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Research paper

Early symptom improvement and other clinical predictors of response to repetitive transcranial magnetic stimulation for depression

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) is a rapidly emerging treatment for depression, but outcome prediction is still a challenge. This study aimed to identify predictors of response to rTMS among baseline clinical factors and early symptomatic improvements.
Methods: This cohort study comprised 136 patients with a unipolar or bipolar depressive episode referred for clinical intermittent theta-burst stimulation or right-sided 1 Hz rTMS at the Uppsala Brain Stimulation Unit. The co-primary outcomes used for logistic regression were response, defined as ≥50 % reduction of Montgomery and Åsberg Depression Rating Scale Self-assessment (MADRS-S) total score, and 1–2 points on the Clinical Global Impression Improvement (CGI-I) scale. Early improvement was defined as ≥20 % reduction in the MADRS-S total score, or ≥ 1 point reduction in each MADRS-S item, after two weeks of treatment.
Results: The response rates were 21 % for MADRS-S and 45 % for CGI-I. A depressive episode >24 months had lower odds for MADRS-S response compared to ≤12 months. Early improvement of the MADRS-S total score predicted CGI-I response (95 % CI = 1.35–9.47, $p = 0.011$), *Initiative*$_6$ predicted MADRS-S response (95 % CI = 1.08–9.05, $p = 0.035$), and *Emotional involvement*$_7$ predicted CGI-I response (95 % CI = 1.03–8.66, $p = 0.044$).
Limitations: No adjustment for concurrent medication.
Conclusions: A depressive episode ≤12 months and early improvement in overall depressive symptoms, as well as the individual items, *Initiative*$_6$ and *Emotional involvement*$_7$, predicted subsequent rTMS response in a naturalistic sample of depressed patients. This could facilitate the early identification of patients who will benefit from further rTMS sessions.

1. Introduction

1.1. Symptom trajectories and early symptom improvement as predictors of response

Repetitive transcranial magnetic stimulation (rTMS) is a safe and effective treatment option for patients with major depressive disorder (MDD) (Dalhuisen et al., 2022; Sackeim et al., 2020). In clinical trials, the pooled response rate for conventional rTMS is 40 % (Vida et al., 2023). A further developed protocol utilizing short stimulation duration, intermittent theta burst stimulation (iTBS), has been assessed as non-inferior to conventional rTMS (Blumberger et al., 2018). The response rates for iTBS varies between 18 and 56 % in clinical trials (Chu et al., 2021). When used in a naturalistic clinical setting, a response rate of 31 % has been reported for conventional rTMS protocols (Bouaziz et al., 2023) and 42.1–58.6 % for iTBS (Ekman et al., 2023; Spitz et al., 2022). However, there seems to be a considerable individual difference. According to a recent analysis of one of the largest rTMS trials to date, treatment response could be divided into four different trajectories: rapid responders, non-responders, and two groups of intermediate responders (Kaster et al., 2019). There is also emerging evidence indicating that specific symptoms within the depressive syndrome have unique trajectories, such as mood and cognition which appears to generally improve by at least 50 % after 36 sessions of rTMS in patients who achieve remission (Sakurai et al., 2022).

In the field of TMS, only a few studies have examined predictors of response early in the treatment course. A subgroup of rapid responders, with a generally significant improvement of depressive symptoms already by the second week of rTMS, was identified in an analysis of the THREE-D study (Kaster et al., 2019). This is in line with a recent trial

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where 66 % of patients, experiencing a reduction of general depressive symptoms by ≥4 points in the Daily Symptom Index (DI-5) score after 10 sessions of rTMS, were responders by session 20 (Gill et al., 2023). Another study highlighted that an improvement of <20 % in the total score of the self-rated Beck Depression Inventory-II (BDI-II) after 10 sessions of rTMS was a negative predictor of response in subsequent treatment sessions (Feffer et al., 2018). To our knowledge, it has thus far not been explored whether early improvements in specific depressive symptoms during rTMS also has a predictive value, as was the case in the antidepressant pharmacotherapy STAR*D trial where early improvement in feeling restless, low energy, feeling slowed down, negative self-view, and sad mood predicted remission (Sakurai et al., 2013).

