



Research paper

A randomized controlled trial of a standard 4-week protocol of repetitive transcranial magnetic stimulation in severe treatment resistant depression



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ABSTRACT

Background: Treatment options for major depressive disorder (MDD) in individuals who are depressed for at least 2 years and failed two or more different types of therapeutic intervention, remain scarce. Being less invasive than electroconvulsive therapy, repetitive transcranial magnetic stimulation (rTMS) might be an alternative treatment option.

Research Question: Does high frequency rTMS applied over the left prefrontal cortex ameliorate depressive symptoms in patients with treatment resistant major depressive disorder and is the efficacy dependent on treatment resistance?

Method: We performed a randomized controlled trial investigating the effect of twenty sessions of real or sham-rTMS, during 4 consecutive weeks. Efficacy was blindly rated with the Hamilton depression rating scale (HDRS-17) at baseline and 1 week after end of treatment, and the Dutch method for quantification of treatment resistance in Depression (DM-TRD) was assessed at baseline.

Results: An interim analysis showed no differences in antidepressant response between real and sham rTMS and we therefore discontinued the RCT after 31 patients. The mean difference of the HDRS score between baseline and post-treatment was 3.7 (± 4.0 ; change 16%), indicating a small but significant improvement across time ($F(1,30) = 25.4; p < 0.01$). There were no differences however between the treatment arms ($F(1,30) = 1.5; p = 0.23$). We did find a negative correlation between the change in HDRS score and DM-TRD in the active rTMS group, but this correlation was not significantly different from the sham group.

Conclusion: “Standard” 4-week rTMS treatment is not effective in chronic, severe treatment-resistant depressed patients. While a replication of our data in this patient group may be ethically difficult, further research with less treatment resistant patients might help in positioning rTMS within the current stepped care approach to depression.

1. Introduction

Major depressive disorder (MDD) is a prevalent psychiatric disorder with a significant impact on quality of life. Despite several treatment options, one out of three patients with depression will not respond to the most common treatment strategies, such as cognitive behavioral therapy and antidepressant medication, either alone or in combination (Rush et al., 2006). In fact, one in five patients with depression will follow a chronic course, as defined by a depressive episode lasting

longer than 2 years (Spijker et al., 2002). Although electroconvulsive therapy (ECT) offers an effective line of treatment for depression in those treatment resistant cases, ECT has a number of drawbacks, such as its invasiveness and cognitive side-effects, which leaves the need for alternative treatment options open.

Repetitive Transcranial Magnetic Stimulation (rTMS) offers an effective and less invasive treatment option in depression, either as a primary treatment or as augmentation to antidepressant medication or psychotherapy, as evidenced by several meta-analyses (Berlim et al.,

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2013; Berlim et al., 2014). rTMS has also been shown to be reasonably effective for patients resistant to two prior antidepressant treatments (Gaynes et al., 2014). However, it remains unclear whether rTMS is a viable treatment option for patients with chronic, treatment resistant depression that lasts longer than two years and who do not respond to both antidepressant and psychological forms of treatment. In addition, it is still an open question whether rTMS could be an alternative for patients who reject, are contraindicated or failed to respond to ECT.

Briefly, rTMS uses an electromagnetic coil to induce an electrical current in the underlying cortex. High frequency rTMS (HF-rTMS) delivers electromagnetic pulses ranging from 5 Hz to 20 Hz, and is known to induce neural excitation (Speer et al., 2009). Two landmark studies (George et al., 2010; O'Reardon et al., 2007) and several meta-analyses (Berlim et al., 2014; Schutter, 2009) have shown that HF rTMS delivered over the left dorsolateral prefrontal cortex (DLPFC) induces significant antidepressant effects in major depression. Accordingly, HF-rTMS over the left DLPFC has been given a level A recommendation (definite efficacy) in recent evidence-based guidelines (Lefaucheur et al., 2014; Arns et al., 2019).

The majority of rTMS studies so far has been conducted in depressed patients with some level of treatment resistance. Yet, definitions of treatment resistance differ and the duration of the depressive episodes in these studies is generally less than one year. Gaynes and colleagues analyzed all sham controlled trials of rTMS in patients with treatment resistant depression (TRD), who had 2 or more prior antidepressant treatment failures (Gaynes et al., 2014). They included 18 TRD studies and found that rTMS, mostly augmented to continued antidepressant treatment, is beneficial compared with sham, with a relative decrease in depression severity of more than 4.5 points on the Hamilton depression rating scale (HDRS-17). However, Gaynes and colleagues did not include a measure of treatment resistance and therefore the relation between level of treatment resistance and chance of response could not be further explored.

