Early report

Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression

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Summary

Background Lesion and neuroimaging studies suggest that left prefrontal lobe dysfunction is pathophysiologically linked to depression. Rapid-rate transcranial magnetic stimulation (rTMS) to prefrontal structures has a lateralised effect on mood in normal volunteers, and several preliminary studies suggest a beneficial effect of rTMS on depression. However, adequately controlled studies have not been conducted.

Methods We have studied the effects of focal rTMS on the depressive symptoms in 17 patients with medication-resistant depression of psychotic subtype. The study was designed as a multiple cross-over, randomised placebo-controlled trial. Sham rTMS and stimulation of different cortical areas were used as controls.

Findings Left dorsolateral prefrontal cortex rTMS resulted in a significant decrease in scores on the Hamilton depression rating scale HDRS (from 25·2 to 13·8) and the self-rated Beck questionnaire BQ (from 47·9 to 25·7). 11 of the 17 patients showed pronounced improvement that lasted for about 2 weeks after 5 days of daily rTMS sessions. No patient experienced any significant undesirable side-effects.

Interpretation Our findings emphasise the role of the left dorsolateral prefrontal cortex in depression, and suggest that rTMS of the left dorsolateral prefrontal cortex might become a safe, non-convulsive alternative to electroconvulsive treatment in depression.

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Introduction

Transcranial magnetic stimulation (TMS) facilitates non-invasive stimulation of the cerebral cortex. Applied over the motor cortex, single magnetic stimuli can, for example, induce motor-evoked potentials in contralateral limb muscles, so conduction in motor pathways of the central nervous system can be investigated. The development of stimulators capable of discharging at frequencies of up to 60 Hz has greatly expanded the applications for TMS in the cognitive and behavioural sciences. Depending on stimulation frequency, intensity, and duration, trains of rapid-rate TMS (rTMS) can transiently block or inhibit the function of a cortical region, and they can enhance the excitability of the affected cortical structures.[1]

Lesion and imaging studies suggest that left prefrontal lobe dysfunction is pathophysiologically linked to primary and secondary depression,[2] and studies of rTMS to prefrontal structures have shown a lateralised effect on mood in normal volunteers.[3,4] Subsequently, Höflich and colleagues applied TMS to two depressed patients and found only slight beneficial effects.[5] However, they stimulated at 0·3 Hz, and with the stimulation coil centred over the vertex, so both hemispheres were simultaneously affected. In a follow-up study, Kolbinger and colleagues[6] studied 15 patients with major depression and reported that those who received 250 TMS stimuli over the vertex at intensities below the motor threshold, on 5 consecutive days, showed improvement in their depressive symptoms. Grisaru and colleagues have also applied low frequency TMS to the vertex of 10 patients with unipolar or bipolar depression and found mild improvement in half of them following a single, one hour session of stimulation.[7] Using focal, high-frequency TMS, George and colleagues found striking beneficial effects of rTMS to the left prefrontal cortex in four of six patients with medication-resistant depression;[8] in one of these patients the beneficial effects of rTMS were associated with normalisation of prefrontal hypometabolism, as shown by positron emission tomography.

All previous studies have failed to control adequately for potential placebo effects of rTMS (clinical improvement) on the depressive symptoms because of the lack of suitable intraindividual sham stimulation conditions. We report the results of a randomised, placebo-controlled trial of rTMS in 17 patients with medication-resistant major depression of the psychotic subtype (DSM-III-R).

Patients and methods

17 right-handed patients (11 women, six men, aged 38–59 [mean 48·6] years) met diagnostic criteria for major depression, psychotic subtype (DSM-III-R). None had bipolar affective disorder, but all had a history of relapsing unipolar major

depression. All had a history of at least three episodes of depression that had been resistant to multiple medications, despite combinations and high dosage. Nine patients had previously received electroconvulsive treatment to which they had responded with significant benefit for several months. All of the 17 agreed to participate in this study before electroconvulsive treatment. They met published safety criteria for rTMS[9] and gave their informed consent to the study, which was approved by the institutional review board. In particular, none had a history of brain surgery or epilepsy; all had normal neurological and general physical examinations; none had concurrent serious medical illnesses requiring long-term treatment; none had previously received TMS.