1.2. Other clinical predictors of response

Literature on clinical characteristics associated with rTMS response remain disparate and scarce, especially concerning iTBS. Although age may impact the rTMS outcome, there is not a common agreement in all studies (Aguirre et al., 2011; Ekman et al., 2023; Fregni et al., 2006; Kaster et al., 2019; Sackeim et al., 2020; Valiengo et al., 2022). Females might have a superior antidepressant response to rTMS in comparison with males (Kedzior et al., 2014; Sackeim et al., 2020). Furthermore, the characteristics of a depressive episode also seem to predict rTMS outcome. Clinical characteristics associated with a decreased likelihood of responding to rTMS include greater severity of depression at baseline, anxiety symptoms, greater levels of treatment resistance and a longer duration of current depressive episode (Ekman et al., 2023; Fitzgerald et al., 2016; Kaster et al., 2023; Trevizol et al., 2020).

1.3. Objectives

This cohort study aimed to describe symptom trajectories in patients with depression undergoing rTMS and to identify predictors of treatment response among baseline clinical factors and early improvements in both overall and specific depressive symptoms.

2. Methods

2.1. Trial design and participants

This cohort study was conducted at Uppsala University Hospital and the patients were recruited between February 7, 2019 and May 25, 2023. All patients referred for clinical rTMS at the Uppsala Brain Stimulation Unit were consecutively approached for potential study participation. Inclusion criteria were being 18 years or older, having a unipolar or bipolar depressive episode, receiving left-sided iTBS or right-sided 1 Hz short rTMS for the first time, and having provided a written informed consent (see flowchart of participants in fig. S1 in the supplementary material). This study was approved by the Research Ethical Review Board in Uppsala and was conducted in accordance with the Declaration of Helsinki as revised 1989.

2.2. rTMS protocols

A magnetic stimulator, MagPro R30 or MagPro X100, MagVenture, was used for the rTMS and iTBS treatments, using either the standard figure-of-eight coil cool-B65 or the slightly angled B-70. Left-sided iTBS was the standard rTMS treatment option for MDD, where the coil was placed over the F3 according to the 10–20 electroencephalogram (EEG) electrode positioning system, targeting the left dorsolateral prefrontal cortex (DLFPC). The iTBS protocol consisted of three pulses at 50 Hz, repeated at 5 Hz for two seconds, followed by an eight-second break, and these trains were repeated 20 times, adding up to 600 pulses.

The second line rTMS protocol was right-sided 1 Hz rTMS, with the coil placed over F4, targeting the right DLPFC. This protocol comprised one minute trains of 1 Hz stimulation followed by a 30-s break, repeated six times, resulting in 360 pulses. This right-sided 1 Hz short rTMS protocol was primarily offered to patients at an increased risk of seizure. From March 2021 and onwards, the local treatment guideline changed so that the right-sided 1 Hz rTMS became the primary protocol for patients with bipolar depression.

For both rTMS protocols, the treatment intensity was set at 120 % of the resting motor threshold (visual inspection of hand twitching). Daily treatment sessions were administered every weekday for four up to normally six weeks, 20 to 30 sessions in total, or until achieving remission, as long as there was a weekly improvement. Treatment was stopped if there was a lack of effect at the 4-week follow-up (i.e. not reaching at least 20 % improvement on MADRS-S).

2.3. Clinical data and symptom ratings

The clinical data, including symptom ratings, were retrieved from each patient's medical record. As per standard procedures, all patients were interviewed by a psychiatrist before initiation of rTMS and after having completed the rTMS treatment course. Most participants were rated by one psychiatrist (author RB). Before initiation of rTMS, starting from the second week and weekly thereafter, all patients continuously rated their current depressive symptoms throughout the treatment using a set of Patient Reported Outcome Measures (PROMs).

The Maudsley Staging Method for Treatment Resistant Depression (MSM) (Fekadu et al., 2009) was performed by a psychiatrist before rTMS. MSM consists of five items: duration of current depressive episode (acute ≤12 months, subacute 13–24 months, or chronic >24 months), severity of the illness (subsyndromal, mild, moderate, severe without psychosis, or severe with psychosis), number of failed antidepressant medication (AD) trials (1–2 antidepressants, 3–4 antidepressants, 5–6 antidepressants, 7–10 antidepressants, or > 10 antidepressants), medication augmentation (if AD medication and other psychopharmaceuticals such as lithium, neuroleptics, and mood stabilizers have been used or not) and history of previous electroconvulsive therapy (ECT) (yes or no). The total score ranges from 3 to 15. Furthermore, the patients filled-in the Alcohol Use Disorders Identification Test (AUDIT) (Bohn et al., 1995) and the Drug Use Disorders Identification Test (DUDIT) (Berman et al., 2005) before initiation of rTMS. AUDIT is a self-reported rating for unhealthy alcohol use, based on the last year. The screening consists of 10-items rated on a 4-point Likert scale, except for items nine and 10, which only have 0, 2, and 4 points as possible responses. The total score ranges from 0 to 40. DUDIT is a self-administered screening instrument including 11 items for drug use. Each item is rated from 0 to 4 points, except for items 10 and 11, which only have 0, 2, and 4 points as possible responses. The total score ranges from 0 to 44.

