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ORIGINAL RESEARCH

Response to deep TMS in depressive patients with previous electroconvulsive treatment

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Background
The efficacy of transcranial magnetic stimulation (TMS) in the treatment of major depression has already been shown. Novel TMS coils allowing stimulation of deeper brain regions have recently been developed and studied.

Objective
Our study is aimed at exploring the possible efficacy of deep TMS in patients with resistant depression, who previously underwent electroconvalsive therapy (ECT).

Methods
Using Brainsway's deep TMS H1 coil, six patients who previously underwent ECT, were treated with 120% power of the motor threshold at a frequency of 20 Hz. Patients underwent five sessions per week, up to 4 weeks. Before the study, patients were evaluated using the Hamilton depression rating scale (HDRS, 24 items), the Hamilton anxiety scale, and the Beck depression inventory and were again evaluated after 5, 10, 15, and 20 daily treatments. Response to treatment was considered a reduction in the HDRS of at least 50%, and remission was considered a reduction of the HDRS-24 below 10 points.

Results
Two of six patients responded to the treatment with deep TMS, including one who achieved full remission.

Conclusions
Our results suggest the possibility of a subpopulation of depressed patients who may benefit from deep TMS treatment, including patients who did not respond to ECT previously. However, the power of the study is small and similar larger samples are needed.

Keywords major depressive disorder; treatment resistant; ECT; deep TMS; rTMS

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Major depression is one of the most common psychiatric problems of the century. National household probability samples of diffuse populations in the United States, reached a lifetime prevalence of major depressive disorder (MDD) as high as 17.9%.[1] Previous systematic review and meta-analysis of second-generation antidepressants in the treatment of MDD demonstrated almost equal response rates for antidepressant and placebo (44.4% and 34.7%).[2] Moreover, up to 15% of depressed patients present a treatment-resistant pattern or refractory depression (TRD), which causes significant social and economic burdens.[3] Electroconvulsive therapy (ECT) proved to be effective as an acute treatment of major depressive episode[4,5] as well as in TRD,[6] with more than 50% of the patients achieving remission.[7] ECT has been declared one of the most effective acute treatments for severe depression.[8] ECT is suggested as a first-line acute treatment for life-threatening depression and a second-line treatment for patients with MDD who do not respond or partially respond to antidepressant drugs.[9] A meta-analysis that included 15 studies found ECT to be superior to pharmacotherapy in the acute treatment of major depression.[10] UK ECT Review Group found ECT to be an effective short-term treatment for depression, and probably more effective than drug therapy.[11]

Michael Faraday's principle that electric currents can be converted into magnetic fields is the basis of transcranial magnetic stimulation (TMS). In TMS, a bank of capacitors is rapidly discharged into an electric coil to produce a magnetic field pulse. When the coil is placed near the head, the magnetic field penetrates the brain and induces an electric field in the underlying region of the cerebral cortex. An electrical field of sufficient intensity will depolarize cortical neurons, generating action potentials.[12] As ECT, repetitive TMS (rTMS) has also been shown to be effective in the acute treatment of major depression.[13-16]

Reports comparing the acute efficacy of ECT and rTMS demonstrated mixed results: rTMS can be an effective option to ECT,[17] rTMS and ECT have comparable therapeutic effects,[15,18-20] rTMS is not as effective as ECT, and ECT was substantially more effective for the short-term treatment of depression.[21,22] ECT has been found to be an effective treatment for 40% of patients who failed to respond to rTMS (nondeep TMS) treatment.[23] A case report of the opposite has been described by Smesny et al.,[24] a patient with resistant major depression failed to respond to five series of ECT but responded to 4 weeks of daily treatments with rTMS.

rTMS applications have demonstrated a reproducible antidepressant effect in patients with refractory depression who initially showed a clinically significant benefit. The duration of effect varied among patients. The benefits were sustained for a mean of nearly 5 months.[25,26] Patients treated with rTMS have been shown to do as well as those treated with ECT at the 3- and 6-month follow-up points.[27,28]

Several studies have dealt with the safety of either rTMS or ECT or both. The review of more than 100 studies showed ECT to be a generally safe procedure, although some serious complications possibly related to ECT have been described. Unilateral ECT was safer than bilateral ECT in the short-term (after five treatments), but not in the longer run (after 3 weeks of treatment).[4]