Before entering patients into the study we attempted cautious withdrawal of all medications to allow evaluation of rTMS without pharmacological interference. However, withdrawal of medication was not tolerated by nine patients; therefore their antidepressant treatments were continued at reduced dosage. Five of this subgroup were treated with imipramine (75–150 mg daily); four received a combination of amitriptyline (20–40 mg daily) and perphenazine (4–8 mg daily); in addition, three received bromazepam (3–6 mg daily). During the 5-month study all patients had fluctuations in the severity of depression. Five of the nine patients whose medication could not be withdrawn experienced transient worsening of the depressive symptoms during the study, leading to hospital admission for 1–6 weeks and adjustment of medications. An additional four patients required transient reintroduction of tricyclic antidepressants (imipramine, 75–100 mg daily). Therefore, only four patients received no antidepressant medications during the study.

Transcranial stimulation was done with a high-speed stimulator (Cadwell Inc, Kennewick, Washington, USA) equipped with a focal figure 8-shaped coil that allowed continuous water cooling to prevent overheating during stimulation.[1,9] During rTMS both the patients and investigators wore earplugs to prevent induction of transient threshold shifts due to loud noise from the discharging coil. Each patient received five courses of rTMS, applied at different scalp positions. Each course consisted of five sessions over 5 (consecutive) days, with each session consisting of 20 trains of 10 s duration separated by 1 min pauses. Stimulation was applied at 10 Hz frequency, at an intensity of 90% of the patient's motor threshold intensity. The choice of these stimulation variables was based on our previous results in normal volunteers,[3] and were within safety guidelines.[9] Motor threshold was assessed by application of single stimuli to the optimum scalp position for activation of the right first dorsal interosseus muscle.[1] Motor threshold intensity was defined as the lowest stimulation intensity that, in ten trials, induced at least five motor evoked potentials of at least 50 μV peak-to-peak amplitude.

TMS was applied with the coil centred over three possible scalp positions: vertex, left, or right dorsolateral prefrontal cortex (DLPFC). Definition of the stimulation positions was based on the measured presumed site of the central sulcus, as defined by the optimum scalp position for activation of the first dorsal interosseus muscle,[10] Tailarach Atlas coordinates, and the electrode positions of the 10–20 system. Stimulation of the vertex was defined as stimulation with the coil centred over Cz of the 10–20 international EEG electrode positions system. Left and right DLPFC stimulation were defined as stimulation with the coil centred over a point 5 cm anterior to the optimum scalp position for activation of the first dorsal interosseus.[11] Given the geometry and size of the stimulation coil used in this study, mathematical models indicated that we would affect an area of about 3×1·5 cm at cortical level.[1] Because of the scalp positions selected, one might infer that, when the stimulator was centred over the vertex, we might have affected sensorimotor cortex bilaterally, supplementary motor cortex bilaterally, parasagittal premotor cortex bilaterally, and possibly anterior cingulate area bilaterally. The DLPFC stimulation was centred primarily over area 46, but it is likely to have affected area 9 also. In any case, the DLPFC stimulation would certainly not spread to the other hemisphere, so, for example, left DLPFC stimulation would be limited to the left hemisphere.

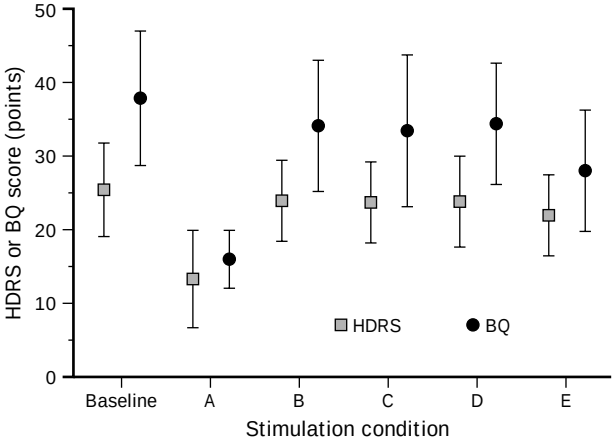

Figure 1: **Hamilton depression rating scale (HDRS) and Beck questionnaire (BQ) scores according to rTMS stimulation condition**