The Montgomery and Åsberg Depression Rating Scale Self-assessment (MADRS-S) (Svanborg and Åsberg, 2001) is a self-rating scale containing nine items: mood{1}, feelings of unease{2}, sleep{3}, appetite{4}, ability to concentrate{5}, initiative{6}, emotional involvement{7}, pessimism{8}, and zest for life{9}. These items will be referred to as: *Depressed mood$_1$, Feelings of unease$_2$, Sleep distrubance$_3$, Appetite loss$_4$, Ability to concentrate$_5$, Initiative$_6$, Emotional involvement$_7$, Pessimism$_8$* and *Zest for life$_9$*. Each item is rated on a scale of 0 to 6 points, where 0 indicates no depressive symptoms and 6 points indicating the worst. The total score ranges from 0 to 54. This self-assessment, along with other PROMs described below, was completed by the patients before the initiation of rTMS, from the second week, and then weekly throughout the treatment. The memory item from the Comprehensive Psychopathological Rating Scale (CPRS memory item) (Åsberg et al., 1978) is a self-rating scale of subjective memory, ranging from 0 to 6 points, where 0 indicates no disturbance of memory and 6 points indicates a complete inability to remember anything. The EuroQol-Visual Analogue Scale (EQ-VAS) (Burström et al., 2014) is the patient's self-rated health ranging from 0 to 100 on a visual analogue scale, where 0 represents the worst imaginable health state, and 100 signifies the best imaginable health state.

Before initiation of rTMS and after having completed the rTMS treatment course, the patients were rated by a psychiatrist using the Clinical Global Impression (CGI) (Guy, 1976). The CGI assesses the severity of illness on a 7-point scale: from "normal, not at all ill" (1 point), "borderline mentally ill" (2 points), "mildly ill" (3 points), "moderately ill" (4 points), "markedly ill" (5 points), "severely ill" (6 points) to "among the most extremely ill patients" (7 points). After the last rTMS session, the patients were rated by a psychiatrist using the CGI-I (Guy, 1976). The CGI-I assesses symptomatic improvement after treatment on a 7-point scale ranging from "very much improved" (1 point), "much improved" (2 points), "minimally improved" (3 points), "no change" (4 points), "minimally worse" (5 points), "much worse" (6 points) to "very much worse" (7 points).

2.4. Outcomes

The primary outcome used for logistic regression analysis was the rTMS response, which was defined as a ≥ 50 % reduction in the MADRS-S total score, based on the patient's last available rating after the initiation of rTMS. The co-primary outcome used for logistic regression analysis was rTMS response defined as "very much improved" (1 point) or "much improved" (2 points) on the CGI—I, based on the clinician's rating after the patient completed the treatment course. The secondary outcome considered was rTMS remission, defined as being rated as either "normal, not at all ill" (1 point) or "borderline mentally ill" (2 points) on the CGI scale, based on the clinician's rating after the patient completed the treatment course. As our study comprises a heterogenous cohort of patients not excluding psychiatric comorbidity we refrained from exploring remission of depression in our regression analyses as many patients probably also will suffer residual symptoms from co-morbid disorders.

2.5. Potential predictors

The baseline predictors included various factors: sex assigned at birth: female or male; age groups: 18–29 years, 30–39 years, or ≥ 40 years; type of depression: unipolar depression or bipolar depression; duration of current depressive episode: acute (≤12 months), subacute (13–24 months), or chronic (>24 months); treatment failures: 1–2 antidepressants, 3–4 antidepressants, 5–6 antidepressants, 7–10 antidepressants, or > 10 antidepressants; medical augmentation: yes or no; and previous ECT: yes or no. Early predictors of response were defined as follows: ≥1 point reduction in all nine MADRS-S individual items, ≥20 % reduction in the MADRS-S total score, and ≥ 1 point reduction in the of CPRS memory item after two weeks of rTMS. This early change of depressive symptoms will hereinafter be referred to as early improvement.

