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Depressive symptom trajectories with prolonged rTMS treatment

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ABSTRACT

Background: A prolonged repetitive transcranial magnetic stimulation (rTMS) treatment course could be beneficial for some patients experiencing major depressive episodes (MDE). We identified trajectories of rTMS response in depressive patients who received an extended rTMS treatment course and sought to determine which trajectories achieved the greatest benefit with a prolonged treatment course.

Method: We applied group-based trajectory modeling to a naturalistic dataset of depressive patients receiving a prolonged course of sequential bilateral rTMS (up to 51 treatment sessions) to the dorsolateral prefrontal cortex. Trajectories of the PHQ-9 with extended treatment courses were characterized, and we explored the association between baseline clinical characteristics and group membership using multinomial logistic regression.

Results: Among the 324 study participants, four trajectories were identified: "linear response, extended course" (N = 73; 22.5 %); "nonresponse" (N = 23; 7.1 %); "slowed response" (N = 159; 49.1 %); "rapid response, standard treatment length" (N = 69; 21.3 %). Only the "linear response, extended course" group showed considerable clinical improvement after receiving additional rTMS treatments. Greater baseline depressive symptoms were associated with linear response and non-response.

Conclusion: Our results confirmed the distinctive response trajectories in depressive patients receiving rTMS and further highlighted that prolonged rTMS treatment courses may be beneficial for a subset of patients with higher initial symptom levels and linear early treatment response.

1. Introduction

Major depression is one of the leading causes of disability worldwide and is associated with significant economic burdens [1,2]. The efficacy of first-line pharmacological treatments for depression remains modest, with as few as 30 % of patients achieving remission [3]. Depressive patients who have failed multiple antidepressant medication treatments are classified as having treatment-resistant depression (TRD) [4]. Amongst patients with TRD, repetitive transcranial magnetic stimulation (rTMS) has been shown to be an effective and safe treatment [5], achieving a remission rate of ~30 % [6]. Although such treatment outcomes are clinically meaningful, especially in the TRD population, a significant portion of individuals still do not benefit from rTMS, leaving much room for improvement [7,8].

One possible approach to improve rTMS courses is to prolong the treatment course [9,10]. The industry-sponsored O'Reardon et al. trial reported that the remission rates were almost two-fold higher with active rTMS at week 6 than at week 4, indicating that longer stimulation periods might be associated with improved efficacy [11]. Furthermore, a significantly higher remission rate was observed in patients who received active treatment during the randomized, blinded phase of the O'Reardon et al. trial and subsequently underwent open-label active

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treatment than those who received sham treatment initially and then switched to open-label active treatment [12]. McDonald et al. found that patients with TRD who do not show a response to 10 Hz left DLPFC rTMS may experience remission by receiving additional sessions [13]. Continued treatment has also yielded a positive response in a notable portion of individuals who initially do not respond to deep rTMS treatment during the acute 4-week phase [14]. Considering these findings, most recent clinical trials have adopted a longer treatment course (4–6 weeks) than early TMS studies (2 weeks). The clinical benefits of an even longer treatment course (>7 weeks) have begun to emerge. In a retrospective naturalistic observational study [15], Razafsha and colleagues found that among 28 nonresponders to a standard 36-session DLPFC-TMS course, offering an additional 36 sessions yielded a 54 % response and 32 % remission rate. In a recent naturalistic study [16], Hutton and colleagues systematically compared clinical outcomes among a large sample of patients (N = 7215) receiving different numbers of rTMS sessions. They found a strong relationship between the treatment course length and the clinical outcomes of rTMS in real-world practice. Patients receiving more rTMS sessions achieved a larger magnitude of symptom reduction. However, it remains unclear how many additional sessions may be required to achieve remission among late responders or which subgroups of patients could benefit from an extended treatment course (>7 weeks).

If prolonged treatment courses do confer additional benefits beyond standard-length courses for some patients, it is important to understand which patients should receive these extended courses, as prolonging a potentially ineffective treatment can delay a potentially effective next step in treatment. Given the known heterogeneity of responses to rTMS [17,18], there may exist only a subset of people whose benefit from a prolonged course would outweigh the associated incremental logistical, administrative, and cost burdens [19]. One approach for quantifying the heterogeneity of response to treatment is through the use of group-based trajectory modeling (GBTM), which can examine treatment response variability and identify subgroups exhibiting similar patterns of change over time [20]. It allows the determination of the optimal treatment duration for different subgroups of patients and the prediction of the membership of subgroups according to the baseline clinical characteristics [21]. We have previously applied this analytic approach successfully to identify response trajectories for a 4–6 week course of left DLFPC rTMS [18], and have compared trajectories between standard and accelerated treatment protocols [17].

