Addiction
RESEARCH REPORT
doi:10.1111/j.1360-0443.2009.02777.x

Efficacy of repetitive transcranial magnetic stimulation in alcohol dependence: a sham-controlled study

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ABSTRACT

Objective To study the anticraving efficacy of high-frequency repetitive transcranial magnetic stimulation (rTMS) of the right dorsolateral pre-frontal cortex (DLPFC) in patients with alcohol dependence. **Methods** We performed a prospective, single-blind, sham-controlled study involving 45 patients with alcohol dependence syndrome (according to ICD-10 DCR), with Clinical Institute of Withdrawal Assessment in Alcohol Withdrawal (CIWA-Ar) scores ≤10. Patients were allocated to active and sham rTMS in a 2 : 1 ratio, such that 30 patients received active and 15 patients sham rTMS to the right DLPFC (10 Hz frequency, 4.9 seconds per train, inter-train interval of 30 seconds, 20 trains per session, total 10 sessions). The Alcohol Craving Questionnaire (ACQ-NOW) was administered to measure the severity of alcohol craving at baseline, after the last rTMS session and after 1 month of the last rTMS session. **Results** Two-way repeated-measures analysis of variance (ANOVA) showed significant reduction in the post-rTMS ACQ-NOW total score and factor scores in the group allocated active rTMS compared to the sham stimulation. The effect size for treatment with time interaction was moderate ($\eta^2 = 0.401$). **Conclusions** Right dorsolateral pre-frontal high-frequency rTMS was found to have significant anticraving effects in alcohol dependence. The results highlight the potential of rTMS which, combined with other anticraving drugs, can act as an effective strategy in reducing craving and subsequent relapse in alcohol dependence.

Keywords Alcoholism, craving, dorsolateral pre-frontal cortex (DLPFC), efficacy, sham control, transcranial magnetic stimulation (TMS).

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Submitted 19 January 2009; initial review completed 21 April 2009; final version accepted 11 August 2009

INTRODUCTION

Alcohol craving presents as an irresistible urge to drink or as intense thoughts about alcohol [1]. This construct also subsumes the intent to use alcohol, anticipation of positive outcome, anticipation of relief from withdrawal symptoms, lack of control over use and cue-induced autonomic responses [2]. Craving is associated biologically with the brain reward centre situated in the medial forebrain bundle comprising the meso–cortico–limbic dopamine pathway [3]. The dorsolateral pre-frontal cortex (DLPFC) is related to craving through the meso–fronto–limbic connections [4]. The development of craving plays an important role in the development of alcohol dependence and maintenance of alcohol-taking behaviour and has also been implicated in relapse [5]. Despite the availability of several anticraving drugs for alcohol dependence, the effectiveness of these agents is limited.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive tool with proven therapeutic efficacy in various neuropsychiatric disorders such as depression [6], schizophrenia [7,8], mania [9,10] and obsessive–compulsive disorder (OCD) [11], etc. Studies have also revealed the potential anti-craving effects of rTMS in substance dependence. In a randomized sham-controlled study, 11 nicotine-dependent subjects were assigned randomly to a course of active and sham rTMS on consecutive days; craving (as measured by a visual analogue scale) was decreased significantly after active stimulation compared to sham stimulation intra-individually [12]. Similarly, in a study involving 14 treatment-seeking smokers, a single session of active high-frequency (20-Hz) rTMS application to the left DLPFC was found to

produce a reduction in cigarette smoking and craving compared to sham; however, the reduction in craving was not significant [13]. In another randomized cross-over study, involving six right-handed patients with cocaine dependence, two sessions of 10-Hz rTMS at 90% of the individual's motor threshold was applied on the left or right DLPFC. The right, but not the left, DLPFC was found to reduce craving transiently by 19% from baseline, which disappeared after 4 hours [14]. In a recent randomized sham-controlled study, 13 subjects meeting DSM-IV criteria for alcohol dependence who were abstinent for a minimum duration of 10 days received active and sham bilateral transcranial direct current stimulation (tDCS) delivered to DLPFC (anodal left/cathodal right and anodal right/cathodal left) for 20 minutes; both anodal left/cathodal right and anodal right/cathodal left decreased alcohol craving significantly compared to sham stimulation, which could not be increased further by visual alcohol cues [4].

