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Simultaneous rTMS and psychotherapy in major depressive disorder: Clinical outcomes and predictors from a large naturalistic study

Lana Donse [a, b], Frank Padberg [c], Alexander T. Sack [a, d], A. John Rush [e, h, i], Martijn Arns [b, f, g, *]

[a] Dept. of Cognitive Neuroscience, Maastricht University, Maastricht, The Netherlands
[b] Research Institute Brainclinics, Nijmegen, The Netherlands
[c] Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Germany
[d] Maastricht Brain Imaging Center, Maastricht, The Netherlands
[e] Duke-National University of Singapore, Singapore
[f] Dept. of Experimental Psychology, Utrecht University, Utrecht, The Netherlands
[g] neuroCare Group, Munich, Germany
[h] Duke Medical School, Durum, NC, USA
[i] Texas Tech University Health Sciences Center, Permian Basin, TX, USA

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) is considered an efficacious non-invasive neuromodulation treatment for major depressive disorder (MDD). However, little is known about the clinical outcome of combined rTMS and psychotherapy (rTMS + PT). Through common neurobiological brain mechanisms, rTMS + PT may exert enhanced antidepressant effects compared to the respective monotherapies.
Objective: The current naturalistic study aimed to evaluate feasibility and clinical outcome of rTMS + PT in a large group of MDD patients. The second aim was to identify clinical predictors of response and remission.
Methods: A total of 196 patients with MDD were treated with at least 10 sessions of simultaneous rTMS and PT. rTMS was applied over the DLPFC, either 10 Hz left or 1 Hz right. Psychotherapy was based on principles of cognitive behavioral therapy (CBT). Symptoms were measured using the BDI each fifth session until end of treatment and at 6-month follow-up. Comparisons were made between responders and non-responders, as well as between the 10 Hz and 1 Hz protocol. Additionally, baseline variables and early BDI change were evaluated as predictors of response/remission.
Major findings and conclusions: 1) Combining rTMS and PT resulted in a 66% response and a 56% remission rate at the end of treatment with 60% sustained remission at follow-up. Compared to previous findings in RCTs, these rates are relatively high; 2) No differences were found between the 10 Hz and 1 Hz TMS regarding clinical outcome; 3) Clinical baseline variables were not predictive of treatment outcomes; 4) Early symptom improvement (at session 10) was highly predictive of response, and may therefore be used to guide rTMS + PT continuation; 5) Based on the current findings in a large naturalistic study, future studies employing a more standardized method are warranted to draw solid conclusions on the unique effect of rTMS + PT.

Introduction

The application of repetitive transcranial magnetic stimulation (rTMS) in major depressive disorder (MDD) as an augmentation treatment strategy for treatment-resistant patients has been extensively investigated in the past decades. In rTMS, a magnetic coil is placed on a specific location on the scalp to modify target brain networks by applying magnetic pulses, inducing an electrical current in underlying cortex [1]. The efficacy of rTMS over the dorsolateral prefrontal cortex (DLPFC) has been established in large multicenter randomized controlled trials (RCTs) [2,3] and meta-analyses [4–7], and is considered an evidence-based treatment

* Corresponding author. Research Institute Brainclinics, Bijleveldsingel 34, 6524 AD Nijmegen, The Netherlands.
E-mail address: martijn@brainclinics.com (M. Arns).

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approach for MDD [8]. A few studies have investigated the generalizability of the effects of rTMS in clinical settings. In a multisite observational study, the response rate in the short term was comparable to those in research populations [9], and a 1-year follow-up study of the same population demonstrated that these effects remained similar in the long term [10]. These studies highlight the clinical significance of rTMS for the treatment of MDD patients. Currently, rTMS is usually applied either as monotherapy or as augmentation to pharmacotherapy. Although response to this approach is better than sham in RCTs, a large proportion of patients does not respond [5]. It is therefore important to seek optimization of the treatment protocol.

The effects of rTMS are exerted through modulating network connectivity [1]. MDD is associated with dysregulation of medial/orbitofrontal networks, including the default mode network (DMN), central executive network (CEN) and salience network (SN) [11,12]. In these networks, hyperconnectivity between prefrontal and anterior cingulate regions is associated with symptoms of MDD, such as rumination and negative bias [13]. Numerous studies have shown that connectivity from the DLPFC to the anterior cingulate cortex (ACC) changes as a result of rTMS [14]. Similarly, symptom changes as a result of psychotherapy (PT) are associated with changes in functional connectivity in fronto-limbic and fronto-cingulate circuitry, particularly from the medial PFC to the ACC and the amygdala [15]. Thus, both rTMS and PT are targeting the same networks through different pathways, inducing changes through neuroplasticity [16,17]. These observations give rise to the question whether simultaneous application of rTMS and PT (rTMS + PT) could lead to more robust and prolonged antidepressant effects.