To better understand the role of prolonged rTMS treatment courses under naturalistic conditions, we conducted an analysis using data from a community-based dataset of depressive patients who received an extended course of rTMS treatments (up to 51 treatment sessions) and used group-based trajectory modeling to identify latent groups. Our objective was three-fold: (1) characterize the patterns of treatment response to rTMS over an extended rTMS treatment course; (2) identify the subgroup of patients who benefit from the additional rTMS treatments; (3) assess associations between previously identified baseline clinical characteristics and data-derived response trajectories.

2. Methods

2.1. Study design

This is a secondary analysis of a naturalistic cohort of depressive patients who received a course of rTMS from January 2019 to April 2021 at one of 19 clinic sites operated by Salience TMS Neuro Solutions (Plano, TX, USA). Patients were included in this analysis if they were over 16 years old, had a primary diagnosis of major depressive disorder (MDD) or bipolar disorder (BD) type I or II, showed resistance to at least two antidepressant trials, and had at least moderate symptom severity (PHQ-9 $\geq$ 10). Patients were required to have a primary diagnosis of a major depressive episode (MDE) occurring in the context of MDD or BD, but were not excluded due to psychiatric comorbidities such as anxiety disorders, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), or attention-deficit/hyperactivity disorder (ADHD). Clinical diagnosis used DSM-5 criteria, and treatment resistance was determined through psychiatric clinical assessment. All individuals were presenting for a course of acute rTMS (i.e., no maintenance rTMS). Individuals in this cohort first received a course of rTMS of standard treatment length; however, then all individuals were assessed for an additional 15 rTMS treatments that were provided to them at no cost. Patients completed informed consent before treatment with rTMS and data collection and provided informed assent and consent to use de-identified treatment data for research purposes. The study protocol was reviewed and approved by the Advarra Institutional Review Board.

2.2. rTMS treatment

Patients were treated with a sequential bilateral protocol, with a low-frequency protocol (1 Hz, 360 pulses, 60 s on, 30 s off) over the right DLPFC followed by a high-frequency protocol (20 Hz, 1200 pulses, 2 s on, 4 s off) over the left DLPFC, at 120 % resting motor threshold (RMT) once daily five times a week [22,23]. These protocols were used to ensure insurance eligibility and minimize the duration of treatment time while also being supported by prior neurophysiological and clinical data [22–24]. All treatments were administered using a MagVenture R30 stimulator and a Cool-B65 coil. Motor thresholds (MTs) were determined by visual inspection by the prescribing provider, using a standardized stepwise intensity titration algorithm, as well as a standardized 4 × 6 cm mapping grid coordinate system covering the primary motor region, to ensure consistency of technique across clinic sites. Treatment targets in the DLPFC were localized via the modified BeamF3 heuristic and applied to the left and right sides [25].

All patients first received a standard-length rTMS course consisting of 36 once-daily treatments. For patients to be eligible to receive a prolonged rTMS treatment course consisting of 15 additional once-daily rTMS treatments (total of 51 treatments), they had to: (1) have a PHQ-9 $\geq$ 5 (i.e., not in remission), (2) have demonstrated good adherence to the treatment protocol (no more than 6 treatments missed during the initial course), and (3) demonstrate medication compliance (maintaining a stable regimen of medication according to clinical interviews). The decision to allow patients to receive additional sessions was based on the PHQ-9 score at the 36th session. Patients then continued on a schedule of once-daily treatment, 5 times a week on weekdays, without interruption, until the additional 15 (up to a maximum of 51) sessions were completed. These 15 additional treatments were provided at no additional cost to the patient.

2.3. Measures

Treatment effects were assessed at baseline, weekly, at treatment 36, and until trial completion, with Patient Health Questionnaire (PHQ)-9 instrument [26]. PHQ-9 is a widely used self-report instrument designed to assess the severity of depressive symptoms in individuals [27]. Consisting of nine items corresponding to the DSM criteria for MDD, it has been shown to have good construct validity [28].

2.4. Statistical analysis

Statistical analyses were conducted in Stata 17.0 (StataCorp LLC, College Station, TX, USA) and R GNU v4.2.1 [29,30]. All codes for data analysis are available at https://github.com/XiaoChenPhD/trajectory_rTMS for validation and replication. For the primary analysis, we intended to identify distinctive subgroups of individual longitudinal trajectories in study participants using a semiparametric approach called GBTM [20,21]. This approach has been previously applied to classify longitudinal trajectories of treatment response of rTMS [17,18]. We implemented this method via a Stata plugin, *traj* [31]. We modeled the error structure of the outcome variable, PHQ-9, as a censored normal

