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ARTICLE

Comparison of repetitive transcranial magnetic stimulation and electroconvulsive therapy in unipolar non-psychotic refractory depression: a randomized, single-blind study

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) can induce significant antidepressant effects and, for some patients, might be an alternative to electroconvulsive therapy (ECT). The results of studies comparing the efficacy of rTMS and ECT are mixed and, therefore, comparison of these two therapies needs to be further explored. Forty-two patients aged between 18 and 65 yr, referred to ECT due to unipolar non-psychotic depression refractoriness entered the trial. They were randomly assigned to receive either rTMS or ECT. Depressive symptom changes were blindly measured by Hamilton Depression Rating Scale, Visual Analogue Scale and Clinical Global Impression at baseline, after 2 wk and after 4 wk of treatment. There was no difference in the antidepressant efficacy of ECT and rTMS. Response rates were relatively low in both groups (40% and 50% respectively), with no significant difference between them ($p = 0.55$). Remission rates were also low for both groups (20% and 10% respectively), also with no significant difference ($p = 0.631$). There was no significant difference in the neuropsychological test performance after either one of these therapies. Both treatments were associated with a degree of improvement in refractory depression and therefore add to the literature that rTMS can be an effective option to ECT as it is a less costly treatment and is not associated with anaesthetic and other ECT risks.

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Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive form of brain stimulation that has been extensively investigated for the treatment of major depression (MD). Although some studies have failed to show clinical improvements in depressed patients after rTMS treatment (Hausmann et al., 2004; Padberg et al., 1999), most of them conclude that rTMS can induce significant antidepressant effects with few, usually mild adverse effects (Conca et al., 1996; Eschweiler et al., 2000; George et al., 1997, 2000; Grunhaus et al., 2000; Holtzheimer et al., 2001; Pascual-Leone et al., 1996; Pridmore, 2000). These positive results raised the question whether the antidepressant efficacy of rTMS treatment might be comparable to that of electroconvulsive therapy (ECT). ECT is the most effective treatment available for depression, but is associated with adverse cognitive effects and needs general anaesthesia with associated risks, especially in patients with clinical comorbidities. Comparatively rTMS appears associated with less undesirable side-effects and no anaesthesia is required (Hasey, 2001). Several studies have compared the efficacy of rTMS and ECT with controversial

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results, some of them showing that rTMS and ECT induce similar antidepressant effects (Grunhaus et al., 2003) and relapse rates (Dannon et al., 2002), whereas other studies show that ECT might have a superior antidepressant response, particularly in patients with psychotic depression (Grunhaus et al., 2000), although with more side-effects than rTMS (O'Connor et al., 2003). One of the reasons for this variability might be the small sample size of these studies. Therefore, to better define the effects of rTMS compared to ECT, we carried out in a larger sample of medication-resistant MD patients a randomized, single-blind clinical trial comparing the effects of rTMS and ECT, evaluating response rates, and differences concerning side-effects profile.

Methods

Participants

Forty-two patients (mean age 43.6 ± 10.5 yr, 20 females) were entered into the study. Patients were eligible if they were referred by their own physicians to receive ECT at the Psychiatric Institute of the University of Sao Paulo due to refractory depression. Patients had to be between 18 and 65 yr, have a unipolar depressive disorder according to DSM-IV criteria – confirmed by a semi-structured interview (SCID – DSM-IV; First et al., 1995), with no psychotic symptoms and a score on the Hamilton Depression Rating Scale (HDRS) (17 items) $\geqslant 22$ (Hamilton, 1960). Refractoriness was defined as a lack of response to at least two antidepressants of different classes (used for at least 4 wk with adequate dosages), with augmentation (with lithium or thyroid hormone for at least one trial). Patients were excluded if they had a past history of epilepsy, past neurosurgery with presence of metal clips, any other neurological or psychiatric diseases, presence of cardiac pacemakers, or pregnancy.

