



## Depressive symptom trajectories associated with standard and accelerated rTMS

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### ABSTRACT

**Background:** To determine if an accelerated rTMS protocol results in distinct depressive symptom response trajectories, compared to a standard rTMS protocol. We also sought to validate previous analyses that identified distinct depressive symptom response trajectories with rTMS treatment using an external dataset.

**Method:** Data from two recent clinical trials comparing accelerated rTMS protocol delivered to the left dorsolateral prefrontal cortex (DLPFC) with standard once-daily rTMS protocol were used to identify depressive symptom response trajectories. The accelerated protocol in Trial 1 was conventional 10-Hz rTMS, while Trial 2 employed intermittent theta burst stimulation (iTBS). Participants were adult outpatients (18–70 years old) with bipolar or unipolar depression and moderate-severe depression (Montgomery Asberg Depression Rating Scale score >19) who had failed to respond to adequate courses of two different antidepressants. We used group-based trajectory modeling to identify MADRS response trajectories, and regression techniques adjusting for baseline depressive symptom severity to determine the association between treatment protocol and depressive symptom response trajectory.

**Results:** Treatment outcomes of 189 participants were analysed. We identified four distinct response trajectories: “nonresponse” (N = 59; 30.7%), “minimal response” (N = 65; 34.1%), “higher symptoms, response” (N = 26; 14.6%), “lower symptoms, response” (N = 39; 20.6%). We failed to find an association between rTMS protocol (accelerated vs standard) with depressive symptom response trajectory even after adjusting for baseline depressive symptom severity.

**Conclusion:** The accelerated rTMS protocol in this study did not impact depressive symptom response trajectories. This work provides further confirmatory evidence that there are distinct depressive symptom response trajectories with rTMS delivered to the left DLPFC.

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### Introduction

Repetitive transcranial magnetic stimulation (rTMS) is an established treatment for patients with major depressive disorder (MDD) who have failed at least one antidepressant medication, known as treatment-resistant depression (TRD) [1]. rTMS is thought to work by focally stimulating cortical regions, such as the

dorsolateral prefrontal cortex (DLPFC) [2] which in turn may modulate large-scale neuronal networks (including the central executive network and default mode network) that have been implicated in the pathophysiology of MDD [3].

While rTMS is effective for TRD, with response rates approaching 50% [4], this still means that a significant portion of individuals do not benefit from rTMS. Amongst those individuals who do respond to rTMS, it can take several weeks before mood changes are observed, which limits the utility of rTMS for individuals requiring urgent response. Furthermore, the manner in which rTMS is delivered currently (5 days per week for 4–6 weeks

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### Abbreviations

|         |   |
|---------|---|
| rTMS    | repetitive transcranial magnetic stimulation  |
| MDD     | major depressive disorder                     |
| MINI    | Mini International Neuropsychiatric Interview |
| HF-rTMS | high-frequency rTMS                           |
| iTBS    | intermittent theta burst stimulation rTMS     |
| BIC     | Bayesian information criterion                |
| VIF     | variance inflation factor                     |
| ECT     | electroconvulsive therapy                     |
| GAD     | generalised anxiety disorder                  |
| OCD     | obsessive compulsive disorder                 |
| PTSD    | post-traumatic stress disorder                |
| SAD     | social anxiety disorder                       |
| PD      | panic disorder                                |
| TRD     | treatment-resistant depression                |
| DLPFC   | dorsolateral prefrontal cortex                |
| MADRS   | Montgomery Asberg Depression Rating Scale     |

[5,6]) limits access to those able to make this substantial time commitment.

These limitations of rTMS have led to the investigation of accelerated rTMS protocols in which multiple treatment sessions are delivered in a single day to achieve a more rapid response of depressive symptoms by delivering the same amount of pulses and treatment sessions over a significantly shorter amount of time [7,8]. These multiple daily treatment sessions result in a significantly greater number of pulses delivered per day than the conventional 3,000 pulses given during an FDA-approved high-frequency rTMS (HF-rTMS) protocol [5,6]. Despite initial promising results from open-label pilot studies [9,10], two recent randomized controlled trials failed to find a difference in either the rapidity of response or ultimate response rates between standard and accelerated rTMS protocols [11,12].

A limitation of the analyses from these two recent studies that examined the speed of response was the use of linear mixed model analyses to examine the rate of change in depressive symptoms over time. This analytic approach does not account for the typical change of depressive symptoms over time, which is generally non-linear [13]. Furthermore, this analytic approach does not account for the possibility of distinct subgroups of depressive symptom trajectories to rTMS, as has been previously demonstrated [13], and whether the proportion of subgroups differ between treatment approaches (i.e. standard and accelerated protocols).