Anterograde and retrograde amnesia appear early in the course of ECT and are cumulative, but with some recovery between treatments. A systematic review of five psychological and medical databases from the years 1980-2007 concluded that autobiographical memory impairment does occur as a result of ECT. Authors found that memory loss was relatively short term (<6 months posttreatment), whereas patients reporting amnesia was more persistent (>6 months post-ECT). ECT predominantly affects memory of prior events that were close to the time of treatment (within 6 months).[29]

Previous studies show that TMS treatment was well tolerated and relatively safe in humans.[30] TMS can induce seizures, but the occurrence of seizures has been rare. TMS has caused seven known cases of seizure since 1996.[30] Although the risk is low, prior history of one or more seizures is considered a relative contraindication for TMS administration.[31] Aggregate safety data obtained recently from a comprehensive clinical development program examining the use of TMS in the treatment of MDD administered to 325 patients (for some patients as long as 12 weeks of continuous daily TMS), showed TMS to be associated with a low incidence of adverse events that were mild to moderate in intensity and demonstrated a largely predictable time course of resolution.[32]

TMS treatment of depression has a theoretical risk of treatment-emergent mania or hypomania (TEM). A review of the literature published from 1966 through 2007 concluded that the rate of TEM was 0.84% for the TMS group and 0.73% for the sham group. The difference was not statistically significant. To date a total of 13 cases of TEM have been reported.[33-36]

A first onset of severe delusions after receiving 13 daily sessions of rTMS monotherapy for treating nonpsychotic major depression have been described. The psychotic symptoms remitted quickly with antipsychotic medication.[37] No other reports of induced delusions are known. In more than 10,000 cumulative treatment sessions, there were no deaths or seizures. Most adverse events were mild to moderate in intensity. Transient headaches and scalp discomfort were the most common adverse events. Auditory threshold and cognitive function did not change. There was a low discontinuation rate (4.5%) because of adverse events during acute treatment.[32] As stated previously, ECT, though rarely, involves some potential serious adverse events, whereas no such documentation exists regarding TMS. In a comparative study, 30 patients with treatment-refractory nonpsychotic major depression received an average of 10 treatments with either unilateral ECT or left prefrontal rTMS and were assessed for objective and subjective cognitive impairments before and about a week after treatment. In patients treated with rTMS, cognitive performance remained

constant or improved, and memory complaints decreased, whereas in the ECT group memory recall deficits emerged and memory complaints remained.[38] A battery of neurocognitive tests relevant to attention, working memory-executive function, objective memory, and motor speed administered to 15 subjects with treatment-resistant major depression before and after a course of rTMS disclosed no worsening of performance on any of the cognitive domains over the baseline-post-rTMS period. On the contrary, evidence of modest but statistically significant improvement in performance was noted in working memory-executive function, objective memory, and fine motor speed domains over the rTMS treatment period.[39] O'Connor et al.[40] conducted a comparative neurocognitive risk-benefit analysis in 28 patients. ECT was associated with transient negative cognitive side effects, most of which dissipate in the days after treatment, whereas deficits of this sort were not apparent after treatment with a 2-week course of rTMS.[40]

Deep TMS is currently being evaluated as a treatment option in major depression and has been shown to be a safe procedure.[41-43] Deep TMS coils are designed to maximize the electrical field deep in the brain by the summation of separate fields projected into the skull from several points around its periphery, while minimizing the accumulation of electrical charge on the surface of the brain. Such accumulation can give rise to an electrostatic field that might reduce the magnitude of the induced electric field both at the surface and inside, thus reducing the depth penetration of the induced electric field.[24] Deep TMS could be more effective than rTMS because of its deeper penetration into brain tissues: The motor cortex could be activated by the H coil at a distance of 5.5 cm compared with 2 cm with the figure-of-eight coil.[41] The deeper penetration should produce greater action on nerve fibers connecting the prefrontal cortex to the limbic system.