distribution, considering its nature as a normally distributed psychometric scale. To account for potential clustering at the lower and upper ends of the PHQ-9 scores, which could be influenced by minimum severity requirements for trial entry and ceiling effects, respectively, we adopted a censored normal model as advised by the procedure's developers [32]. The optimal number of response trajectories and the optimal polynomial degree within each trajectory were determined using the Bayesian information criterion (BIC), which quantifies the improvement in model fit achieved by incorporating additional groups or shape parameters while also penalizing the increase in complexity. The BIC log Bayes factor approximation is calculated as the BIC difference between a more complex model and a less complex model, multiplied by 2 ($2 \times \Delta$BIC), which has been shown to be an acceptable approximation to the log Bayes factor criterion [33]. Three considerations were included in determining the optimal number of groups and the order of the final polynomial equation: 1) The more complex model was favored when the log Bayes factor approximation is larger than 10; 2) models that included small trajectory groups (<5 % of the sample) were rejected. 3) The average posterior probability of group membership of the final model for all trajectories was required to be larger than 70 %. One-way ANOVA and χ^2 tests were performed to compare baseline clinical characteristics among all four trajectory groups. Post-hoc comparisons were performed using the Tukey HSD test.

Only those patients who were not in remission at the end of 36 initial treatments (week 7) received 15 additional treatments, which led to a high rate of non-random missing values for weeks 8–10 within each trajectory. Accordingly, to ensure the model fitted with the full data (the 51 entire treatments) was not biased by missing values, we independently estimated models with data from the 36 treatment course and the prolonged 51 treatment course. Models with an identical number of trajectories and good interrater agreement between week 7 and week 10 data were favored. χ^2 tests were performed to determine whether the ratios of missing values differed among subgroups.

We constructed the model using a two-stage process similar to our previous studies [17,18]. We first determined the number of groups with the order of polynomial degree defining each group's trajectories fixed at quadratic. We then determined the polynomial degree in each trajectory by examining BIC for all possible permutations of linear, quadratic, and cubic trajectories. The model that comprised a combination of linear, quadratic, and cubic polynomials, which provided the best explanation for the observed response trajectories (based on the lowest BIC), was considered the most optimal fitting model.

To determine the clinical significance of extended treatment courses amongst the trajectories, we conducted a secondary analysis to compare PHQ-9 scores at week 7 and week 10 between response trajectories that included at least 10 patients by the end of the extended treatment course. Clinical significance was quantified using Cohen's *d*. An effect size of $d = 0.2$ indicates a small effect, $d = 0.5$ denotes a medium effect, and $d \geq 0.8$ represents a large effect [34]. We only included participants without missing values for week 7 and week 10 in this secondary analysis. PHQ-9 remission (PHQ-9 score <5) and response (PHQ-9 change $\geq$ 50 % from baseline) for week 7 and week 10 were also calculated. To compare outcomes between week 7 and week 10 within trajectories, we used a paired *t*-test for PHQ-9 values and McNemar's χ^2 tests for response and remission rates. We also performed a categorical comparison among the four depressive symptom trajectories in terms of PHQ-9 remission and response rates for weeks 1–10.

Once distinct trajectories had been identified, we then determined the associations between the prognostic factors (e.g., baseline clinical and demographic characteristics) and the trajectory group membership using weighted multinomial logistic regression. These regressions were weighted based on the probability of each individual's group membership to address the measurement error arising from the uncertainty of group membership. We chose the trajectory with the largest membership as the reference group. Because the limited sample size of the present study, especially data for weeks 8–10, may dampen the fitness of the regression model with a large number of exploratory covariates, we a priori included age, sex, baseline depressive symptom severity, and anxiety comorbidity as the covariates, based on our prior findings [17,18]. Model discrimination and fit were assessed in independent logistic models for each response trajectory and are reported using the c-statistic and the Hosmer-Lemeshow test, respectively. We explored the relationship between medication use and treatment outcomes by sequentially adding predictors regarding medication use (i.e., antidepressant use, benzodiazepine use, augmenting use, and anticonvulsant use) to the initial model. In light of a recent study [16], we also performed an exploratory analysis on the association between the change of PHQ-9 scores after week 1 and the trajectory group membership.