Therefore, the objective of the present work was to conduct a re-analysis of the recently conducted randomized controlled trials comparing accelerated and standard rTMS [11,12] using group-based trajectory modeling, an analytic technique that accounts for non-linear depressive symptom trajectories. Our hypothesis was that there would be a difference in the proportions of depressive symptom response trajectories between accelerated and standard rTMS protocols. Our secondary objective was to determine if our previous findings examining depressive symptom trajectories with rTMS could be replicated using an external, independent dataset [13].

### Methods

This analysis consisted of data from two recently completed clinical trials by the senior author – hereafter referred to as Trial 1 [11] and Trial 2 [12] – that were parallel superiority trials comparing an accelerated rTMS protocol (multiple treatments per

day) with a standard once daily rTMS protocol. In Trial 1, HF-rTMS was applied in both the accelerated and standard protocols. In Trial 2, HF-rTMS was applied in the standard protocol while intermittent theta burst stimulation (iTBS) was applied in an accelerated manner. A recent, large-scale, definitive study demonstrated non-inferiority of clinical outcomes for iTBS compared to HF-rTMS in treating unipolar depression [4]. Further details about Trials 1 and 2 can be found in their original publications.

### Participants and setting

Both trials were conducted at an Australian academic hospital with Trial 1 conducted from March 2013 to April 2016 and Trial 2 from May 2016 to December 2018. Patients in both trials were recruited via referral from external clinicians. The studies were approved by Alfred Hospital and Monash University Human Research and Ethics committees, and participants provided written informed consent.

Participants in both trials were outpatients between the age of 18 and 70 with a current major depressive episode (bipolar or unipolar) confirmed using the Mini International Neuropsychiatric Interview [14]. Participants were required to meet the following inclusion criteria: moderate-severe depression severity as indicated by Montgomery Asberg Depression Rating Scale (MADRS) score >19 [15], failure to respond to adequate courses of two different antidepressants [16], were on stable psychotropic medication for the 4 weeks preceding trial entry and agreeable to make no medication changes during the course of treatment. Participants were excluded for the following reasons: rTMS contraindication (such as metallic implants in head, cardiac pacemakers, or cochlear implants), had any co-occurring psychiatric disorder (except for an anxiety disorder), had a history of substance abuse/dependence in 6 months preceding trial entry, were pregnant, had a previous stroke, neurodegenerative disorder, or a major neurological illness.

### Study design

For both trials, participants were randomized in a 1:1 ratio to either the accelerated rTMS (HF-rTMS in Trial 1, iTBS in Trial 2) or standard rTMS (HF-rTMS in Trial 1 and 2) protocols. Standard rTMS was delivered once daily 5 days per week over four weeks for a total of 20 treatments. Accelerated rTMS was delivered according to the following schedule:

- Week 1: 3 treatment days, 3 sessions per day (9 total)
- Week 2: 2 treatment days, 3 sessions per day (6 total)
- Week 3: 1 treatment day, 3 sessions per day (3 total)
- Week 4 (Study 2 only): 1 treatment day, 3 sessions per day (3 total)

For days with multiple treatment sessions they were provided at 15–30 min intervals. One missed session was allowed per week and only one missed session in a row. The treatment course was extended by the number of missed treatments. Randomization occurred through the use of a single random number sequence. While treatment technicians and patients could not be blinded to the allocation given the nature of the intervention, outcome assessors were blinded to treatment allocation.

### rTMS procedure

The resting motor threshold (RMT) was measured for the abductor pollicis brevis (APB) on the left motor cortex in all subjects using standard published methods [17]. Stimulation localization for Trial 1 was achieved by measuring 6 cm anterior to the site of

optimal APB stimulation and in Trial 2 using the BeamF3 method [18]. Further details are available in the original publications [11,12]. For both trials, the device used was a MagPro X100/R30 stimulator with a B70 fluid-cooled coil (MagVenture, Farum, Denmark). For standard rTMS, standard settings for HF-rTMS were used: 10 Hz for 4.2s train with 25s inter-train intervals applied at 120% of RMT, for a total of 3150 pulses per day or 63,000 over the treatment course. For accelerated HF-rTMS the same settings were used except 83 trains were provided in each of the three treatment sessions with 15 s inter-train interval (10,500 pulses per day across the three sessions, or 63,000 pulses in total). For accelerated iTBS, triplet 50 Hz bursts repeated at 5Hz, 2 s on, 8 s off, 600 pulses/session over 3 min at 120% of RMT were applied in each iTBS session. This totalled 12,600 pulses over the course of 21 treatments.

