SHORT REPORT

No benefit derived from repetitive transcranial magnetic stimulation in depression: a prospective, single centre, randomised, double blind, sham controlled ''add on'' trial

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Repetitive transcranial magnetic stimulation (rTMS) has been reported to demonstrate slight effects in the treatment of depression. Hence, a novel bilateral versus unilateral and sham stimulation design was applied to further assess rTMS' antidepressant effects.

Forty one medication free patients with major depression, admitted to a psychiatric unit specialising in affective disorders, were consecutively randomised into 3 groups. Group A1 (n = 12) received unilateral active stimulation consisting of high frequency (hf) rTMS over the left dorsolateral prefrontal cortex (LDLPC) and subsequent sham low frequency (lf) rTMS over the right dorsolateral prefrontal cortex (RDLPC). Group A2 (n = 13) received simultaneous bilateral active stimulation consisting of hf-rTMS over the LDLPC and lf-rTMS over the RDLPC. Group C (n = 13) received bilateral sham stimulation. Stimulation was performed on 10 consecutive workdays. All patients received antidepressant medication on the first day of stimulation, which was continued during and after the stimulation period. As no significant difference in antidepressant outcome between group A1 and A2 was found, the two groups were pooled. The time course of the outcome variables Hamilton depression rating scale ($HDRS_{21}$) and Beck depression inventory (days 0, 7, 14, 28) by repeated measures analysis of variance revealed no significant group differences (in terms of a group by time interaction), whereas there was a significant effect of time on all three outcome variables in all groups. The results suggest that rTMS as an ''add on'' strategy, applied in a unilateral and a bilateral stimulation paradigm, does not exert an additional antidepressant effect.

Repetitive transcranial magnetic stimulation (rTMS) is a technique that allows for non-invasive modulation of the excitability and function of distinct cortical brain areas.[1] The ability of rTMS to specifically up[2] or down-regulate[3] cortical activity using high frequency rTMS (hf-rTMS) or low frequency rTMS (lf-rTMS), respectively, has led to the specific interest in the use of rTMS in the modulation of hypoactivity syndromes. Although data of imaging studies do not always concur, hypoactivity is seen in major depression as it is associated with reduced left prefrontal metabolism in both unipolar and bipolar presentations.[4 5] Consequently, most rTMS studies in depression addressed their attention to hf-rTMS applied to the left dorsolateral prefrontal cortex (LDLPC).[6 7]

A meta-analysis,[8] including nine open studies, and 23 controlled comparisons suggest that clinical significance of rTMS in depression is modest. The lack of substantial clinical response led some researchers to focus on attempts to increase efficacy of rTMS. Altering stimulation frequency, duration, and/or locus of application were tried, thus inducing different patterns of neurophysiological activity. On the background of the theory of mood lateralisation[9] it might be argued that if an interhemispheric balance of frontal activity is essential for euthymia, an lf-rTMS induced downregulation of the right dorsolateral prefrontal cortex (RDLPFC) would achieve the same interhemispheric balance as an upregulation of the LDLPC using hf-rTMS. In fact, clinical data corroborate the efficacy of lf-rTMS applied to the RDLPC.[10 11] Thus, the combination of lf-rTMS to the right and an hf-rTMS to the left side was theorised to be possibly more effective.[12] We hypothesised that bilateral rTMS (20 Hz over LDLPC and 1 Hz over RDLPC) is superior to unilateral rTMS (20 Hz over LDLPC) and that there is a speeding up effect in the add on group in comparison to the usual care group medicated with antidepressants alone.

METHODS

The study, which was fully approved by the local ethics committee, was designed as a single centre, prospective, double blind, sham controlled ''add on'' trial.

Forty one medication free patients with major depressive disorder, admitted for treatment to a psychiatric unit, were consecutively randomised into three groups. Subject inclusion criteria were DSM IV established diagnosis of a major depressive disorder without psychotic features, and a score of at least 18 on the 21 item Hamilton depression rating scale ($HDRS_{21}$).[13] Patients with contraindications to TMS, major medical problems, or suicidal ideation were not enrolled. Written informed consent was obtained prior to participation. In order to speed up the expected antidepressant effect, an ''add on'' study paradigm was chosen, and antidepressant medication was commenced on the first day of stimulation and maintained throughout the stimulation period. Dosage remained constant during the trial. The choice of medication was done on naturalistic basis. At entry, patients on antidepressant medication underwent a fivefold half life washout period. Lorazepam as a comedication at a dosage of 1 mg to 5 mg was permitted.