3. Results

3.1. Response trajectories

From the initial 390 patients in the naturalistic cohort, we excluded 66 patients who initially had moderate symptoms at initial assessment but mild depressive symptoms (PHQ-9 score < 10) at baseline, yielding an analytic cohort for this study consisting of 324 participants. Models were estimated independently using week 7 and week 10 data. Data from weeks 8–10 showed high missing value ratios and may violate the assumption of missing at random (Fig. S2, Table S2, Table S6). Accordingly, only those models showing agreement were favored. The addition of trajectory groups led to an improvement in model fit, as indicated by the increase in BIC (Table 1). Nevertheless, the 5-group solution was not accepted due to the poor agreement between models fitted using week 7 and week 10 data and also including a small trajectory group (<5 % of the sample) when using initial 7 week data. The BIC log Bayes factor approximations provided strong evidence that a 4-group model better fits the data than a 3-group model. The model was best described by combining cubic and quadratic polynomial components. We found that there was good interrater agreement (unweighted kappa = 0.85, $p < 0.001$) for assigning response trajectories and polynomial components when week 7 or week 10 data were used (Fig. 1 and Fig. S1). Average posterior probabilities were high for all 4 groups (range, 0.90 - 0.97). The baseline characteristics of included participants are presented in Table 2. The demographic and clinical characteristics of patients with a diagnosis of bipolar I or II are shown in Table S5. In our final analytical cohort (N = 324), 270 patients (83.33 %) had no prior rTMS treatment course. For those having previous rTMS treatment courses, the average number of previous treatment courses was 1.24 (SD = 0.64), and the average number of days between the last rTMS treatment course and the current course was 321.74 (SD = 254.96). The response and remission rates for the entire sample were 56.79 % and 34.26 %, respectively, by week 7 and steadily increased to 63.27 % and 37.96 % by the end of week 10 (Table S1). Only patients receiving additional rTMS sessions were required to maintain a stable medication

Table 1
Values of BIC by the number of groups for models with all quadratic polynomial components and associated BIC Log Bayes factor approximation. Models were estimated independently using week 7 and week 10 data. Only those models showing agreement were favored.

Number of Groups	Week 7 data		Week 10 data	
	BIC	2 × ΔBIC	BIC	2 × ΔBIC
1	−7379.73	NA	−8150.28	NA
2	−6885.77	987.92	−7621.91	1056.74
3	−6708.26	355.02	−7436.48	370.86
4[a]	−6633.53	149.46	−7358.00	156.96
5[b]	−6622.00	23.06	−7319.87	76.26

Abbreviations: BIC, Bayesian information criterion; NA, not applicable.
[a] Selected model.
[b] Model included a small trajectory group (<5 % of the sample) and was rejected.

Table 2
Demographic and clinical characteristics of participants receiving prolonged rTMS treatments, by symptom trajectory group.

Characteristic	Total sample, N = 324	Rapid response, standard treatment length, N = 69	Slowed response, N = 159	Linear response, extended course, N = 73	Nonresponse, N = 23	F/χ^2	*p*
Age (years)	44.14 (16.97)	46.03 (17.00)	44.71 (16.80)	42.05 (16.99)	41.17 (18.11)	0.95	0.42
Sex							
Female	219 (67.59 %)	44 (63.77 %)	113 (71.07 %)	50 (68.49 %)	12 (52.17 %)	3.86	0.28
Male	105 (32.41 %)	25 (36.23 %)	46 (28.93 %)	23 (31.51 %)	11 (47.83 %)		
Baseline depressive symptoms[a]	17.07 (4.33)	14.52 (3.98)	16.35 (3.86)	19.11 (3.07)	23.17 (3.41)	41.27	<0.001
Bipolar disorder	23 (7.10 %)	2 (2.90 %)	15 (0.63 %)	4 (5.48 %)	2 (8.70 %)	3.54	0.32
Anxiety comorbidity							
No anxiety comorbidity	143 (44.14 %)	33 (47.83 %)	64 (40.25 %)	34 (46.58 %)	12 (52.17 %)	2.13	0.55
Any anxiety comorbidity[b]	181 (55.86 %)	36 (52.17 %)	95 (59.75 %)	39 (53.42 %)	11 (47.83 %)		
SSRI/SNRI use	223 (68.83 %)	45 (65.22 %)	114 (71.70 %)	48 (65.75 %)	16 (69.57 %)	1.36	0.72
TCA use	17 (5.25 %)	3 (4.35 %)	8 (5.03 %)	5 (6.85 %)	1 (4.35 %)	0.54	0.91
Other antidepressant use	117 (36.11 %)	22 (31.88 %)	64 (40.25 %)	24 (32.88 %)	7 (30.43 %)	2.37	0.50
Benzodiazepine use	117 (36.11 %)	21 (30.43 %)	56 (35.22 %)	27 (36.99 %)	13 (56.52 %)	5.20	0.16
Augmenting agent use	72 (22.22 %)	15 (21.74 %)	36 (22.64 %)	17 (23.29 %)	4 (17.39 %)	0.38	0.94
Anticonvulsant use	58 (17.90 %)	14 (20.29 %)	29 (18.24 %)	14 (19.18 %)	1 (4.35 %)	3.24	0.36
Lithium use	10 (3.09 %)	5 (7.25 %)	4 (2.52 %)	0 (0.00 %)	1 (4.35 %)	6.61	0.09
Session numbers	37.30 (11.03)	33.65 (7.26)	39.27 (9.71)	37.07 (14.20)	35.30 (14.53)	4.62	0.003
Session length (weeks)	9.03 (2.98)	8.07 (2.25)	9.45 (2.70)	9.20 (3.65)	8.45 (3.73)	3.88	0.01
All values are n (%) except age, session numbers, and session length, which reported as mean (SD)							

