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Therapeutic Studies

Relative Effects of Repetitive Transcranial Magnetic Stimulation and Electroconvulsive Therapy on Mood and Memory: A Neurocognitive Risk–Benefit Analysis

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Abstract

Objective:
Two procedures for treating major depressive disorder were compared with regard to their respective effects on mood and cognition.

Background:
Fourteen patients underwent treatment with electroconvulsive therapy and 14 underwent treatment with repetitive transcranial magnetic stimulation. Patients were tested on three occasions: before initiation of treatment, at the end of treatment, and 2 weeks after the end of treatment.

Methods:
Electroconvulsive therapy was applied unilaterally approximately three times per week for 2 to 4 weeks. Repetitive transcranial magnetic stimulation was applied in sessions of 1600 stimuli at 10 Hertz and 90% of motor threshold intensity to the left dorsolateral prefrontal cortex daily (Monday through Friday) for 2 consecutive weeks.

Results:
Results indicate that electroconvulsive therapy had a more positive effect on mood than did a 2-week trial of repetitive transcranial magnetic stimulation. With regard to cognitive outcome measures, electroconvulsive therapy exerted a deleterious but transient effect on various components of memory that were no longer detected 2 weeks after the end of treatment; however, there was evidence of persistent retrograde amnesia after treatment with electroconvulsive therapy. As a group, repetitive transcranial magnetic stimulation patients experienced only a modest reduction in depression severity but there was no evidence of anterograde or retrograde memory deficits in the aftermath of treatment with repetitive transcranial magnetic stimulation.

Conclusions:
Findings suggest that electroconvulsive therapy is associated with transient negative cognitive side effects, most of which dissipate in the days after treatment. Deficits of this sort are not apparent after treatment with a 2-week course of repetitive transcranial magnetic stimulation.

Key Words: electroconvulsive therapy, major depressive disorder, memory, neuropsychology, transcranial magnetic stimulation

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Major depressive disorder (MDD) is a public health problem that has tremendous personal and social consequences. Estimates are that 20% of Americans have an episode of depression some time during their adult lives. Most patients with MDD respond promptly to antidepressant medications, but a significant number fail multiple medication trials. Many of these patients with medication-resistant MDD are treated successfully with electroconvulsive therapy (ECT). ECT often results in total remission of depressive symptoms for an extended period of time. However, ECT is not a wholly benign procedure and side effects can include headache, disorientation, and cognitive deficits.[1,2] A number of investigators have shown that ECT has an adverse effect on memory so that new learning is temporarily disrupted.[3–5] In many cases there are permanent lacunae in memory for events that occurred before the treatment sessions.[6–9] Because of the potential adverse effects of ECT on memory there

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is a clinical mandate to investigate alternative therapies for treatment of MDD.

Over the past decade, repetitive transcranial magnetic stimulation (rTMS) has been explored for treatment of MDD. rTMS is a noninvasive procedure involving the application of electrical current pulses, induced by a strong pulsating electromagnetic field. The therapeutic efficacy of rTMS is still being investigated and there have been studies that do not support rTMS as a potent treatment of MDD;[10,11] however, a number of other investigations have demonstrated that rTMS applied to the left prefrontal cortex is associated with decreased depression in patients with MDD.[12–16] The procedure is practically painless and has not been associated with significant negative cognitive side effects. To the contrary, in some instances, rTMS has been associated with improvement on tasks of attention and learning.[17,18] Such improvement may reflect diminished depression but there is also reason to believe that rTMS has independent positive effects on some components of cognition.[17] For example, several studies designed to assess the safety of rTMS found apparent beneficial effects of rTMS on memory and attention.[19,20]