## Measures

### Clinical assessments and prognostic factors

All clinical assessments were conducted by trained raters blinded to treatment allocation. All sociodemographic and clinical characteristics were measured at baseline and included: age, sex, employment status, medication use and history, illness duration and onset, and comorbid psychiatric disorders. The MADRS was measured at baseline, weekly during treatment.

### Outcomes

The primary outcome was the proportion of study participants classified to each depressive symptom trajectory.

### Statistical analysis

We used an approach that has been previously used for identifying longitudinal response trajectories with rTMS treatment [13]. This approach used a semiparametric group-based trajectory modeling strategy to classify study participants into subgroups based on identifying heterogeneous longitudinal polynomial trajectories. This was implemented via the procedure PROC TRAJ in SAS version 9.4 statistical software (SAS Institute, Inc) [19,20]. The outcome variable – MADRS – is a normally distributed psychometric scale for which we estimated the error structure as a censored normal distribution. As the scores on the MADRS may be susceptible to clustering at the lower end of the scale (due to minimum severity requirements for trial entry), and at the upper end of the scale (due to ceiling effects), we used a censored normal model to account for these characteristics as recommended by the developers of this procedure [20]. We also visually inspected histograms of the total MADRS score each week to verify our assumption of normality. We determined the optimal number of response trajectories in the model and optimal polynomial degree in each trajectory, using the Bayesian information criterion (BIC). BIC measures improvement in model fit gained by adding additional groups or shape parameters but also penalizes added complexity. The BIC log Bayes factor approximation, defined as  $2 \times [\Delta\text{BIC}]$  (where  $\Delta\text{BIC}$  is the BIC difference between a more complex and less complex model), has been shown to be an acceptable approximation to the log Bayes factor criterion [21] and was used to determine the number of response trajectories that best fit the observed data. A log Bayes factor approximation  $>10$  was used as the criterion for favoring the more complex model [20].

We first determined the best-fitting number of response trajectories with the maximum degree of the fitted polynomial fixed at cubic, since prior work has demonstrated that depressive symptom trajectories generally follow linear, quadratic or cubic trajectories [22,23]. Next, we determined the polynomial degree in each trajectory by systematically reducing the polynomial degree

for each trajectory with the smallest point estimate until all trajectories consisted of linear polynomial degrees. The combination of linear, quadratic, and cubic polynomials that best explained the observed response trajectories (lowest BIC), was considered the best fitting model. We next assessed model fit by calculating the average posterior probability of group membership (70% minimum for each group), determining the percentage of the total sample within each trajectory (5% minimum for each group), and calculating the odds of correct classification ( $>5$  considered adequate).

For our primary research question – to determine accelerated vs standard rTMS protocol response trajectories for depression – we used a multinomial multivariable logistic regression adjusting for baseline depressive symptom severity to determine if treatment allocation was associated with response trajectory group membership. The limited sample size available in this study, in contrast to previous work [13], precluded exploratory analysis of covariates associated with response trajectory. We therefore *a priori* chose baseline depressive symptom severity as the most important covariate to adjust for in the regression model. The effect size for rTMS treatment protocol was reported as an odds ratio (OR) with 95% confidence interval (CI). The regressions were weighted by the probability of group membership to account for measurement error introduced by the uncertainty of group membership. We conducted sensitivity analyses of treatment stimulation parameters (HF-rTMS vs iTBS) by including this as an additional covariate in the primary regression model to determine the association of treatment stimulation parameters with response trajectory. Given that rTMS is predominantly used for unipolar depression without psychotic features [1], we conducted two additional analyses to characterize the impact of including individuals with bipolar depression or depression with psychotic features in our primary analysis: (1) a comparison of the response trajectory group memberships for individuals with bipolar depression or psychosis using the chi-squared test of association, and (2) a repeat of the primary analysis identifying response trajectories excluding individuals with bipolar depression or psychosis. The reference group for all regression analyses was chosen *a priori* to be the response trajectory with the largest membership. We also conducted a categorical comparison of response (reduction in MADRS score  $\geq 50\%$  from baseline) and remission (MADRS  $\leq 10$ ) over time between each response trajectory. Statistical tests were two-tailed with alpha set to 0.05.

