


Repetitive transcranial magnetic stimulation in major depression

A three-arm parallel-group dose-response randomized pilot trial

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Abstract

Background: The optimal dose (number of pulses per session) of repetitive transcranial magnetic stimulation (rTMS), using the H-coil, in major depressive disorder (MDD) has not previously been reported.

Objective: To explore the relationship between rTMS dose and antidepressant effect, and collect data for the design of a definitive trial.

Methods: This was a double-blind, three-arm parallel-group, randomized [1:1:1], pilot trial conducted in Stockholm, Sweden (September 2014 to September 2016). The primary outcome was change in depression severity measured with the Montgomery Åsberg Depression Rating Scale (MADRS) after 4 weeks. Participants (n = 29) with MDD were randomized to 1000, 2000, or 4000 pulses of rTMS for 20 sessions during 4 weeks.

Results: At 4 weeks, the 3 treatment groups reduced the mean MADRS (95% CI) by 11.6 (4.0–19.2), 9.1 (5.0–13.3), and 11.3 (4.1–18.5) points respectively. Eleven participants met criteria for response and 10 for remission. No serious adverse events occurred. Ratings of subjective memory improved in all groups. Exploring the effect of dose and time, 4000 pulses had the largest reduction in MADRS during the first 2 weeks. A comparison of change in MADRS between 2000 and 4000 pulses after 2 weeks will require a sample size of 66 patients at power .80 and alpha .05.

Conclusions: It is feasible to conduct a definitive trial investigating whether a higher number of magnetic pulses per treatment session gives a more rapid antidepressive response.

Abbreviations: CGI-I = Clinical Global Impression-Improvement scale, CGI-S = Clinical Global Impression-Severity scale, CPRS-Memory = item 17 “failing memory” of the Comprehensive Psychopathological Rating Scale, DLPFC = dorsolateral prefrontal cortex, ECT = electroconvulsive therapy, GSE-My = Global Self-Evaluation-Memory, ITT = intent-to-treat, MADRS = Montgomery Åsberg Depression Rating Scale, MDD = major depressive disorder, MT = motor threshold, QIDS-SR16 = The Quick Inventory of Depressive Symptomatology, Self-Report 16 items, rTMS = repetitive transcranial magnetic stimulation, rTMS1000 = rTMS group 990 pulses/session, rTMS2000 = rTMS group 1980 pulses/session, rTMS4000 = rTMS group 3960 pulses/session, TRD = treatment resistant depression.

Keywords: dose-response, H-coil, left dorsolateral prefrontal cortex, major depressive disorder, repetitive transcranial magnetic stimulation

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Highlights

- We examined the effect of three different doses of H-coil rTMS in MDD.
- The higher dose showed the largest treatment effect during the first two weeks.
- There were minimal differences between the groups after four weeks.
- No serious adverse events occurred, indicating safety of the higher dose.
- There was a slight improvement of subjective memory in all treatment groups.

1. Introduction

Major depressive disorder (MDD) is a severe and common disorder. The lifetime prevalence of having a major depressive episode is estimated at 12.5%.^[1] In 2017 depressive disorders was ranked as the leading cause of non-fatal health loss.^[2] The suicide risk for patients with mood disorders has been estimated to be 13 to 26 times higher than the risk for the general population.^[3,4] MDD also increases the risk of developing ischemic heart disease, RR 1.56 (95% CI 1.30–1.87), contributing to its mortality.^[5] About half of patients respond and one-third remit using first-line treatment with selective serotonin reuptake inhibitors.^[6] About 30% of patients with MDD have not reached remission after 2 to 4 trials with pharmacological or cognitive behavioral therapy (i.e., treatment-resistant depression, TRD).^[7] Hence there is a need for additional treatment modalities.

Repetitive transcranial magnetic stimulation (rTMS) is used in TRD with response- and remission rates estimated at 30% and 19% respectively^[8] which is about 50% better than the third treatment step of the STAR*D trial (13.7%).^[7]

rTMS involves sending repetitive alternating currents (pulses) through a metal coil that via electromagnetic induction affects neuronal activity at the focus of stimulation as well as interconnected neuronal networks. The pulses are delivered in series (trains) with pauses in between (intertrain intervals). There is an infinite way of combining different rTMS parameters such as coil design, target area, stimulus intensity, frequency of pulses (pulses per second), frequency of sessions (sessions per day), train duration, intertrain interval, the total number of pulses per session and length of the treatment course.