In order to compensate for individual differences in topography, we assessed the prefrontal cortex by three

Abbreviations: BDI, Beck depression inventory; HDRS, Hamilton depression rating scale; hf-rTMS, high frequency repetitive transcranial magnetic stimulation; LDLPC, left dorsolateral prefrontal cortex; lf-rTMS, low frequency repetitive transcranial magnetic stimulation; MRI, magnetic resonance imaging; MT, motor threshold; RDLPC, right dorsolateral prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation

Table 1 Sociodemographic data and patients' characteristics

	Group A1 (LDLPC) n = 12	Group A2 (L+RDLPC) n = 13	Group C (sham) n = 13	Total n = 38
Age mean (SD)	47.33 (13.34)	45.23 (11.95)	47.00 (11.31)	46.50 (11.90)*
Gender				
Male (%) (n)	50 (6)	38.5 (5)	30.8 (4)	39.5 (15)*
Female (%) (n)	50 (6)	61.5 (8)	69.2 (9)	60.5 (23)
Number of episodes				
⩽2 (%) (n)	58.3 (7)	50.0 (6)	53.8 (7)	54.1 (20)*
>2 (%) (n)	41.7 (5)	50.0 (6)	46.2 (6)	45.9 (17)
Duration of illness (years)				
⩽5 (%) (n)	41.7 (5)	33.3 (4)	53.8 (7)	43.2 (16)*
>5 (%) (n)	58.3 (7)	66.7 (8)	46.2 (6)	56.8 (21)
N Citalopram/Seropram 20 mg/d	8	7	7	22
N Milnacipran/Ixel 50 mg/d	2	2	2	6
N Mirtazapin/Remeron 30 mg/d	1	1	2	4
N Reboxetin/Edronax 4 mg/d	1	3	2	6

LDLPC, left dorsolateral prefrontal cortex; RDLPC, right dorsolateral prefrontal cortex.
Data not available for number of episodes and duration of illness for one patient.
*Not significant.

dimensional magnetic resonance imaging (MRI). The optimal positions of the LDLPC and RDLPC were located on the scalp with a marking pen.

All patients received rTMS on 10 consecutive workdays. We delineated three groups called A1 (active unilateral stimulation), A2 (active bilateral), and C (control/sham group).

Group A1: patients (n = 12) received hf-rTMS applied to the LDLPC (20 Hz, 100% of motor threshold (MT), 10 trains of 10 s duration with a 90 s intertrain interval, resulting in a total of 2000 stimuli per session for 2×5 days). Five minutes following active LDLPC stimulation, the RDLPC received sham lf-rTMS.

Group A2: patients (n = 13) underwent active hf-rTMS of the LDLPC, as described above, followed by active lf-rTMS over the RDLPC (1 Hz, for 10 min, 120% of MT, resulting in a total of 2600 stimuli per session for 2×5 days).

Group C: patients (n = 13) who served as a control group received bilateral sham stimulation, hf-rTMS to the LDLPC, followed by lf-rTMS to the RDLPC.

Stimulation was performed using a figure 8 shaped focal coil attached to a Magstim Rapid Stimulator (Magstim Company Limited, Spring Gardens, Whitland, UK). Active rTMS was applied with the coil's maximal output spot centered over the marked position on the scalp; the handle of the coil in a perpendicular orientation relative to the ipsilateral central sulcus. Sham stimulation was achieved by placing the same coil on the patient's head as described above. The sham coil was disconnected from the stimulator. At the same time, a second, active coil was held 10 cm behind the patient's head. This coil produced the acoustic artifact as required by randomisation group. This kind of sham stimulation was chosen in order to avoid a sham paradigm shown to be somewhat active.[14]

Patients were asked to relax on a chair. Surface electromyographic electrodes were attached over the first dorsal interosseous muscle bilaterally and the patient's individual motor threshold at rest was determined daily, bilaterally, using a figure 8 coil.[15] Patients were evaluated by blinded trained psychiatrists using the 21 item HDRS and the Beck depression inventory (BDI)[16] on days 0, 1, 3, 5, 7, 10, 14, and 28.

Baseline comparisons of three (two active) treatment groups were performed by analysis of variance (t test), Kruskal-Wallis test (Mann-Whitney U test), or χ^2 test (Fisher's exact test) depending on the variable type. Outcome was measured by the mean percentage change of BDI and $HDRS_{21}$ between baseline day 14 and day 28. Group comparisons regarding these measures were performed by analysis of variance. The time course (day 0, 7, 14, 28) of these measures was analysed by repeated measures analysis of variance, considering time as a within subject factor and treatment group as a between subject factor, giving special emphasis to the time×treatment interaction.