To address the efficacy of rTMS in treatment resistant depression, several randomized controlled trials have directly compared rTMS with ECT. A meta-analysis of 9 of such trials concluded that ECT was more effective than rTMS, with response rates of 64 and 49% respectively. ECT was particularly more effective for patients with psychotic depression (Ren et al., 2014). This suggests that rTMS may be a viable alternative for ECT or in cases when ECT has failed to sort effects in patients with a non-psychotic depression. To our knowledge, no studies have explicitly studied the efficacy of rTMS in chronic TRD patients where the ongoing episode lasted for longer than two years.

We therefore conducted a randomized sham-controlled trial to investigate the effects of a standard 4-week protocol of high frequent rTMS over the left DLPFC on top of usual care in well-defined chronic, treatment resistant depressed patients, who were not eligible or had already received ECT. Treatment effect was assessed by a pre-post change in depressive symptoms measured with the HDRS-17 (Hamilton, 1960). In addition, a measure of treatment resistance was included to evaluate treatment effects relative to the level of treatment resistance.

2. Materials and methods

2.1. Patients

Adults patients with chronic, treatment resistant depression, were recruited from the outpatient clinic of the academic department of psychiatry of the Radboud UMC Nijmegen and mental health care institute Pro-Persona Nijmegen in the Netherlands between 2013 and 2018.

Major depressive disorder was diagnosed by the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996) by trained psychiatrists (PvE, IT). Inclusion criteria were adults with a current depressive episode, without psychotic features, that lasted at least 2 years and failed

to respond to at least two adequate trials of antidepressants and one adequate trial of cognitive behavior therapy, in accordance with criteria for treatment resistance as described by Ruhé and colleague (Ruhé et al., 2012). We used the Dutch method for quantification of treatment resistance in Depression (DM-TRD) to quantify the level of treatment resistance (Peeters et al., 2016). Concomitant usage of antidepressant medication was allowed because there is no evidence that medication has a negative influence on the antidepressant effect of rTMS (Pridmore, 2000), but instead may lead to additive effects. Moreover, discontinuation of medication could result in aggravation of depressive symptoms thereby endangering the safety of the patient. We excluded patients with a history of substance abuse or dependence, bipolar or other psychotic disorders, a history of traumatic brain injury, claustrophobia, metal implants, and pregnancy for women.

The study was approved by the local ethics committee (CMO region Arnhem-Nijmegen, the Netherlands). All participants gave written informed consent prior to participation. The randomized controlled trial was registered with the ISRCTN (ISRCTN 15,535,800). In accordance with the medical ethical committee, we agreed upon an interim analysis in case of clinical reasons such as evidence for treatment failure or serious adverse events.

2.2. Design

The study design is a sham-controlled randomized controlled trial. Patients were randomly assigned to receive 20 sessions of either active rTMS (10 Hz) or sham rTMS sessions to the left DLPFC over the course of four weeks (standard 4-week protocol). The Magstim Rapid 2 TMS with a focal, 8-figure shaped 70 mm coil was used. At the first day of each treatment week and for both groups, the resting motor threshold (resting MT) was estimated from the right abductor pollicis brevis muscle based on a standardized method (Schutter and Van Honk, 2006). Treatment intensity was fixed at 110% of the individual resting MT throughout the experiment.

The DLPFC was localized according to EEG method using an international system for electrode placement (Klem et al., 1999). Each rTMS session consisted of 60 trains, administering 10 Hz pulses at an angle of 45° relative to the medial-sagittal plane, each train lasting 5 s with a resting period of 25 s between each train. This resulted in a total stimulation time of 30 min with 3000 pulses per session, 5 days consecutively, for 4 weeks, adding to a total of 60,000 pulses. Sham rTMS was applied by tilting the coil 45° away from the scalp (Fitzgerald et al., 2003). Auditory protection in the form of earplugs were given during treatment sessions.

2.3. Outcome measures

Depressive symptoms were evaluated with the Hamilton depression rating scale 17 item score (HDRS-17) at baseline, after 5, 10, 15, 20 sessions and one-week post-treatment, by trained raters who were blind to the randomization. The primary outcome was the difference in HDRS one week after the last treatment in comparison with baseline. The secondary outcome measures were response (defined as $\geq 50\%$ decrease of the baseline HDRS score) and remission (defined as a HDRS score ≤ 7) one week after the last treatment in comparison with baseline. During the course of the study, patients were monitored for side-effects on a daily basis by interview. Spontaneously reported side-effects and adverse events were registered and subjects were questioned for the presence of headache, scalp pain or other known side effects.