In light of its potential therapeutic efficacy and lack of side effects, rTMS appears promising as a form of treatment of MDD. However, it is not clear whether rTMS represents a therapeutic alternative to ECT. There have only been a few studies comparing the relative effects of ECT and rTMS. In one study Grunhaus et al[21] compared the antidepressant effects of these procedures with patients who received 20 days of treatment with rTMS and patients who received a standard clinical protocol of ECT. They found that ECT was more beneficial for patients with psychotic depression whereas ECT and rTMS had equal effects on nonpsychotic depression.[21] In a subsequent paper these investigators reported that the mood-enhancing properties of rTMS were as robust as those associated with ECT 3 to 6 months after treatment.[22] Two more recent studies have drawn attention to the therapeutic usefulness of rTMS. Janiack et al[23] demonstrated that a standard clinical protocol of ECT and 10 to 20 trials of rTMS had comparable therapeutic effects when administered to patients with severe depression. In a single case study a patient with ECT-resistant depression was treated with rTMS for 4 weeks, and this was found to be quite effective.[24] Further support for rTMS as a treatment of MDD came from a study by Primidore.[25] Patients who were undergoing treatment with unilateral ECT were given eight sessions of rTMS in lieu of four (of six) sessions of ECT. The combination of ECT and rTMS did not diminish the extent of antidepressant efficacy and was associated with less cognitive morbidity than treatment with ECT alone.

A critical analysis of the benefits and risks of ECT versus rTMS is important to provide useful information for clinicians working with MDD patients. Such information would facilitate clinical decisions regarding whether therapeutic gains that result from either treatment are worthwhile or whether they are offset by associated negative cognitive side effects. In the current investigation a standard clinical application of ECT and a frequently used protocol for rTMS were compared with respect to mood and cognition. The balance between therapeutic efficacy and side effects was investigated with similar outcome measures and at similar points in time. In light of previous work it was expected that ECT would have greater antidepressant effects but that ECT would lead to more pronounced difficulties on tasks of working memory and long-term memory than would rTMS.

METHODS

Patients

Patients with major depressive disorder, referred to the ECT service or to the Laboratory of Magnetic Stimulation at Beth Israel Deaconess Medical Center (BIDMC), were offered participation in the study. There were two groups of patients with 14 patients in each. All patients met DSM-IV cri-

teria for MDD. Depression severity was measured with the 28-item Hamilton Rating Scale of Depression (HRSD).[26] Only patients with pretreatment HRSD scores of 18 or higher were included in the study. ECT patients varied with respect to psychotropic medications. Patients enrolled in the rTMS protocol underwent at least a 2-week washout of all psychotropic medications, and were thus medication-free at the time of initiation of treatment. Therefore, patients entered into the ECT protocol received ECT as an add-on to their medication regimen, while patients entered into the rTMS protocol had to withdraw medications. For both groups of patients exclusion criteria included psychosis, acute suicidality, other current Axis I diagnoses in DSM IV, known CNS pathology, pacemakers, electronic or metallic implants, severe cardiac pathology, personal or first-degree family history of a seizure disorder, and inability to give informed consent.

As seen in Table 1 there were no between-group differences with regard to age, education, baseline memory performance, and estimates of verbal IQ derived on the basis of the American New Adult Reading Test.[27] However, groups differed with respect to level of baseline depression. Before the initiation of treatment, patients in the rTMS group had an average HRSD score of 29, whereas ECT patients had an average score of 39 on the HRSD. However, differences in baseline depression severity were not associated with worse performance on measures of anterograde and retrograde memory; to the contrary, ECT patients performed slightly better than did the rTMS patients on most tasks of memory at baseline (Table 1).

Electroconvulsive Therapy Procedure

Electroconvulsive therapy was conducted approximately three times per week. The number of sessions varied according to clinical response (range 6–12). Patients included in this study had electrode placement in a right unilateral distribution. Dosage intensity was 2.5 times the patient's seizure threshold, and was determined during an initial titration procedure. Testing of ECT patients was conducted a minimum of 2 hours after ECT administration to minimize the effects of anesthesia and post-ECT confusion (range 2–4 hours). In all cases, memory testing was conducted only when it had been determined that the patient was alert and oriented. All patients were alert, and all were able to sustain focused vigilance at the time of testing.