The total number of pulses per session is the definition of treatment “dose” which we investigated in this study. One meta-analysis showed no association between treatment response and the total number of pulses per day,^[8] whereas another found a negative correlation between the total number of pulses per session and improvement of depression.^[9] Higher stimulus intensity (100% of motor threshold (MT)) has been shown to be more effective than subthreshold intensity (90% of MT).^[10] A possible dose-response relationship has, to our knowledge not previously been studied within a trial designed with this as the primary objective. Detailed knowledge of dose-response relations can contribute to the optimization of rTMS treatment protocols.

In a study comparing electric field characteristics of various coils in a spherical head model, the H1-coil stimulated larger volumes than the conventional figure-8 coil,^[11] and has thereby

been hypothesized to be more effective. Supporting this, is that targeting the intended treatment location—left dorsolateral prefrontal cortex (DLPFC)—is associated with treatment response.^[12,13] Due to poor anatomical specificity, using the figure-8 coil with the “5-cm rule” (stimulating 5 cm anterior to the location in motor cortex causing twitching of the thumb) has been estimated to result in an actual treatment location outside of DLPFC in about 30%.^[14,15]

Additionally, according to a comparative review investigating the efficacy of electroconvulsive therapy (ECT), figure-8 and H-coil rTMS after 4 weeks of treatment; suggesting the H-coil (responders 44%) might be better than the conventional figure-8 coil (responders 22%).^[16] When comparing the standardized effect sizes of the 2 randomized studies that led to the FDA-approval of the H-coil (0.76) and the figure-8 coil (0.36 to 0.56); the H-coil seems more favorable.^[17,18]

To adequately power a randomized controlled trial (RCT) of the relationship between dose and antidepressant effect, estimates and variances of the treatment effect is required. Thus, the research aim of this pilot trial was to examine the relationship between number of stimuli per session and antidepressant effect and to collect data (estimates, 95% confidence intervals, and variances) on the primary outcome measure from which a sample size of a definitive RCT can be estimated.

2. Materials and methods

The study (clinicaltrials.gov; NCT03265340) was performed in accordance with the World Medical Association Declaration of Helsinki after approval by the regional ethical review board in Stockholm (2014/368–31) and reported according to CONSORT.^[19,20] It was a single-center, double-blind, three-arm parallel design, dose-response, pilot trial with simple randomization [1:1:1], conducted in Stockholm, Sweden. Active enrollment of 33 patients took place from September 2014 through September 2016. Patients were recruited from 2 psychiatric tertiary care clinics (outpatients and inpatients), and by newspaper advertisement. All study procedures took place after written and oral consent. The trial ended when the predefined number of participants was reached.

2.1. Study overview

The inclusion criteria were an ongoing episode of Major Depressive Disorder (MDD) as defined by ICD-10 (F32, F33) according to the Mini International Neuropsychiatric Interview 6.0,^[21] age >18 years, and a Montgomery Åsberg Depression Rating Scale (MADRS)^[22] score ≥ 20 . Exclusion criteria were psychotic symptoms, a lifetime history of any non-mood psychotic disorder or bipolar disorder, current (within the last month) substance or alcohol abuse/dependence; fluoxetine treatment last 3 weeks, major neurological disorders (e.g., Parkinson's, stroke, dementia), severe psychomotor retardation, pregnancy, acute medical disorders, presence of any contraindications for repetitive transcranial magnetic stimulation (rTMS) (e.g., history of epilepsy, ferromagnetic material head/neck implants), ECT within 2 months before inclusion and previous rTMS treatment ever.

The screening procedure, including a medical- and psychiatric interview, was performed by a trained psychiatrist (CJE, KJ, MA, UB). Eligible patients were included. Participants were free to withdraw at any time without prejudice. Antidepressants were

tapered and discontinued at least 5 half-lives before randomization. Anxiolytic and hypnotic drugs were allowed during treatment at the discretion of the clinician. Patients were randomly assigned to rTMS group 990 pulses/session (TMS1000), rTMS group 1980 pulses/session (rTMS2000), or rTMS group 3960 pulses/session (rTMS4000); receiving 990, 1980 and 3960 pulses per treatment session respectively.

A total of 20 treatments were conducted during 4 consecutive weeks, with 5 treatments per week. Subjects were allowed to make up for missed treatments. However, those who missed more than 2 consecutive treatments, or more than 5 in total were discontinued. Missed treatments were added to the treatment course to achieve a total of 20 treatments.