Patients referred to ECT and eligible for the study were invited to enter the study. All subjects gave written informed consent to participate in the study, which had been approved by our Institutional Ethical Committee. The study was conducted with close adherence to the principles of the Helsinki Declaration.

Patients were randomized to receive ECT or rTMS to the left dorsolateral prefrontal cortex (LDLPFC) according to a computer-generated list. Of the 42 randomized patients, five patients of the ECT group were excluded from the study – three of them did not complete 2 wk of treatment (they received four sessions and the treatment was suspended by their treating physicians; it was not possible to assess clinical improvement or side-effects) and the other two patients did not attend the follow-up evaluation after 2 wk (due to personal problems). Two patients randomized to receive rTMS were also excluded. One of them developed a dissociative state (not previously diagnosed) after the first application of rTMS, which lasted about 5 min, with no further complications. After intensive neurological and clinical evaluations with negative findings, the patient was withdrawn of the study. The other patient received 5 d rTMS and developed hypomanic symptoms and was withdrawn from the study. In summary, 35 patients completed the study (20 in the rTMS group and 15 in the ECT group).

Medications

The use of antidepressants, antipsychotics and mood stabilizers was not allowed during the treatment period. Patients on antidepressants were instructed to taper them off under close medical supervision. The washout period was 1 wk for any antidepressive medications, except for fluoxetine (3 wk) and MAO inhibitors (2 wk). Benzodiazepines were used if necessary to treat anxiety and/or insomnia, and its use was computed as a covariable. If necessary, patients were hospitalized for the washout of medication and study participation to assure their safety.

Objectives

The primary objective of the study was to compare depression symptoms improvement between both treatments, as measured by HDRS scores and also by a Visual Analogue scale (VAS) and the Clinical Global Impression (CGI) Scale. Secondary outcomes included a neuropsychological evaluation of both groups at baseline, after 2 wk and after 4 wk of treatment.

Experimental design

A detailed neuropsychological and psychiatric evaluation was performed at baseline (T0) (24 h before the first session), after 2 wk of treatment (T1), and after 4 wk of treatment (T2).

Interviews were performed by raters blinded to the patients' group assignment (ECT vs. rTMS) and patients were instructed not to disclose which treatment they were receiving. These evaluations included HDRS, CGI, VAS for depression, and a neuropsychological battery. ECT was performed over 4 wk (or less, in case the patient had a clinical improvement). In cases which more ECT sessions were needed

(according to the treating physician), treatment was continued after the final evaluation (outside the protocol).

rTMS was administered over 4 wk. If the patient did not improve or showed a worsening after 2 wk, study participation was terminated and ECT was then initiated. Therefore, the patient was rated as a non-responder to rTMS.

ECT methods

A brief pulse MECTA, SpECTrum 5000Q® British model (MECTA Corporation, Lake Oswego, OR, USA) was used. This device has British standards and is capable of twice the charge of American devices (1152 mC vs. 576 mC respectively).

ECT was performed according to standards approved at our institution and in agreement with the American Psychiatric Association guidelines (APA, 2001).

During each ECT session, patients received 100% oxygen. Etomidate (1.0–1.5 mg/kg i.v.) was the anaesthetic used. Although methohexital is the most commonly used anaesthetic for ECT worldwide, it is not available in Brazil. For muscle relaxation, succinylcholine (0.5–1.25 mg/kg i.v.) was used. Patients also received atropine (0.4–1.0 mg i.v.).

Treatment begun with right unilateral ECT (d'Elia, 1970). If there was no antidepressant response after 2 wk, bilateral ECT was performed. In the first treatment, seizure threshold was calculated according to the method of limits (Beyer et al., 1998). In the following treatments, a mean charge of 4.5 times the threshold was given three times a week (Mondays, Wednesdays and Fridays). If a patient was transferred to bilateral ECT, a mean charge of 1.5 times the threshold was given. Both motor and EEG seizure duration were monitored.

rTMS methods

A Dantec Magpro® (Medtronic, Minneapolis, MN, USA) magnetic stimulator was used, with a figure-of-eight coil (70 mm). Patients were seated in a comfortable chair and used earplugs. A tightly fitting swimming cap was worn to mark the site of stimulation and help keep the placement of the TMS coil constant across and during each session.