Such an enhanced effect has been observed in studies combining PT with pharmacotherapy [18,19] and rTMS with pharmacotherapy [20]. Even stronger additive effects may be expected from rTMS + PT, as both target network plasticity in a similar way through different pathways. Furthermore, PT may be a preferable add-on strategy to rTMS, as it is desirable for many patients to quit medication. The main disadvantages of pharmacological treatment consist of undesirable side effects, cumulative drop-out rates, and non-response in a significant proportion of the patients, as demonstrated in the systematic antidepressant treatment of STAR*D [21]. Moreover, psychotherapy is often better tolerated as a next-step treatment than medication augmentation and switch strategies [22]. Although psychotherapy and medication are equally effective in the short term, follow-up outcomes are favorable for psychotherapy [18,19,23]. It may therefore be hypothesized that a combination of rTMS and PT could lead to stronger and longer lasting effects, using a well-tolerated treatment approach.

Moreover, non-invasive brain stimulation techniques including rTMS exert effects on cognitive functions that psychotherapy may rely on, such as explicit learning or top-down emotional control [24]. In neurorehabilitation, combined application of rTMS and cognitive rehabilitation therapies has been shown to result in beneficial effects [25], mainly in the motor [26] and language domain [27,28] as well as unilateral neglect [29]. A similar effect may apply to the behavioral effect of rTMS + PT in psychiatry. Indeed, a case report demonstrated that combined rTMS and CBT is feasible and possibly more effective than either treatment alone [30], supporting this hypothesis, but no other studies to date have reported on the clinical outcome of this promising approach.

Therefore, the present study aimed to evaluate the feasibility and clinical outcome of the simultaneous application of rTMS + PT in a large, representative population of MDD patients. The second aim was to identify possible predictors of treatment outcome.

Method

Design and participants

The current study was a naturalistic open-label study. All patients enrolled at three outpatient mental health care clinics (neuroCare Clinic Nijmegen, neuroCare Clinic The Hague, and Psychologenpraktijk Timmers Oosterhout) between May 2007 and November 2016 were screened for inclusion. Inclusion criteria were 1) a primary diagnosis of non-psychotic MDD or dysthymia, 2) BDI$\geq$14 at baseline, 3) treatment with at least 10 sessions of rTMS over the DLPFC or response within these 10 sessions, and 4) informed consent. Exclusion criteria to ensure safety for rTMS were previous ECT treatment, epilepsy, traumatic brain injury, current psychotic disorder, wearing a cardiac pacemaker or metal parts in the head, and current pregnancy.

Treatment procedure

Prior to treatment, patients completed an intake procedure, including a structured clinical interview (MINI International Neuropsychiatric Interview (MINI)) [31] for the diagnosis of MDD or dysthymia; if the MINI could not be completed due to time limits, patients with a diagnosis in accordance with DSM-IV or DSM-5 criteria obtained elsewhere were considered eligible for treatment as well. In addition, EEG was used to rule out contraindications for rTMS.

All patients were treated with either a high frequency (HF) protocol over the left DLPFC or a low frequency (LF) protocol over the right DLPFC, or both sequentially. rTMS was performed using a Magstim Rapid2 (Magstim Company, Spring Gardens, UK) or a Deymed DuoMag XT-100 stimulator with a figure-of-8 coil, 70 mm diameter. For the HF protocol, rTMS was administered at 10 Hz over the left DLPFC, 110–120% of the resting motor threshold (MT), 30 trains of 5s duration, inter-train interval (ITI) 30s, 1500 pulses per session. The LF protocol consisted of rTMS at 1 Hz over the right DLPFC, 110–120% MT, 120 trains of 10s duration, ITI 1s, 1200 pulses per session. In case of both protocols, the LF protocol was administered first with a shorter duration of 1000 pulses per session and subsequently the HF protocol at full length. The DLPFC was localized using either the 5-cm rule or the Beam F3/F4 method (see Ref. [32] for details).

Furthermore, rTMS treatment was complemented with psychotherapy by a psychologist trained in both rTMS and CBT. The therapist performed psychotherapy while the rTMS protocol was running (as shown in Fig. 1). Psychotherapy always consisted of evidence-based methods, mainly cognitive-behavioral therapy (CBT) [33,34], but the specific approach was tailored to the clinical needs of the patient, according to a decision procedure as usual in mental health care, in some cases including other evidence-based techniques indicated for comorbidities such as schema therapy or EMDR. Each treatment session had a total duration of 45 min. An rTMS protocol lasted 20 min, but psychotherapy was continued until 45 min. Sessions took place with a minimum frequency of two to three times per week and a maximum frequency of two per day.