2.2. Blinding and randomization

The participants were randomly allocated to one of the 3 treatment groups in a ratio of 1:1:1, by simple randomization using a computer-generated randomization list. The randomization list was generated and concealed from the researchers by a third party. After obtaining informed consent, the research nurse telephoned the third party for allocation consignment. Subjects were blinded to treatment allocation firstly by receiving information that they would be attached to the rTMS equipment for 41 minutes and that it would make noise during the first part, followed by a second silent period. Secondly, they were not informed that the differences in dose were the number of pulses per session. Patients were further instructed not to discuss the treatment experience with the raters.

The rTMS treatment was administered by unblinded trained staff at the 2 sites. Trained psychiatrists at each site, “raters,” were blinded by treatment allocation not being visible in medical charts. Further, the staff administering the treatment were told not to discuss/mention treatment dose with raters.

2.3. Outcome measures

Raters performed weekly assessments throughout the treatment period. The treatment effect was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS)^[22]; Clinical Global Impression-Improvement scale (CGI-I)^[23]; Clinical Global Impression-Severity scale (CGI-S)^[23] and the Quick Inventory of Depressive Symptomatology, Self-Report 16 items (QIDS-SR16).^[24]

Subjective memory disturbance was rated using the 7-point variant of item 17 “failing memory” of the Comprehensive Psychopathological Rating Scale (CPRS-Memory)^[25] and the Global Self-Evaluation-Memory (GSE-My).^[26] Alcohol use was assessed by the Alcohol Use Disorder Identification Test-Consumption (AUDIT-C).^[27]

The primary efficacy outcome measure MADRS was measured at baseline, weekly and last visit. Standard criteria for antidepressant response and remission were applied. Response was defined as a decrease of 50% or more in the MADRS from baseline to the last visit. Remission was defined as an absolute score of 9 or less. The QIDS-SR16, CGI-S, and CPRS-Memory were measured at baseline and last visit. The CGI-I and GSE-My were measured at last visit.

2.4. rTMS device

The treatment was given using a Magstim Rapid stimulator (Magstim Company, Ltd, Carmarthenshire, Wales, UK) with an H1-coil (Brainsway Inc., Jerusalem, Israel).

2.5. Procedure

Before stimulation, patients were provided with earplugs to lessen any possible adverse effects on hearing, due to the loud clicking noise generated. The motor threshold (MT) was assessed weekly and was established using the visualization method.^[28] First the location in the motor cortex where stimulation causes twitching of the contralateral thumb was located. Next, the stimulus intensity was titrated until the number of motor responses elicited was 5 out of 10 stimulations. Then, the coil was placed 6 cm anterior to the aforementioned location targeting the left the dorsolateral prefrontal cortex (DLPFC). During the first 3 treatments, the staff was allowed to titrate stimulation intensity up from 100% to 120% of the individual motor threshold (MT) in order to improve subjects’ tolerability to the treatment.

The treatment was delivered in two-second trains of 18Hz at 120% MT, with an intertrain interval of 20 seconds. The number of pulses, dose, or duration of treatment differed between the 3 treatment groups. rTMS1000 received 990 pulses (10 minutes of treatment), rTMS2000 received 1980 pulses (20 minutes of treatment) and rTMS4000 received 3960 pulses (40 minutes of treatment) at each treatment session. All subjects were attached to the rTMS equipment for 41 minutes as part of the previously described blinding procedure.

2.6. Data analysis

Since this was a pilot study, a formal sample size calculation was not required. However, assuming rTMS has a moderate to large standardized treatment effect, following the rules of thumb proposed by Whitehead et al, 10 patients per treatment arm are required to calculate the sample size of an 80% powered main study.^[29]

Descriptive data are presented with estimates and variance at baseline, after end of treatment and as the difference from baseline to end of treatment. Exploratory inferential statistics were conducted on the modified intent-to-treat (ITT) analysis set. However, no conclusions on the effectiveness of the intervention were made from the results as recommended by CONSORT. The modified ITT analysis set was defined as those who underwent at least one rTMS session at 120% MT. Missing data were imputed as last-observation carried forward.

Depression severity was assessed using the unidimensional scales MADRS (primary outcome measure) and QIDS-SR16 (secondary outcome measure). The change from baseline over time was modeled via repeated measures ANOVA methodology (STATA/SE, version 13.0). The change from baseline was modeled as a function of treatment group (treatment), treatment progression (time), and the treatment*time interaction as fixed effects. As for the remaining measures, the groups were compared using the non-parametric Kruskal Wallis test for ordinal variables and Pearson’s Chi-Squared test for categorical variables.