2.6. Statistics

First, data were visually examined and plotted. Data distributions were described using means and standard deviations (SD), and median and interquartile ranges (IQR). Second, data were plotted in linear graphs to visualize symptom trajectories. Binary logistic regressions were used to analyze the clinical characteristics at baseline and early improvement as predictors of rTMS response. Clinical characteristics at baseline and early improvement in all of MADRS-S nine individual items were entered into a multivariate logistic regression analysis to explore the independent predictive value of an individual baseline characteristics or items. To identify the MADRS-S response rate, all participants with an available MADRS-S rating were included in an Intention-To-Treat (ITT) analysis. Each patient's last available rating was used, irrespectively of how many weeks they had been treated. Patients with only baseline ratings were categorized to the MADRS-S non-responder group. Only patients who had CGI-I and CGI ratings post treatment were included in the analyses of CGI-I response and CGI remission. All patients with any MADRS-S rating after initiation of rTMS or available CGI-I rating were included in the logistic regression analyses to predict response. We also performed a sensitivity analysis by running the same prediction analyses in the subsample of patients who completed the treatment course Per-Protocol (at-least four weeks of rTMS). The statistical analyses were performed using IBM SPSS Statistics for Windows, Version 28.0.

3. Results

3.1. Participants demographic and clinical characteristics

Demographic and clinical baseline data regarding the study participants are presented in Table 1. The mean of MADRS-S total score corresponds to moderate depression, bordering on severe depression. Most of the study participants were females, had a unipolar depression, and received left-sided iTBS. Thirty-two of the study participants received less than four weeks of treatment (see Fig. S1 in supplementary).

Table 1
Demographic and clinical baseline data.

Baseline data	N total	Mean (SD)	Median (IQR)
Age	136	35 (13)	32 (15)
MSM total score	132	9 (2)	9 (2)
AUDIT	125	3 (4)	2 (5)
DUDIT	128	0 (2)	0 (0)
MADRS-S	134	34 (7)	34 (8)
CPRS memory item	132	3 (1)	3 (2)
EQ-VAS	130	27 (13)	30 (15)
CGI	128	5 (1)	5 (1)
	N total	**N (%)**	
Female/male	136	80 (59)/56 (41)	
Unipolar/bipolar depression	136	110 (81)/26 (19)	
MSM subcategories			
Duration of current episode:	132		
Acute ≤12 months		45 (34)	
Subacute 13–24 months		15 (11)	
Chronic >24 months		72 (55)	
Severity of illness:	132		
Subsyndromal		0 (0)	
Mild		1 (1)	
Moderate		62 (47)	
Severe without psychosis		66 (50)	
Severe with psychosis		3 (2)	
Treatment failures:	132		
1–2 antidepressants		27 (21)	
3–4 antidepressants		40 (30)	
5–6 antidepressants		46 (35)	
7–10 antidepressants		16 (12)	
>10 antidepressants		3 (2)	
Medication augmentation:	132		
No		46 (35)	
Yes		86 (65)	
Previous ECT:	132		
No		104 (79)	
Yes		28 (21)	
iTBS		115 (85)	
1 Hz		21 (15)	

Abbreviations: SD=Standard deviation, IQR = Interquartile range, MSM = Maudsley Staging Method for Treatment Resistant Depression, AUDIT = Alcohol Use Disorders Identification Test, DUDIT = Drug Use Disorders Identification Test, MADRS-S = Montgomery and Åsberg Depression Rating Scale Self-assessment, CPRS memory item = the memory item from the Comprehensive Psychopathological Rating Scale, EQ-VAS = EuroQol-Visual Analogue Scale, CGI=Clinical Global Impression, Medication augmentation = antidepressants and other psychopharmaceuticals, such as lithium, neuroleptics, and mood stabilizers; iTBS = left-sided intermittent theta-burst stimulation, 1 Hz = right-sided 1 Hz short repetitive transcranial magnetic stimulation.

3.2. Outcome data

According to MADRS-S response, 21 % (n = 28) of the study participants were responders (n total = 135), while response assessed using CGI-I resulted in 45 % (n = 42) responders (n total = 94). Among participants with available CGI-I and MADRS-S ratings (n total = 93), 24 % (n = 22) were MADRS-S responders. Finally, 20 % (n = 19) of all patients were remitters after having completed the rTMS treatment course according to CGI (n total = 96).

3.3. Descriptive statistics

Considering each item in MADRS-S separately, all nine items decreased numerically during rTMS treatment. *Sleep disturbance*$_3$ and *Appetite loss*$_4$ started at lower baseline scores compared to the other items (Fig. 1). Depressive symptoms were generally rated lower after treatment compared to before initiation of rTMS. There was a decrease in depressive symptoms over the first seven weeks of rTMS according to the mean of MADRS-S total score, and subsequent confidence intervals (CI) did not overlap with baseline CI (Fig. 2). Most of the study participants completed the rTMS treatment course after five weeks, leading to larger CI intervals thereafter.