The total number of sessions was guided by clinical decisions and thus varied for each individual patient. Decisions to continue treatment were based on response to treatment (satisfactory or unsatisfactory response could both be a reason to end treatment), clinical evaluation of symptom severity, and the patient's own request. The first decision rule was to continue rTMS if a decrease of at least 20% in BDI score was obtained after 10 sessions; the effect was evaluated each subsequent fifth session. If no response occurred by session 20–25, it was advised to abort treatment. If the BDI indicated remission over the course of sessions, defined as a

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Fig. 1. This picture shows the setting of rTMS + PT in which the psychologist (right) performs psychotherapy simultaneously with rTMS.

stable score ≤12 for 5 sessions, the patient was given the option to end treatment, phase out sessions (gradually lowering the frequency of sessions) or extend with maintenance sessions (one session each 6–8 weeks). However, if the symptoms appeared to be in remission but still showed a remarkable decrease, treatment was continued until BDI scores were stabilizing.

Outcome measures

The Beck Depression Inventory, second edition, Dutch version (BDI-II-NL) score was used as primary outcome measure. Response to treatment was defined as ≥50% reduction in BDI score from baseline to the last visit; remission as a BDI score ≤12 [35]. These definitions were used at the last acute treatment visit to define outcomes.

The Depression, Anxiety and Stress Scale (DASS) [36] was used as secondary outcome. The DASS is a self-report questionnaire and consists of three scales: depression (DASS D), anxiety (DASS A), and stress (DASS S). Each scale consists of 14 items with a 4-point severity score, with a maximum total score of 42 on each scale. The patient is asked to fill in the items based on experiences in the previous week.

Both questionnaires were filled out at baseline, each fifth session throughout treatment, at the last visit, and at 6-month follow-up. For non-responders and drop-outs, the last available BDI score was used as last visit measure (last observation carried forward). For patients receiving maintenance sessions, the measure closest to 6 months after the last visit was used as follow-up score.

Analyses

Firstly, to evaluate treatment outcome of rTMS + PT for the total sample, paired t-tests were used to test changes in BDI and DASS scores from baseline to last visit. Repeated-measures analysis of variance (ANOVA) was used to assess BDI changes over the course of treatment, using the scores of each fifth session. A separate repeated-measures ANOVA was conducted for the group of patients that completed follow-up.

Secondly, comparisons were made between responders and non-responders. Differences in demographic and clinical baseline variables were evaluated using independent samples t-tests for continuous variables (age, baseline severity) and chi-square tests for categorical variables (gender, rTMS protocol, suicide risk, MINI diagnosis). Mixed design ANOVA with session (baseline/session 10/last visit) and response (response/non-response) was performed to evaluate differences in symptom severity over the course of treatment. Similarly, a mixed ANOVA was conducted to compare rTMS protocols (LF/HF) over the course of treatment (baseline/session 10/last visit).

Lastly, clinical baseline variables and early treatment-emergent changes were tested as predictors of treatment (non-)response. Since previous reports suggest that age, age of onset and baseline symptom severity may serve as clinically useful predictors [37–39], these were selected as candidate variables. Negative predictive values (NPVs) and positive predictive values (PPVs) were calculated for each individual predictor, and if these did not meet a predefined criterion of at least 0.8, combinations of various predictors were used [39]. Variables meeting the criterion of 0.8 were included in a receiver operating characteristic (ROC) curve to determine sensitivity and specificity. Youden's index [40] was used to identify possible cut-off values.

Results

Demographic and clinical baseline variables

The total sample consisted of 196 patients, 98 female and 98 male, aged 18–78 (43.2 ± 12.9). Treatment resistance was not systematically recorded, but post-hoc review of the files indicated that >97% of the sample met the criteria of treatment-resistance, defined as at least one previous antidepressant treatment without response. Clinical baseline and treatment variables are specified in Table 1. Patients underwent on average 20.9 (SD = 7.5) sessions. Out of 196 patients starting treatment, 179 completed 10 sessions, 106 completed 20 sessions, 22 completed 30 sessions, 6 completed 40 sessions, and 3 continued until 50 or more sessions.

Total sample treatment outcome

Mean BDI scores were significantly reduced after rTMS + PT compared to baseline, $t(194) = 21.13$, $p < 0.001$, $d = 1.54$. Similarly, significant reductions were observed at DASS D, $t(168) = 15.76$,

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Table 1
Clinical baseline and treatment variables of the total sample (with *n* or *M* (*SD*)).