A PUBMED search revealed no studies on the anti-craving efficacy of rTMS in alcohol dependence. Neuroimaging studies have revealed DLPFC to be a major component of the neural substrate for craving associated with various psychoactive substances, including alcohol [4]. It has been suggested that the brain substrates for craving can be influenced by cortical rTMS application because of the cortex's massive interconnections and redundant cortical–subcortical loops [15]. The rationale for choosing the right DLPFC is supported by the above-mentioned studies, which found reduction in craving on rTMS application to the right DLPFC, whereas it was not effective on application to the left DLPFC. Further, high-frequency rTMS application to the right DLPFC has been hypothesized to produce trans-synaptic suppression of the left DLPFC (i.e. the dominant hemisphere in right-handed individuals) via transcallosal connections [16]. Therefore, we planned to examine the change in craving parameters following high-frequency rTMS stimulation of the right DLPFC in patients with alcohol dependence at the Center for Cognitive Neurosciences, Central Institute of Psychiatry, Ranchi, India.

MATERIALS AND METHODS

This was a prospective, hospital-based, single-blind, sham-controlled rTMS study conducted over a period of 9 months from March to November 2008. Figure 1 shows the Consolidated Standards of Reporting Trials (CONSORT) diagram of flow of participants through the trial. The study sample was collected using the purposive sampling method. The sample consisted of 45 (excluding 10 dropouts) right-handed male patients aged between 18–60 years with a diagnosis of alcohol dependence syndrome according to ICD-10 Diagnostic Criteria for Research [1], having Clinical Institute of Withdrawal Assessment in Alcohol Withdrawal (CIWA-Ar) [17] scores of $\leq$10, and giving written informed consent. Patients with comorbid psychiatric, major medical or neurological disorders or with a pacemaker or metal in any part of the body were excluded from the study. The Handedness Preference Schedule, Hindi version [18] was used to determine the handedness of the patients. Before the beginning of rTMS session, Severity of Alcohol Dependence Questionnaire Form-C (SADQ-C) [19] and Alcohol Craving Questionnaire (ACQ-NOW) [2] were administered to measure the severity of alcohol dependence and baseline craving, respectively. Patients were assigned alternatively to the active and sham groups in a 2 : 1 ratio, i.e. the first two patients received active rTMS, the third patient sham rTMS, and so on. Eventually, 30 patients received active and 15 patients sham rTMS. The motor threshold (MT) for the left abductor pollicis