The sample size calculation for a definitive trial, comparing the rTMS2000 and rTMS4000 after 2 weeks of treatment, was based on the mean change in MADRS and the SD of the change in the respective groups, with power set at .80 and alpha .05 (G*Power). The overall significance level for this pilot study was .05 using two-tailed tests.

3. Results

A total of 33 participants fulfilled both inclusion and exclusion criteria, signed informed consent and were randomized consecutively. Twenty nine patients tolerated at least 1 treatment session

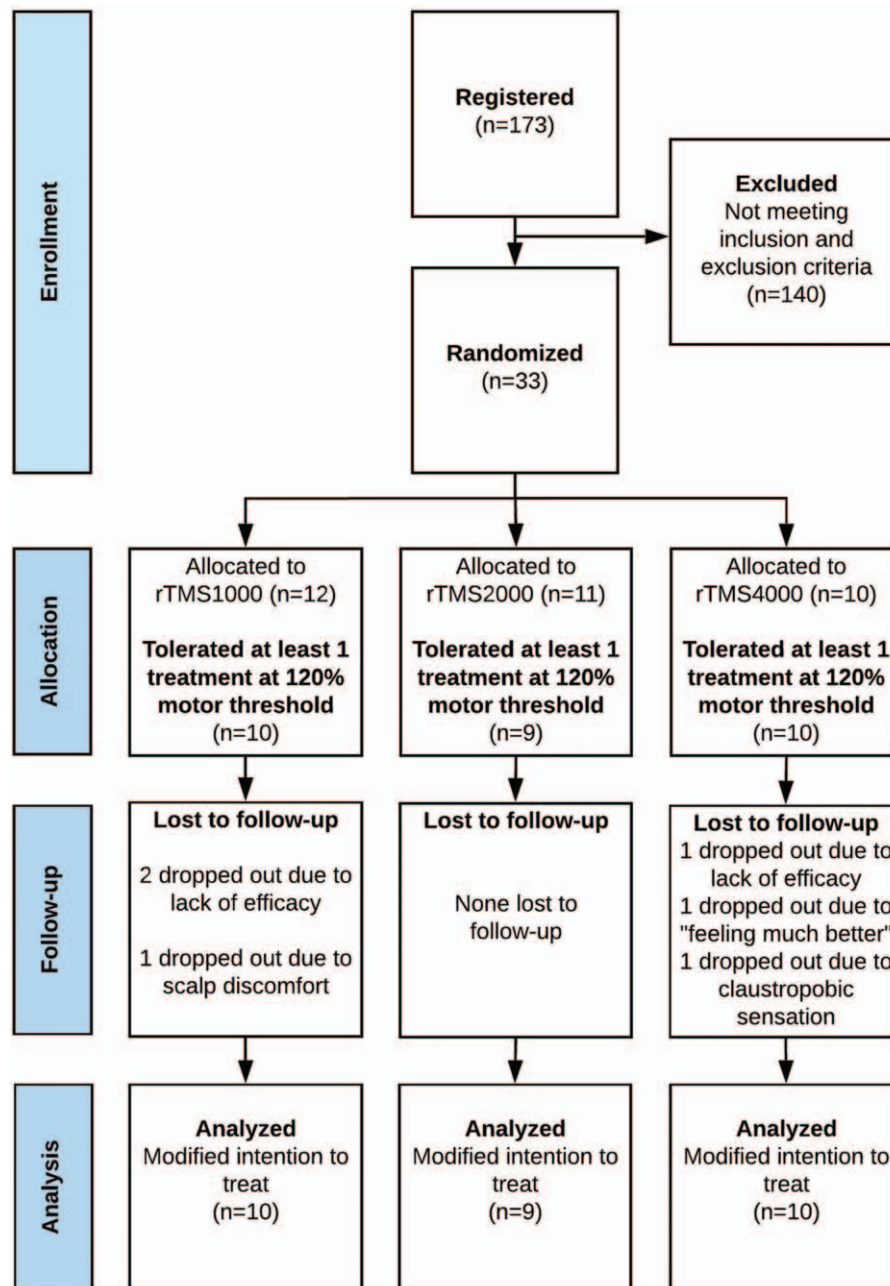


Figure 1. CONSORT flowchart.

at 120% MT constituting the modified ITT analysis set. Twenty three participants completed the treatment course. A CONSORT flowchart is shown in Figure 1.

