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ORIGINAL INVESTIGATION

H-coil repetitive transcranial magnetic stimulation for the treatment of bipolar depression: an add-on, safety and feasibility study

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Abstract

Objectives. The H1-Coil is a novel transcranial magnetic stimulation (TMS) device capable of inducing a magnetic field with a deeper and wider distribution than standard coils. This pilot study evaluated the safety and feasibility of the H1-Coil as adjuvant treatment for bipolar depression (BPD). *Methods.* Nineteen patients diagnosed as having BPD and under treatment with psychotropic medication were enrolled in the study. They received daily prefrontal repetitive TMS (rTMS: 20 Hz, 2 s on, 20 s off, totaling 1680 stimuli) every weekday for four consecutive weeks. The primary outcome measure was the change from baseline in the Hamilton Depression Rating Scale (HDRS-24) score a week after the last treatment session. *Results.* A significant mean decrease of 12.9 points in the HDRS-24 scale ($P < 0.001$) was found. Response rate was 63.2% and remission rate was 52.6%. Treatment was well tolerated in terms of headache and overall discomfort, and there were no significant change in cognitive functioning or mood switches. One patient had a short induced generalized seizure without complications. *Conclusions.* An add-on H-coil rTMS treatment protocol in BPD subjects indicated improvement in bipolar depression symptoms. Sham-control studies to further determine the efficacy and safety of the H-Coil for BPD are warranted.

Key words: *Bipolar depression, transcranial magnetic stimulation, cognitive function, affective disorder*

Introduction

Depressive symptoms are dominant in approximately one-third of the time during the course of bipolar disorder (BPD) and are the major cause of disability and impairment (Judd et al. 2002). The treatment for BPD consists mainly of mood stabilizers. The role of antidepressants during the depressive phase of the illness has not been fully established. A recent large effectiveness study (STEP-BD) found no superiority of adjunct antidepressants to a mood stabilizer in the treatment of BPD, leaving clinicians with limited tools for dealing with this long-lasting, disabling phase of the illness (Sachs et al. 2007).

Advances in brain stimulation techniques have raised new hopes for BPD treatment. Repetitive transcranial magnetic stimulation (rTMS) has proven effective, and was recently given FDA approval as a treatment for unipolar depression (Holtzheimer et al. 2001, McNamara et al. 2001, Burt et al. 2002, Kozel and George 2002, Aarre et al. 2003, Martin et al. 2003, Couturier 2005, O'Reardon et al. 2007). Surprisingly, very few rTMS studies and case reports have been conducted with patients who suffer from bipolar depression. Two small randomized controlled trials (RCTs; Dolberg et al. 2002, Nahas et al. 2003,) and one open study (Dell'Osso et al. 2009) have tested the efficacy of rTMS in BPD, as have a few case studies (Erfurth et al. 2000, Tharayil et al. 2005, Tamas et al. 2007). The first RCT (Nahas et al. 2003) was a 2-week study on 23 subjects assigned to either sham treatment or rTMS (left prefrontal stimulation at 5Hz, 110% motor threshold for 8 s, with an off period of 22 s, and a 20-min session duration). The rTMS treatment was an adjunct to the mood

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stabilizers valproic acid or carbamazepine. There was no significant decrease in the primary outcome measure which was the change from baseline in the Hamilton Depression Rating Scale (HDRS) scores (Nahas et al. 2003). In comparison to the sham condition, however, the results of the treatment arm indicated a trend towards an improvement in mood-related symptoms. The other double-blind, randomized, sham-controlled study (Dolberg et al. 2002) enrolled 20 bipolar depressed patients randomized to receive 20 treatment days of rTMS (10 patients) or 10 treatment days of sham followed by 20 treatment days of active rTMS (10 patients). The results of that study demonstrated significant improvement in depression rating scales after the 10 treatment days (2 weeks) of active rTMS compared to sham. This difference disappeared when the two groups went on to receive 2 more weeks of active treatment (4 weeks of active treatment vs. 2 weeks of sham + 2 weeks of active treatment). A recent open-label study (Dell'Osso et al. 2009) tested the efficacy of low frequency, navigation-guided rTMS treatment (3 weeks of 1 Hz, 110% MT, 300 stimuli/day to the right dorsolateral prefrontal cortex) as a supplement to mood stabilizers in 11 subjects with type I or type II bipolar depression who did not respond to previous pharmacological treatment. Six of the subjects (54.5%) had decreased HDRS-21 scores of >50% (defined as response) and four subjects (36.3%) had an HDRS score <8 (defined as remission) on the last treatment day.