Motor threshold was determined according to published guidelines (Rossini and Rossi, 1998). A pair of surface electrodes was placed over the right abductor pollicis brevis muscle. These electrodes were connected to a Dantec Electromyograph (Medtronic). Electromyography was used to measure the motor threshold (MT). MT was defined as the lowest TMS intensity required to elicit motor-evoked potentials (MEPs) of $\geqslant 0.05$ mV in the contralateral resting abductor pollicis brevis muscle in at least 5 of 10 trials with the coil over the optimal scalp position.

During the rTMS treatment the left prefrontal area was targeted by placing the coil over a point 5 cm anterior and in the same parasagittal plane from the optimal position for induction of MEPs in the right abductor pollicis brevis muscle (Pascual-Leone et al., 1996). The coil was held tangentially to the skull with the handle pointing occipitally and aligned parallel to the midline of the subject's head.

Sessions were performed five times a week for 4 wk (total of 20 sessions). The following parameters were used: intensity 100% MT; frequency of 10 Hz; trains of 10 s and intertrain interval of 20 s; 25 trains per session. Therefore, a total of 2500 pulses were administered each session (overall total of 50 000 pulses). This is slightly outside the current safety guidelines (Wassermann, 1998). However pilot studies at our institution found this stronger stimulation (within secure intertrain intervals) to be safe and more effective than when shorter trains (consistent with safety guidelines) were applied.

Patients that did not respond to this course of rTMS sessions were scheduled to receive a course of ECT after the completion of the protocol.

Neuropsychological evaluation

A trained, licensed neuropsychologist blinded to the patients' treatment group conducted the neuropsychological evaluation. The main goal was to evaluate memory deficits, which are often seen with ECT. Cognitive side-effects of rTMS are less well characterized although they seem to be relatively minor (Schulze-Rauschenbach et al., 2005). Tests included subsections of the Weschler Adult Intelligence Scale – Revised (vocabulary and cubes) (WAIS-R; Wechsler, 1981), subsections of the Wechsler Memory Scale (digit span) (WMS; Wechsler, 1987) and the Rivermead Behavioral Memory Test (RBMT; Wilson et al., 1991). Baseline testing was performed 24 h before the beginning of treatment. The other two subsequent evaluations were performed after 2 wk and 4 wk (on the morning before receiving either one of the treatments).

Statistical analysis

The primary outcome was the clinical response [indexed by HDRS scores, patients' subjective perception of improvement (VAS), and the physician's

Table 1. Demographic and baseline clinical characteristics

Variable	Group		*p*
	ECT	TMS	
Sex (*n*, %)			0.433*
Male	8 (53.3)	8 (40.0)	
Female	7 (46.7)	12 (60.0)	
Race (*n*, %)			0.631*
Caucasian	12 (80.0)	18 (90.0)	
Black	3 (20.0)	2 (10.0)	
Educational level (*n*, %)			0.443*
Basic	1 (6.6)	2 (10.0)	
Mean	10 (66.7)	9 (45.0)	
Superior	4 (26.7)	9 (45.0)	
Age (yr ± S.D.)	46.0 (10.6)	41.8 (10.2)	0.252**
HDRS score (± S.D.)	32.1 (5.0)	30.1 (4.7)	0.926**
Duration of illness (months ± S.D.)	103.6 (73.4)	110.7 (44.6)	0.882***
No. of previous episodes (± S.D.)	2.9 (0.9)	3.6 (1.2)	0.099***
No. of previous hospitalizations (± S.D.)	0.9 (1.4)	0.1 (0.3)	0.055***
Approximate duration of current episode (months ± S.D.)	10.5 (3.0)	11.5 (5.1)	0.987***
Family history of depression[a] (*n*, %)			0.467*
No	10 (76.9)	12 (63.2)	
Yes	3 (23.1)	7 (36.8)	

ECT, Electroconvulsive therapy; TMS, transcranial magnetic stimulation; HDRS, Hamilton Depression Rating Scale.