3.4. Baseline predictors of response

Individuals aged ≥40 had significantly lower odds for rTMS response compared to younger age groups regarding MADRS-S response in the univariate analysis and CGI-I response in the multivariate analysis (Table 2). A duration of depressive episodes lasting >12 months in the univariate analysis and > 24 months in the multivariate analysis showed lower odds for MADRS-S response compared to episodes lasting ≤12 months. In the univariate analysis, patients with bipolar depression or medical augmentation had higher odds for the MADRS-S response than patients with unipolar depression or no medical augmentation. However, patients with a history of previous ECT had lower odds for MADRS-S response in the multivariate analysis.

3.5. Early predictors of response

Univariate analyses with MADRS-S response as the outcome identified an early improvement of *Depressed mood*$_1$ and *Initiative*$_6$ as statistically significant early predictors (Table 3). In the multivariate analysis, adjusted for the other eight MADRS-S items, only *Initiative*$_6$ remained significant. Univariate analyses with CGI-I response as the outcome identified an early improvement of *Depressed mood*$_1$, *Appetite loss*$_4$, *Initiative*$_6$ and *Emotional involvement*$_7$ as statistically significant early predictors. However, in the multivariate analysis, only *Emotional involvement*$_7$ remained significant. *Appetite loss*$_4$ showed borderline significance. In addition, early improvement of *Pessimism*$_8$ was statistically significant in the multivariate analysis.

Early improvement in the MADRS-S total score was not a significant predictor of MADRS-S response, with an odds ratio (OR) of 1.97 (95 % CI of 0.81–4.78). However, early improvement in the MADRS-S total score was a significant predictor of CGI-I response, with an OR 3.57 (95 % CI of 1.35–9.47).

Early improvement in the CPRS memory item was not a statistically significant predictor of either MADRS-S response (OR 1.05, [95 % CI 0.44–2.51]) or CGI-I response (OR 1.10, [95 % CI 0.47–2.57]).

3.6. Sensitivity analysis in the per-protocol sample

The results from the analyses of the predictors in the Per-Protocol sample (n = 104) were all in the same direction as the ITT analyses (see supplementary text and tables).

4. Discussion

4.1. Summary of main results

This cohort study observed a decrease in all self-rated depressive symptoms throughout a clinical treatment course of rTMS. A longer, more chronic, depressive episode was found to predict a poorer MADRS-S response compared to a shorter duration. Early improvement in the MADRS-S total score and the individual item *Emotional involvement*$_7$ predicted a CGI-I response. Furthermore, the MADRS-S response was predicted by an early improvement in *Initiative*$_6$.

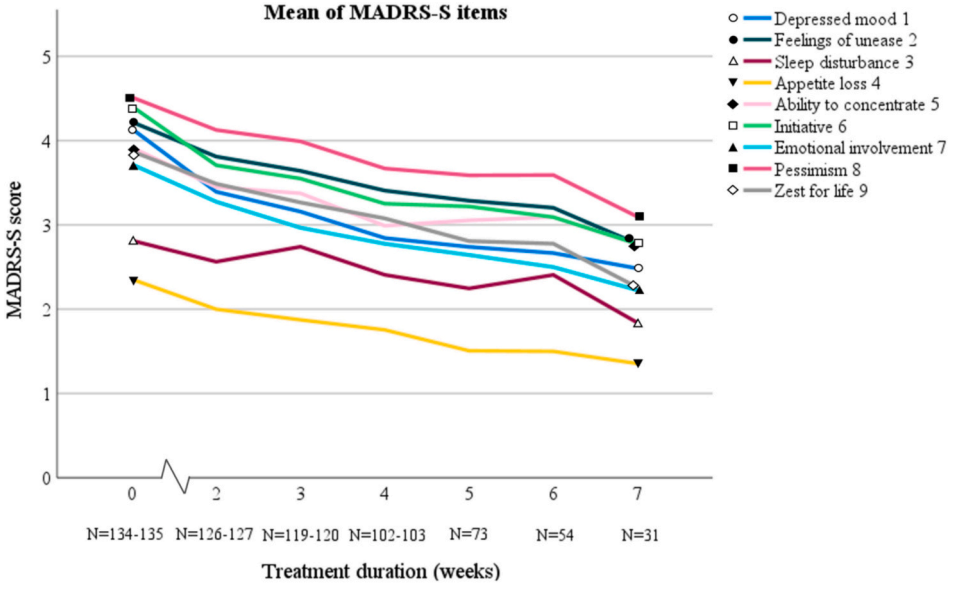

Fig. 1. Mean of the study participants' score at baseline (W = 0), after two weeks of treatment, and thereafter on a weekly basis until last day of treatment, separately for Montgomery and Åsberg Depression Rating Scale Self-assessment (MADRS-S) nine items. No ratings were collected after the first week of treatment, and not all patients received treatment for nine weeks. Ratings at weeks 8 and 9 did not have enough data to be shown.