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin and norepinephrine reuptake inhibitors; patient health questionnaire - 9 item (PHQ-9); generalized anxiety disorder (GAD).
[a] The total score of the patient health questionnaire - 9 item (PHQ-9).
[b] Here, anxiety comorbidity includes generalized anxiety disorder (GAD), unspecified anxiety, and panic anxiety.

regimen, leading to a small proportion of the sample (11.42 %) undergoing medication adjustments. None of these patients received additional treatment sessions.

The final group-based trajectory model using week 10 data showed the longitudinal course of depressive symptoms in prolonged rTMS treatments and is depicted in Fig. 1. Trajectories where N < 10 were not plotted due to excessively wide confidence intervals. We labeled these groups according to their relative starting position and response trajectory as follows: "linear response, extended course" (N = 73; 22.53 %), with a steady linear improvement and no apparent plateau throughout the entire treatment course; "nonresponse" (N = 23; 7.10 %), in which no clear change exhibited regarding symptom severity in initial 36 treatments and no one achieved remission; "slowed response" (N = 159; 49.07 %), with a rapid improvement by week 3–4, followed by a slowed progress around PHQ score of 9 to week 10; "rapid response, standard treatment length" (N = 69; 21.30 %), which rapidly improved to the remission by week 2–3, then slowly improved even further by week 7. All participants in this group discontinued at week 7 and received no extended treatment course. There was no significant difference regarding baseline characteristics except for depressive symptoms, session numbers, and session lengths (week). Post-hoc tests showed that the "nonresponse" group was characterized by higher baseline PHQ-9 scores compared to the other 3 groups. In contrast, the baseline PHQ-9 scores of the "rapid response, standard treatment length" group were lower than the other 3 groups. The session number and treatment length of the "slower response" group was significantly larger than the "response,

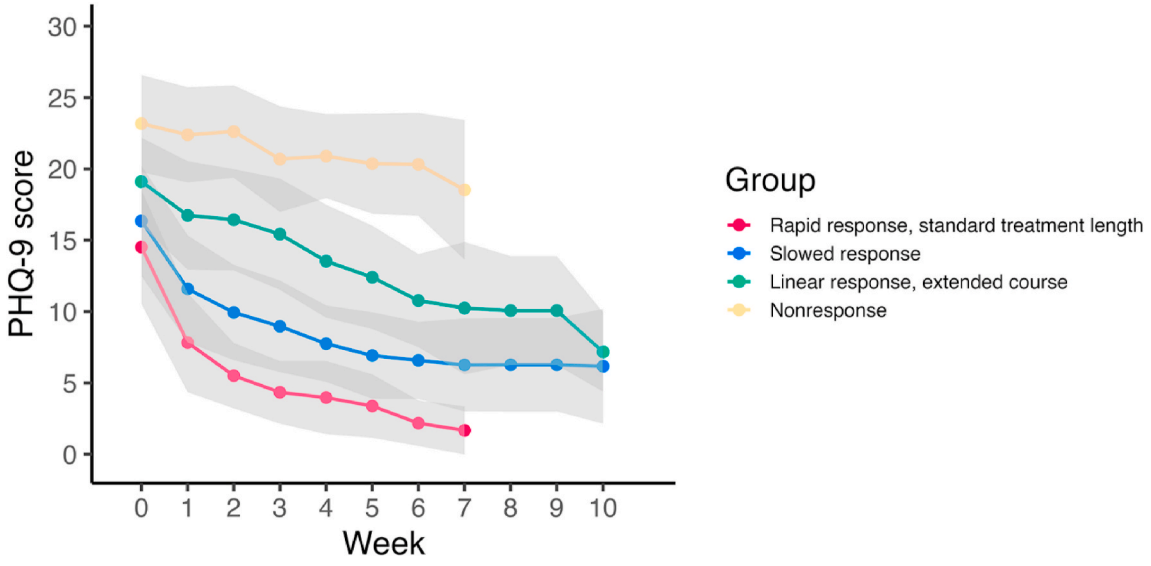

Fig. 1. Trajectories of depressive symptom responses over 10 weeks of rTMS treatment. Note two trajectories ("Nonresponse" group and "Rapid response, standard treatment length" group) after week 7 were not plotted due to the excessively small sample size (N < 10). Abbreviations: rTMS, repetitive transcranial magnetic stimulation; PHQ-9, Patient Health Questionnaire - 9 item.

standard treatment length" group. As expected, the missing value ratios differed significantly among the four groups in weeks 8–10 (*ps* < 0.001, Table S2). The average number of sessions for the entire sample was 37.30 (SD = 11.03), ranging from 2.00 to 51.00. The average treatment length for the whole sample was 9.03 weeks (SD = 2.98), ranging from 0.14 to 20.29 weeks (Table 2).