* Level of statistical significance according to χ^2 association test or Fisher's exact test (one frequency lower then <5).

** Statistical significance according to *t* test.

*** Statistical significance according to Mann–Whitney test.

[a] Information on three patients was missing.

subjective perception of improvement (CGI)]. Secondary outcomes included cognitive side-effects.

Initially, baseline characteristics were compared between the two groups using two-tailed *t* tests for continuous variables and χ^2 for categorical variables. The primary outcome (clinical response) was considered as a decrease equal to 50% or more in HDRS scores when comparing T0 (baseline) to T2 (end of treatment). Remission was considered as a final score (T2) of $\leqslant 7$ on the HDRS. Because there were seven dropouts (five in the ECT and two in the rTMS group), we also performed an intention-to-treat (ITT) analysis for the HDRS changes in which we assumed no further improvement and used the last observation to the missed values to perform this analysis. The difference in the response rate between the two groups was analysed using χ^2 and the difference in the remission rate was analysed using Fisher's exact test as the number of events per cell was low. A further analysis in which HDRS scores were used as a continuous measure was performed using a two-way analysis of variance (ANOVA) with repeated measures on time (two factors: group – ECT and rTMS; and time – T0, T1 and T2).

Results

Demographic and clinical characteristics are shown in Table 1. No statistical differences were observed between the two groups. Duration of the disorder ranged from 8 to 228 months (mean 107.7 months, S.D. = 57.8). Most of the patients did not present a family history of depression (62.2%). Atypical symptoms were not observed. Two patients in each group

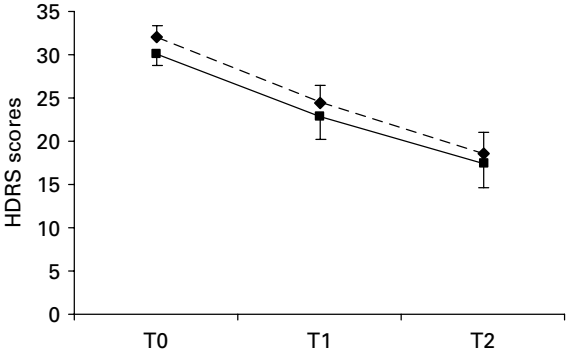

Figure 1. Hamilton Depression Rating Scale (HDRS) scores along time in both groups (±S.D.). - - ◆ - -, ECT; —■—, rTMS.

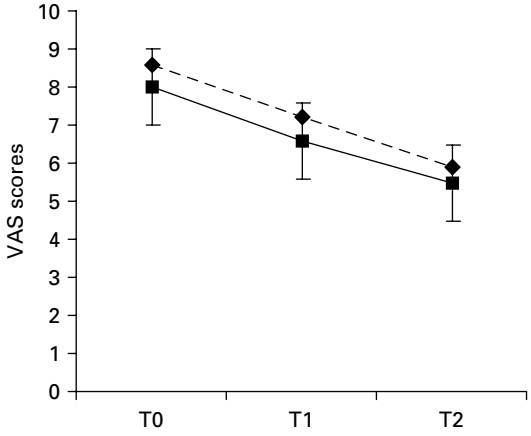

Figure 2. Visual Analogue scale (VAS) scores along time in both groups (±S.D.). - - ◆- -, ECT; —■—, rTMS.

reported suicidal ideation, with no planning – these patients were treated as in-patients. Approximate duration of episode of depression ranged from 7 to 24 months (mean 11.1 months, S.D. = 4.3). Benzodiazepines were seldom used (two patients in each group used 10 mg diazepam for insomnia for one night only during the study).