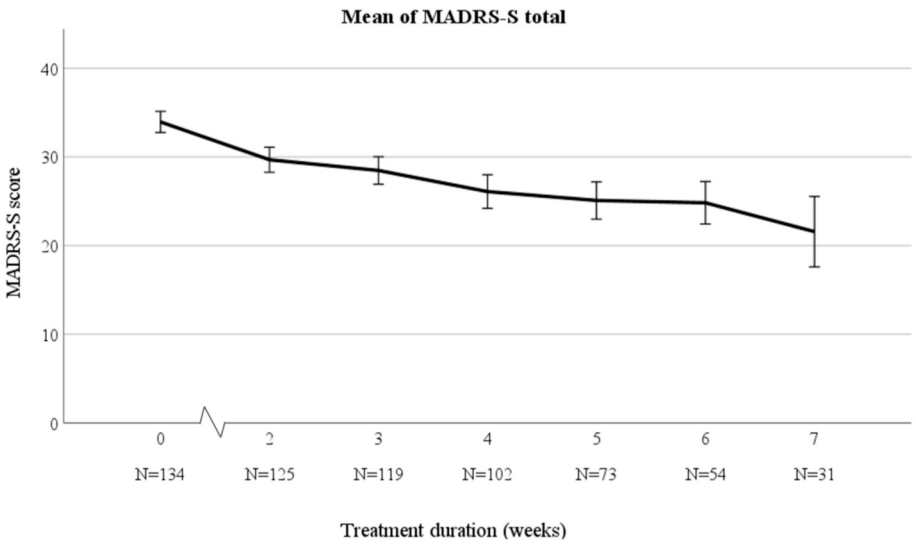

Fig. 2. Mean of the study participants' Montgomery and Åsberg Depression Rating Scale Self-assessment (MADRS-S) total score at baseline (W = 0), after two weeks of treatment, and thereafter on a weekly basis until the last day of treatment. No ratings were collected after the first week of treatment, and not all patients received treatment for nine weeks. Error bars are 95 % confidence interval (CI). The majority of the study participants completed the rTMS treatment course after five weeks, upon which time the CI becomes increasingly larger. The ratings at weeks 8 and 9 did not have enough data to be shown.

Table 2
Baseline predictors of response.

	Univariate				Multivariate			
	MADRS-S response		CGI-I response		MADRS-S response		CGI-I response	
Baseline predictors	OR (95 % CI)	P	OR (95 % CI)	P	OR (95 % CI)	P	OR (95 % CI)	**P**
Female	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Male	0.41 (0.16–1.05)	0.062	0.91 (0.40–2.09)	0.821	0.49 (0.15–1.63)	0.245	1.79 (0.63–5.05)	0.271
Age 18–29	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
30–39	1.66 (0.67–4.12)	0.273	1.19 (0.47–3.02)	0.718	3.24 (0.97–10.84)	0.057	1.17 (0.40–3.37)	0.776
≥40	0.20 (0.04–0.95)	0.043	0.37 (0.12–1.16)	0.087	0.28 (0.05–1.63)	0.155	0.25 (0.06–0.96)	0.044
Unipolar depression	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Bipolar depression	3.97 (1.56–10.10)	0.004	2.47 (0.91–6.69)	0.076	3.28 (0.82–13.11)	0.093	1.80 (0.48–6.76)	0.386
≤12 months	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
13–24 months	0.12 (0.01–0.98)	0.047	1.39 (0.28–6.79)	0.685	0.25 (0.02–2.83)	0.260	5.00 (0.74–33.96)	0.099
>24 months	0.24 (0.10–0.60)	0.002	0.47 (0.19–1.15)	0.097	0.25 (0.07–0.93)	0.039	0.62 (0.20–1.93)	0.412
1–2 antidepressants	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
3–4 antidepressants	0.42 (0.13–1.39)	0.155	0.42 (0.12–1.45)	0.172	1.24 (0.25–6.02)	0.794	0.40 (0.09–1.79)	0.231
5–6 antidepressants	0.68 (0.23–2.01)	0.483	0.80 (0.25–2.55)	0.706	3.07 (0.64–14.77)	0.162	1.44 (0.34–6.20)	0.622
7–10 antidepressants	0.34 (0.06–1.85)	0.212	0.50 (0.12–2.14)	0.350	1.12 (0.13–9.65)	0.917	0.66 (0.11–4.05)	0.655
>10 antidepressants	1.19 (0.09–15.04)	0.894	0.80 (0.04–14.89)	0.881	15.21 (0.39–600.94)	0.147	0.60 (0.02–17.44)	0.768
No Augmentation	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Augmentation	3.74 (1.21–11.61)	0.022	2.32 (0.96–5.64)	0.062	3.05 (0.78–12.02)	0.110	2.56 (0.80–8.25)	0.115
No previous ECT	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Previous ECT	0.24 (0.05–1.08)	0.063	0.78 (0.25–2.41)	0.667	0.14 (0.03–0.79)	0.026	0.83 (0.22–3.16)	0.780