## Results

A total of 193 participants (119 in Trial 1, 74 in Trial 2) underwent randomized treatment assignment, of whom 189 (115 in Trial 1, 74 in Trial 2) received their allocated intervention and comprised the analytic cohort for this study. The four excluded participants dropped out prior to receiving the allocated intervention. The participant study characteristics are presented in Table 1. Using the analytic approach outlined in our Methods section, we identified four distinct longitudinal response trajectories, which best fit the observed data (Table 2). These response trajectories were best described by a combination of quadratic and linear polynomial components. Visual inspection of the distribution of total MADRS score each week supported our assumption of an approximately normal distribution (Supplemental Fig. S1).

The longitudinal course of depressive symptoms for each of the four trajectories is depicted in Fig. 1. We descriptively labelled each response trajectory as follows: “nonresponse” (N = 59; 30.7%) in which there was essentially no symptom change and no patients achieving response; “minimal response” (N = 65; 34.1%) in which there was minimal symptom change; “higher symptoms, response” (N = 26; 14.6%) in which there was a high baseline symptom

**Table 1**  
Baseline characteristics of study participants by response trajectory.

|   | Total Sample<br>(N = 189)       | Lower symptoms, response<br>(N = 39) | Higher symptoms, response<br>(N = 26) | Minimal response<br>(N = 65)    | Nonresponse<br>(N = 59)         |
|---|---------------------------------|--------------------------------------|---------------------------------------|---------------------------------|---------------------------------|
| <b>Demographic Characteristics</b>      |                                 |                                      |                                       |                                 |                                 |
| Age (years)                             | <b>Mean (SD)</b><br>47.2 (13.3) | <b>Mean (SD)</b><br>50.7 (11.3)      | <b>Mean (SD)</b><br>43.5 (10.0)       | <b>Mean (SD)</b><br>46.8 (14.0) | <b>Mean (SD)</b><br>46.9 (14.5) |
|   | <b>Median (IQR)</b>             | <b>Median (IQR)</b>                  | <b>Median (IQR)</b>                   | <b>Median (IQR)</b>             | <b>Median (IQR)</b>             |
| Duration of current episode (years)     | 18.0 (9.0–26.0)                 | 17.0 (11.0–27.0)                     | 22.5 (12.5–24.5)                      | 20.0 (9.0–29.0)                 | 13.0 (6.0–23.0)                 |
| Age of depressive symptom onset (years) | 23.0 (17.0–36.0)                | 26.0 (21.0–42.0)                     | 19.0 (15.0–28.0)                      | 22.0 (16.0–31.0)                | 23.5 (17.0–43.0)                |
| Number of depressive episodes           | 1.0 (1.0–3.0)                   | 2.0 (1.0–6.0)                        | 2.0 (1.0–5.0)                         | 1.0 (1.0–2.0)                   | 1.0 (1.0–2.0)                   |
|   | <b>N (%)</b>                    | <b>N (%)</b>                         | <b>N (%)</b>                          | <b>N (%)</b>                    | <b>N (%)</b>                    |
| Female                                  | 101 (53.4%)                     | 24 (61.5%)                           | 16 (61.5%)                            | 25 (38.5%)                      | 36 (61.0%)                      |
| Employed                                | 59 (31.2%)                      | 16 (41.0%)                           | 6 (23.1%)                             | 29 (44.6%)                      | 8 (13.6%)                       |
| Handedness                              |                                 |                                      |                                       |                                 |                                 |
| Right                                   | 148 (78.3%)                     | 30 (76.9%)                           | 20 (76.9%)                            | 53 (81.5%)                      | 45 (76.3%)                      |
| Left                                    | 16 (8.5%)                       | 4 (10.3%)                            | 2 (7.7%)                              | 5 (7.7%)                        | 5 (8.5%)                        |
| Ambidextrous                            | 12 (6.3%)                       | 4 (10.3%)                            | 2 (7.7%)                              | 4 (6.2%)                        | 2 (3.4%)                        |
| <b>Clinical Characteristics</b>         |                                 |                                      |                                       |                                 |                                 |
| Bipolar disorder                        | 24 (12.7%)                      | 2 (5.1%)                             | 8 (30.8%)                             | 7 (10.8%)                       | 7 (11.9%)                       |
| Melancholic features                    | 132 (69.8%)                     | 25 (64.1%)                           | 19 (73.1%)                            | 45 (69.2%)                      | 43 (72.9%)                      |
| Psychotic depression                    | 6 (3.2%)                        | 0 (0%)                               | 1 (3.8%)                              | 4 (6.2%)                        | 1 (1.7%)                        |