One hypothesis explaining the moderate clinical effects of rTMS in depression could be the limited depth of direct stimulation by standard rTMS coils. In comparison, the H1-Coil induces a magnetic field with larger distribution and depth than the standard TMS coils, without a significant increase in the intensity of the electric field induced in superficial cortical regions (Roth et al. 2002, Zangen et al. 2005). Phantom brain (a spherical homogeneous volume conductor) measurements have shown that when using 120% of the average motor thresholds of the study subjects, the H-coil can reach an effective field at a depth of 3 cm beneath the surface, while the standard figure-8 coil can reach a depth of less than 1 cm (Roth et al. 2007). In two studies using the H-coil: a safety study in healthy volunteers (Levkovitz et al. 2007) and a safety and feasibility study in major depression (Levkovitz et al. 2009), the stimulation was well tolerated and an improvement in depressive symptoms was found. No cognitive deterioration or other serious adverse effects were evident.

The purpose of the current study was to explore the safety and feasibility of H1-Coil rTMS as an adjuvant treatment to mood stabilizers and antidepressants for BPD.

Methods

Subjects

Patients diagnosed as having BPD (type I or II) and currently experiencing an episode of depression according to DSM IV criteria were recruited for this study. Other inclusion criteria were age between 18 and 65 years, an HDRS (17 items) score of >18, a stable mood stabilizer regimen for at least 2 weeks before study entry and a stable regimen of antidepressants, if taken, for at least 4 weeks prior to study entry (for a full list of medications see Table I). The following were considered to be mood stabilizers: valproate, lithium, carbamazepine, lamotrigine, olanzapine, quetiapine and risperidone. A therapeutic level was necessary for valproate, lithium and carbamazepine (50–120 μg/ml, 0.6–1.2 mmol/l, and 4–12 μg/ml, respectively) taken during the 2 weeks before enrollment. Exclusion criteria were any other Axis I disorder, any known risk factor for seizures, a mood cycle of less than 4 weeks, psychotic features in the current episode of depression, substance abuse during the past year, and a high suicide risk based on clinical assessment or a suicide attempt during the past year.

The study was approved by the local and national review board (IRB) committees, and was conducted at the Shalvata Mental Health Center, associated with the Sackler Faculty of Medicine at Tel-Aviv University, Israel. The mental health center accepts referrals from a pre-determined catchment area.

Twenty apparently healthy volunteers were enrolled to serve as a control group for the cognitive assessment and did not receive any rTMS treatment. They were recruited by advertisements posted around the mental health center. They had no Axis I psychiatric disorder, as assessed by an interview for mental health history. They were not reimbursed and were free to withdraw at any time without prejudice. The Beck Depression Inventory II (BDI-II) scores (highest BDI-II score of 8) ruled out the presence of depression among the controls. They were matched in age and education level to the depressed patients.

All study participants signed an informed consent form prior to their inclusion in the study.

Study design

The screening procedure included a structured clinical interview by a trained senior psychiatrist clinician (YL or EVH) in order to determine suitability according to the inclusion and exclusion criteria. During the active treatment phase, daily rTMS sessions were scheduled in a 5-day sequence for four consecutive weeks. A total of 20 sessions were conducted (Visits 1–20). A follow-up assessment was

Table I. Demographic data, disease history and medication taken during the study of the bipolar depressed subjects (n = 19).

	Age	Education (years)	Gender (M/F) 1 = male 2 = female	Duration of current episode (months)	Number of anti depressants in current episode	Duration of current treatment	Age of first episode (years)	Past depressive episodes (no.)	Past psychiatric hospitalizations (no.)	Medications
A234	34	15	1	30	5	12	31	1	0	Divalproate (800 mg) Lamotrigine (75 mg)
B236	56	12	1	14	1	6	36	5	2	Paroxetine (60 mg) Lamotrigine (75 mg) Carbamazepine (400 mg) Olanzepine (5 mg)
C230	26	14	2	11	3	2	22	3	0	Duloxetine (60 mg) Lamotrigine (250 mg) Escitalopram (10 mg) Mirtazapine (15 mg)
C233	38	15	2	16	1	10	19	10	0	Bupropion (450 mg) Fluoxetine (20 mg) Lamotrigine (100 mg)
C237	39	15	2	6	1	7	32	2	2	Lamotrigine (200 mg) Venlafaxine (300 mg)
D235	47	15	2	2.5	0	0	20	5	3	None
D240	58	15	2	3	0	12	30	10	12	Carbamazepine (800 mg) Quetiapine (700 mg) Zopiclone (7.5 mg) Biperiden (2 mg)
D249	56	12	2	2		2	31	6	0	Milnacipran (50 mg) Duloxetine (60 mg) Olanzapine (5 mg)
D430	52	14	2	18	2	3	23	10	0	None
E241	31	9	1	12	1	12	14	15	3	Divalproate (800 mg) Citalopram (20 mg) Risperidone (1 mg)
E245	30	10	1						3	Lamotrigine (100 mg) Paroxetine (20 mg) Risperidone (1 mg)
F238	59	15	1	11	2	10	20	15	0	Olanzapine (5 mg) Trazodone (300 mg) Desipramine (125 mg) Lamotrigine (100 mg)