The nonresponse group and the rapid response group with a standard treatment length were excluded from the secondary analysis due to the small remaining sample sizes for week 10 (N = 7 and N = 0, respectively). In examining the clinical significance of a prolonged treatment course for the remaining two trajectory groups, both groups showed statistically significantly decreased PHQ-9 scores ($t = 2.73$, $p = 0.01$, slowed response; $t = 4.14$, $p < 0.001$, linear response group). Nonetheless, the linear response group yielded a large effect size (Cohen's $d = 1.10$), while the rapid response group showed a small effect size (Cohen's $d = 0.39$) (see Table 3). For the outcomes of secondary categorical comparisons, we observed an increase in the overall remission rate from 3.40 % (week 1) to 37.96 % (week 10) and significant differences among trajectories in remission rates throughout the entire treatment course (Table S3).

3.2. Associated characteristics for each symptom trajectory

Table 4 presents the outcomes of the multinomial logistic regression model concerning group membership. Lower baseline self-reported depression severity (PHQ-9 score) was associated with membership in the group of rapid response with a standard treatment course (odds ratio = 0.87, 95 % CI = 0.86, 0.89). In contrast, more severe baseline self-reported depression was related to the membership in nonresponse group (odds ratio = 1.73, 95 % CI = 0.89, 3.37) and linear response group (odds ratio = 1.21, 95 % CI = 1.12, 1.31). The adequacy of model discrimination (c-statistic, 0.66-0.94) and fit (Hosmer-Lemeshow test *ps* > 0.05) was indicated by individual logistic regression models for each response trajectory. No significant effect of medication use on the rTMS treatment outcomes was revealed (all *ps* > 0.05, Table S3). A significant association between the PHQ-9 reduction rate after week 1 and the group membership was observed (Table S4).

4. Discussion

In this study, we described the longitudinal depressive symptom response trajectories using data from a naturalistic cohort in which patients received prolonged rTMS treatments. We found four distinct trajectories that were similar to those previously identified in a standard rTMS treatment course [18]. One of the four groups (which comprised 22.53 % of this analytic cohort) demonstrated clinically significant benefit from prolonged rTMS treatments. Examination of characteristics that predict a trajectory group identified, similar to previous work, that baseline symptom severity was the most important predictor.

Prior research has indicated that extended rTMS treatment courses may prove advantageous for some patients [13,14,35]. A review of patients who received bilateral TBS treatments found that a significant number of patients could only achieve remission with longer treatment courses (>6 weeks) [35]. In another double-blind placebo-controlled study, Yip and colleagues found a large proportion of non-responders after 4 weeks of daily rTMS treatments achieved responder status when the treatment was continued for 16 more sessions [14]. Our results showed that a subset of patients comprising the linear response group (22.53 % of the sample) may benefit from a prolonged course. We further showed that two groups of patients (those with minimal improvement during a standard treatment course, or those with rapid response during acute treatment and a slowed progress during standard treatment), only have limited incremental improvement, even with additional treatments. These two groups, comprising a majority of patients, would not appear to achieve an improvement in depressive symptoms even after extending the treatment course up to 10 weeks, highlighting the need to select appropriate patients. Considering the time and financial expenses linked to the rTMS [36], the decision to extend an rTMS treatment course should be considered in the context of the patient's baseline depression severity and the response during the initial treatment course. Specifically, for patients demonstrating minimal symptom reduction throughout the initial treatment course ("non-response"; 7.10 % of patients), or patients showing a rapid symptom reduction in the early stage of treatment ("rapid response, standard treatment length", 21.30 % of patients) there is limited utility in prolonging the treatment course. Patients who demonstrate continued ongoing incremental improvement throughout the treatment course ("linear response, extended course", 22.53 % of patients) are the best candidates for prolonged treatment courses. Patients who respond quickly, then have a more gradual response afterwards ("slowed response"; 49.07 % of patients) could be considered on an individual basis depending on patient preferences.

Our results of four trajectories of treatment response, including rapid, linear response, and non-response groups, were generally in line with previous findings in adult patients with depression treated with either standard (one treatment per day) or accelerated (more than one treatment per day) high frequency/intermittent theta burst stimulation targeted on the left DLPFC [17,18]. Nevertheless, a notable difference in trajectory patterns was revealed: unlike previous studies, we observed two rapid response groups. However, only one group with a smaller proportion of patients achieved remission, while the other group with a larger proportion of patients' reduction rates of symptom severity were much slower after the initial 4 weeks' quick response. Two factors may potentially contribute to this discrepancy. First, the current study administrated a sequential bilateral rTMS protocol (high-frequency stimulation on the left DLPFC and low-frequency stimulation on the right DLPFC), which was different from the prior work (only included stimulation on the left DLPFC). Second, a self-rated clinical assessment, PHQ-9, was utilized to classify participants into different trajectories in the current study, while prior research used inventories rated by trained raters who were blind to treatment allocation.