Repetitive Transcranial Magnetic Stimulation Procedure

Repetitive transcranial magnetic stimulation was administered in daily sessions of 1600 stimuli in 20 trains of 8-second duration with 24-second inter-train intervals. Stimulation parameters were 10 Hertz at an intensity of 90% of the motor threshold. Motor thresh-

TABLE 1. Demographics and baseline assessments

	ECT Group X ± SD (N = 14)	rTMS Group X ± SD (N = 14)	*t*	*p*
Age	48.4 ± 12.0	51.2 ± 12.2	0.63	ns
Education	15.8 ± 3.0	17.1 ± 3.9	1.05	ns
AMNART Errors	19.7 ± 9.4	16.1 ± 7.7	1.11	ns
HRSD	38.07 ± 8.1	29.3 ± 4.9	3.54	0.001
RVLT Total	44.8 ± 11.4	43.2 ± 11.8	0.38	ns
Working memory	10.92 ± 2.5	10.43 ± 3.0	0.34	ns
TNET	63.8 ± 18.3	55.4 ± 20.1	1.13	ns

ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation; AMNART, American National Adult Reading Test; HRSD, Hamilton Rating Scale; RVLT, Rey Auditory Verbal Learning Test; TNET, Transient News Events Test; ns, not significant.

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old was defined following the guidelines of the International Federation of Clinical Neurophysiology.[28,29] These parameters are well within current safety guidelines.[30] A focal 70-mm double cone coil was centered over the left dorsolateral prefrontal cortex as defined in previous studies of rTMS in depression, based on distance from the motor cortex.[15,31] rTMS sessions occurred for a period of 2 weeks with five sessions per week.

Neuropsychologic Assessment Procedure

Patients were tested on three occasions. Baseline testing was conducted on the first day of treatment with ECT or rTMS. A second test session occurred at the end of the treatment course. For ECT patients, the end of treatment was determined according to clinical outcome and ranged from 2 to 4 weeks (6 to 12 sessions) after the first treatment session. End of treatment of the rTMS patients was fixed by the research protocol. Patients were tested after the 10-day trial of rTMS (a period of 2 weeks) without regard to their clinical response to treatment. A third test session occurred 2 weeks after the final (ECT or rTMS) treatment session. This third test session therefore took place 4 weeks after the first rTMS and on average, 4 to 6 weeks after the initial ECT. Testing was conducted by a research assistant who was blinded to experimental hypotheses but who was not blinded to treatment allocation.

Neuropsychological and psychiatric outcome measures were chosen to provide information regarding changes in mood and memory. Emotional well being was assessed with a 28-item Hamilton Depression Rating Scale (HRSD).[26] The examiner had been formally trained and rated for interrater reliability. Various components of memory were examined. Working memory was assessed with the Letter Number Sequencing subtest from the Wechsler Memory Scale-III (WMS-III).[32] The Letter Number Sequencing Task (LN) required the individual to sequentially organize a string of letters and numbers that were read in a random fashion. Scores on this task ranged from 0 to 30. Both patient groups performed in the average range on this test at baseline and there were no group differences (Table 1).

New learning was assessed with the original and alternate versions of the RAVLT (Rey Auditory Verbal Learning Test).[33] The cumulative number of 15 words learned over five trials (range 0–75) comprised the measure acquisition. Both groups demonstrated average acquisition abilities and there were no group differences with respect to performance on this test before initiation of treatment (Table 1). Retention was measured by free recall of list items after a 20-minute delay interval (range 0–15).

Retrograde memory was evaluated with a revised version of the Transient News Events Test.[34] This test was developed to examine memory for events that had been in the news for a limited period of time during the past 25 years. Items on this test were popular news events and people (e.g., Joseph Buttafucco, the Unabomber, and Louise Woodward) that had been reported in *The New York Times* an average of 60 times on a given year and that had fallen off in frequency in successive years. Details of the event or famous person were queried. There were a total of 25 questions, each of which was worth up to four points (range 0–100). Because only a limited number of TNET items were available, the same test was administered on all three sessions. There were no group differences with respect to performance on this test before initiation of treatment (Table 1).

Even though patients were not given the answers to TNET items it is possible that earlier exposure to test items (i.e., a practice effect) may have enhanced recall on repeat administrations. None of the other tests used in the study were sensitive to practice effects, though participation in the study might have had a generic effect on performance. In this instance, one might expect performance to be slightly enhanced across sessions as the participant became more familiar with the

examiner and more relaxed in the testing situation.