Clinical baseline variables		
MINI diagnosis	MDD	83
	Dysthymia	9
	MDD and dysthymia	24
	MDD and anxiety disorder	31
	MDD, dysthymia, and anxiety	13
	MDD and other comorbidity	14
	Mixed anxious/depressive disorder	1
	No formal MINI diagnosis, but diagnosis elsewhere conform DSM criteria	16
Suicide risk	None	50
	Low	40
	Moderate	42
	High	27
Age of onset ($n = 123$)		24.0 (13.0)
Number of previous episodes ($n = 33$)		5.1 (3.9)
Treatment variables		
rTMS protocol	HF (10 Hz left)	74
	LF (1 Hz right)	115
	Both sequentially	7
Treatment site	Nijmegen	177
	The Hague	4
	Oosterhout	15
Total number of sessions		20.9 (7.5)
Maintenance	Number of patients	39
	Average number of maintenance sessions	4.9 (2.5)
Relapse	Number of patients reporting relapse	48
	Average time from last session to relapse	10.2 (11.9) months
	Average number of sessions after relapse	7.1 (5.7)

$p < 0.001$, $d = 1.48$, DASS A, $t(167) = 13.08$, $p < 0.001$, $d = 1.05$, and DASS S, $t(167) = 13.51$, $p < 0.001$, $d = 1.23$. See Table 1 for mean scores at baseline, the last visit, and the change in these scores. The overall response was a 55.9% reduction in depression severity as measured by BDI. The reduction in BDI over the course of treatment was significant $F(3.70, 385.01) = 153.36$, $p < 0.001$, $\eta^2 = 0.60$. Post-hoc tests showed that BDI score decreased significantly each fifth session over the course of treatment, except for the difference between session 10 and 15 (Fig. 2).

Response and remission

Treatment response was defined as ≥50% reduction in BDI score from baseline to last visit. Based on this criterion, the sample consisted of 130 responders and 66 non-responders. Thus, the response rate was 66.3%. The remission rate was 56.0%, with 109 out of 196 patients achieving remission (BDI≤12).

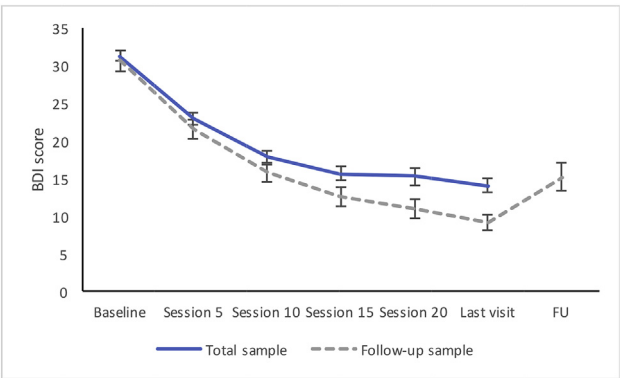

Fig. 2. BDI change over the course of treatment for the total group ($N = 196$) and the follow-up group ($n = 73$). Error bars represent standard error of the mean (*SEM*).

No differences between responders and non-responders existed in age ($t(194) = 1.32$, n.s.), gender ($\chi^2(1) = 1.34$, n.s.), diagnosis ($\chi^2(7) = 6.90$, n.s.), suicide risk ($\chi^2(3) = 4.59$, n.s.), or rTMS protocol ($\chi^2(2) = 0.51$, n.s.).

BDI at baseline was significantly higher in non-responders than responders, $t(194) = 2.21$, $p < 0.05$, $d = 0.3$, and in non-remitters than remitters, $t(194) = 5.87$, $p < 0.05$, $d = 0.8$. A mixed design ANOVA (session × response) was used to test differences in BDI over the course of treatment between responders and non-responders. Measurements of three time points were used: baseline, session 10, and the last visit, as these were available for most patients ($n = 177$; Table 2). A significant main effect over sessions was observed, $F(1.90, 336.45) = 284.08$, $p < 0.001$, $\eta^2 = 0.62$. Overall BDI score was significantly different between responders and non-responders as well, $F(1, 177) = 85.06$, $p < 0.001$, $\eta^2 = 0.33$. Finally, the interaction effect was significant, $F(1.90, 336.45) = 84.50$, $p < 0.001$, $\eta^2 = 0.32$ (Fig. 3). Repeated contrasts revealed a significant interaction effect from baseline to session 10, $F(1, 177) = 34.50$, $p < 0.001$, $\eta^2 = 0.16$, as well as from session 10 to the last visit $F(1, 177) = 54.26$, $p < 0.001$, $\eta^2 = 0.24$.