Abbreviations: MADRS-S response = ≥50 % reduction of Montgomery and Åsberg Depression Rating Scale Self-assessment total score, CGI-I response = 1–2 points on Clinical Global Impression Improvement, OR = Odds ratio, CI=Confidence interval, P=*P*-value, AD = antidepressants, Augmentation = Medication augmentation with antidepressants and other psychopharmaceuticals, such as lithium, neuroleptics, and mood stabilizers; ECT = Electroconvulsive therapy.

4.2. Comparisons with previous studies

4.2.1. Symptom trajectories

In the present study, all MADRS-S individual items showed numerical decreases during the rTMS treatment. *Sleep disturbance*$_3$ and *Appetite loss*$_4$ started at numerically lower baseline scores compared to the other items. A recent study investigating trajectories of individual depressive symptoms demonstrated that somatic symptoms and neurovegetative symptoms such as appetite, weight change, and sleep problems, were not improved by rTMS as distinctly as the other items in the 16-item Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR$_{16}$) and the 28-item Hamilton Depression Rating Scale (HAMD$_{28}$) after rTMS (Sakurai et al., 2022). This finding is congruent with the results in the present study, since the numerically lower baseline scores for *Sleep disturbance*$_3$ and *Appetite loss*$_4$ might not display an improvement in the same order of magnitude as the other individual depressive symptoms. Even though MADRS-S and QIDS-SR$_{16}$ are different rating scales, shared items such as *Depressed mood*$_1$ in MADRS-S versus sad mood in QIDS-SR$_{16}$, *Ability to concentrate*$_5$ versus concentration or decision-making, and *Zest for life*$_9$ versus suicidal ideation, visually had similar trajectories during rTMS in both studies.

4.2.2. Efficacy of rTMS

There is a similarity between the CGI-I response in the present study and the findings of Ekman et al. (2023), a Swedish register-based study using the same definition of CGI-I response. Another naturalistic observational study reported 46 % PHQ-9 responders and 58.6 % MADRS responders after iTBS (Spitz et al., 2022). These response rates

Table 3
Early predictors of response.

	Univariate				Multivariate			
	MADRS-S response $N = 126$*		CGI-I response $N = 93$**		MADRS-S response $N = 125$		CGI-I response $N = 92$	
Early predictors ≥*1 point reduction*†:	OR (95 % CI)	P	OR (95 % CI)	P	OR (95 % CI)	P	OR (95 % CI)	P
Depressed $mood_1$	2.77 (1.08–7.10)	0.034	2.60 (1.09–6.18)	0.031	2.03 (0.67–6.14)	0.213	2.11 (0.71–6.22)	0.177
Feelings of $unease_2$	1.65 (0.71–3.84)	0.247	1.07 (0.47–2.45)	0.870	1.29 (0.50–3.29)	0.600	0.66 (0.25–1.77)	0.408
Sleep $disturbance_3$	1.68 (0.71–3.97)	0.242	2.18 (0.92–5.18)	0.077	1.26 (0.47–3.41)	0.647	2.13 (0.74–6.11)	0.159
Appetite $loss_4$	1.99 (0.85–4.64)	0.113	2.92 (1.25–6.83)	0.014	2.02 (0.81–5.07)	0.134	2.68 (1.00–7.18)	0.050
$Concentration_5$	1.06 (0.46–2.47)	0.886	1.47 (0.65–3.35)	0.354	0.58 (0.22–1.55)	0.281	0.92 (0.33–2.52)	0.865
$Initiative_6$	3.53 (1.38–9.07)	0.009	2.37 (1.02–5.50)	0.044	3.13 (1.08–9.05)	0.035	2.46 (0.85–7.15)	0.098
Emotional $involvement_7$	1.75 (0.75–4.07)	0.197	2.48 (1.07–5.72)	0.034	1.24 (0.43–3.61)	0.692	2.99 (1.03–8.66)	0.044
$Pessimism_8$	1.72 (0.74–4.02)	0.208	0.94 (0.41–2.16)	0.882	0.77 (0.27–2.24)	0.633	0.24 (0.07–0.80)	0.020
Zest for $life_9$	1.79 (0.76–4.20)	0.183	1.36 (0.58–3.18)	0.477	1.09 (0.38–3.12)	0.872	0.79 (0.27–2.31)	0.666