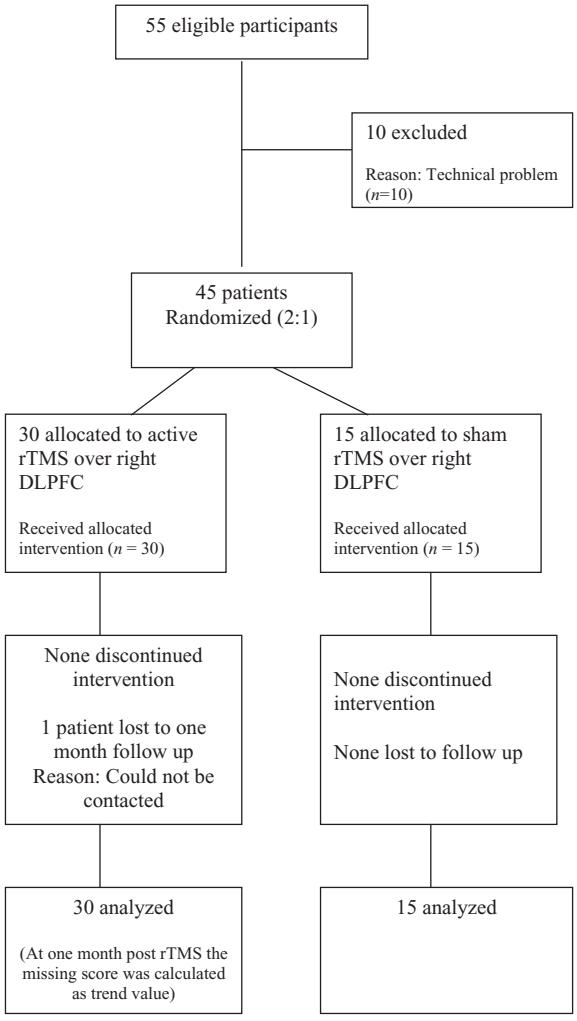

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) diagram showing the flow of participants through each stage of the trial. rTMS: repetitive transcranial magnetic stimulation, DLPFC: dorsolateral pre-frontal cortex

brevis (APB) was determined using the Neuropack Sigma evoked potential measuring system (Nihon Kohden, Japan) using a figure-of-eight-shaped coil at 1 Hz frequency according to the Rossini–Rothwell algorithm [20]. According to this, MT was defined as the lowest intensity, which produced five motor evoked potential (MEP) responses of at least 50 μV in 10 trials. Ten daily sessions of rTMS treatments (using the Magstim Rapid® device; Magstim Company Ltd., Whitland, Wales, UK) were administered over the right DLPFC (at 110% of the MT determined) with an air-cooled figure-of-eight coil, angled tangentially to the head. At right PFC, active high-frequency (10 Hz) stimulation was administered for 4.9 seconds per train, with inter-train interval of 30 seconds, and a total of 20 trains per session. Each patient received approximately 1000 pulses per day. The sham group was administered rTMS with the same parameters, but using a figure-of-eight sham coil. ACQ-NOW was administered following the last rTMS session to measure the changes in craving parameters. During the study period both the groups received Zolpidem 12.5 mg tablets on an as-required basis at night for insomnia along with vitamin B complex capsules. After completion of the rTMS sessions, the patients either received anti-craving drugs (such as naltrexone, acamprosate, disulfiram, carbamazepine, fluoxetine) or did not, as decided by the treating team. ACQ-NOW score was again documented after 4 weeks of the last active or sham rTMS session.

Statistical analysis

The data were analysed using the Statistical Package for Social Sciences (SPSS version 10 for Windows®computer program; SPSS Inc., Chicago, IL, USA). The alpha level was set at $P < 0.05$ (two-tailed) for statistical hypothesis testing with exact probability levels for test statistics as shown in the text. Group differences in clinical characteristics between the active and sham groups were made using an independent-sample *t*-test for normally distributed data. Repeated-measures analysis of variance (ANOVA) was performed for the ACQ-NOW total score, ACQ-NOW factor scores, i.e. factor 1 (urges and desires to use alcohol), factor 2 (intent to use alcohol), factor 3 (anticipation of positive outcome), factor 4 (anticipation of relief from withdrawal and negative outcome) and factor 5 (lack of control over alcohol use) and general craving index (GCI) score with two factors: group (active and sham) and time (pre-rTMS, post-rTMS and 1 month after rTMS). Pearson's correlation was calculated between socio-demographic and clinical variables with craving scores. One patient was lost to follow-up at 1 month, in whom the missing ACQ-NOW scores were allotted by trend values obtained on SPSS version 10.

RESULTS

In our study, 55 patients with the diagnosis of alcohol dependence syndrome fulfilling the inclusion and exclusion criteria were recruited initially, of whom 10 patients dropped out. Of 45 patients, active rTMS was administered to 30 patients and 15 patients received sham stimulation. Sample characteristics are summarized in Table 1. The mean age of patients was 39.36 [standard deviation (SD) 8.93] years (range 24–55 years) in the active group and 38.20 (SD 6.85) years (range 29–52 years) in the sham group. There was no significant difference in the socio-demographic and clinical variables between the active and sham groups. The motor threshold between the two groups was comparable. There was no significant difference in the socio-demographic and clinical characteristics between the study sample and dropouts.