(Continued)

Table I. *(Continued)*.

	Age	Education (years)	Gender (M/F) 1 = male 2 = female	Duration of current episode (months)	Number of anti depressants in current episode	Duration of current treatment	Age of first episode (years)	Past depressive episodes (no.)	Past psychiatric hospitalizations (no.)	Medications
F239	63	16	1	18	1	3	23	10	0	Escitalopram (10 mg) Oxacarbamazepine (900 mg) Tofranil (500 mg) Alprazolam (1.5 mg)
G231	40	15	2		0					Carbamazepine (400 mg) Venlafaxine (150 mg) Risperdone (2 mg) Lorazepam (3 mg)
H232	53	12	2		1	9	48	2	3	Lamotrigine (300 mg) Mianserin (120 mg) Olanzepine (10 mg) Clonazepam (1.5 mg)
D242	55	12	2	26	0	2	38	5	2	Risperidone (2 mg) Clonazepam (1.5 mg)
H244	48	16	2	2	2	2	24	20	0	Lithium (900 mg) Clonazepam (0.5 mg)
B245	47	16	1	13	5	11	21	10	0	Fluoxetine (50 mg) Lithium (900 mg)
B246	54	12	1	2	0	5	27	50	30	Lamotrigine (200 mg) Clonazepam (1 mg)
Mean ± SD	45.47 ± 11.61	13.68 ± 1.63	8\11	11.28 ± 8.48	1.41 ± 1.58	6.53 ± 4.19	27.29 ± 8.39	9.94 ± 11.72	3.33 ± 7.24	

conducted 1 week after the last active treatment (Visit 21) and was defined as the primary efficacy time point.

Clinical assessments for efficacy were performed at baseline and Visits 4, 10, 15, 20, and 21. The primary efficacy outcome measure was defined as any change in the Hamilton Depression Rating Scale (HDRS-24) from baseline (Visit 1) to the primary efficacy time point at the follow-up visit 1 week after end of treatment (Visit 21). Secondary outcome measures were: the response rate defined as a 50% decrease in the HDRS-24 from baseline to the final follow-up visit, remission rates defined as HDRS-24 scores of <10 on the final follow-up visit, changes in the Hamilton Anxiety Rating Scale (HAM-A), changes in the CGI-Severity (CGI-S) and CGI-Improvement (CGI-I) questionnaires and changes in the self-report BDI-II, and the Pittsburgh Sleep Quality Index (PSQI).

Safety was assessed during the study by means of a variety of measures. Following the completion of each treatment session, the scalp was inspected for possible skin lesions. The subjects were also asked to rate their current headache intensity on a self-graded questionnaire by marking an "X" on a 10-cm visual analogue scale (VAS, 1-10) within 5 min after the rTMS session. A medical assessment was conducted by a psychiatrist at visits 1, 4, 10, 15, and 20, in which the subjects were asked to report any physical changes related to rTMS treatment. Blood pressure and pulse rates were measured, and the Young Mania Rating Scale (YMRS) was used as a safety measure for evaluating the risk of mood switch at the same visits. Another safety measure was a battery of cognitive tests (the Cambridge Neuropsychological Test Automated Battery, CANTAB), administered at baseline, Visit 11 and at the final follow-up visit. The CANTAB tasks were divided into four domains: psychomotor speed (reaction time), visuospatial memory (paired associative learning), sustained attention (rapid visual information processing), and frontal lobe-related/executive functions (Stockings of Cambridge [SOC] and Spatial Working Memory [SWM]).