LF vs. HF rTMS protocol

A mixed design ANOVA (session × protocol) was used to test changes in BDI over the course of treatment between patients treated with the HF and LF protocol. Patients treated with both protocols were excluded from this analysis, as this subgroup was very small ($n = 7$). Again, measurements of three time points were used: baseline, session 10, and last visit (Table 2). A significant main effect of session was observed, $F(1.80, 306.44) = 253.90$, $p < 0.001$, $\eta^2 = 0.60$. No differences in overall BDI score were found between the HF and LF protocol groups, $F(1, 170) = 0.73$, $p = 0.39$. Finally, no interaction effect was found, $F(1.80, 306.44) = 0.59$, $p = 0.50$ (Fig. 3).

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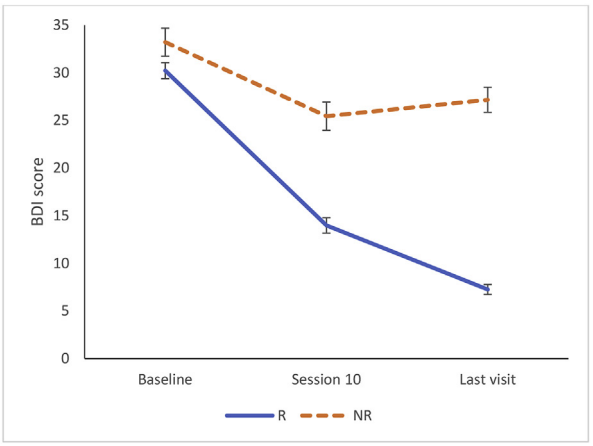
Table 2
BDI and DASS scores of the total group ($n = 196$), responders vs. non-responders, HF vs. LF protocol, and the follow-up sample ($n = 73$).

		Baseline	Session 10	Last visit	Change	% change
Total sample						
BDI		31.3 (10.0)	17.9 (11.2)	14.1 (12.2)	17.2 (11.3)	55.9 (34.3)
DASS D		28.6 (10.0)		12.1 (11.7)	16.1 (13.3)	49.3 (75.1)
DASS A		13.7 (8.7)		5.6 (6.5)	8.1 (8.1)	55.1 (53.6)
DASS S		22.4 (10.5)		10.1 (8.7)	11.8 (11.3)	39.7 (107.5)
BDI	R	30.2 (9.1)	14.0 (8.7)	7.3 (5.67)	22.8 (7.7)	76.2 (15.0)
	NR	33.2 (11.6)	25.4 (11.7)	27.2 (10.4)	5.8 (8.9)	15.0 (24.5)
BDI	HF	29.9 (8.9)	17.4 (10.5)	12.8 (10.6)	17.2 (11.6)	56.7 (34.3)
	LF	31.5 (10.3)	17.7 (11.3)	14.7 (12.7)	16.7 (11.1)	54.8 (35.1)
Follow-up sample		**Baseline**	**Session 10**	**Last visit**	**Follow-up**	**% change**
BDI		29.4 (9.3)	13.5 (8.2)	8.0 (7.1)	13.8 (11.4)	51.3 (41.9)
DASS D		27.0 (10.3)		6.5 (6.6)	11.8 (11.5)	52.8 (45.1)
DASS A		14.1 (9.1)		4.0 (4.4)	7.2 (7.5)	27.7 (145.1)
DASS S		22.3 (10.7)		7.3 (6.2)	12.5 (10.4)	33.7 (64.3)



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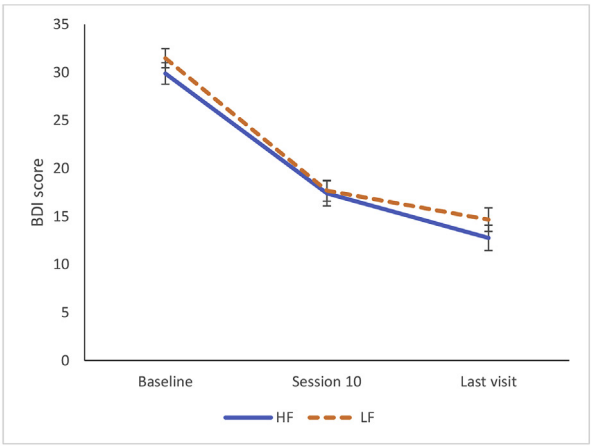

b.

Fig. 3. Differences in BDI score over time between responders and non-responders (a) and patients treated with HF and LF rTMS protocol (b). Error bars represent *SEM*.

Maintenance and relapse

A total of 39 patients underwent maintenance sessions, with an average of 4.9 sessions (Table 1). These maintenance sessions were performed with a frequency of once every 6–8 weeks. Furthermore, 48 patients reported relapse and 42 of those came back for rTMS treatment. In this group, relapse occurred on average at 10.23 months after the last visit. Patients who came back for rTMS treatment after relapse underwent 7.12 additional sessions on average.