With regard to cognitive side effects in deep TMS, in a randomized controlled study of deep TMS conducted in Israel, 32 healthy volunteers (nine of which were tested for the H1 coil presented in this report) were evaluated for possible cognitive impairment. Cognitive evaluation was conducted using the Cambridge Neuropsychological Test Automated Battery (CANTAB), which is sensitive to cognitive changes caused by a wide range of central nervous system disorders and medication side effects. No deterioration in cognitive functions was found, except for a transient short-term effect of the H1 coil on spatial recognition memory on the first day of rTMS (but not in the following treatment days). Questionnaires conducted for emotional or mood alterations showed no significant changes except for reports on "detachment" experienced by subjects treated with the H1 coil. In addition, stimulation with the novel H coils was found to be well tolerated, with no adverse physical or neurologic outcomes.[42]

Contraindications to deep TMS are essentially the same as those for rTMS. Absolute contraindications include history of any metal object in the head, known history of any metallic particles in the eye, implanted cardiac pacemaker or any intracardiac lines, implanted neurostimulators, surgical clips or any medical pumps, history of cochlear implants, and a history of seizure or heat convulsion. Relative contraindications include epilepsy or seizure in first-degree relatives; history of head injury; frequent or severe headaches, migraines; hearing loss; drug abuse or alcoholism, pregnancy, or not using a reliable method of birth control; and systemic and metabolic disorders.

The aim of this study was to show that patients with major depression and ECT failure may respond to deep TMS.

Materials and methods

Our study was approved by the institutional review board of Beer-Yaacov Mental health institution and the national medical devices review board in Israel. Outpatients were recruited by psychiatrists working in Beer-Yaacov's facilities. One patient, a German citizen, coming to know of the study through National Institute of Health clinical trail domain, applied independently.

Deep TMS is currently being evaluated as a treatment option in major depression, and has been shown to be a safe procedure.[41,42] The innovative design of Brainsway H coils (Har Hotzvim, Israel) is intended to generate sufficient magnetic field strength to stimulate neurons deep inside the brain mass without posing a hazard.[42] This forms the basis of the Brainsway H coils used in their deep rTMS device. The coils are designed to maximize the electrical field deep in the brain by the summation of separate fields projected into the skull from several points around its periphery. The device also minimizes the accumulation of electrical charge on the surface of the brain, which can give rise to an electrostatic field that might reduce the magnitude of the induced electric field both at the surface and inside, and reduce the depth penetration of the induced electric field.[44] The unique shape of the device's base includes wire coils containing several wire strips, set tangentially to the surface of the scalp. Each set of strips is connected in series and contains current flowing in the same direction, therefore generating a field that extends into the brain in a specified orientation from each location along the scalp. Computerized theoretical calculations were made to optimize the coil design for maximizing the percentage of stimulation in depth relative to the cortical regions. These, in conjunction with tests performed in a phantom model,[44,45] demonstrated the ability to stimulate, by means of the H coil, the deep brain regions. When given in 120% of motor threshold (MT) the magnetic field intensity using an H1 coil measured in the frontal zone reaches MT intensity in depth of 4.5 cm. In contrast, using the figure-of-eight coil given in 120% of MT a magnetic field intensity measured in the frontal zone reaches MT intensity in depth of 1.5 cm.[45]

According to calculations, if given in 120% of MT, H1 magnetic field is both deeper and both more "frontal" (that is reaches more frontal zones of the frontal lobe) than the figure-of-eight coil.[45]

It may be assumed then that the activation of deep brain regions and their interconnecting fibers may serve as a new approach in treating neuropsychiatry illnesses with prominent advantage over the standard coil, unable to affect regions as deep as the H coil. Deep TMS could be more effective than rTMS because of its deeper penetration into brain tissues.[41] The deeper penetration should produce greater action on nerve fibers connecting the prefrontal cortex to the limbic system.

We used the Brainsway H1 coil to create the magnetic field. We connected the windings to a Magstim cable and a connector which we than connected to a Magstim Rapid 2 stimulator (Magstim, Whitland, Wales, UK). The most effective electric field produced by the H1 coil is oriented in an anterior-posterior axis, with hemispheric preference for the left hemisphere.

The first step in the treatment procedure was to locate the "hot-spot" on the patient's scalp, for example, the exact point in which a minimum magnetic field will cause a motor response in the form of twitching of the contra lateral finger muscles in the hand. As the H1 coil preferentially stimulates the left motor cortex, the muscles of the right hand twitches. After locating the "hot-spot," we advance the coil 5 cm in a line parallel to the sagittal suture of the skull.[42] The coil stimulates both the left and the right dorsolateral prefrontal cortex, but produces greater stimulation of the left.[41,43-45] Patients were treated with 120% power of the MT at a frequency of 20 Hz. Each train of pulses included 40 pulses within 2 seconds. The intertrain interval was 20 seconds. Forty-two such trains of pulses were given in a total of 1680 pulses per treatment session.