In accordance with our previous research [17,18], we found that more severe baseline depressive symptoms decreased the odds of membership in the "rapid response, standard treatment length" group while increasing the odds of membership in the "linear response, extended course" and "nonresponse" groups. Fitzgerald et al. [8] pooled data from 11 rTMS clinical trials and found that the less severe baseline depressive symptoms were associated with better clinical outcomes after

Table 3
Secondary analyses on the differences in the severity of depressive symptoms, response rates, and remission rates between week 7 and week 10.

		Week 7	Week 10	*t*/McNemar's χ^2	*p*	Cohen's *d*
Slowed response, N = 48[a]	PHQ-9	7.58 (3.02)	6.16 (4.01)	2.73	0.01	0.39
	Response rate (%)	52.08	68.75	4.08	0.04	NA
	Remission rate (%)	14.58	31.25	3.06	0.08	NA
Linear response, extended course, N = 29[a]	PHQ-9	10.90 (3.95)	7.17 (2.78)	4.14	<0.001	1.10
	Response rate (%)	44.83	82.76	7.69	0.01	NA
	Remission rate (%)	0.00	10.34	1.33	0.25	NA

Abbreviation: PHQ-9, patient health questionnaire - 9 item.
[a] Participants without missing values at week 7 and week 10 were included.

Table 4
Baseline characteristics predicting symptom trajectories.

	Rapid response, standard treatment length, N = 69		Slowed response, N = 159		Linear response, extended course, N = 73		Nonresponse, N = 23	
Characteristic	Odds Ratio	95 % CI	Odds Ratio	95 % CI	Odds Ratio	95 % CI	Odds Ratio	95 % CI
Age	1.01	0.53–1.93	1	(Reference)	0.99	0.54–1.83	0.98	0.18–5.37
Sex	1.28	0.69–2.36	1	(Reference)	1.23	0.02–90.44	2.75	2.66–2.85
Baseline PHQ-9	0.87[a]	0.86–0.89	1	(Reference)	1.21[a]	1.12–1.31	1.73[a]	0.89–3.37
Anxiety Disorder[b]	0.72	0.60–0.87	1	(Reference)	0.71	0.24–2.14	0.56	0.19–1.65

[a] Statistical significance at $p < .05$.
[b] Anxiety disorder included: general anxiety disorder (GAD), panic disorder, and unspecified anxiety disorder.

receiving rTMS. Moreover, higher baseline symptom severity may be an indicator of membership in the "linear response, extended course" group, the only group showing considerable improvement after receiving an extended rTMS course. We failed to find a significant association between benzodiazepine use and the odds of group membership. Nevertheless, the benzodiazepine use did increase the odds of membership in the "non-response" group (odds ratio = 1.84), which is in line with the previous findings that benzodiazepine use led to a poorer treatment outcome after receiving a rTMS treatment [37] and our previous research [18]; however, could be the result of confounding by comorbid anxiety symptoms [38]. Exploring the potential associations between additional covariates and response trajectories requires future studies with larger sample sizes to allow for more covariates in the multinomial regression model. In line with our previous research [18], the "nonresponse" group only took up a small proportion of the entire sample.

The results of the present study may have important broader implications for research on biomarkers to predict TMS treatment response and non-response. Namely, the successful demonstration of a candidate biomarker depends on having accurate labels for the 'responder' and 'non-responder' patients. For TMS biomarker studies using short courses of treatment (e.g., 20 sessions or fewer), the slower-responding subgroups may be inaccurately labeled as 'non-responders' rather than slow responders, degrading the apparent predictive accuracy of the biomarker. The results of the present study therefore highlight the need for adequate course length in future studies seeking biomarkers for TMS outcome prediction. The present work may also have implications for interpreting the relatively high rates of response and remission reported in recent accelerated TMS regimens under the fMRI-guidance [39,40]. These regimens, importantly, delivered 50 sessions rather than the more common course length of ~30 sessions. The results of the present study indicate that even in the absence of MRI-guidance, increasing the number of sessions from 30 to 50 could yield some increase in response and remission rates. While there is comparatively less evidence on the rTMS protocols used in this work, the clinical outcomes of the current study are remarkably similar to the outcomes of more commonly used stimulation protocols, typically reporting response and remission rates of 50 % and 30 %, respectively, which supports the efficacy of the protocols for this study [41].