2.4. Data analysis

Data analysis was performed using IBM SPSS 25 Statistics. Student's *t*-test and likelihood ratios were performed to test differences in demographic clinical characteristics between the two treatment arms (active and sham treatment). To test for differences in treatment effect

between the groups a mixed ANOVA with HDRS scores as dependent variable and time and treatment arm as within-subject factor and between group factor respectively.

A correlation analysis was carried out between the change in HDRS score and the level of treatment resistance measured by the DM-TRD for both treatment groups.

We performed an initial power analysis to calculate the sample size based on earlier studies showing a clinically meaningful change in depressive symptoms of 3 points on the HDRS between an intervention and a sham group with a pooled standard deviation around 6. Using these numbers for a power of 80% and a one-sided p-value of 0.05, 50 patients per group would be needed.

In line with the procedure attuned with the medical ethical committee, the responsible clinician (PvE) requested an intermediate analysis for clinical considerations, that is the observation that patients did not seem to show a treatment response. Therefore, after 31 patients had finished the trial, an interim analysis was performed by the senior author and based on these results we decided to end the trial based due to futility. In the following, we present the results of 31 patients.

3. Results

3.1. Demographic and clinical characteristics

31 subjects were randomly assigned to receive real ($n = 15$) or sham rTMS ($n = 16$). Table 1 shows the demographic and clinical characteristics of both treatment arms, including the level of treatment resistance, age of onset, duration of episode and previous treatment with ECT. Apart from concurrent antidepressant use, none of the demographic and clinical variables differed between the two groups. Antidepressant use was higher in the sham group (88%) in comparison with the active group (47%; $p = 0.01$). A complete overview of medication use during the trial is shown in Table 2. Medication was kept constant during the whole study period, except for minimal changes in benzodiazepine usage.

3.2. Treatment effect

The interim analysis which resulted in stopping the study because of futility showed that none of the patients in the active condition had achieved treatment response. The overall mean HDRS score at baseline was $23.4 (\pm 4.1)$ and $19.7 (\pm 5.6)$ at 1 week after end of treatment (5 weeks after baseline), resulting in a mean decrease in HDRS of $3.7 (\pm 4.0)$; change of 16%. The decrease in HDRS score for the separate groups was $3.1 (\pm 4.2)$; 13% in the active group and $4.1 (\pm 3.9)$; 18% in the sham group.

Results of the interim analysis in the form of a mixed ANOVA indicated that there was a main effect of time ($F(1,30) = 25.4$; $p < 0.01$), but not for treatment ($F(1,30) = 1.5$; $p = 0.23$), and there was no interaction between time and treatment ($F(1,30) = 0.45$; $p = 0.50$). Including concurrent antidepressant use did not have any effect on the results. In total there was only one patient showing a reduction of more than 50% in HDRS score, who had undergone sham treatment. There were no patients fulfilling criteria for remission.

3.3. Relation with treatment resistance

We correlated the DM-TRD score with change in HDRS score before and after treatment and found a significant correlation in the active group ($r = 0.57$; $p = 0.027$), which was not present in the sham group ($r = -0.20$; $p = 0.46$). A Fisher-Z test did not reveal a significant difference in correlations between the two groups ($z = -1.11$, $p > 0.1$). A scatter plot of the relation between DM-TRD and change in HDRS-score is shown in Fig. 2. The results indicate that more severe treatment resistance is associated with a lower degree of response to active rTMS treatment. There was no correlation between duration of

Table 1

Demographic and clinical characteristics of both treatment arms.