Primary outcome – depression improvement

There were no significant differences between the groups for baseline HDRS scores (ECT group: 32.1 ± 5.0; rTMS group: 30.1 ± 4.7; $p = 0.926$). Two-factor repeated-measures ANOVA (subject group and time of evaluation) showed no group effect ($p = 0.495$) and no group × time interaction ($p = 0.949$). However, there was a significant effect of time ($p = 0.001$), demonstrating that scores changed similarly in both groups during the study. We repeated this analysis, but instead of completers only, we included all patients (ITT analysis), and obtained similar results: no group effect ($p = 0.12$) and no interaction effect ($p = 0.86$); but a significant time effect ($p < 0.0001$). Post-hoc analysis showed a significant difference for both groups of patients between T0 and T1 ($p = 0.01$ for the ECT group; and $p = 0.003$ for the rTMS group), and T0 and T2 ($p = 0.01$ for the ECT group; and $p = 0.001$ for the rTMS group). However, between T1 and T2, although there was a trend towards depression improvement, this difference did not reach significance ($p = 0.07$ for the ECT group, $p = 0.06$ for the rTMS group) (Figure 1).

Similarly to the results of the HDRS, there were no significant differences between the groups for baseline VAS ($p = 0.860$). Two-factor repeated-measures ANOVA (subject group and time of evaluation) showed no group effect ($p = 0.388$) and no group × time interaction ($p = 0.942$). However, there was a significant effect of time ($p = 0.001$). Post-hoc analysis showed that patients scored significantly less depression after 4 wk of treatment compared to the baseline for both groups ($p < 0.0001$ for the ECT group, $p < 0.0001$ for the rTMS group). However, the comparison between T0 and T1 was significantly different only for the rTMS group ($p = 0.045$) (Figure 2), possibly suggesting a slightly faster response rate to rTMS than ECT.

Finally, CGI scores also showed similar behaviour, i.e. ANOVA showed neither significant main effect of group ($p = 0.432$) nor significant interaction group vs. treatment ($p = 0.672$), but there was a significant main effect of time ($p < 0.0001$). Post-hoc analysis, showed a significant difference between T2 and T0 for both groups ($p < 0.001$ for the ECT group, $p < 0.001$ for the rTMS group), but not between T0 and T1 and T1 and T2 (Table 2).

The percentage of responders (reduction of $\geqslant 50\%$ on HDRS scores) was 40% ($n = 6$) in the ECT group and 50% ($n = 10$) in the rTMS group (Figure 3). This difference was not significant ($p = 0.557$). Likewise, there was no significant difference ($p = 0.631$) in the percentage of remissions (final score $\leqslant 7$ on HDRS) in both groups $\sim 20\%$ ($n = 3$) in the ECT group and 10% ($n = 2$) in the TMS group (Figure 3). Performing an ITT analysis and given that dropout patients only completed the baseline evaluation, we found 30% responders in the ECT group and 45% in the rTMS group (no significant difference between the two groups, $p = 0.35$); and 9% of remissions for the rTMS and 15% for the ECT group ($p = 0.65$).

Table 2. Clinical Global Impression (CGI) scores along time (±S.D.)

Time of evaluation	Treatment	
	ECT	RTMS
T0	4.7 (0.8)	4.3 (0.8)
T1	4.0 (1.0)	3.7 (1.1)
T2	3.2 (1.5)	3.1 (1.3)

ECT, Electroconvulsive therapy; TMS, transcranial magnetic stimulation.

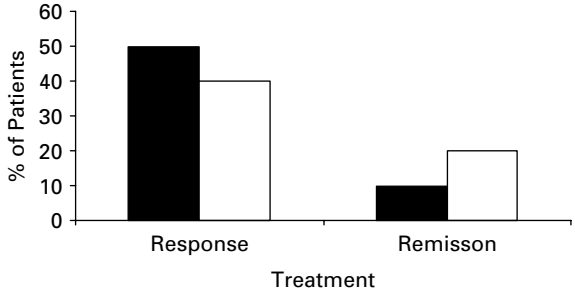

Figure 3. Rate of response and remission in both groups (completers). □, ECT; ■, rTMS.