Symbols represent mean score (and SD) of raw scores for all 17 patients at baseline (weeks before first rTMS session), and at end of each week of rTMS session. Stimulation condition A=real left DLPFC stimulation; B=real right DLPFC stimulation (control); C=sham left DLPFC stimulation (control); D=sham right DLPFC stimulation (control); E=real vertex stimulation (C_z, control). Order of different stimulation conditions was randomised across patients. To generate these analyses, months of the same stimulation condition were arranged together, therefore, sequence A–E does not represent a real ordering in time.

In addition, stimulation over the left and right DLPFC was applied either with the coil resting flat on the scalp, as required to achieve induction of adequate cortical stimulation (real TMS), or with the coil angled at 45° and only the edge of the coil resting on the scalp (sham-TMS). The sham TMS induces a contraction of the scalp and face muscles and a subjective sensation similar to that achieved with real TMS, but fails to induce a significant cortical stimulation.[12–14] Therefore, we applied rTMS in five possible conditions, depending on stimulation site and real versus sham stimulation. Based on previous experience,[2–6,8] we expected to find significant effects of stimulation on the depressive symptoms only after real left DLPFC rTMS. The four control rTMS courses were stimulation to Cz, real right DLPFC rTMS, and sham TMS to left and right DLPFC.

Depressive symptoms were assessed by means of the 21-item version of the Hamilton-depression rating scale,[15] before the study and at the end of each week. The evaluator was unaware of the stimulation condition. In addition, we asked patients to self-rate their mood on Beck's questionnaire.[16]

The study was designed as a multiple placebo-controlled, cross-over study. The patients were not informed about the hypothesis that only real (left DLPFC) rTMS should ameloriate their depression, whereas no such benefit was expected from the other real or sham stimulation conditions. None had had rTMS previously and had no preformed notions about what to expect. They were merely informed that the study was designed to assess the effects of different forms of stimulation of different brain areas on depression. As mentioned above, the evaluator completing the Hamilton scale was also unaware of the stimulation conditions.

In each patient the study lasted 5 months. In each month, the patients underwent rTMS daily for the first 5 days. Thereafter they were followed weekly, with Hamilton scale and Beck scores obtained every Friday. The order of the different rTMS conditions was randomised and counterbalanced across patients. Throughout the 5 months, all patients were treated with nimodipine at a constant dose of 30 mg three times daily. Nimodipine was chosen because of its mood-stabilising effects and the fact that it appears to prolong the beneficial effects of ECT.[17] Some of the patients also continued to receive other antidepressant medication. We decided not to use carbamazepine

for mood stabilisation because of its inhibitory effects on the cortex, which might have confounded the rTMS effects.

Scores of the Hamilton scale and the Beck questionnaire were obtained at baseline, the week before the study, and weekly throughout the study. Therefore, we had a baseline measurement 1 week after medication withdrawal or stabilisation, and four measurements 1–4 weeks after each rTMS condition. Statistical analyses of the results used repeated ANOVA. In a first approach, two-way ANOVA was conducted for the Hamilton and Beck scores, at baseline and on the week of stimulation, according to stimulation condition. Subsequently, Hamilton and Beck scores at the end of each week of stimulation were expressed as percentage of the scores on the previous Friday to control for possible lasting effects of the preceding stimulation condition. Again, two-way ANOVA was applied on these relative scores. We also examined the time course of the Hamilton and Beck scores in the 4 weeks after a given stimulation condition. For the ANOVA we used Scheffe's post-hoc testing of significance, assuming a significance level of $p<0·05$.