Study device

The H1-Coil rTMS sessions were conducted using a Magstim Super Rapid stimulator (Magstim, UK) with the novel H1-Coil, which is an extracorporeal device positioned on the patient's scalp prior to stimulation. The optimal spot on the scalp for stimulation of the right abductor pollicis brevis muscle was located, and the motor threshold (MT) was established by delivering single stimulations to the motor cortex. The MT was measured by gradually increasing the stimulation intensity (using single pulse mode, applying one pulse every 5 s, i.e. 0.2 Hz) and recording electrical activity in the abductor pollicis brevis using surface electrodes. MT was defined as the lowest intensity of stimulation able to produce motor-evoked potentials of at least 50 μV in five out of 10 trials. The coil was then placed 5.5 cm anterior to the motor spot (i.e. the prefrontal cortex), and spatial coordinates were recorded with markings on a cap placed on the subject's head to ensure placement reproducibility. The MT was determined each time, and all pulses were delivered by an expert physician in trains of 20 Hz at 120% of the measured MT. Each rTMS session consisted of 42 trains with a 2-s duration for each, and a 20-s inter-train interval (a total of 1680 magnetic pulses delivered per session).

Statistical analysis

The demographic data are presented in a tabular format. The means and standard deviations (SD) of continuous variables and a count and percentage of categorical variables were compiled. Baseline values of the BPD subjects and the controls were compared by *t*-tests, chi-square tests, or Fisher's exact test, depending on the type of data. Paired *t*-test was used to compare the clinical rating scale data at the screening and baseline visits. The slope of change in clinical rating scales over 5 weeks (from baseline until Visit 21) was estimated from repeated measures analysis of variance models (SAS Proc MIXED). The change from baseline value was modeled as a function of the time in weeks for each rating scale.

Eight factors (age, gender, number of past depressive episodes, number of past psychiatric hospitalizations, motor threshold at baseline, number of manic episodes, duration of the current episode, and number of antidepressants used in the current episode) were tested for prognostic characteristics. Each of them was included separately in the repeated measures analysis models. A repeated measure analysis of variance model (SAS Proc MIXED) was developed for each of the CANTAB tests. The change from baseline to each visit was modeled as a function of the subject category (i.e. control or BPD patient), baseline value, number of visit, and subject's clinical status by visit interaction. The adjusted means of the various tests between the subjects category were compared (LSMEANS command with PDIFF option) at each visit. A P value of ≤ 0.05 was considered significant. No adjustment for multiple testing was carried out. All analyses were performed using SAS version 9.1 or higher. The database was locked on 22 March 2009.

Results

Thirty-one subjects were screened for this study. Nineteen BPD patients met the inclusion/exclusion

criteria. Demographic data, medical history and a list of medications taken during the study are presented in Table I. Two subjects were excluded from the study after 4 and 17 treatment days due to noncompliance with the study protocol. The two patients did not complain of any physical side effects. A significant decrease of 12.9 points in HDRS-24 score (the primary efficacy outcome measure) was evident at the follow-up visit (the primary efficacy time point) (Figure 1; $P < 0.001$). The response rate at the follow-up visit was 63.2% (12/19) and the remission rate was 52.6% (10/19). The data of the two subjects who had been excluded prior to visit 21 were included. There was a significant change from baseline throughout the study protocol for the CGI-S ($P < 0.0001$) and HAM-A ($P = 0.0052$) scores, but not for the BDI-II ($P = 0.1374$) and PSQI ($P = 0.3613$; Table II) values.

We looked for correlations between eight factors (age, gender, number of past depressive episodes, number of past psychiatric hospitalizations, number of past manic episodes, duration of the current episode, and number of antidepressants used during the current episode) and the clinical outcome measures in order to detect possible prognostic characteristics. The number of past depressive episodes and the number of antidepressants used during the current episode were negatively correlated with improvement as assessed by the CGI [$F(1,16) = 4.85$; $P = 0.0449$, $F(1,16) = 13.83$, $P = 0.0023$]. There were no significant correlations for the other tested parameters. In an attempt to identify a correlation between severity of depression and response to H-Coil rTMS in our sample, we divided the subjects into three groups according to depression severity based on the HDRS-24 score at baseline (mild = 20–24, moderate = 25–30, severe = >30). Our results failed to reveal any association between response rates and severity of depression.