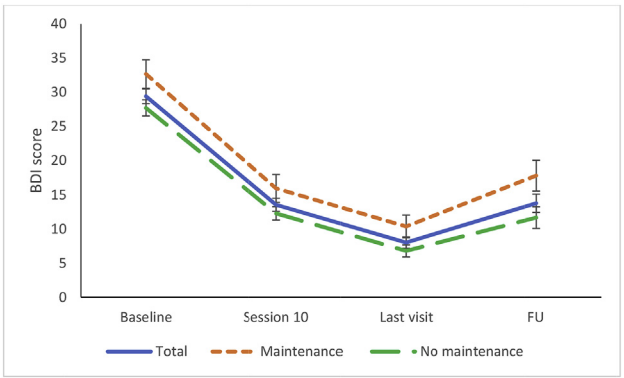

Fig. 4. Changes in BDI over time for the follow-up sample and for patients who received maintenance sessions versus those who did not. Error bars represent *SEM*.

Follow-up

Seventy-three patients completed BDI and DASS at 6-month follow-up (Table 2). A repeated-measures ANOVA showed significant differences from baseline to each fifth session until session 20, last visit, and follow-up, $F(2.90, 145.22) = 69.65$, $p < 0.001$, $\eta^2 = 0.58$. Scores at follow-up were slightly higher than at the last visit, but remained significantly lower than at baseline (Fig. 2).

In the follow-up group, 46 (63.0%) were responders. Out of 66 initial responders at end of treatment, 43 (65.2%) retained response at follow-up. Thirty-nine (53.4%) patients were in remission at follow-up; out of 60 remitters at end of treatment, 36 (60.0%) still met remission criteria after 6 months.

No valid comparison of follow-up data could be made between responders and non-responders, since only 7 of the non-responders completed follow-up. When comparing patients who received maintenance treatment to those who did not, there was a significant difference between groups, $F(1, 71) = 8.22$, $p < 0.01$, $\eta^2 = 0.10$. No time × maintenance interaction was found, $F(2.13, 151.29) = 0.50$, $p = 0.62$. Patients who received maintenance sessions had a higher score over sessions than those who did not (Fig. 4), possibly indicating that those with higher severity throughout treatment were more likely to receive maintenance treatment.

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Response prediction

Clinical baseline variables and early treatment-emergent changes were tested as predictors of successful treatment response and remission. NPVs and PPVs were calculated for each individual predictor based on discriminant analyses, and if these did not meet the criterion of at least 0.8, combinations of clinical baseline predictors with early treatment change were used.

No individual clinical baseline predictor reached a PPV or NPV of 0.8 (Supplement 1). Change in BDI from baseline to session 10 resulted in a satisfactory PPV, but not NPV for response. Combinations of the clinical baseline variables with change in BDI early in treatment did not result in satisfactory NPVs either. In other words, change in symptom severity from baseline to session 10 can serve as a useful treatment-emergent predictor of treatment response, but none of the individual or combined clinical variables can predict non-response. For BDI percentage change at session 10, an ROC curve was computed, which resulted in an area under the curve (AUC) of 0.796 (Fig. 5). Thus, this model discriminated well between responders and non-responders; therefore, sensitivity and specificity as well as Youden's index for possible cut-off points were calculated (Supplement 2).

The cut-off value that discriminated best between responders and non-responders was a reduction in BDI score of at least 40% at session 10, with a sensitivity of 71.2% and a specificity of 75.0%, $J = 0.462$.

As for prediction of remission, none of the individual predictors were clinically meaningful according to the predefined cut-off of 0.8 (Supplement 1). A satisfactory NPV was found for the combination of BDI change from baseline to session 10, baseline severity, and age of onset. However, combining these variables in an ROC curve (Fig. 5) resulted in an AUC of 0.670, indicating that the discriminating value of this model remained poor.

Discussion

The aim of the present study was to evaluate the clinical outcome of rTMS treatment combined with psychotherapy in a large, representative population of MDD patients. Most importantly, the results demonstrate a remission rate of 56% compared to earlier studies of rTMS monotherapy with remission rates up to 37% [9,39]. In addition, a response rate of 66% was found, compared to 29–58% in monotherapy studies [9,38]. This outcome is promising, since the high remission rate suggests an additional and clinically meaningful effect of simultaneous rTMS and psychotherapy beyond either treatment strategy alone. However, as valid comparisons with previous studies are not possible due to differences in outcome measures and procedure, future studies performing direct comparisons of rTMS monotherapy and rTMS + PT are strongly warranted.