Statistical Analyses

Baseline group differences on the mood ratings and cognitive tasks were compared with unpaired *t* tests using SPSS. Treatment-related differences were analyzed with SPSS according to a 2 × 3 repeated measure analysis of variance. Between-subject factors were the two (ECT and rTMS) groups. The test sessions (baseline, end of treatment, and follow-up) were the within-subject factors. For all statistical analyses significance was set at $p < 0.05$.

RESULTS

Mood Ratings

Both groups demonstrated reduced depression over the course of treatment (Figure 1). ECT patients demonstrated a marked decline in severity of depression from baseline (HRSD mean = 39, SD = 7.25) to the end of treatment (HRSD mean = 15.3, SD = 11.7). At the time of the 2-week follow-up, ECT patients continued to show a significant reduction in depression (HRSD mean = 20.4, SD = 9.5). In contrast, rTMS patients showed only a modest effect with respect to severity of depression from time of baseline (HRSD mean = 29.33, SD = 4.90) to the end of treatment (HRSD mean = 25.6, SD = 7.7). This slight reduction in depression severity was also seen during the 2-week follow-up session (HRSD Mean = 24.8, SD = 9.5). None of the participants in the rTMS group demonstrated 50% reduction in depression severity on the HRSD. While the magnitude of the response of rTMS patients was slight, it is noteworthy that 80% of the group did show a mild reduction in depression.

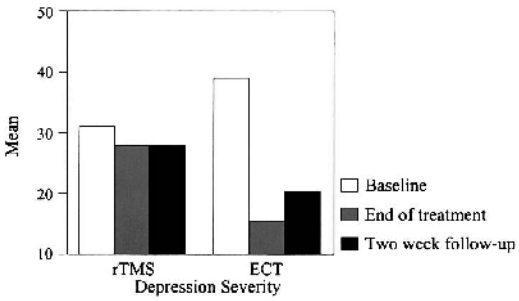

FIGURE 1. Severity of Depression: Mean score on the Hamilton Rating Scale of Depression.

Repeated measure ANOVA reveled the main effect of the treatment session ($F = 41.03$; $p < 0.01$). There were no significant differences between groups ($F = 0.43$; $p > 0.05$). However, there was a significant interaction between the treatment session and treatment group with respect to changes in levels of depression ($F = 21.4$; $p < 0.01$).

Working Memory

Letter Number Sequencing

Because of scheduling conflicts we could not administer the LN task to one patient from the ECT group. Hence, comparisons are based on 13 ECT and 14 rTMS patients. ECT and rTMS patients performed equally well on the LN task at baseline. ECT patients obtained a mean LN score of 10.92 (SD = 2.49) and rTMS patients obtained a mean LN score of 10.42 (SD = 3.00). There was evidence of mild decline on the LN task at the end of ECT (mean LN = 9.23, SD = 1.83) and improvement at the 2-week follow-up (mean LN = 11.15, SD = 1.46). ECT patients did not demonstrate a significant change in LN performance when baseline performance was compared directly with the 2-week follow-up results ($p > 0.05$). The rTMS patients demonstrated mild improvement on the LN task over all sessions (end of treatment mean LN = 10.71, SD = 3.83; 2-week follow-up mean LN = 11.14, SD = 3.08). Repeated measure ANOVA revealed a main-effect-of-treatment session on LN ($F = 3.09$; $p < 0.05$) but there was not a main-effect-of-treatment group ($F = 0.12$; $p > 0.05$). There was no significant interaction between treatment sessions and groups with respect to LN ($F = 2.11$; $p > 0.05$).

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New Learning

Acquisition

New learning was measured with a 15-item word list (RVLT). Acquisition was defined according to free recall of the 15 words repeated over five trials (range 0–75). As seen in Figure 2, patients demonstrated similar performances during baseline testing at which time ECT patients obtained a mean RVLT acquisition score of 43.78 (SD = 11.07) and rTMS patients obtained a mean acquisition score of 43.71 (SD = 12.09). ECT patients demonstrated reduced acquisition at the end of treatment (RVLT mean = 29.14 SD = 7.93) and improved acquisition at the 2-week follow-up session (RVLT mean = 46.92, SD = 10.80). The difference between baseline acquisition and performance on the acquisition task during the 2-week follow-up session was not significant ($p > 0.05$). In contrast, rTMS patients demonstrated relatively stable acquisition across test sessions (end of treatment RVLT mean = 43.00, SD = 10.09; 2-week follow-up RVLT = mean 44.07, SD = 10.43).