Safety and tolerability

H-Coil rTMS treatment was well tolerated by the subjects. The average degree of headache as evaluated by a VAS scale of 1–10 at 5 min after each treatment session was 2.92 (SD = 4.83), 3.26 (SD = 3.91), 0.91(SD = 1.78), 1.59 (SD = 2.89) and 1.07 (SD = 2.15) on Visits 1, 4, 10, 15 and 20, respectively. Hemodynamic measurements revealed neither increases nor decreases in mean blood pressure or pulse rate (127/78 and 75 at baseline and 124/83 and 72 at Visit 20). Inspection of the scalp (conducted before and immediately after each session) revealed no skin lesions. There were no mood switches to hypomanic or manic states as assessed by the YMRS. One patient had an induced generalized seizure that lasted for less than 10 s, was self-limited, and did not cause any physical injury. The patient had post-ictal amnesia and confusion that resolved after 30 min. She had been taking lithium 900 mg/day (blood level of 0.79 before entering the study), and the seizure occurred on the 12th treatment day, at the 19th rTMS train. Her MT was 51% of stimulator maximum intensity, meaning that stimulation intensity was 61% of maximum power output. No other medical condition existed and no other medication taken.

Assessment of cognitive functions did not reveal any negative impact on cognition. Significant differences in all of the measured cognitive fields were found at baseline between the BPD patients and the controls. The BPD patients' baseline performance was significantly poorer (Table III). The slower processing time of the BPD subjects at baseline compared to the controls was no longer evident on cognitive assessments administered after 10 days of treatment nor at the final follow-up visit (Table III). The significant difference between the two groups that had been seen on the SWM task at baseline was no longer present at the time of the second assessment (Table III). No correlations were found

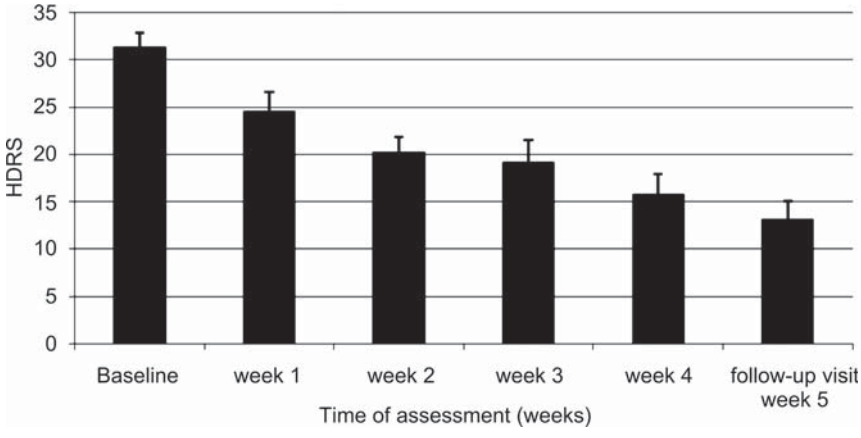

Figure 1. Hamilton Depression Rating Scale (HDRS) scores from baseline to the follow-up visit 1 week after the last treatment day.

Table II. Slopes of changes from baseline in the clinical scales over 5 weeks.

	Estimate	Standard error	DF	*t* value	Pr > |*t*|	95% CI
HDRS	–12.89	2.91	69	–4.43	<0.0001	[–18.70 to –7.08]
CGI-S	–2.71	0.49	66	–5.57	<0.0001	[–3.69 to –1.74]
CGI-I	–2.23	0.45	66	–4.99	<0.0001	[–3.12 to –1.34]
BDI	–5.12	3.40	69	–1.50	0.1374	[–11.91 to 1.68]
PSQI	–2.14	2.33	69	–0.92	0.3613	[–6.80 to 2.51]
HAM–A	–5.49	1.90	69	–2.88	0.0052	[–9.29 to –1.69]

HDRS, Hamilton depression rating scale; CGI-S, clinical global impression severity; CGI-I, clinical global impression improvement; BDI, Beck depression inventory; PSQI, Pittsburgh sleep quality index; HAM-A, Hamilton anxiety rating scale.

between the patients' cognitive performance and their HDRS-24 scores either at baseline or at any other time.

Discussion

This preliminary study is the first to examine the effect of add-on deep-TMS stimulation of prefrontal regions in the treatment of BPD. The results suggest a possible positive therapeutic effect of the H-coil deep-TMS on depressive symptoms in BPD when used as adjuvant therapy together with mood stabilizers and antidepressants. The improvement in depressive symptoms was indicated by an improvement in the HDRS and CGI values over time. Improvement was also observed in the HAM-A scores. Response rates according to the HDRS at the primary efficacy time-point (the last follow-up visit) reached as high as 63.2%, and remission rates were 52.6%. Our results substantiated those of a recent open-label trial (Dell'Osso et al. 2009), which evaluated right dorsolateral low frequency rTMS in BPD subjects, and showed a 54.5% response rate and a 36.3% remission rate. The poorer results reported in the two RCTs described earlier (Dolberg et al. 2002, Nahas et al. 2003) could be related to the shorter duration of treatment, seeing as longer rTMS protocols have proven to be more effective in the treatment of depression.