ECT group analysis

There was no significant difference in any variables concerning the ECT parameters between the responders and non-responders in the ECT group. These variables included seizure threshold, mean electric charge, charge on the last treatment, duration of seizures, and number of treatments (Table 3). No patient was shifted to bilateral ECT during the trial.

Secondary outcome

There was no significant difference between the two groups in the neuropsychological tests performance after 2 wk and 4 wk of treatment. However, it is important to note that for most of the tests, patients in the ECT group had a trend of worsening in the neuropsychological performance after 2 wk and 4 wk of treatment, while for the rTMS groups, the tests did not change or showed a slight improvement after the treatment. For instance, for the RBMT profile, the ECT group showed worsening after 2 wk and 4 wk (T0 = 14.2 ± 3.6; T1 = 11.0 ± 6.9; T2 = 12.5 ± 9.7); whereas in the rTMS group, there was a trend of improvement after 2 wk and 4 wk of treatment (T0 = 16.4 ± 5.5; T1 = 17.9 ± 4.6; T2 = 17.3 ± 4.4) (see Table 4).

Discussion

The results of this study showed that the efficacy of rTMS was similar to that of ECT in the treatment of severe medication-resistant depression (40% and 50% respectively). It can be considered a low response rate for ECT but this was achieved in a population with severe depression, as characterized by the mean duration of the present episode, resistance to pharmacological treatment, number of previous depressive episodes, and baseline HDRS. In addition, there was no additive effect with antidepressants as all the patients washed out their antidepressants before starting the study. For chronic, refractory depression, ECT efficacy is known to be reduced (Abrams, 2002; APA, 2001; Prudic et al., 1990, 1996; Shapira et al., 1996) and is a main concern for ECT practitioners. In fact, among patients who have not responded to one or more adequate antidepressant trials, response rate to ECT is around 50–60% (Prudic et al., 1996). Furthermore, the results showed that there was no significant difference in the neuropsychological performance after either one of these therapies.

Six prior studies comparing the efficacy of ECT and rTMS for depression have been reported (Grunhaus et al., 2000, 2003; Janicak et al., 2002; O'Connor et al., 2003; Pridmore et al., 2000; Schulze-Rauschenbach et al., 2005). Although these studies varied in the design, most of them show a similar antidepressant effect of rTMS and ECT, except the study by O'Connor et al. (2003).

Grunhaus et al. (2000) published the first study comparing ECT to rTMS. This was an open study with 40 patients. They found that ECT had a greater antidepressant efficacy than rTMS for psychotic patients, but it was equivalent for non-psychotic depression. Results from this study were limited because evaluation was not blinded and ECT patients continued to receive antipsychotics whereas rTMS patients received only benzodiazepine.

Pridmore et al. (2000) published the first randomized controlled study comparing unlimited (until remission or response plateau) numbers of rTMS and ECT for a major depressive episode. Patients ($n = 32$) were non-responsive to one antidepressant and a single-blinded evaluation was performed. This study showed the best improvement rate published with rTMS to date (55.6% improvement in HDRS scores).

Janicak et al. (2002) published the third study, showing the preliminary results of a randomized

Table 3. Electroconvulsive therapy (ECT) parameters and clinical response

	All patients ($n=15$)		Patients dichotomized by presence of clinical response		
	Mean	S.D.	No	Yes	p value[a]
Seizure threshold (mC)	93.9	125.2	130.1 (152.4)	39.7 (28.2)	0.328
Mean electric charge (mC)	422.8	361.3	464.5 (381.6)	360.4 (353.2)	0.529
Electric charge on the last treatment (mC)	524.4	440.0	599.4 (446.3)	411.9 (445.0)	0.388
Mean duration of motor seizure (s)	51.9	18.4	53.2 (21.6)	50.0 (13.9)	0.864
Mean duration of EEG seizure (s)	55.4	29.2	102.5 (134.0)	52.2 (11.7)	0.607
Number of treatments	10.0	1.5	9.3 (0.9)	11.0 (1.8)	0.066

[a] According to Mann–Whitney test.