Table 1 Sample characteristics.

Variables	*Active (mean ± SD) (n = 30)*	*Sham (mean ± SD) (n = 15)*	*t(df = 43)*	*P*
Age	39.36 ± 8.93	38.20 ± 6.85	0.44	NS
Education	12.13 ± 3.47	10.73 ± 2.52	1.39	NS
Alcohol use (duration)	15.30 ± 7.09	13.46 ± 6.74	0.83	NS
Age of onset	24.03 ± 7.43	24.73 ± 7.70	–0.29	NS
Years of dependence	7.00 ± 6.36	4.33 ± 3.53	1.51	NS
CIWA-Ar total score	3.10 ± 1.47	3.73 ± 1.70	–1.29	NS
SADQ total score	48.46 ± 10.21	52.66 ± 6.33	–1.46	NS
SADQ–A score	13.96 ± 1.80	14.33 ± 1.39	–0.69	NS
SADQ–B score	26.36 ± 7.15	29.40 ± 4.20	–1.51	NS
SADQ–C score	8.13 ± 1.92	8.93 ± 1.75	–1.35	NS
Motor threshold	50.33 ± 3.69	52.33 ± 4.58	–1.58	NS

CIWA-Ar: Clinical Institute Withdrawal Assessment of Alcohol scale, revised scores; SADQ: severity of alcohol dependence questionnaire; NS: not significant; SD: standard deviation.

For ACQ-NOW total score, the repeated-measures ANOVA showed a significant effect of treatment over time as shown by the interaction effect (Pillai's trace $F = 14.05$, df = 2/42, $P < 0.0005$) (Table 2). The effect size of for the treatment with interaction for ACQ-NOW total score was 0.401 (eta^2). A significant effect of treatment over time was found for ACQ-NOW factor scores and GCI except for factor 2 ($P = 0.066$) (Table 2). Anticraving drugs were prescribed to 23 patients (76.7%) in the active group and 11 patients (73.4%) in the sham group; there was no difference between the groups. In the active group, four of 29 patients (13.8%) relapsed and in one patient the relapse status could not be known, because he was lost to follow-up, whereas in the sham group, five of 15 (33.33%) patients relapsed, with no significant group difference between the active and sham groups.

In the active group, years of formal education was found to correlate positively with post-rTMS ACQ-factor 1 ($r = 0.399$, $P = 0.029$) and factor 3 ($r = 0.415$, $P = 0.023$) scores, with a trend towards positive correlation with post-rTMS ACQ–total and GCI scores. The age of onset of alcohol use was found to correlate negatively with post-rTMS ACQ–total score ($r = –0.415$, $P = 0.023$), ACQ-factor 1 ($r = –0.385$, $P = 0.036$), factor 2 ($r = –0.401$, $P = 0.028$), factor 3 ($r = –0.392$, $P = 0.032$), factor 5 ($r = –0.442$, $P = 0.015$) and GCI ($r = –0.415$, $P = 0.023$) scores. Similarly, years of alcohol dependence was found to correlate positively with post-rTMS ACQ–factor 1 score ($r = 0.399$, $P = 0.029$), with evidence of a trend towards positive correlation with post-rTMS ACQ–total, factor 5 and GCI scores. A trend towards positive correlation was found between total duration of alcohol use in years and post-rTMS ACQ–factor 5 score. This being an exploratory analysis, we conducted several correlations between socio-demographic and clinical characteristics with the craving scores. Considering the large number of analyses, there is a possibility that some of the significant correlations are due to chance.