In a complementary study, Hutton and colleagues [16] found that a subset of patients (~13.51 % of the sample) who received extended rTMS treatment (>36 sessions) showed additional clinical benefits after the standard rTMS treatment course (36 sessions). Given the naturalistic nature of this study, the decision on the rTMS treatment course was based on the clinicians' real-time observations regarding the intervention's effectiveness. This prevents most patients showing no response or slowed reduction of symptom severity from receiving additional rTMS sessions. Moreover, Hutton et al. grouped patients according to the number of rTMS sessions administered, while the present study identified groups based on the differences in symptom trajectories. Thus, the patients receiving additional sessions in Hutton et al. may belong to the "linear response, extended course" group from the present study. Interestingly, the proportion of the "linear response, extended course" group in the present study (22.53 %) was higher than the proportion (~13.51 %) of the study conducted by Hutton et al., which indicated that a subset of patients who may benefit from a prolonged course may not receive additional sessions currently in the real world.

Results from the current study should be interpreted with respect to limitations. The ratio of missing values for week 7–10 data was high. In addition, data were not randomly missing after week 7 due to the study design, which probably violated the statistical assumption of GBTM [42]. We independently fitted models using the initial 7-week data and the entire 10-week data and ensured the correspondence between these two models to address this issue partially. This high and non-random missing rate might also lead to the rapid decline in the linear response group in weeks 9–10, but it could also be a demand characteristic. Participants may report fewer depressive symptoms simply because they were willing to extend their treatment courses and had expectations about TMS's treatment outcomes. Some factors may influence the treatment course duration in the current study. Here, patients receiving additional treatment sessions had to have a ≥5 PHQ-9 score and demonstrate adherence to treatment protocol and medication compliance. Future work should examine factors influencing treatment protocol adherence and medication compliance. Another limitation is that only self-reported measures of depressive symptoms (i.e., PHQ-9) were analyzed. Self-reported measurements allow individuals to directly express their own experiences and perceptions of their depressive symptoms and are easy to administer in a longitudinal study. Although the alignment between self-reported and clinician-rated instruments has been reported to be good [43], notable discrepancies exist [44]. Existing evidence showed the correlation between PHQ-9 scores and the total scores of the Hamilton Rating Scale for Depression (HAMD) was strong, but the consistency was modest [45,46]. Thus, comparing the present study's findings and results from studies using clinical-rated instruments (e.g., HAMD) should be cautious. It is worth noting that all patients included in this study were able to access rTMS treatment at a private clinic (i.e., through insurance or private pay), such that our results may not be generalizable to individuals who may be more socioeconomically disadvantaged. However, as long as an individual was able to access the standard (i.e., 36 treatments), the extended treatment course was offered at no cost to the individual. Our retrospective analysis of an existing real-world dataset implicated similar trajectories of patients receiving an extended rTMS treatment course. Still, its retrospective nature prevented it from ruling out some pivotal confounding issues. Future prospective clinical trials are needed to compare prolonged and standard rTMS treatment trajectories. The naturalistic approach in this research also made it difficult to exclude the potential impact of confounding biases (placebo effect, antidepressant medications, the natural course of depression, etc.) [47]. Nevertheless, the present findings provide valuable and tangible guidance for psychiatrists in clinical practice and complement data from well-controlled randomized clinical trials.

5. Conclusion

The present study identified four depression response trajectories in a real-world clinical dataset with a prolonged rTMS course using group-based trajectory modeling. Further analysis showed that a minority of

patients with a linear response trajectory achieve additional benefits from prolonged rTMS courses. Higher baseline depressive severity was associated with linear and non-response trajectories. Our findings demonstrated the robustness of our previously discovered four-trajectory model in an extended treatment course of rTMS and highlighted the selective clinical benefit from a prolonged rTMS treatment course. Patients' baseline severity of depressive symptoms and response trajectories in the early treatment course could be leveraged to decide whether they could achieve a considerable clinical improvement from additional rTMS sessions.

CRediT authorship contribution statement

Xiao Chen: Formal analysis, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Daniel M. Blumberger:** Conceptualization, Funding acquisition, Methodology, Resources, Software, Writing – review & editing. **Jonathan Downar:** Conceptualization, Data curation, Funding acquisition, Project administration, Resources, Writing – review & editing. **Victoria J. Middleton:** Data curation, Investigation. **Naima Monira:** Data curation, Investigation. **Jennifer Bowman:** Data curation, Investigation. **Joseph Kriske:** Data curation, Investigation. **John Kriske:** Data curation, Investigation. **Nancy Donachie:** Data curation, Investigation. **Tyler S. Kaster:** Conceptualization, Funding acquisition, Methodology, Resources, Software, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.04.010.

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