3.1. Patient disposition

The study included 29 depressed patients, randomly assigned to 3 treatment groups. The demographic and disorder related parameters are summarized in Table 1. The CGI-S median score of 4 for the study cohort corresponded to a depression severity of moderately ill. The groups were similar on baseline depression scores with an average MADRS of 27 and self-rated QIDS-SR16

of 18. Regarding baseline subjective memory impairment in the study sample, the median CPRS-Memory was 2 (occasional increased lapses of memory).

3.2. Dropouts

Six participants dropped out of the study before completing treatment, 3 in group rTMS1000 and 3 in group rTMS4000 (Fig. 1). In the rTMS4000 group, 1 participant dropped out because of “feeling much better”. In this case, records indicated the participant was in remission 1 week after dropout, CGI-S: 1 (normal, not at all ill).

Table 1
Baseline demographics and clinical features.

	rTMS1000	rTMS2000	rTMS4000
n	10	9	10
n (%) female	6 (60)	3 (33)	3 (30)
Education N (%)*			
Lower secondary education	3 (30)	1 (11)	1 (10)
Upper secondary education	3 (30)	3 (33)	4 (40)
Postsecondary non-tertiary education	2 (20)	0 (0)	1 (10)
First stage of tertiary education	2 (20)	4 (44)	4 (40)
Age mean (SD)	51 (15)	62 (15)	49 (13)
Duration of current depressive episode mean (SD)	27 (46)	39 (67)	14 (18)
Previous depressive episodes mean (SD)	4.2 (3.1)	2.9 (2.8)	4.6 (5.2)
Duration since first-time debut of MDD in years, mean (SD)	23 (10)	22 (15)	16 (12)

* 1 missing data rTMS2000.

3.3. Clinical measures

The primary outcome measure was the change in MADRS from baseline (T0) to after 4 weeks of treatment (T4). In Figure 2 the mean MADRS is plotted against time, for each treatment group. For the individual participants in the respective groups, MADRS score is plotted against time in Figure 3. rTMS1000, rTMS2000, and rTMS4000 reduced the mean (95% CI) MADRS by 11.6 (4.0–19.2), 9.1 (5.0–13.3); and 11.3 (4.1–18.5) respectively.

Descriptive data of the secondary outcomes for the study sample is described in the text and separated by treatment group in table Table 2. Repeated measures ANOVA analysis revealed a significant reduction in MADRS from baseline to last visit for the study sample [$F(4,104)=23, P<.001$] as well as for each treatment group respectively [rTMS1000 $F(4,108)=21, P<.001$; rTMS2000 $F(4,108)=18, P<.001$; rTMS4000 $F(4,108)=23, P<.001$]. There was no significant treatment*time interaction $F(8,104)=0.73, P=.66$. Neither the secondary outcome measure QIDS-SR16 revealed a significant treatment*time interaction $F(2,18)=0.84, P=.45$.

Eleven of the 29 participants met criteria for clinical response and 10 were in remission at treatment completion. The mean reduction in CGI-S (95% CI) was 1.1 (0.6 to 1.6), where a reduction in 1 step from 4 to 3 corresponds to moving from moderately to mildly ill. Furthermore, the CGI-I measured at last

visit was on average 2.6 (2.1–3.1), corresponding to between much- and minimally improved.

Regarding subjective memory disturbance, the participants scored on average (95% CI) 4.4 (4.1–4.8) on GSE-my (slight improvement) and a mean reduction in CPRS-memory of 0.6 (0.1–1.1) (slight improvement). There were no significant differences between the groups on any of the primary or secondary outcomes.

3.4. Ancillary analysis

Although the groups did not seem to differ at the prespecified endpoint T4, exploration of the data revealed diversion at T1 and T2 between the groups. The largest difference in decrease in MADRS was shown at T2 favoring group rTMS4000 (11.7 ± 8.6 SD) over rTMS2000 (6.4 ± 5.8 SD). See Figure 1. A sample size calculation revealed that 66 patients would be required to detect a difference of 5 points in MADRS after 2 weeks of treatment (power .80; 2-sided α .05) between rTMS4000 and rTMS2000.

3.5. Safety and tolerability

Mild temporary headaches were the most common side-effects, reported in eleven of the patients. The proportion of patients experiencing any adverse effect was 6/10 in rTMS1000, 6/9 in rTMS2000 and 3/10 in rTMS4000. One patient in group rTMS1000 dropped out due to scalp pain and twitching of the facial muscles. Another subject, in group rTMS2000, experienced transient confusion, manifested as incoherent speech, after the thirteenth treatment. This subject completed the treatment course, and the confusion did not recur. Two patients reported toothaches; 2 reported tiredness post treatment and 1 patient reported transient worsening of tinnitus. There were no serious adverse events such as tonic-clonic generalized seizures.