Repeated measure ANOVA revealed a main-effect-of-treatment session ($F = 9.69$; $p < 0.01$) but there was no main-effect-of-treatment group (1.36; $p > 0.05$) with respect to acquisition. The treatment session by treatment group interaction was significant ($F = 7.67$; $p < 0.01$).

Retention

Free recall of the RVLT 15-item word list after a 20-minute delay interval comprised the measure of retention. Groups did not differ with respect to baseline retention: ECT patients retained an average of 8.07 (SD = 4.49) words and rTMS patients retained an average of 9.76 (SD = 3.08) words. ECT patients displayed reduced retention at the end of treatment (mean retention = 2.14, SD = 1.99) and subsequent improvement at the 2-week follow-up (mean retention = 8.92, SD = 4.14). There was no significant difference for ECT patients when baseline performance was compared directly with the 2-week follow-up results ($p > 0.05$). rTMS patients demonstrated stable retention across test sessions (end of treatment mean retention = 8.23, SD = 2.80; 2-week follow-up mean retention = 8.31, SD = 4.07).

Repeated measure analyses revealed a significant effect-of-treatment session ($F = 9.76$; $p < 0.01$) and a significant effect-of-treatment group ($F = 5.31$; $p < 0.05$) on re-

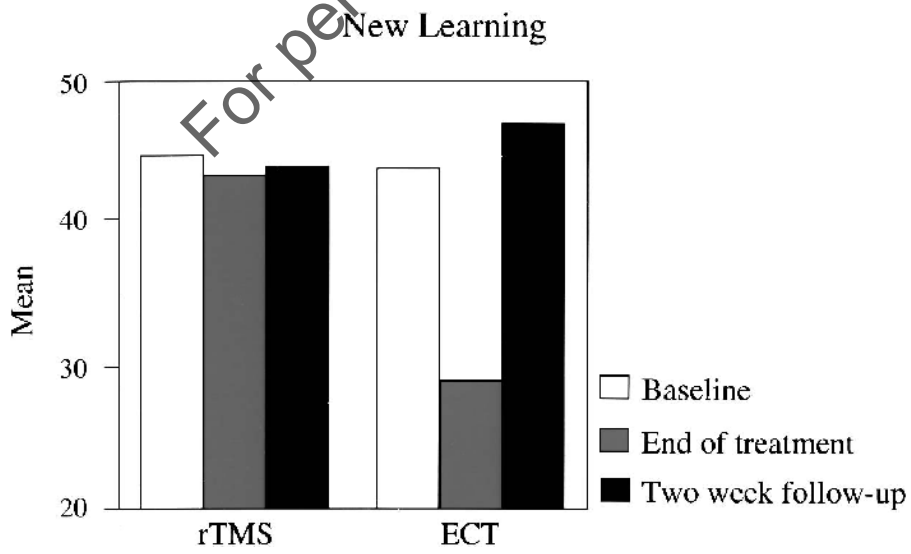

FIGURE 2. New Learning: Mean number of words recalled on the Rey Auditory Verbal Learning Test over five trials

tention. There was evidence of a significant interaction between treatment group and session (F = 7.41; $p < 0.01$).

Retrograde Memory

Recall of item information from the TNET comprised the measure of retrograde memory. Unlike the other tests of memory used in this study, the TNET is sensitive to practice effects; hence, improvement on repeat administrations may be caused by the direct effect of previous exposure to items. Because of scheduling conflicts, data from 10 ECT and 11 rTMS patients were available for analysis. As can be seen in Figure 3, groups did not differ with respect to baseline TNET performance (ECT mean TNET = 64.30, SD = 19.40; rTMS mean TNET = 55.63, SD = 18.12) but differences emerged over the course of treatment sessions. ECT patients displayed reduced TNET recall at the end of treatment (mean TNET = 39.10, SD = 13.21) and subsequent improvement at 2-week follow-up (mean TNET = 59.20, SD = 20.67). In contrast, rTMS patients demonstrated mild improvement across test sessions (end of treatment mean TNET = 57.81, SD = 18.33; 2-week follow-up mean TNET = 61.54, SD = 19.12).