Table 4. Cognitive measures between groups

	Test scores [mean (S.D.)]						
	ECT group			rTMS group			
Measure	T0 (baseline)	T1 (2 wk)	T2 (4 wk)	T0 (baseline)	T1 (2 wk)	T2 (4 wk)	p[a]
Total vocabulary (WAIS-R)	38.2 (20.2)	35.3 (21.2)	37.0 (25.3)	37.5 (13.8)	42.3 (12.3)	42.4 (12.4)	n.s.
Total cubes (WAIS-R)	21.2 (14.9)	20.8 (13.0)	22.8 (17.9)	22.6 (13.5)	22.1 (12.4)	27.5 (13.5)	n.s.
Estimated IQ (WAIS-R)	91.5 (18.9)	91.4 (32.8)	91.3 (27.3)	91.7 (15.6)	94.1 (13.5)	96.1 (13.0)	n.s.
Direct digits (WMS)	7.7 (3.6)	8.5 (4.6)	6.5 (3.2)	6.3 (2.3)	6.3 (2.6)	6.1 (3.2)	n.s.
Indirect digits (WMS)	5.5 (3.9)	4.5 (2.9)	4.7 (4.2)	4.8 (2.2)	5.3 (3.1)	5.3 (3.0)	n.s.
Numbers (WAIS)	13.2 (7.4)	13.0 (7.3)	11.2 (7.0)	11.4 (4.1)	11.6 (5.9)	11.7 (6.0)	n.s.
RBMT (profile)	14.2 (3.6)	11.0 (6.9)	12.5 (9.7)	16.4 (5.5)	17.9 (4.6)	17.3 (4.4)	n.s.
RBMT (classification)	7.2 (1.3)	4.3 (3.3)	5.3 (4.7)	7.5 (2.8)	8.3 (2.0)	7.9 (2.1)	n.s.

ECT, Electroconvulsive therapy; TMS, transcranial magnetic stimulation. WAIS-R, Wechsler Adult Intelligence Scale – Revised; WMS, Wechsler Memory Scale; RBMT, Rivermead Behavioral Memory Test; n.s., not significant.
[a] Group × time interaction.

trial comparing the two treatments. They studied 25 patients and found a similar response rate in both groups with a percentage of change on HDRS scores of 55% for the rTMS group and 64% for the ECT group. This was the only comparative study that used bilateral ECT since the beginning of the treatment.

O'Connor et al. (2003) conducted a study focusing on the cost–benefit analysis of antidepressant efficacy and side-effects. They found ECT more effective, but with side-effects that were absent in the rTMS group.

Grunhaus et al. (2003) published another randomized controlled comparison of ECT and rTMS in severe and medication-resistant non-psychotic MD ($n=40$). Indeed, this study has several methodological similarities with our study. For instance, both studies had similar study design (randomized, controlled, single-blind study), patients' characteristics (unipolar non-psychotic MD), medication use (only benzodiazepine), number of TMS sessions (20 sessions) and frequency of rTMS (10 Hz). Differences between these two studies concerned some TMS parameters, such as total number of pulses (50 000 in our study and 24 000 in Grunhaus et al.'s study) and neuropsychological evaluation (neuropsychological battery in our study and only mini-mental status examination in Grunhaus et al.'s study). The cited study reported a response rate for ECT of 48.2% and for rTMS of 45.5%, which was similar to our findings (40% and 50% respectively), in spite of the greater severity of symptoms and strict refractoriness criteria in our study.

This might explain the higher remission rate in the Grunhaus et al. study (however, the authors used a cut-off of 8 in the HDRS).

Finally, a recently published study (Schulze-Rauschenbach et al., 2005) comparing the two treatments specifically aimed at the evaluation of the cognitive side-effects of both techniques ($n = 30$). The authors found a marked reduction of depression as measured by HRSD scores (decrease of 35% with ECT and 39% with rTMS) and a clinical response (final HRDS score decreased by $\geqslant 50\%$ from baseline) of 46% on the ECT group and 44% on the rTMS group. Several methodological issues, such as non-random assignment, low dosage for both treatments, short treatment duration (only 2 wk of rTMS), and use of medications during treatment might have limited the clinical outcome of this study.