4. Discussion

Exploring the relationship between dose and antidepressant effect—the primary research aim of this pilot trial—rTMS4000 (double dose compared to the conventional rTMS2000) showed the largest decrease in depression severity during the first 2 weeks. However, differences between the groups after 4 weeks (primary endpoint) were minimal. A sample size calculation revealed that 66 patients would be required to detect a difference in antidepressant effect after 2 weeks of treatment. Additionally, the previously not studied dose rTMS4000 was safe and well tolerated. All patients allocated to this group tolerated at least 1 session at 120% MT. Only 1 patient dropped out in rTMS4000 due to intolerable side effects (claustrophobic sensation), compared to 1 patient in rTMS1000 (scalp discomfort) and none in rTMS2000.

To further increase the antidepressant effect, the most effective combinations of rTMS parameters must be chosen. The relationship between clinical effect and the number of stimuli per session in H-coil rTMS has previously not been studied. Identifying such a relationship may facilitate the development of more efficient protocols, improving responses to treatment. Since we wanted to explore the previously not studied doses rTMS1000 and rTMS4000, comparing these to the conventional rTMS2000, a randomized double-blinded pilot-trial was a necessary first step. Hence, we could evaluate safety, tolerability and ultimately exploring the effect of dose on depression severity.

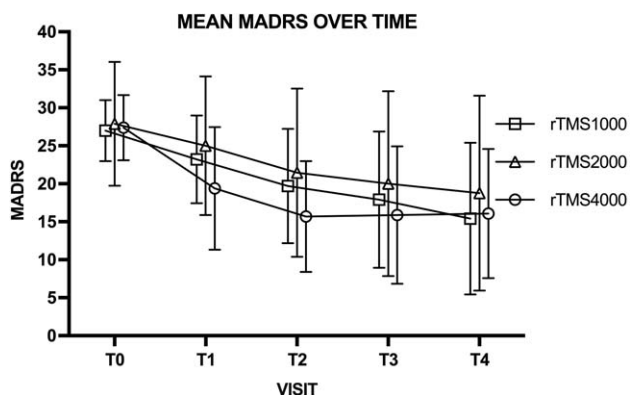


Figure 2. Mean MADRS plotted over time by treatment group. Error bars indicate standard deviations.