The question remains whether the combination of rTMS and psychotherapy results in an enhanced effect through neuroplasticity as hypothesized, or whether it is merely a dose-response relationship. The combination of two treatment strategies can be interpreted as an increase in dose. In the current study, no standard 'dosages' in the form of total treatment duration or a standardized number of sessions per week were applied, albeit in comparison to the FDA approved rTMS protocol of 3000 pulses per session, the TMS dose in this study was at a relatively low 1200–1500 pulses per session. Future studies could incorporate and compare different standardized operationalizations of dosage to rule out this explanation for the relatively high response and remission rates.

Moreover, imaging studies could shed more light on the question whether the enhanced effect is dependent on changes in brain network connectivity through different pathways. Advances in imaging technology allow for the simultaneous application of non-invasive brain stimulation (NIBS) and fMRI or EEG [41,42,53]. These methods could be used to provide insight into the effects that are elicited by each treatment approach and their interaction, both at the time of stimulation and over the course of treatment. Theoretically, effects of rTMS and PT may synergistically interact, but also negatively interfere with each other [24]. This may be observed on a functional level, where cognitive domains involved in PT may be strengthened by rTMS: e.g. 1 Hz rTMS of the right DLPFC may enhance episodic memories through reconsolidation in healthy subjects [54]. Thus, by combining NIBS and PT, it may be possible to dismantle cognitive components of PT in terms of their underlying physiology.

Neuroimaging studies in depression, however, do not suggest that fMRI connectivity networks and hubs where rTMS and CBT (but also pharmacotherapy) show their modulatory action, do simply overlap [52,55]. Innovative approaches are needed to investigate in more detail differences and potential synergistic effects between rTMS plus PT vs. rTMS and PT monotherapy: e.g. 1) EEG connectivity analyses applied to the specific DLPFC-sgACC network implicated in MDD and treatment response (e.g. see [51]: and [2]) more advanced data driven network connectivity approaches to obtain biotypes of response to various rTMS approaches (e.g. see Ref. [52]).

Results at 6-month follow-up suggest a relatively stable effect on the long term, with symptom severity slightly higher than at the last visit, but significantly lower than at baseline. Moreover, 63% of the follow-up sample still met response criteria and 53% met remission criteria. Although this outcome might be biased since

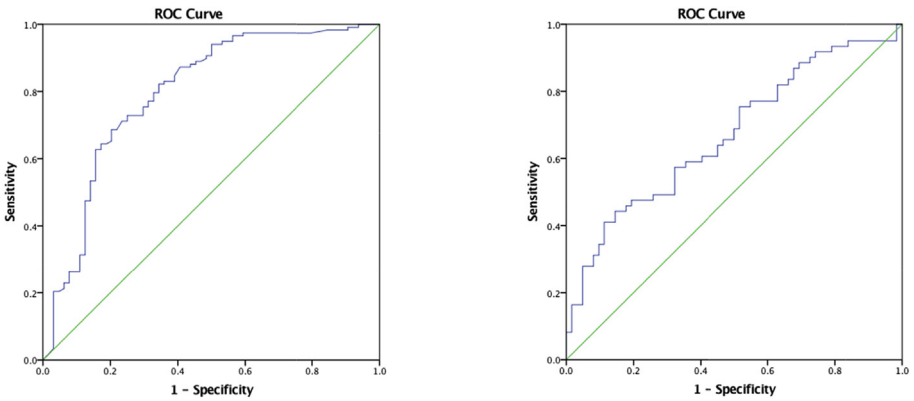

Fig. 5. ROC curves of the discriminant models predicting response with BDI change at session 10 (left) and predicting non-remission with a combination of BDI change at session 10, BDI baseline severity and age of onset (right).

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mainly responders were likely to return follow-up questionnaires, it suggests that rTMS + PT results in a sustainable reduction of depressive symptoms. The results of the current study are comparable to an earlier report on long-term outcome of rTMS treatment in a naturalistic setting, in which sustained response was found in 56.8% of the patients and sustained remission in 50% [10]; in the current sample, these percentages were 65.2% and 60%, respectively. Compared to long-term outcome in primary care, in which 25% of patients typically achieve and maintain remission up to 18 months after treatment [43], and to antidepressant medication with remission rates of 13–36.8% after one year [44], outcomes of rTMS treatment at follow-up can be considered favorable. The question whether the combination with psychotherapy has an additional effect in the long term remains to be answered in future studies using head-to-head comparison.

Within the follow-up sample, patients who received maintenance sessions had significantly more severe depressive symptoms throughout treatment than patients who did not. This is probably the result of selection bias, where patients with more severe symptoms and higher relapse risks are more frequently advised to continue with maintenance sessions after treatment. The current study cannot rule out the potential incremental value of maintenance sessions because of the difference in symptom severity between those groups; an RCT would be necessary to draw solid conclusions. Earlier reports do suggest that additional rTMS sessions are associated with prolonged treatment effects [45]; therefore, future studies should use a systematic follow-up procedure when evaluating maintenance sessions.