Results

All patients tolerated rTMS without complications; in particular, no seizure was induced. Seven patients after some rTMS sessions complained about minor headaches that were promptly controlled with paracetamol or salicylates. These complications were not related to the stimulation condition, and did not prompt the patients to request discontinuation of the study, which was offered in every instance. Therefore, at the chosen stimulation variables, rTMS can be considered safe and without significant side-effects.

At completion of the study, nine patients related having felt a pronounced improvement only after real left DLPFC stimulation. Three others reported having felt improvement after both real left DLPFC and vertex stimulation. Two patients reported improvement after real left and right DLPFC stimulation. The remaining patient indicated improvement after real and sham left DLPFC stimulation, although she felt that the real stimulation had been better. However, these subjective recollections at the end of the study were not fully supported by the patient's own weekly ratings on the Beck and Hamilton scores. In all patients, the lowest Beck scores followed real left DLPFC stimulation. At the end of the week of stimulation the Hamilton scores were lowest for conditions other than real left DLPFC rTMS in only two patients. In both subjects, this occurred after right DLPFC stimulation and, in both, the Hamilton scores at the end of the subsequent week had continued to drop after left but had increased again after right DLPFC rTMS, ie, in these two patients there was a suspected worsening of depressive symptoms.

Mean Hamilton and Beck scores for all patients according to rTMS condition are shown in figure 1. Analysis of variance of Hamilton scores according to stimulation condition showed a significant interaction ($p<0·001$), with real left DLPFC stimulation resulting in the lowest scores. The beneficial effects of the real left DLPFC stimulation were confirmed by patients' self-ratings on the Beck questionnaire. Analysis of variance of the Beck scores according to rTMS condition gave highly significant results ($p<0·0001$), again with real DLPFC rTMS inducing the lowest scores. The degree of improvement in the Hamilton or Beck scores after real left DLPFC stimulation was not related to the timing of that stimulation condition during the 5-month study.

To test our hypothesis that beneficial effects on depressive symptoms would result only from real left DLPFC stimulation, we did a more conservative analysis of the results, calculating for each patient mean Hamilton and Beck control scores from all ratings after any other rTMS condition (figure 2). Analysis of variance for both scores, according to real left DLPFC stimulation versus control, showed significant interactions (Hamilton, $p<0·0005$; Beck, $p<0·0001$). Six patients showed no benefit from real left DLPFC stimulation. However, the lack of response to rTMS was not related to severity of the depression at baseline (as measured by the Hamilton and Beck scores), to whether or not patients were taking antidepressant medication during the rTMS sessions (3 non-responders were taking medication, three were not), to whether they were admitted to hospital (n=2) or treated as outpatients (n=4), or to which point during the study we applied left DLPFC stimulation (month 1 in one case, month 3 in two cases, month 4 in two cases, month 5 in one case). Similarly, there was no relation between previous electroconvulsive treatment and rTMS response; seven patients showing a good response to rTMS had previously received electroconvulsive therapy, whereas the six non-responders to rTMS included two patients previously treated successfully with electroconvulsive therapy.

Our study design allowed analysis of the duration of the beneficial effects of real left DLPFC rTMS on the