Repeated measure analyses revealed a main-effect-of-treatment session (F = 11.94; $p < 0.01$) whereas there was not a significant main-effect-of-group (F = 0.30; $p > 0.05$). There was evidence of a significant interaction between treatment group and treatment session (F = 12.29; $p < 0.01$).

DISCUSSION

Findings from this investigation suggest that a standard clinical protocol of ECT exerted a more robust effect on depressive symptoms than did a research application of rTMS. ECT resulted in significant reduction in depressive symptoms and this effect was sustained 2 weeks after the end of treatment. By contrast, patients who underwent treatment with rTMS did not demonstrate the same degree of therapeutic response. While the majority (80%) of rTMS patients experienced some reduction of depressive symptoms, the magnitude of the therapeutic response was quite small, and none of the rTMS patients demonstrated 50% reduction in severity of depression. These findings are consistent with recent studies indicating that rTMS is associated with either modest or no antidepressant effects.[10,11] However, they differ from other studies emphasizing rTMS as a therapeutic alternative to ECT for treatment of MDD.[21–25]

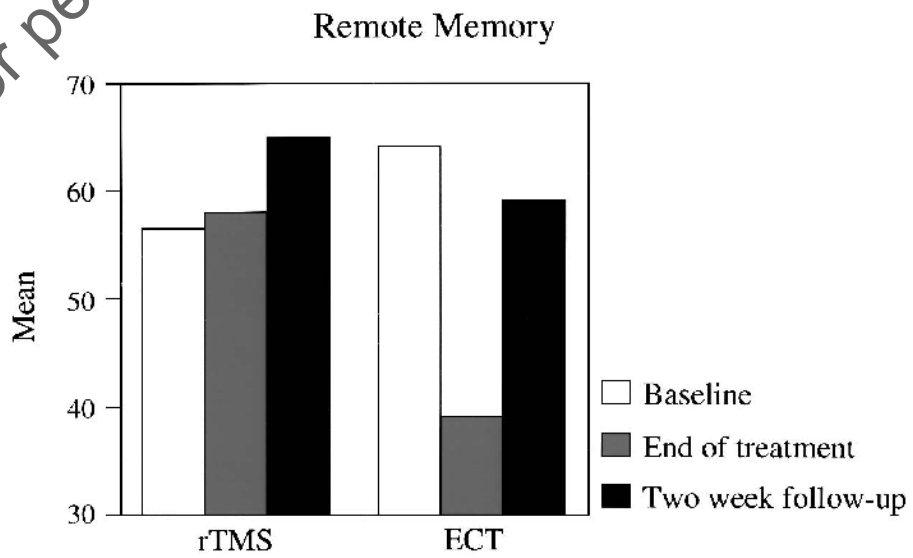

FIGURE 3. Remote Memory: Mean number of items recalled from the Transient News Events Test.

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It may be that differences between treatment protocols in the current investigation exerted inadvertent effects on the outcome of the study. In this investigation ECT was conducted in a clinical setting where therapeutic response was monitored by a psychiatrist. Treatment continued until some relief from depression was observed. In contrast, rTMS was conducted according to a previously established research protocol so that treatment was terminated after 10 days regardless of therapeutic response. It is likely that rTMS would have been more effective in alleviating the depressed mood of participants if treatment was carried out according to clinical outcome rather than according to protocol requirements. Of note, patients in previous studies emphasizing the beneficial effects of rTMS[23] received more treatment sessions than did those who participated in the current investigation.

A comparison of the cognitive side effects of ECT versus rTMS revealed that a clinical application of ECT was associated with transient negative side effects that were not seen in the aftermath of 10 sessions of rTMS. At the end of treatment patients in the ECT group demonstrated deficits on tests of working memory, acquisition, retention, and retrograde memory. However, it is important to note that substantial cognitive recovery occurred 2 weeks after treatment with ECT and that a direct comparison of baseline performance and end-of-treatment performance did not yield statistical differences with regard to performance on tasks of working memory and new learning. At the 2-week follow-up test session, ECT-induced memory problems had, for the most part, completely subsided even though the mood-enhancing benefit of ECT was still present. This pattern of transient cognitive deficit followed by recovery of cognitive abilities has been described in other ECT studies.