The treatment was generally well tolerated in terms of discomfort. One patient experienced a generalized tonic-clonic seizure. Due to the small sample size, it is not possible to estimate whether the H-coil rTMS treatment has a greater risk of inducing a seizure compared to other forms of rTMS. No seizures were induced in any of the patients in a previous study by our team, in which we applied the H-coil rTMS on 65 unipolar depressed subjects without concomitant medication and followed the same treatment protocol as described for the current study (20 Hz, 2 s, 120% MT) (Levkovitz et al. 2009). Another earlier safety study (Levkovitz et al. 2007) on eight healthy subjects using 20 Hz, 1 s, 120% MT did not show any seizure activity. A possible contributor to seizure induction in the patient described in the current study was the concomitant use of lithium which could increase the risk of seizure by lowering the motor threshold. Lithium is known to prolong seizure activity during electroconvulsive therapy (Girish et al. 2003), and a previous case report of rTMS-induced seizure lends credence to the possibility that concomitant use of lithium by our patient might have contributed to seizure induction (Tharayil et al. 2005). The actual role of lithium in increasing the risk of seizure induction by rTMS is not yet known. Data on a much larger patient population treated with H-coil rTMS for BPD with and without

Table III. Comparison of the cognitive test results between the BPD subjects and the healthy controls at baseline, after 10 treatment days (2nd test), and 1 week after the last treatment day (3rd test).

Cognitive test	Baseline			2nd test		3rd test	
CANTAB test	DF	*t* value	Pr > |*t*|1	*t* value	Pr > |*t*|2	*t* value	Pr > |*t*|3
SOC problems solved in minimum moves	37	3.41	0.0016	3.49	0.0013	2.31	0.0273
RVP A'	37	4.44	0.0001	3.06	0.0050	2.87	0.0091
PAL total errors	37	–3.43	0.0015	–2.56	0.0180	–2.24	0.0315
SWM between errors	37	*–3.41*	*0.0016*	*–1.47*	*0.1506*	*–2.04*	*0.0491*
RTI five choice reaction time	37	*–2.21*	*0.0358*	*–1.23*	*0.2268*	*–1.66*	*0.1065*
RTI five choice movement time	37	–2.47	0.0180	–2.07	0.0461	–2.24	0.0317

SOC, Stocking of Cambridge; PAL, paired associative learning; RVP, rapid visual processing; SWM, spatial working memory; RTI, reaction time.
Italic entries indicate values for which difference was eliminated throughout the treatment between the patients and the control group.

concurrent lithium would be required in order to estimate the risk of seizure induction by the H-Coil in general and with concurrent lithium treatment.

No deterioration in the cognitive functioning (as measured by the CANTAB) of the BPD patients was observed. Furthermore, there was an improvement in reaction time and spatial working memory, although this improvement did not correlate with a decrease in the severity of depression. Again, a larger sample might have reached a clearer conclusion about the possible positive effects of either the use of rTMS or the improvement in depression on cognitive functions.

Since this is an add-on study, the subjects were being treated concurrently with mood stabilizers and antidepressants at a steady dosage throughout the rTMS treatment. The type of antidepressants taken by the subjects varied widely. As such, we cannot draw conclusions about the relative efficacy of any given antidepressant in combination with rTMS. Furthermore, among the different mood stabilizers used by the patients, some, such as lithium and lamotrigine are believed to have antidepressant properties. Therefore, it is rather difficult to define the role of concurrent medications in the outcome of rTMS treatment.

The design of the current study has several limitations; it was an open study, a small sample size and an add-on design. This makes it impossible to rule out a possible placebo effect and expectancy bias, and the possibility of improvement having been the result of other factors, such as the natural course of the illness cannot be discounted. Nevertheless, given the chronic and severe nature of BPD and the lack of available satisfactory therapeutic options, the results of this current pilot study suggest a possible new treatment that requires further examination. In light of this pilot study, a randomized controlled study is warranted.

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Statement of interest

Drs. Levkovitz, Zangen and Roth have financial interests in Brainsway, Inc.

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