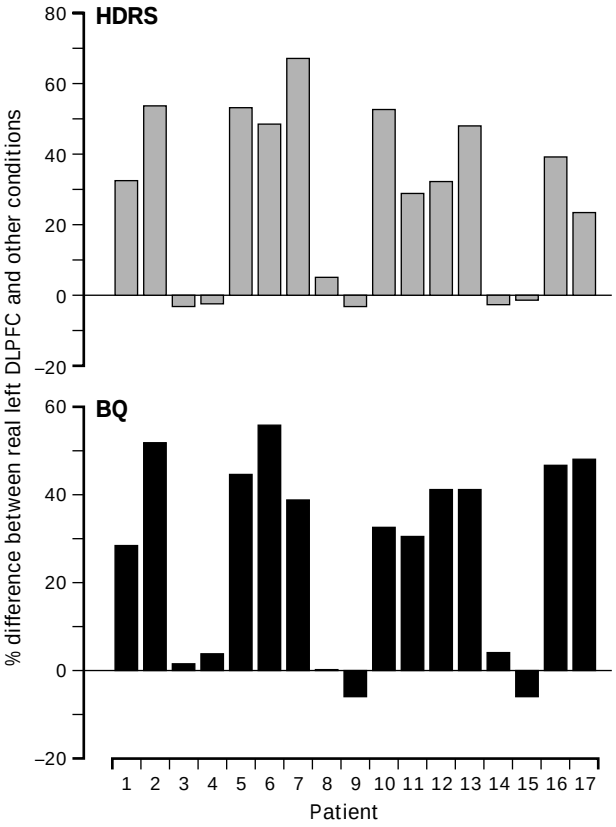

Figure 2: **Difference in Hamilton depression rating scale (HDRS) and Beck questionnaire (BQ) scores between week of left DLPFC stimulation and weeks of all other stimulation conditions**

Bars=results for indiviudual patients. Positive and negative values respectively express percentage improvement or worsening of depressive symptoms after left DLPFC stimulation compared with control conditions.

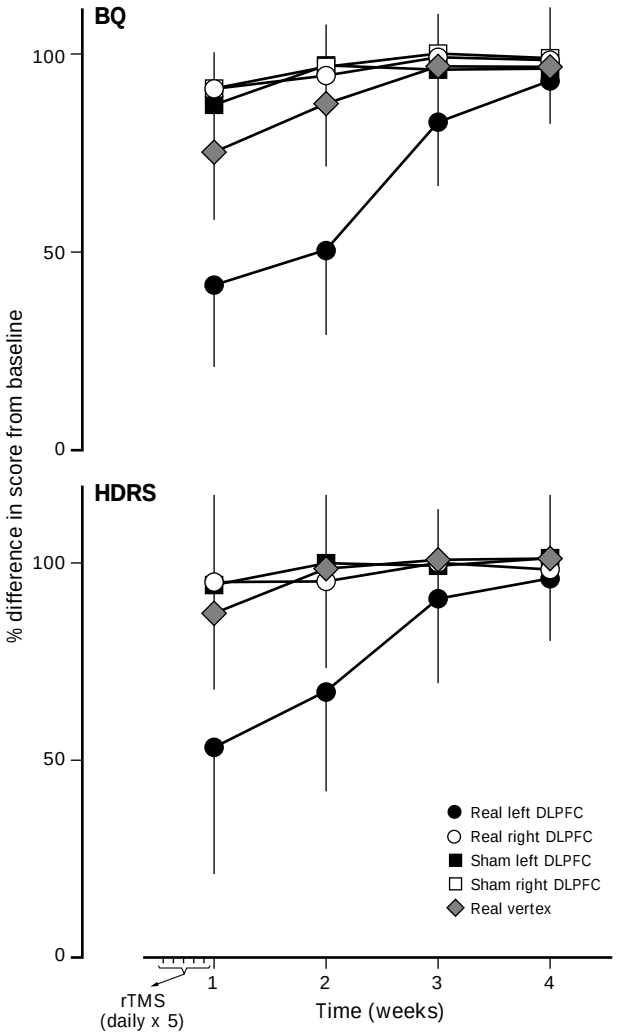

Figure 3: **Scores (mean and standard deviation) in Hamilton depression rating scale (HDRS) and Beck questionnaire (BQ) according to rTMS stimulation condition**

Mean results for all 17 patients are expressed as percentage difference from baseline scores. Baseline score is represented by score on Friday preceding week with daily rTMS—ie, last rating of preceding rTMS condition. Stimulation conditions A–E as in figure 1.

depressive symptoms (figure 3). Paired comparison of the Hamilton and Beck scores in the weeks after rTMS with the baseline scores revealed significant differences for the first and second weeks. No significant differences were found for the third and fourth weeks after rTMS. Furthermore, we normalised the depression scores for each patient in each rating day relative to the score on the last week before a week with daily rTMS, thus controlling for possible lasting effects of the preceding stimulation condition despite the 3 weeks of follow-up. Analysis of variance for Beck and Hamilton scores, split by weeks of study session (1–4) according to stimulation condition, showed significant interaction only for the first and second weeks. In both cases, left DLPFC stimulation resulted in significantly lower scores. These findings suggest that, with this design, the beneficial effects tapered off over about 14 days.