Abbreviations: MADRS-S response = ≥50 % reduction of Montgomery and Åsberg Depression Rating Scale Self-assessment total score, CGI-I response = 1–2 points on Clinical Global Impression Improvement, Early predictors = ≥1 point reduction in all of MADRS-S nine individual items after two weeks of treatment, OR = Odds ratio, CI=Confidence interval, P=P-value.

† <1 point reduction of MADRS-S items (ref).

* Except $Sleep\ disturbance_3$, $N = 125$.

** Except $Pessimism_8$, $N = 92$.

were higher in both patient and clinician ratings compared to the present study.

4.2.3. Predictors of rTMS outcome

In line with an earlier study of patients treated with various rTMS protocols (Fitzgerald et al., 2016), the present study found that patients with a shorter duration of the current depressive episode were more likely to respond well to rTMS, compared to those with a longer duration. Further, a study on the response to ECT has also identified shorter duration of the depressive episode as a positive predictor of treatment outcomes (Haq et al., 2015).

In the present study, early improvement seemed to be a positive predictor of rTMS response. This finding is in accordance with previous results from the few available studies (Gill et al., 2023; Kaster et al., 2019). To our knowledge, the present study is the first to identify early improvements in specific depressive symptoms as positive predictors of rTMS response. According to a study of patients treated with citalopram, early improvement in the items in $QIDS\text{-}SR_{16}$ related to low energy and feeling slowed down was considered as a significant predictor of remission (Sakurai et al., 2013). These predictors could be seen as consistent with our findings, particularly regarding the early improvement in *Initiative*$_6$ as a predictor of MADRS-S response. However, a general interest in $QIDS\text{-}SR_{16}$ could not predict remission, as its counterpart *Emotional involvement*$_7$ in MADRS-S was a predictor of CGI-I response.

4.3. Limitations

The effect of concurrent medication has not been accounted for which is a limitation. The aim of the present study's ITT principle was to avoid potential bias due to the exclusion of patients during the treatment course. On the other hand, some of the patients who were included in the analyses terminated rTMS before completing four weeks of treatment, for reasons unrelated to the treatment itself. These patients might have achieved response or remission if they would have completed the treatment course. Therefore, the inclusion of this subgroup of patients in the analyses might have resulted in lower rates of response and remission. However, using the Per-Protocol (PP) principle excludes these patients, who are common in this clinical context. Thus, a strength of the chosen study design is its clinical use and relevance, since not all patients are fully compliant with rTMS. In contrast, an advantage of the PP principle is that it clarifies the effectiveness of rTMS, which occurs under optimal treatment conditions. Nevertheless, the results from our sensitivity analysis Per-Protocol presented in the supplementary that were in the same direction as the ITT analysis, mitigates any potential concerns regarding choosing ITT as primary analysis. Our effort to achieve a clinically relevant sample of patients by consecutively approaching all patients referred for clinical rTMS was an attempt to promote the generalizability of the findings. However, 24 % of all patients referred for clinical rTMS declined to participate in this study. This process of selecting participants could introduce selection bias. A larger study sample size would generate more reliable results and potentially better statistical power to detect meaningful relationships and differences.

In conclusion, not only baseline clinical factors such as the duration of depressive episodes, but also early improvements in both overall and specific depressive symptoms, such as *Initiative*$_6$ and *Emotional involvement*$_7$, predict responses to rTMS in patients with unipolar and bipolar depression. This finding could be useful in the clinical setting to identify early improvements in depressive symptoms as a guidance for psychiatrists in determining which patients may or may not benefit from further rTMS treatment sessions.

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CReDiT authorship contribution statement

Moa Winninge: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – Original draft, Visualization. **Martin Cernvall:** Methodology, Validation. **Robert Bodén:** Conceptualization, Methodology, Validation, Investigation, Data curation, Resources, Project administration, Funding acquisition.

All authors critically reviewed and revised the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of competing interest

None of the authors have anything to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.06.054.

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