Burt et al. (2002) published a meta-analysis in which studies comparing ECT and rTMS for the treatment of depression were analysed. The study of Janicak et al. (2002) was not included due to methodological issues. Also not included were the studies of Schulze-Rauschenbach et al. (2005) and O'Connor et al. (2003) because they were published after. This meta-analysis included 112 cases and although the results showed that ECT has a superior antidepressant effect compared to rTMS, this difference did not reach significance. Furthermore, the difference was smaller if psychotic patients were excluded from the analysis. The pooled data showed that improvement in HDRS was 47.13% for patients who received rTMS and 54.47% for patients who received ECT. It is intriguing that these are the best results observed for rTMS (almost twice as large compared to sham-controlled clinical trials evaluating rTMS for depression compared with sham stimulation) and the worst results observed for ECT (compared to other ECT trials). The reasons for this are unknown. Refractoriness of the samples, unilateral position of electrodes, relatively low charge of ECT used (2.5 times seizure threshold), and higher number of rTMS sessions may partially explain this disagreement. Publication bias might be another explanation for this phenomenon.

Our study has three main limitations that should be considered. First, there was no placebo group. The main reasons for this were the severity of the depression of our patients and the ethical issue of the use of sham ECT. Furthermore, ECT has been long demonstrated as the most effective treatment for depression. Therefore, our trial might be viewed as a comparison of rTMS against an established, effective therapy. Second, the sample size of this study, even though it is larger than in most prior trials, remains small and therefore we might have been underpowered to detect a difference between these two treatments, incurring in a type II error. However, the results showed that there was no statistical trend towards any treatment and the absolute values of depression improvement were similar in both groups. Finally, our neuropsychological battery might not have been adequate to detect memory changes following ECT treatment, especially with unilateral ECT (deficits of orientation, anterograde memory and delayed recall of non-verbal material), or our sample was too small to show this difference. This result was unexpected, since ECT is classically known and criticized for its cognitive side-effects, especially memory impairment. Indeed, O'Connor et al. (2003) found prominent memory side-effects in the patients treated with ECT and a lack of such deleterious effects in the rTMS patients. Schultze-Rauschenbach et al. (2005) also found a higher rate of memory impairment with ECT than with rTMS. The benign cognitive side-effect profile in our sample might be partially explained by the ECT technique applied: mostly unilateral and with high charge (~ 4.5 times seizure threshold). This procedure is known to minimize ECT cognitive impairment (Sackeim et al., 2000), which would tend to diminish the difference between ECT and rTMS. Nevertheless, in our study patients in the ECT group had a higher frequency of headache and confusion after ECT treatment compared to rTMS treatment.

An important point refers to safety parameters and efficacy. According to the safety guidelines (Wassermann, 1998), with a frequency of 10 Hz and an intensity of 100% MT, train duration should not exceed 5 s. In the current study we used 10 s. On the other hand, intertrain interval (an important variable regarding risk of seizure induction) (Chen et al., 1997; Rosa et al., 2004) was safe (20 s). No patients showed any signs of partial or generalized seizure. Perhaps the efficacy found can be related to a more intense stimulation (2500 pulses per session; total of 50 000 pulses).

The present results show a similar response rate between ECT and rTMS, enlarging the body of literature supporting rTMS as an important tool in the treatment of unipolar depression. This result gives additional evidence to support the use of rTMS as an alternative treatment in severe cases of MD, with the advantage of avoiding general anaesthesia and other ECT-related complications (e.g. cardiovascular and pulmonary), as well as being more cost-effective than ECT. New strategies, such as the combined use of

rTMS with antidepressants might further augment the antidepressant efficacy of rTMS as recently suggested by Rumi et al. (2005).

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Statement of Interest

None.

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