Prediction of treatment outcome based on clinical variables was performed using NPVs and PPVs with a predefined criterion of 0.8. None of the individual clinical baseline variables met this criterion, underscoring the emerging idea that clinical factors alone are not sufficient to predict treatment response [38], and that predictions based on biological factors may be more informative and have greater clinical utility [46,47]. Change in symptom severity early in treatment could predict positive treatment response; moreover, only the combination of baseline severity, age of onset, and change in symptom severity after 10 sessions could predict non-remission. This is also in line with previous studies showing that early symptom change combined with clinical factors have a clinically meaningful predictive value [39]. These results suggest that response and remission cannot be predicted at baseline, but after 10 sessions of treatment, change in symptoms may be used as a sufficiently strong predictor of response to make clinical decisions. This is highly relevant in the application of rTMS, since it could be used as to guide treatment decisions to continue or discontinue rTMS treatment and hence help improve the cost-to-benefit ratio for rTMS.

An example of how BDI change early in treatment may guide treatment decisions is to use the percentage change to predict positive response. In the current sample, a reduction of at least 40% at session 10 discriminated best between responders and non-responders. Therefore, patients who have achieved less than 40% change at session 10 may be advised to proceed with add-on strategies such as using bilateral rTMS (sequential HF and LF). The efficacy of such strategies and decision rules should be evaluated in future clinical studies.

An additional finding that may guide clinical decisions is that no differences in clinical outcome were found between patients treated with the HF and the LF protocol. This is an especially important finding; as LF rTMS is better tolerated by patients and is considered a safer protocol [48,49], the application of this protocol in clinical practice may be preferable. Although reports on clinical guidelines suggest that stronger evidence exists for the efficacy of HF rTMS, this is mainly attributable to the smaller number of placebo-controlled studies into LF rTMS [8] and recent adequately powered RCTs demonstrate no substantial differences [50].

Limitations of the current study include some of the points mentioned above, such as the lack of a direct comparison between rTMS only, rTMS + PT and psychotherapy only, and the lack of non-responders participating in the follow-up sample. In addition, some clinical factors that may affect treatment outcome were not systematically registered, such as level of treatment-resistance and chronicity. Post-hoc review of patient files revealed that more than 97% of patients in our sample would have met eligibility criteria similar to the FDA regulations for rTMS, meaning that they had undergone at least one failed antidepressant treatment. In this sense, our sample may be rather comparable to previous randomized controlled rTMS studies [2,3]. However, it is recommended for future studies to systematically measure clinical variables, including treatment resistance in order to also quantitatively analyse the relationship between level of previous treatment resistance and TMS treatment response. In addition, considering that current findings were obtained in a naturalistic setting in which external validity is high but internal validity and reliability are limited, replication of our findings in randomized controlled trials is mandatory.

In conclusion, the main additional effect of rTMS + PT appears to be a considerable remission rate at the end of treatment. These effects were sustainable in most patients, and favorable compared to long-term outcomes of other treatment approaches, especially considering the high level of treatment resistance of this population. Thus, the outcome of rTMS with simultaneous psychotherapy can be considered clinically meaningful. Clear clinical guidelines can be derived from these findings. Firstly, rTMS can be combined with psychotherapy to achieve a higher likelihood of remission – although future studies using a more standardized approach than in the current naturalistic study are necessary to provide more clarity on the role of clinical factors such as treatment resistance. In addition, as HF and LF are equally effective, LF may be preferred as patient tolerability and safety of this protocol is higher. Finally, change in symptoms after session 10 may guide clinical decisions in the continuation of treatment, with larger reductions predicting positive response. Further investigation in RCTs performing direct comparisons with either therapy alone, as well as studies into the working mechanism and prediction of treatment response are warranted to optimize its application.

Disclosures

MA reports options from Brain Resource (Sydney, Australia); he is director and owner of Research Institute Brainclinics, a minority shareholder in neuroCare Group (Munich, Germany), and a co-inventor on 4 patent applications (A61B5/0402; US2007/0299323, A1; WO2010/139361 A1) related to EEG, neuromodulation and psychophysiology, but does not own these nor receives any proceeds related to these patents; Research Institute Brainclinics received funding from Brain Resource (Sydney, Australia) and neuroCare Group (Munich, Germany), and equipment support from Deymed, neuroConn and Magventure, however data analyses and writing of this manuscript were unconstrained.

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FP has received speaker's honorarium from Mag&More GmbH (Munich, Germany) and the neuroCare Group (Munich, Germany)

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.brs.2017.11.004.

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