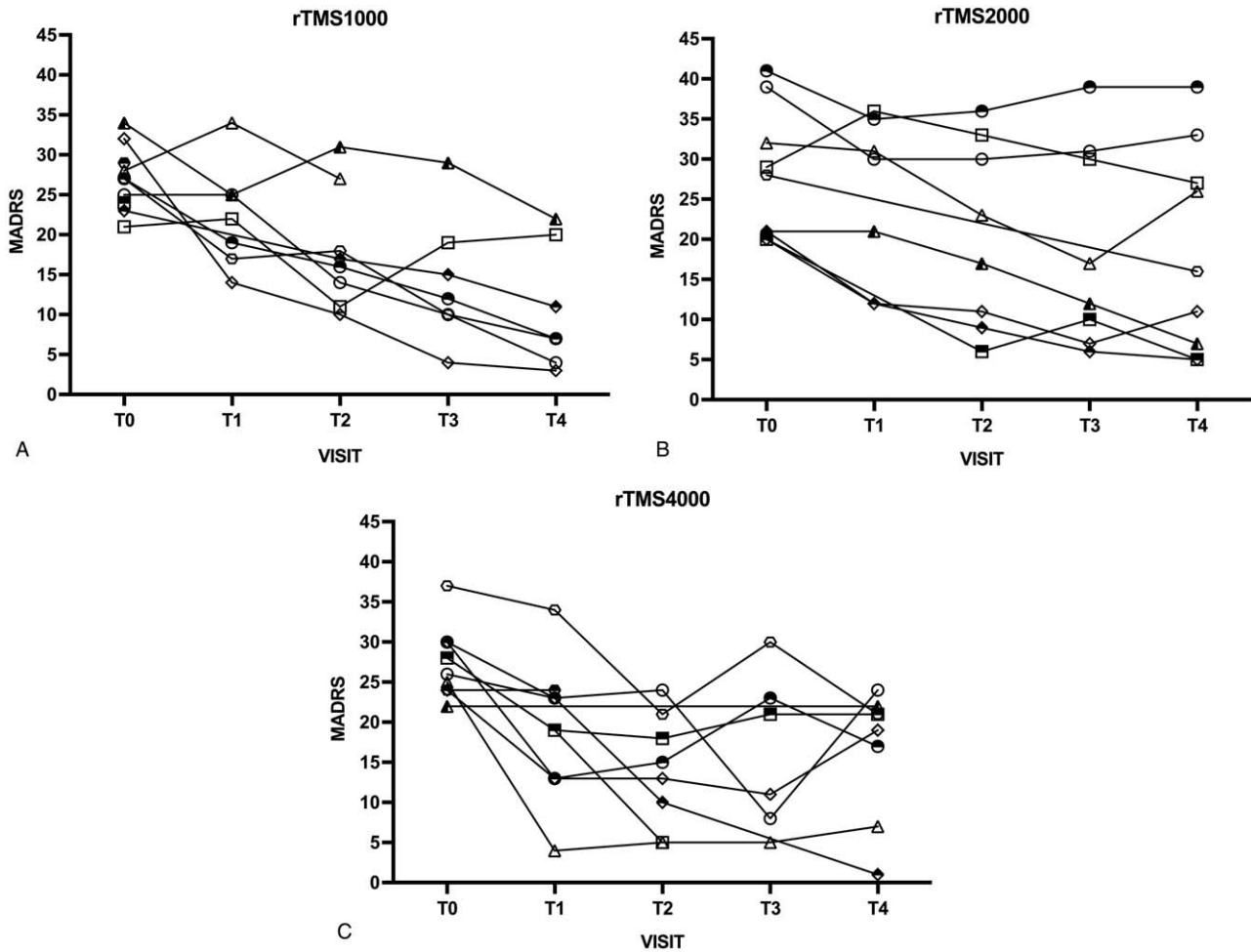


Figure 3. Individual MADRS scores for the respective treatment groups plotted over time.

Table 2

Descriptive data presented within each treatment group as estimates and variance at baseline (pre), end of treatment (post) and as the difference from baseline to end of treatment (change).

			rTMS1000	rTMS2000	rTMS4000
MADRS	pre	mean (SD)	27.0 (4.0)	27.9 (8.2)	27.4 (4.3)
	post	mean (SD)	15.4 (10.0)	18.8 (12.8)	16.1 (8.5)
	change	mean (95% CI)	-11.6 (-19.2 to -4.0)	-9.1 (-13.3 to -5.0)	-11.3 (-18.5 to -4.1)
QIDS-SR16	pre	mean (SD)	17.1 (4.5)	17.2 (5.1)	17.2 (2.4)
	post	mean (SD)	12.9 (7.0)	13.0 (6.2)	12.4 (5.1)
	change	mean (95% CI)	-4.2 (-8.6 to 0.2)	-4.2 (-7.0 to 1.5)	-4.8 (-8.6 to -1.0)
CGI-S	pre	mean (SD)	4.1 (0.3)	4.1 (0.8)	4.3 (0.5)
	post	mean (SD)	2.9 (1.3)	3.0 (1.7)	3.2 (1.6)
	change	mean (95% CI)	-1.2 (-2.1 to -0.3)	-1.1 (-1.9 to -0.3)	-1.1 (-2.3 to -0.1)
CGI-I	post	mean (95% CI)	2.0 (1.1 to 2.9) [*]	2.9 (2.1 to 3.7)	2.9 (1.7 to 4.0) [†]
CPRS-Memory	pre	mean (SD)	2.7 (1.3)	2.7 (1.4)	1.8 (1.4)
	post	mean (SD)	2.1 (1.4)	2.2 (1.5)	1.0 (1.5)
	change	mean (95% CI)	-0.6 (-1.8 to 0.6)	-0.4 (-1.0 to 0.1)	-0.8 (-1.8 to 0.2)
GSE-My	post	mean (95% CI)	4.7 (3.8 to 5.6) [†]	4.3 (3.8 to 4.9)	4.3 (3.5 to 5.0) [†]
Response	post	% (95% CI)	50 (19 to 81)	33 (7 to 70)	30 (7 to 65)
Remission	post	% (95% CI)	40 (12 to 74)	33 (7 to 70)	30 (7 to 65)

^{*} 3 missing data.

[†] 2 missing data. Response defined as a decrease of 50% or more in the MADRS from baseline to end of treatment and remission defined as an absolute score of 9 or less.

In line with our hypothesis of a dose-response effect, higher stimulus intensity has shown superiority over subthreshold intensity.^[10] Additionally, delivering rTMS at a faster rate, 18 sessions over 3 weeks compared to 20 sessions delivered over 4 weeks^[30] showed comparable results at 4 week endpoint, indicating treatment can be completed faster.