Patients signed an informed consent form that was approved by the Ministry of Health and the local ethics committee. They then completed a psychiatric interview and SCID (version 2/2000). Patients were also evaluated with the Hamilton Depression Rating Scale (24 items) (HDRS), the Hamilton Anxiety Rating Scale (HARS), and the Beck Depression Inventory (BDI) at baseline. Participants were evaluated with the aforementioned scales after 5, 10, 15, and 20 daily treatments. We considered treatment response to be a reduction in HDRS of at least 50%, and remission to be a reduction of the score below 10 points.

Subjects

We enrolled six patients with treatment-resistant major depression according to DSM-IV-TR criteria. All patients were drug resistant and had undergone treatment with at least two antidepressant courses adequate in both dosage and duration. Also, patients were defined as ECT nonresponders, according to their psychiatrists' evaluations. Five of them had undergone one course of ECT and the sixth had undergone two different courses. Before and during study enrollment, three patients were treated with antidepressants (one with mianserin, one with venlafaxine and mirtazapine, and one with trazodone) and three patients were antidepressant free, one of them using only zopiclone. During the study, no pharmacological changes were made (Tables 1 and 2).

Clinical evaluation and results

Average HDRS of our six subjects was 31 (mean = 31 ± 3.8), average HARS was 25 (mean = 25 ± 8.9), and average BDI was 34 (mean = 34 ± 7) before the treatment. After five treatments, average HDRS dropped to 24 (mean = 24 ± 8.4), average HARS dropped to 18 (mean = 18 ± 7.3), and average BDI dropped to 28 (mean = 28 ± 11.3).

After 10 treatments average HDRS dropped to 17 (mean = 17 ± 7, repeated measures ANOVA $P = .003$, F value = 10.6, Lambda = 21.33), average HARS dropped to 14 (mean = 13.7 ± 7, repeated measures ANOVA $P = .0001$, F value = 24.873, Lambda = 49.745), and average BDI was 31 (mean = 31 ± 9.34, repeated measures ANOVA $P = .4234$, F value = 0.938, Lambda = 1.876). All patients completed 10 treatments. Two patients dropped out after the tenth session: one patient, a non-Israeli citizen, decided to go back to his homeland claiming he did not improve enough; another patient disclosed suicidal thoughts and therefore we decided to refer her back to her psychiatrist. Altogether, four patients completed 15 treatments with an average HDRS of 19.8 (mean = 16.833 ± 10, repeated measures ANOVA $P = .001$, F value = 9.36, Lambda = 28, paired t test = 0.017),

Table 1 Patient demographics

Patients	Age (y)	Sex	Years of education	Age MDD onset	Current episode (y)	No. of lifetime episodes	No. of past ECT courses	Past psychotherapy/ cognitive therapy	Family history MDD
1	23	Male	12	20	4	2	1	Yes	No
2	28	Female	15	8	1	2	2	Yes	No
3	41	Female	15	14	1	4	1	Yes	No
4	39	Male	Religious, not assessed	9	1	3	1	Yes	No
5	59	Female	15	14	2	3	1	Yes	No
6	55	Female	16	37	0.5	>10	1	No	Yes

Table 2 Type of ECT and number of courses

Patients	Type of ECT and no. of courses	Total no. of courses
1	13 unilateral courses	13
2	Patient started 8 unilateral courses switching to 17 bilateral courses, altogether 25 courses	25
3	12 courses of unilateral in a first ECT treatment, followed by a second treatment of additional 12 unilateral courses, altogether 24 courses	24
4	Patient started 4 unilateral courses switching to 8 bilateral courses, altogether 12 courses	12
5	8 unilateral courses	8
6	12 unilateral courses	12

average HARS of 17 (mean = 14.3 ± 8, repeated measures ANOVA $P \leq .0001$, F value = 25.26, Lambda = 75.8, paired *t* test = 0.001), and average BDI of 30 (mean = 29.5 ± 10.2, repeated measures ANOVA $P = .4758$, F value = 0.875, Lambda = 2.626, paired *t* test = 0.115). After 15 sessions, two patients dropped out because of unsatisfactory response to treatment, after consulting with their treating psychiatrists. Two patients (Table 3) completed 20 sessions with further improvement: one attained remission and the second attained response.