One aspect of memory remained defective in the wake of ECT. Two weeks after completion of the treatment course, ECT patients demonstrated a modest, but persistent, retrograde amnesia manifested by diminished recall of information from the TNET. This finding is particularly striking and stands out in marked distinction to the rTMS patients who demonstrated improved performance over the three test sessions on this test. Of note, a number of other investigators have shown that ECT may result in loss of information from retrograde memory.[6–9] It may well be that the ECT-induced seizure disrupts consolidation of recently acquired information before its secure representation in neocortical areas. Because the information is never firmly established in long-term memory, recovery is not seen at a later point in time. Similar problems with consolidation have been described in patients with temporal lobe epilepsy.[35,36] Further studies focused on the time parameters during which memories are refractory to ECT-induced retrograde amnesia would be worthwhile.

In the aftermath of treatment rTMS patients demonstrated mild improvement on tests of working memory and retrograde memory and relative stability on tests of verbal learning and retention. Hence, it can be concluded that rTMS does not adversely affect attention and memory, findings that are consistent with those of several safety studies.[30,31] The tasks chosen for the memory testing in this study are not considered sensitive to practice or learning effects. Nonetheless it may be the case that this mild improvement was because the participant became more familiar with the examiner and more relaxed in the testing situation.

Limitations of the Study

There are a number of drawbacks to this investigation that pose limitations on the findings. This study was conducted in a hospital setting with patients who were referred for either ECT or rTMS on the basis of clinical information available to their treating psychiatrist. The clinical nature of the study prohibited random assignment to either form of treatment. It may be that inherent differences between groups confounded some of the outcome measures. For instance, ECT patients were more severely depressed than

were rTMS patients at baseline. One might expect that an increased level of depression would exert a negative effect on cognitive performance. While this did not prove to be the case in this study, it is possible that other extraneous factors associated with the treatment group did affect outcome measures. For instance, it is likely that some ECT patients expect to suffer cognitive problems in the wake of treatment.[37] Consequently, it may be that the cognitive deficits observed at the end of ECT were in part influenced by patients' expectations. In addition, even though all ECT patients were alert and all were able to sustain focused vigilance at the time of testing, it is entirely possible that they encountered difficulties on more challenging cognitive tasks because of the residual effects of anesthesia and postictal confusion.

There were other clinical constraints that may have affected study findings and that ultimately limit the extent to which findings can be generalized. Efficacy data were obtained at the end of treatment of both groups rather than in accordance with a fixed time schedule. Future studies should compare these procedures according to a fixed time schedule as well as in relation to the end of treatment variable. Furthermore, differences in medication regimens may have played a role with regard to the differences in antidepressant efficacy of ECT and rTMS. Patients in the ECT group received ECT as an add-on to their stable medication regimen whereas patients in the rTMS group underwent a medication taper and wash-out and received rTMS without the adjunct of any other medications. However, it is unlikely that concurrent antidepressant medications would have been significantly more effective, as other recent trials of rTMS with concurrent medications have shown similarly discrete antidepressant efficacy.[38]

Perhaps the most obvious limitation of this study concerns the fact that ECT was carried out according to a standard clinical application whereas treatment with rTMS took place in the context of a research protocol. This difference might have influenced results in favor of ECT. This problem was unavoidable given the clinical setting in which the study took place. It should also be noted that previous studies demonstrating equal efficacy for ECT and rTMS used clinical outcome to determine the number of ECT treatments and a fixed schedule to determine the number of rTMS treatments. Alternately, in those investigations a lengthier course of rTMS was used.[21,23] If rTMS had been carried out over a longer time period with more treatment sessions the outcome of the study may have been quite different.

In conclusion, findings from the study indicate that a clinically monitored course of ECT is more effective for treating depression than a 2-week trial of rTMS, but that under these conditions, ECT was associated with *transient* negative effects on some components of memory and persistent effects on one task of retrograde amnesia. Despite limitations it should be noted that this study is among the few that have examined the relative benefits and risks of ECT and rTMS using tasks of emotional well being and cognitive performance.

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