Contrary to our hypothesis, meta-analyses have either shown no association between the number of stimuli per session and antidepressant effect^[8] or even a negative correlation.^[9] As the included studies are heterogeneous regarding treatment parameters and properties of the study populations, we believe drawing conclusions on adequately powered clinical trials examining treatment parameters head-to-head is preferable.

In our pilot study, all 3 treatment-groups, as well as the group as a whole, had a significant effect of time on the change in MADRS after 4 weeks. For the study sample, response and remission rates were 38% and 34%, comparable to 37% and 30% in the H-coil rTMS sham-controlled study.^[17] To our knowledge, this is the first time that results from double the conventional dose of H-coil rTMS was reported. No serious adverse events occurred, indicating 4000 pulses per treatment is safe. Other studies found safety delivering more than twice as many pulses per session (6800)^[31] compared to the FDA-cleared 3000 pulses/session, with the figure-8 coil. Furthermore, we found impairment of subjective memory after treatment completion; in fact, on average all treatment groups had non-significant improvements.

Consistent with our research aim, we explored the dose-response relationship, finding the largest decrease in depression severity in the highest dose-group after 2 weeks. During the following 2 weeks, administration of rTMS4000 provided little additional effect, whereas the lower dose regimens caught up. Perhaps there is a ceiling effect, in administering high dose rTMS, beyond proceeding 2 weeks acute course treatment has little effect. In our study sample we found rTMS4000 to be safe and showing faster antidepressant effect. If confirmed in a definitive trial, this would be beneficial for patients seeking alleviation from the burden of depression. If indeed, the length of the acute treatment course could be reduced to 2 weeks, this would also increase availability since one of the largest obstacles is committing to the time-consuming once daily, four-week long course.

This pilot trial carries several methodological limitations. The first one is the attempted blinding of the subjects. Some of the participants might have figured out their treatment allocation. This could have been examined by asking them for their assumption at the end of treatment. However, even if participants would have figured out their designated treatment allocation, bias was limited by beforehand clarifying that the effects of different doses are unknown. In this study design, we cannot rule out that the apparent faster treatment response in rTMS4000 could be due to a larger placebo effect. Taking this into consideration, we propose changing the study protocol, of a definitive RCT to replace rTMS1000 with a placebo arm receiving sham treatment. Additionally, we suggest changing the primary endpoint to after 2 weeks, keeping assessment at 4 weeks as secondary endpoint to avoid suboptimal treatment length.

Secondly, participants dropping out of treatment were not encouraged to participate in planned rating, which could have introduced bias in both directions depending on the reason for dropout. For example, rTMS1000 had the highest rate of dropouts due to lack of efficacy (n=2). By failing to measure

those dropouts on important outcome measures such as CGI-I at the end of treatment could have inflated the treatment effect of that group. On the contrary rTMS4000 had 1 participant dropping out due to “feeling much better” and failing to measure depression severity of that participant after the end of treatment could have resulted in a deflated treatment effect of this group. To reduce this bias in the definitive trial, we suggest asking participants dropping out of treatment to keep participating in planned ratings.

Finally, recruitment to the study was slower than predicted, and thus we had to add recruitment via advertising in the local newspapers. A large proportion of our subjects were recruited this way, which means the population might not be representative of treatment-resistant depressions in psychiatric outpatient clinics. However, important baseline characteristics such as depression severity and duration of the current episode did not differ from those of study participants in naturalistic studies on depression.^[7]

5. Conclusion and future directions

Based on the results from this pilot we suggest conducting a double-blinded RCT comparing clinical effect between sham treatment, the standard 2000 pulses/session and the higher 4000 pulses/session after two- and 4 weeks of treatment. If treatment response indeed comes faster with the double dose, this could have clinical importance in alleviating symptoms more rapidly and perhaps reducing in-care hospital stays. If shortening the treatment length could be achieved, this could also increase the availability of the treatment.

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Author contributions

All authors discussed the results and contributed to the final manuscript. KJ contributed to data collection, analysis and wrote the first draft of the manuscript; MA contributed to conceptualization of the study, study design, protocol writing, data collection, analysis and manuscript writing, UB contributed to study design, protocol writing, data collection, analysis and manuscript writing, CE contributed to study design, protocol writing, data collection, analysis and manuscript writing, JL contributed to conceptualization of the study, study design, protocol writing, data analysis and manuscript writing.

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