Only one patient receiving sham rTMS developed a seizure after the third rTMS session, which was within 6 days of stopping the lorazepam tablet given during detoxification. One patient developed scalp pain and withdrew consent from the study, and in the remaining eight patients the rTMS sessions had to be terminated prematurely because of technical problems with the rTMS unit. Transient headache was reported by five patients receiving active treatment following the rTMS session, which lasted from less than an hour to 4 hours. Of these, three patients required analgesics such as paracetamol tablets to control headache. The most common complaint of the patients receiving active treatment was pain during delivery of the stimulation train, which improved spontaneously after completion of the session. The patients receiving sham stimulation did not complain of any discomfort during the sessions. Anxiety was reported by four patients during first rTMS session, which resolved after giving a detailed explanation of the benign nature of the procedure.

DISCUSSION

Our study reveals a significantly greater reduction in craving scores in patients receiving active rTMS compared to sham stimulation. The effect size of the efficacy of rTMS was moderate ($\eta^2 = 0.401$) for most of the craving scores. The mean age of the participants in both the active and sham groups was found to be greater than that in the study by Camprodon *et al.* [14] (age range 19–23 years), but less than the study by Boggio *et al.* [4] (mean age 41.3, SD 5.7 years). The mean age of onset of alcohol use in both the groups was greater than that described by Boggio *et al.* [4] (mean 15.0, SD 4.6 years). All the patients were abstinent for more than 10 days before the beginning of the rTMS session, whereas the abstinence period was 41 (SD 51.3) days (a minimum of 10 days) in the study by Boggio *et al.* [4] The rTMS session was started 3 days after the completion of detoxification (duration = 7–10 days) with the intention of preventing the interference of lorazepam in determination of the motor threshold. The abstinence period was minimized in our study in order to complete the rTMS sessions within the average duration of stay of the patient in the institute, which is approximately 1 month.

In our study, ACQ-NOW was used in view of its ability to measure the multi-dimensional aspects of craving with high internal consistency and reflect the changes in alcohol craving with rTMS treatment. The significantly lower craving as revealed by ACQ-NOW scores following rTMS sessions in the active group, compared to sham stimulation, suggests the potential anticraving efficacy of high-frequency rTMS in alcohol dependence. Increased activity in the meso–limbic dopaminergic pathway has been implicated in craving associated with alcohol dependence [3]. Several dopaminergic antagonists such as clozapine and olanzapine have demonstrated a significant effect in reducing alcohol craving [4]. The application of rTMS to the DLPFC could have modulated the altered activity in the mesolimbic pathway through the meso–fronto–limbic connections. High-frequency rTMS application to the right DLPFC resulted possibly in trans-synaptic suppression of the left DLPFC [16], which reduced alcohol craving in our patients.

Years of alcohol dependence was found to correlate positively with post-rTMS ACQ–factor 1 score ($r = 0.399$), with evidence of a trend towards positive correlation with post-rTMS ACQ–total, factor 5 and GCI scores. Type 2 alcoholism has been described to be associated

Table 2 Repeated-measures analysis of variance (ANOVA) of ACQ-NOW scores (pre-rTMS, post-rTMS and 1 month post-rTMS) between the active ($n = 30$) and sham ($n = 15$) groups.