Discussion

This placebo-controlled trial of the effects of rTMS in depression confirms and expands previous results.[5–8] In 1995, Kolbinger and colleagues[6] reported a parallel-design, semi-blinded study of the antidepressant efficacy of TMS on major depression. They studied 15 patients in one placebo group, who received sham-TMS, and two treatment groups. One treatment group received stimuli above the motor threshold intensity, and the other group received stimuli of an intensity below motor threshold. As in our study, subjects received TMS on five consecutive days. Hamilton depression scale ratings indicated a non-significant reduction of symptoms in both treatment groups, and no change in the symptoms of the control group. The improvement in the below-threshold group was greater than that of the above-threshold group. On a self-rating scale, there was no change in the above-threshold and the control group, but strong trend toward improvement in the below-threshold group. However, Kolbinger and colleagues used a Madaus 200 MagStim ME with a circular stimulation coil of 14 cm, and stimuli were delivered at a frequency of 0·25–0·50 Hz with the coil centred at the vortex.[6] These are critical differences from our study. First, low-frequency stimulation, as used by Kolbinger and colleagues seems to induce a post-stimulation inhibition of the underlying cortex, whereas higher-frequency, low-intensity stimulation (as we used) increases the excitabiity of the underlying cortex.[18] Second, a circular coil centred over the vertex, results in stimulation of both hemispheres, affecting bilateral dorsolateral, prefrontal, parasagittal, and parietal regions, whereas we used a much more focal stimulation technique. Therefore, because of the technical differences, our results are difficult to compare with those of Kolbinger and colleagues, even though both studies strongly suggest that there is therapeutic potential for rTMS in depression, as a possible alternative to electroconvulsive therapy.

TMS has advantages over electroconvulsive therapy. It is practically painless, does not require anaesthesia, is not coupled with the induction of a seizure, and has fewer risks and cognitive side-effects. However, questions need to be answered. For example, further work is needed to explore other rTMS characteristics and to find out the optimum stimulation intensity, train duration, stimulation frequency, and number of sessions. Such studies might provide insight into why six of our subjects did not respond to rTMS (figure 2). We have limited our study to depression of the psychotic subtype; certainly the effects of rTMS on patients with other depressions should be studied. Psychotic depression is often more difficult to treat than other subtypes and is often medication resistant. The role of mood-maintaining medications in the duration of the effects and whether other drugs might prolong the beneficial effects of rTMS are unclear. We are disappointed by the transience of the therapeutic effect of rTMS. Perhaps more days of stimulation—for example, 10 rather than 5 days—might prolong the beneficial effects. Quantitative studies of possible cognitive side-effects of the applied rTMS are required, even though no clinically undesirable effects were noted, and previous safety studies have not reported them.[9]

Our results, and their further development, may advance understanding of the pathophysiology of mood disorders, and help clarify the mode of action of electroconvulsive therapy.[19,20] The results strongly suggest that focal rTMS to left prefrontal structures might obtain results similar to those of electroconvulsive therapy, without requiring induction of seizures. Induction of

generalised convulsive activity has been traditionally considered a necessary condition of electroconvulsive therapy efficacy,[21] but the evidence on which this belief is grounded can be questioned.[20] It would certainly be hasty to advocate the replacement of electroconvulsive therapy by rTMS, but we hope that this study will encourage the development of a subconvulsive mode of treatment of depression using rTMS. Ultimately, the relevant clinical questions are whether, for a given patient, rTMS would be an effective treatment, and whether rTMS would be more beneficial than, or at least equally beneficial to, electroconvulsive therapy.

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