3.24 ± 4.64	n.s. ¹
Smoking, years	28.63 ± 11.16	27.35 ± 7.51	n.s. ¹
FTND	5.00 ± 1.61	4.75 ± 1.63	n.s.

Values are given as mean ± SD.

¹ Given the large difference in variance between the groups, nonparametric tests were calculated additionally. The results stayed the same.

Analysis

Questionnaire data were analyzed by means of analyses of variance (ANOVA) with the factors 'group' (treatment vs. sham) and 'time' (pre vs. post). Abstinence data were analyzed by means of contingency table statistics and odds ratios were calculated. Participants that could not be contacted via telephone after the treatment (dropouts) were considered relapsing participants². As we had a directional hypothesis based on previous studies administering rTMS or tDCS to the dlPFC (i.e. a higher abstinence rate in the treatment group), hypothesis testing was one-sided. The alpha level was set at 5%.

Results

Questionnaire Data

The two groups did not differ with respect to level of addiction (FTND), number of cigarettes per day, years of smoking, age at the onset of smoking and number of attempts to quit. See table 1 for a summary of the sample characteristics.

The 2 × 2 ANOVAs for the other questionnaires yielded significant main effects for time (all p values < 0.001). SER scores on 'confidence of staying abstinent' increased, whereas QSU scores decreased from pre- to posttreatment. Neither significant group effects nor significant group-by-time interactions indicating differential treat-

ment effects in the groups were found. See table 2 for a summary of the results.

Abstinence Data

Analyses revealed that for the 3-month follow-up the treatment group displayed an increased abstinence rate as compared to the sham group, a difference that could not be observed after 6 and after 12 months (table 3). Dropouts were equally distributed across the groups at 3 months ($\chi^2 = 0.85$, $p = 0.36$) and 6 months ($\chi^2 = 1.30$, $p = 0.25$), but not at 12 months ($\chi^2 = 2.90$, $p = 0.09$), where a higher dropout rate was seen in the sham group. Thus, the 12-month findings should be interpreted very cautiously and are only given for reasons of completeness. See table 3 for a summary of the results.

Discussion

The current study investigated whether CBT for smoking cessation might benefit from add-on treatment with iTBS and revealed a beneficial effect, i.e. a higher abstinence rate in the verum as compared to the sham group, at 3 months after the end of therapy. This is rather remarkable given a treatment of only 4 iTBS sessions. At 6 and 12 months, no lasting beneficial effects of iTBS were found, indicating that such a short add-on treatment may only be helpful in the short or intermediate term and improve the CBT outcome. For instance, for maintaining anti-depressive effects by means of rTMS/TBS, repetition of the treatment cycle was found to be crucial for longer-lasting effects [e.g. 41, 42]. Extending the duration of the iTBS sessions or offering booster sessions might thus be beneficial in supporting long-term nicotine abstinence. In this respect, in a sham-controlled study, Amiaz et al. [22] administered 10 daily rTMS sessions to the left dlPFC, which reduced craving and cigarette consumption directly afterwards, dissipating eventually, however. Yet in a subgroup being stimulated directly after exposure to smoking-related cues, a trend towards lower cigarette consumption after 6 months was found. Methodological differences between Amiaz et al. [22] and our study greatly limit comparability and the drawing of valid conclusions. Besides other protocol differences (rTMS vs. iTBS; cue exposure-related vs. -unrelated stimulation; single vs. add-on therapy), we stimulated the right dlPFC. Future studies need to investigate potential laterality differences in the application of rTMS or iTBS. Given the results, it is difficult to determine mediating neurobiological factors. From the available literature (see 'Introduction') a posi-

² When dropouts were excluded and only the remaining participants included in the further analyses, the results stayed the same.