RESULTS

Of the 41 patients recruited for the study, 38 patients completed the two week protocol. Three patients, each per group, terminated the study prematurely. No seizure like phenomena was observed.

Patients overall did not differ significantly with regard to their age or gender. Patients did not differ in terms of duration of illness, nor in the number of suffered episodes

Table 2 HDRS and BDI scores in the time course and results of repeated measures analysis of variance

	Baseline mean (SD)		Day 7 mean (SD)		Day 14 mean (SD)		Day 28 mean (SD)		Analysis of variance			
									Time		Group×time	
	A1+A2	C (sham)	A1+A2	C (sham)	A1+A2	C (sham)	A1+A2	C (sham)	F (3,34)	p Value	F (3,34)	p Value
$HDRS_{21}$	32.3 (5.9)	33.7 (3.7)	23.6 (8.5)	25.2 (8.2)	17.6 (9.0)	21.8 (8.2)	15.8 (9.5)	20.2 (10.9)	43.04	<0.001	0.64	ns†‡
BDI	32.0 (10.4)	31.2 (11.8)	22.3 (11.4)	28.4 (12.8)	16.9 (11.6)	21.2 (14.3)	14.8 (12.5)	19.6 (15.8)	26.00	<0.001	1.41	ns†‡

$HDRS_{21}$, Hamilton depression rating scale; BDI, Beck depression inventory.
†p Value for testing the general hypothesis of no group×time interaction.
‡p Value for testing the hypothesis of no interaction between group and the time contrast ''baseline versus all other times''.

(table 1). There were no significant differences between the three groups (A1, A2, and C) as well as between the pooled treatment groups (A1+A2) and the sham group in terms of HDRS and BDI scores at baseline (day 0). As there were also no significant differences between the two active treatment groups (groups A1 and A2) regarding HDRS and BDI, over the course of treatment (day 7, 14, and 28), we pooled the data of the two groups for comparison to the control group (group C). At day 14 and 28 there was no statistical difference between rTMS (A1+A2) and controls (group C) in mean percentage decrease of the $HDRS_{21}$ total score and the BDI.

When testing the time course of the outcome variables $HDRS_{21}$ and BDI (days 0, 7, 14, 28) by repeated measures analysis of variance, there was a significant effect of time on outcome variables in both groups, whereas there were no significant group differences in terms of a group by time interaction (table 2). The size of the interaction term for the $HDRS_{21}$ amounted to 2.8 (95% confidence interval (CI) −2.8 to 8.5) for day 14 versus baseline and to 3.0 (95% CI −3.8 to 9.8) for day 28 versus baseline, where a positive (negative) value indicates a favour for group A1+A2 (group C). The corresponding values for the BDI were 5.0 (−3.2 to 13.2) and 5.7 (−3.8 to 15.0), respectively.

DISCUSSION

There may be multiple reasons for the lack of additional antidepressant response. It might be that the sample was too small to allow an additional rTMS induced antidepressant effect to emerge statistically. However, in terms of BDI, actively treated patients (group A1+A2) performed somewhat better than controls when comparing scores on days 7, 14, and 28 with baseline (indicated by the nearly significant interaction between groups and the linear time contrast of baseline *v* all other times, $p = 0.10$). This should not be overestimated, as none of the other variables gave rise to a significant group difference or a statistical trend

In the present study antidepressant regimens were heterogeneous (table 1). Thus it cannot be excluded that the medication induced antidepressant effect in the sham group (C) was higher than in the active treated groups (A1+A2). Such a phenomenon could have equalised or prevented the potential rTMS-induced ''add on'' effect from emerging statistically. However, our data concur with Garcia-Toro *et al*,[6] who did not find an additional benefit ($n = 11$) in an ''add on'' hf-rTMS trial over the LDLPC using a single antidepressant, namely sertraline. In fact, a meta-analysis[8] was able to show that adjunctive antidepressant medication neither enhances nor detracts from rTMS therapeutic effects. This study confirms our previous results in a different sample of patients, where there was no difference in antidepressant outcome comparing unilateral versus bilateral stimulation.[17] An open ''add on'' study based on this theoretical background reports four responders out of seven in a sample of medication resistant depressive outpatients.[18] But our data are in line with a recently published controlled study reporting no differences in terms of antidepressive outcome between unilateral versus bilateral stimulation.[19]

In conclusion, the analysed sample of depressed inpatients did not have an additional benefit neither from a bilateral in comparison to the unilateral stimulation, nor from the expected speeding up effect of the add on paradigm in comparison to an antidepressant medication.[19]

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