	Active ($n = 15$)	Sham ($n = 16$)	Total ($n = 31$)	P Value
Female sex, no. (%)	9/15 (60%)	13/16 (81%)	22/31 (71%)	0.19 ^b
Age, years				
mean (SD)	47.3 (11.5)	49.7 (11.0)	48.6 (11.1)	
range	25–67	31–73	25–73	0.57 ^a
Level of education (1–5) ^c				
mean (SD)	2.6 (1.2)	2.8 (1.4)	2.7 (1.3)	0.76 ^a
range	1–5	1–5	1–5	
DM-TRD,				
mean (SD)	18.7 (2.4)	18.2 (2.8)	18.4 (2.5)	
range	14–21	12.5–23	12.5–23	0.61 ^a
Previous ECT, no. (%)	6/15 (40%)	9/16 (56%)	15/31 (48%)	0.36 ^b
Current antidepressant usage, no. (%)	7/15 (47%)	14/16 (88%)	21/31 (68%)	0.01 ^{* b}
Age of onset, years,				
mean (SD)	28.8 (12.1)	25.2 (10.4)	26.9 (11.2)	0.38 ^a
range	11–50	12–50	11–50	
Duration current episode, months				
mean (SD)	54.6 (26.2)	57.9 (54.8)	56.3 (42.7)	0.83 ^a
range	24–100	24–180	24–180	
First / recurrent depression	4/15	1/16	5/31	0.11 ^b
Number of episodes,				
mean (SD)	2.9 (1.2)	3.5 (1.3)	3.2 (1.3)	0.17 ^a
range	1–5	1–5	1–5	
HDRS-17 baseline				
mean (SD)	24.1 (4.2)	22.7 (3.8)	23.4 (4.1)	0.33 ^a
range	14–31	18–29	14–31	
HDRS-17 end				
mean (SD)	21.0 (5.4)	18.6 (4.2)	19.7 (5.6)	0.23 ^a
range	10–29	9–28	9–29	
Responders, no. (%)	0/15 (0%)	1/16 (6%)	1/31 (3%)	0.11 ^b

Table 1 Demographic and clinical characteristics of both treatment arms. Abbreviations: SD: standard deviation; ECT: electroconvulsive therapy; DM-TRD: Dutch method for quantification of treatment resistance in Depression, range 2–26, higher = more resistant; HDRS-17: Hamilton depression rating scale 17-item, range 0–52.

^a T-test for independent samples (2-tailed).

^b Likelihood Ratio (2-sided).

^c Educational level is coded level 1 to 5 (5 = academic), according to the Dutch education system.

current episode and change in HDRS score (active: $r = 0.035$, $p = 0.90$; sham: $r = 0.002$, $p = 0.81$), indicating that the level of treatment resistance may be a better predictor for treatment response than the level of chronicity.

3.4. Side effects

3.4.1. Treatment was overall well tolerated by the patients

Nine out of 15 patients in the active group and 10 out of 16 patients in the sham group reported mild to moderate headache symptoms, whereby the frequency of reported headaches was comparable in the two groups (44 vs 37%). There were no serious adverse events, such as epileptic seizures, observed during the trial.

4. Discussion

The aim of this RCT was to investigate the effect of a standard 4-week protocol with 20 sessions of high frequency rTMS delivered to the left dorsolateral prefrontal cortex (60,000 pulses in total) in chronic, treatment resistant MDD patients. We performed an interim analysis after completion of 31 patients and decided to discontinue the RCT due to futility reasons as only one patient under sham treatment fulfilled the response criteria. In this study, we included patients with a severe level

Table 2
Medication.

Subject - condition	Antidepressant	Antipsychotic	Moodstabilizer	Benzodiazepine	Other
1 -rTMS	–	–	–	–	–
2 -rTMS	fluoxetine & mirtazepine	–	–	alprazolam & temazepam	promethazine
3 -sham	nortriptyline	–	lithium	lorazepam & clonazepam	–
4 -sham	nortriptyline	–	lithium	–	–
5 -rTMS	–	–	–	lorazepam	melatonin
6 -rTMS	–	quetiapine	–	–	–
7 -sham	fluoxetine	–	–	–	–
8 -sham	nortriptyline	–	–	–	–
9 -rTMS	–	perphenazine	–	temazepam	–
10 -sham	–	–	–	–	melatonin
11 -rTMS	tranylcypromine	–	–	–	melatonin
12 -sham	clomipramine	–	–	lorazepam	–
13 -rTMS	tranylcypromine	–	–	temazepam	–
14 -rTMS	–	–	–	alprazolam	–
15 -sham	–	olanzapine	–	–	–
16 -rTMS	venlafaxine & mirtazapine	quetiapine	–	temazepam & lorazepam	–
17 -sham	tranylcypromine	–	–	lorazepam & temazepam & midazolam	melatonin & levomepromazine
18 -rTMS	amitriptyline	quetiapine	–	flurazepam	methylphenidate
19 -sham	bupropion	quetiapine & haloperidol	–	lorazepam	levomepromazine & promethazine
20 -sham	venlafaxine & trazodon	quetiapine	lithium	–	–
21 -rTMS	tranylcypromine & mirtazapine	haloperidol & olanzapine	–	lorazepam	levomepromazine & promethazine
22 -sham	tranylcypromine	–	–	alprazolam & zopiclon	levomepromazine
23 -rTMS	–	–	–	oxazepam	melatonin
24 -sham	mirtazapine	haldol	–	lorazepam	promethazine
25 -rTMS	clomipramine	aripiprazol	–	temazepam	melatonin
26 -sham	venlafaxine	quetiapine	–	lorazepam	–
27 -rTMS	–	–	–	–	–
28 -sham	sertraline	–	–	–	–
29 -rTMS	–	–	–	oxazepam	levomepromazine
30 -sham	tranylcypromine	–	–	oxazepam	promethazine
31 -sham	venlafaxine	quetiapine	–	–	–
total (%)	21/31 (68%)	11/31 (35%)	3/31 (10%)	19/31 (61%)	13/31 (42%)