Table 2. Group statistics for the investigated questionnaires

Questionnaire	iTBS treatment (n = 38)		Sham iTBS (n = 36)		Statistics
	pre	post	pre	post	
SER temptation	75.08±13.91	46.32±18.93	76.31±13.52	45.39±16.85	$F_{1,72} = 212.32^*$
SER confidence	54.03±15.84	72.95±19.25	54.94±16.32	73.72±19.05	$F_{1,72} = 48.95^*$
QSU	83.63±36.79	56.5±33.78	81.89±35.88	47.66±16.65	$F_{1,70} = 61.28^*$

pre = Pretreatment (prior to CBT meeting 1); post = posttreatment. Values are given as mean ± SD; * $p < 0.001$.

Table 3. Descriptive statistics for the abstinence data in the two treatment groups

	iTBS treatment (n = 38)		Sham iTBS (n = 36)		Statistics OR (95% CI)
	abstinent	relapse ¹	abstinent	relapse ¹	
3 months	19	19 (9)	10	26 (12)	2.60 (1.15, 5.86)*
6 months	12	26 (12)	10	26 (16)	1.20 (0.52, 2.78)
12 months	10	28 (19)	5	31 (25)	2.21 (0.82, 6.01)

OR = Odds ratio.

¹ Participants for whom information was not available were counted as dropouts (given in parentheses; as dropout was not randomly distributed between groups at month 12, results cannot be interpreted and are only given for reasons of completeness) and were considered relapsed participants. * $p < 0.05$ (one-sided).

tive modulation of prefrontal structures or neural circuits that involve these structures might be assumed, but this needs to be confirmed in systematic neurobiological studies.

Questionnaire data did not reveal any additional benefits of iTBS. General improvements across the groups could be shown. The QSU indicated the expected reduction in craving, which is the primary aim of CBT. This was accompanied by changes in the SER, which indicates increased confidence of staying abstinent and decreased temptation to smoke. Most likely, these results can be ascribed to CBT; however, a small moderating or additive effect with iTBS in other variables than those assessed in the present study cannot be ruled out.

Although the results of add-on iTBS are promising, several caveats have to be considered. First, the presented data are the results of a pilot study in which certain aspects were not systematically assessed, e.g. objective abstinence (CO levels), number of cigarettes smoked per day/week by relapsers, or use of nicotine replacement products. Second, follow-up telephone interviews may reduce data accuracy and reliability. Objective measures (e.g. breath CO, urine or saliva cotinine) could circum-

vent potential biases of retrospective self-report. Third, participants were TMS-naïve and blind to group assignment; yet, it cannot be ruled out that they might have hypothesized about it. However, posttreatment interrogation of assumed group assignment indicated actual blindness. Consistently, Herwig et al. [43] showed that TMS novices could not distinguish rTMS treatment from sham rTMS. Fourth, dropouts were increasing over time and differed between the groups at 12 months, which should be interpreted cautiously; labeling dropouts as relapsing participants may not reflect reality and bias the results (however, see footnote 2). Fifth, although we were correctly applying hypothesis-driven one-sided testing, it needs to be stated that two-sided testing only results in a trend effect. Nonetheless, given this study's pilot character and including power aspects (i.e. balancing type I and type II error) to detect potential effects of such a modern add-on therapy, we consider even a trend effect an important finding. Sixth, 4 sessions of iTBS may not be sufficient to enable longer-lasting effects; especially when treatment time is restricted, offering booster sessions after a specific interval may be an available option. Such sessions could be accompanied by additional CBT group

meetings to consolidate effects and increase relapse prevention. Seventh, we regarded craving the crucial mediating factor in achieving abstinence. However, changes in craving did not differ between groups, indicating that craving was not a substantial mediator between iTBS and abstinence in our study. Unlike reduced craving following rTMS of the right dlPFC [20, 21], the expected processes could not be shown after iTBS. It may be that different neurobiological processes are triggered in the two protocols, which influence addictive behavior; this question, however, will have to be addressed in more basic research studies.

To summarize, despite the above-mentioned limitations that should not be neglected, this pilot study reports for the first time a possible effect of an iTBS protocol in aiding smoking cessation. Further studies are needed to answer the currently unresolved open questions.

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