Side effects

One patient reported three side effects: a foul smell appearing after five sessions that disappeared after the 19th treatment, a bad taste appeared after 15 sessions that also disappeared after the 19th treatment. A repulsive smell sensation caused by specific materials (e.g., perfumes or plastics) started after the 19th treatment and continued for 40 days after treatment cessation. The sensation of bad taste disappeared during treatment. There were no other side effects or serious adverse events (Figure 1).

Table 3 Ratings of HDRS, HARS, and BDI before and after treatments

Patients	Before study	After 5 treatments	After 10 treatments	After 15 treatments	After 20 treatments
1					
HDRS	26	12	12		
HARS	21	12	11		
BDI	25	29	22		
2					
HDRS	31	20	22	17	15
HARS	16	15	7	11	5
BDI	38	11	38	33	21
3					
HDRS	34	30	10		
HARS	24	12	7		
BDI	38	35	35		
4					
HDRS	31	19	12	7	7
HARS	22	17	16	14	11
BDI	25	18	18	15	14
5					
HDRS	35	35	28	35	
HARS	42	31	28	30	
BDI	39	37	42	44	
6					
HDRS	26	28	18	20	
HARS	25	22	13	13	
BDI	39	40	31	28	

Discussion

Our results demonstrated an improvement with deep TMS in ECT nonresponder patients. A comparison of the acute efficacy of ECT and rTMS is difficult to conduct simply because ECT can be applied in different ways and in different number of sessions. The same is true of rTMS: the frequency, intensity, or number of pulses per session differ between rTMS studies of depression. Beyond that, no large study comparing a specific method of ECT (e.g., bifrontal) to a specific method of rTMS (e.g., high frequency to DLPFC) has been performed yet. What is clear, and is also strengthened by this study, is that patients who have major depression are divided into subpopulations: those who will respond better to ECT and those who will respond better to rTMS or deep TMS. To date, there are no clues as to the preferred treatment for a specific patient. Regarding safety, generally speaking, accumulated data suggest rTMS to be safer than ECT though ECT in itself is a safe procedure. Cognitive sequel of treatment is more likely to appear after ECT treatment than after rTMS treatment.

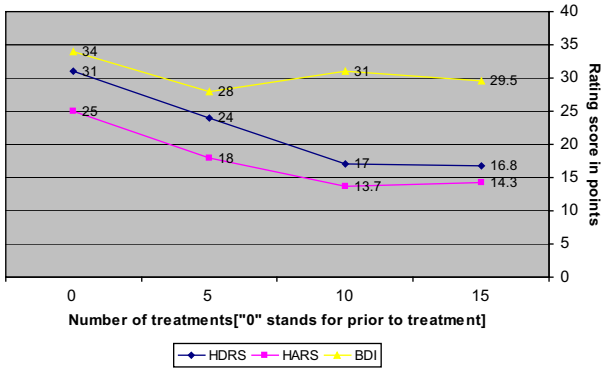

Figure 1 HDRS, HARS, BDT average scores at the different time points: prior to treatment and after 5, 10 and 15 sessions.

Our study suggests that some patients who failed to respond to ECT may respond to deep TMS. Deep TMS cannot be stated to be advantageous to ECT in its side effects because patients with major depression have not been studied for cognitive sequel after deep TMS treatment. Deep TMS cognitive side effects have been evaluated in healthy volunteers[22] and in depressive patients (oral communication, Dr. Abraham Zangen, June 2009).

Conclusions

A subpopulation of major depressive patients, resistant to treatment with ECT, may benefit from deep TMS. The cognitive sequel of deep TMS in depressed patients remains to be elucidated. Patients participating in this study did not complain of memory loss or other cognitive side effects. Questions regarding cognitive side effects were presented during evaluations, but no cognitive battery was used in this specific patient group.

The major limitation of this study is the lack of proper and quantified measurement of depressive parameters before and after ECT treatments. The treating psychiatrist from the community clinics reported ECT attempts to be unsuccessful, but patients underwent no HDRS evaluation as performed in this study; therefore, they may have improved to a certain extent, an improvement that may have gone unnoticed. The evaluations and treatments performed in this study were all performed by psychiatrists who were involved in the different phases of TMS treatment. The power of the study is small.

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