Table 2 Medication usage during the trial.

of treatment resistance, which we measured and staged by means of the DM-TRD. We correlated the DM-TRD with the symptom relieve expressed in the HDRS and found a significant negative association between severity of treatment resistance and symptom improvement in the active rTMS group, while there was no relation with duration of episode. These findings indicate that a standard 4-week protocol of rTMS is not effective in severe treatment resistant, chronic depression. The level of treatment resistance instead of the level of chronicity may be the most contributing factor to estimate the probability of treatment response in TRD patients, which is in line with a recent two stage model

of TRD to operationalize criteria for the level of treatment resistance in MDD patients (Conway et al., 2017).

The patients examined in this study are a difficult group to treat, due to both chronicity and multiple treatment failures. In general, failure to respond to initial treatments diminishes the chance to respond to other treatments as well. Measuring treatment resistance has long been a challenge in the field of psychiatry (Ruhé et al., 2012). Ruhé and colleagues described that a widely accepted and applicable measurement for TRD is important for several reasons. Firstly, different definitions cause different prevalence rates and a uniform approach is

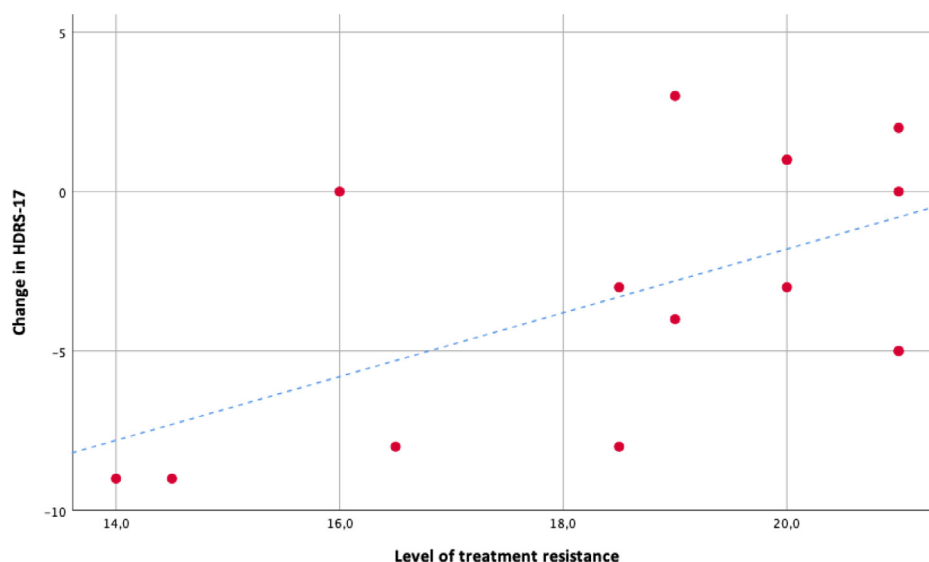


Fig. 1. Scatter plot of the change in HDRS-17 after treatment plotted against the level of treatment resistance (score DM-TRD) in the active group.

needed. Secondly, identifying risk factors involving the development of TRD and its different stages may help. Thirdly, predicting a high risk of TRD prior to or during the early stages of depression may help initial treatment guidance, for example, referral to more intensive therapy such as in tertiary care. Fourthly, an applicable measurement can be used broadly, improving characteristics and homogeneity description in next-step treatments.