Craving scores		*Pre-rTMS*	*Post-rTMS*	*1 month post-rTMS*	*Pillai's trace F (df = 2,42)*	*P*	*Effect size (η^2)*
ACQ-T	Active (mean ± SD)	245.16 ± 23.47	43.43 ± 18.05	44.25 ± 73.76	941.65**	<0.0005	0.978
	Sham (mean ± SD)	244.53 ± 28.72	86.73 ± 11.15	89.93 ± 103.80			
ACQ-T × group					14.05**	<0.0005	0.401
ACQ-1	Active (mean ± SD)	51.83 ± 5.16	7.20 ± 4.38	8.60 ± 16.63	750.09**	<0.0005	0.973
	Sham (mean ± SD)	53.20 ± 5.18	19.26 ± 3.28	19.40 ± 23.26			
ACQ-1 × group					13.80**	<0.0005	0.397
ACQ-2	Active (mean ± SD)	42.53 ± 9.87	6.40 ± 3.77	6.71 ± 13.48	228.36**	<0.0005	0.916
	Sham (mean ± SD)	42.66 ± 12.73	13.86 ± 5.19	15.06 ± 19.16			
ACQ-2 × group					2.90	0.066	0.121
ACQ-3	Active (mean ± SD)	44.53 ± 6.08	7.46 ± 4.12	7.30 ± 12.70	383.78**	<0.0005	0.948
	Sham (mean ± SD)	42.46 ± 10.22	15.60 ± 3.39	15.33 ± 18.46			
ACQ-3 × group					9.78**	<0.0005	0.318
ACQ-4	Active (mean ± SD)	54.60 ± 4.10	5.83 ± 3.67	8.03 ± 17.40	910.78**	<0.0005	0.977
	Sham (mean ± SD)	56.46 ± 4.51	14.46 ± 6.64	17.33 ± 23.83			
ACQ-4 × group					5.09*	0.010	0.195
ACQ-5	Active (mean ± SD)	51.66 ± 5.62	16.53 ± 4.93	13.59 ± 14.08	739.81**	<0.0005	0.972
	Sham (mean ± SD)	49.73 ± 5.37	23.53 ± 3.70	22.80 ± 19.69			
ACQ-5 × group					15.76**	<0.0005	0.429
GCI	Active (mean ± SD)	7.90 ± 0.75	1.40 ± 0.58	1.42 ± 2.37	941.75**	<0.0005	0.978
	Sham (mean ± SD)	7.88 ± 0.92	2.79 ± 0.35	2.89 ± 3.34			
GCI × group					14.05**	<0.0005	0.401

ACQ: ACQ-NOW Alcohol Craving Questionnaire; ACQ-T: total score; ACQ-1: factor 1—urges and desires to use alcohol score; ACQ-2: factor 2—intent to use alcohol score; ACQ-3: factor 3—anticipation of positive outcome score; ACQ-4: factor 4—anticipation of relief from withdrawal and negative outcome score; ACQ-5: factor 5—lack of control over use score; GCI: general craving index score. *Significance at $P < 0.05$, **Significance at $P < 0.0005$ (two-tailed); SD: standard deviation.

with early age of onset and greater duration of alcohol use with poor response to treatment, which corroborates our findings [21].

In the present study rTMS was found to be well tolerated by the patients, with a benign adverse effect profile as found in previous studies [14,22]. Only one patient receiving sham rTMS developed a seizure after the third rTMS session. The possible reason for seizure could be premature benzodiazepine withdrawal [23], without having any relation to rTMS application.

Our study was limited by lack of double-blinding, which could result in rater bias during the psychopathology assessment. Assignment of the sample to active and sham treatment was conducted by purposive sampling, which does not involve random selection. Hence, it not a true randomization method and may potentially introduce bias. The dorsolateral pre-frontal cortex of patients was located using the '5-cm rule' [24], which does not take into consideration the shape and size of a person's head. This may result in some variations in the exact site of stimulation in the pre-frontal cortex. The sham coil that was used in our study has been designed to look and sound like an active coil by incorporating a metal shield that diverts the majority of the magnetic flux generated by the internal coil, such that a minimal (less than 3%) magnetic field is delivered to the cortex. Even then, the sham coils do not feel like active TMS, which generates a tapping sensation and resultant pain on the scalp. Thus the nature of sham stimulation remains a limitation of our study.

Further studies are required to optimize TMS parameters such as frequency of stimulation, number of trains, duration of each train, intertrain interval and number of sessions which will be effective in alcoholism without producing other adverse events. The period of rTMS to maintain the gains produced need to be examined with longer follow-up studies. Neurophysiological variables such as quantitative electroencephelogram, evoked potentials and frontal activation tasks should be measured along with rTMS in alcohol dependence for more comprehensive assessment of the treatment effect.

Declarations of interest

None.

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