Gaynes and colleagues (Gaynes et al., 2014) found in their systematic review and meta-analysis a beneficial effect of rTMS compared with sham in TRD patients. TRD criteria for studies to be included in the review were at least two adequately performed, failed trials with antidepressants. This review did not show a preference for a specific treatment protocol. The main difficulty to assess efficacy of rTMS treatment is that many studies differ in the characteristics of the treatment such as the given pulses per treatment, number of treatment days, intensity of rTMS varying between 90% to 160% MT and stimulation frequencies varying from 1 Hz to 20 Hz. Importantly, no description of staging or treatment resistance was described in any of the studies.

In the present study, we used the most commonly evaluated treatment protocol, i.e. high-frequency stimulation over the left dorsolateral-prefrontal cortex with 60,000 pulses over the course of 4 weeks (George et al., 2010; O'Reardon et al., 2007). However, we do have to consider that a longer treatment course might have positively influenced the outcome of this study. For example, Bakim and colleagues (Bakim et al., 2012) stimulated treatment resistant patients with 20 Hz pulses for 2 s plus 28 s intertrain interval during 20 trains for 30 sessions (6 weeks course) over the left DLPFC, leading to a total number of pulses of 24,000. This caused a significant response (>50% decrease) in HDRS score. Although the patient sample was not chronically depressed and less treatment resistant than our sample, it is remarkable that the most prominent effect in this study was found between the 4th and 6th week. We only stimulated for 4 weeks in line with the majority of the studies and one may have to consider longer treatment protocols. In this context, new possibilities like deep transcranial magnetic stimulation (DTMS) have also arisen for treatment resistant patients. Berlin and colleagues described having a response and remission rate of 70.6% and 41.2% respectively with DTMS for TRD (Berlin et al., 2014). The average number of failed pharmacological interventions was around 5 antidepressants and patients had to retain their medical regime 4 weeks prior and during the study. In this open label study, patients received 20 Hz stimulation for 2 s and 20 s waiting time, 75 trains with a deep brain stimulator. Other ways to optimize rTMS for treatment resistant MDD may be the application of theta burst stimulation, which may induce more potent neuroplastic effects in comparison with conventional rTMS (Chung et al., 2015), or by combining rTMS with psychotherapy, to probe additional effects of different treatment modalities (Donse et al., 2018).

Finally, with respect to the limitations of the study, we have to consider that the method of sham stimulation used in the present study could have caused small effects within the brain. A solution for this would be to use a sham coil, although each 'placebo' method has its own limitations (Duecker and Sack, 2015). Moreover, in our group a substantial number of patients even had undergone ECT prior to participating in this trial, contributing to a very high level of treatment resistance. Future studies should standardly use measures of treatment resistance to take the level of TRD precisely into account. Despite the evidence for the stimulation setup we used, we cannot rule out that a more intensive or advanced rTMS protocol (i.e. longer treatment period, more sessions, bilateral, priming or deep stimulation etc.) would have resulted in a more beneficial outcome. Future studies should investigate this severe treatment-resistant group with rTMS protocols that have proven to be more effective than the standard high frequency protocol that we used.

5. Conclusion

"Standard" rTMS treatment for 4 weeks over the left DLPFC is not be effective in chronic, severe treatment-resistant depressed patients. While a replication of our data in this severe patient group may be ethically difficult, further research with less treatment resistant patients might show a more beneficial outcome. Also, a meta-regression analysis of rTMS studies that report on the level of treatment resistance is needed to indicate the range of treatment resistance that most likely benefits from "standard" rTMS treatment. Our results indicate that the most optimal place of "standard" rTMS seems to be a more moderate level of TRD and an intermediate step in the stepped care model of depression. Future studies in severe TRD should consider more advanced protocols with proven superior efficacy.

Our results suggest that measures of treatment resistance should be standardly integrated in treatment planning with rTMS. When rTMS is conducted in severe treatment resistant patients, we recommend to extend the standard treatment protocols to at least 6 weeks of treatment to increase the chances of a beneficial outcome.

CRedit authorship contribution statement

P.F.P. van Eijndhoven: Conceptualization, Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing. **J. Bartholomeus:** Formal analysis, Writing - original draft. **M. Möbius:** Investigation, Writing - review & editing. **A. de Bruijn:** Investigation, Writing - review & editing. **G.R.A. Ferrari:** Writing - review & editing. **P. Mulders:** Writing - review & editing. **A.H. Schene:** Writing - review & editing. **D.J.L.G. Schutter:** Conceptualization, Methodology, Writing - review & editing. **J. Spijker:** Conceptualization, Writing - review & editing. **I. Tendolkar:** Conceptualization, Formal analysis, Writing - review & editing.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.05.055.

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