| Anorexia nervosa                        | 1 (0.5%)                        | 0 (0%)                               | 0 (0%)                                | 0 (0%)                          | 1 (1.7%)                        |
| Bulimia nervosa                         | 7 (3.7%)                        | 3 (7.7%)                             | 0 (0%)                                | 2 (3.1%)                        | 2 (3.4%)                        |
| Panic disorder                          | 41 (21.7%)                      | 7 (17.9%)                            | 7 (26.9%)                             | 8 (12.3%)                       | 19 (32.2%)                      |
| OCD                                     | 18 (9.5%)                       | 1 (2.6%)                             | 7 (26.9%)                             | 5 (7.7%)                        | 5 (8.5%)                        |
| PTSD                                    | 23 (12.2%)                      | 3 (7.7%)                             | 7 (26.9%)                             | 4 (6.2%)                        | 9 (15.3%)                       |
| Social phobia                           | 72 (38.1%)                      | 5 (12.8%)                            | 16 (61.5%)                            | 23 (35.4%)                      | 28 (47.5%)                      |
| GAD                                     | 115 (60.8%)                     | 16 (41.0%)                           | 20 (76.9%)                            | 39 (60.0%)                      | 40 (67.8%)                      |
| Alcohol abuse and/or dependence         | 20 (10.6%)                      | 7 (17.9%)                            | 3 (11.5%)                             | 5 (7.7%)                        | 5 (8.5%)                        |
| Substance use disorder (non-alcohol)    | 2 (1.1%)                        | 0 (0%)                               | 0 (0%)                                | 0 (0%)                          | 2 (3.4%)                        |
| <b>Treatment Characteristics</b>        |                                 |                                      |                                       |                                 |                                 |
| Current antidepressant                  | 129 (68.3%)                     | 31 (79.5%)                           | 21 (80.8%)                            | 40 (61.5%)                      | 37 (62.7%)                      |
| Current antipsychotic                   | 48 (25.4%)                      | 6 (15.4%)                            | 8 (30.8%)                             | 14 (21.5%)                      | 20 (33.9%)                      |
| Current benzodiazepine                  | 64 (33.9%)                      | 10 (25.6%)                           | 12 (46.2%)                            | 17 (26.2%)                      | 25 (42.4%)                      |
| Current mood stabiliser                 | 27 (14.3%)                      | 7 (17.9%)                            | 4 (15.4%)                             | 10 (15.4%)                      | 6 (10.2%)                       |
| Number of medication trials (lifetime)  |                                 |                                      |                                       |                                 |                                 |
| 0–2                                     | 16 (8.5%)                       | 10 (25.6%)                           | 0 (0%)                                | 4 (6.2%)                        | 2 (3.4%)                        |
| 3–5                                     | 74 (39.2%)                      | 16 (41.0%)                           | 11 (42.3%)                            | 24 (36.9%)                      | 23 (39.0%)                      |
| 6–8                                     | 35 (18.5%)                      | 5 (12.8%)                            | 4 (15.4%)                             | 14 (21.5%)                      | 14 (23.7%)                      |
| 9+                                      | 38 (20.1%)                      | 5 (12.8%)                            | 8 (30.8%)                             | 14 (21.5%)                      | 11 (18.6%)                      |
| History of ECT                          | 32 (16.9%)                      | 5 (12.8%)                            | 4 (15.4%)                             | 11 (16.9%)                      | 12 (20.3%)                      |
| rTMS Protocol                           |                                 |                                      |                                       |                                 |                                 |
| Accelerated HFL/iTBS                    | 94 (49.7%)                      | 17 (43.6%)                           | 13 (50.0%)                            | 33 (50.8%)                      | 31 (52.5%)                      |
| Standard                                | 95 (50.3%)                      | 22 (56.4%)                           | 13 (50.0%)                            | 32 (49.2%)                      | 28 (47.5%)                      |
| <b>Baseline Depressive Symptoms</b>     | <b>Mean (SD)</b>                | <b>Mean (SD)</b>                     | <b>Mean (SD)</b>                      | <b>Mean (SD)</b>                | <b>Mean (SD)</b>                |
| MADRS                                   | 31.9 (5.6)                      | 26.7 (5.0)                           | 35.8 (4.3)                            | 29.7 (3.5)                      | 36.1 (4.3)                      |

OCD = Obsessive compulsive disorder; PTSD = Posttraumatic stress disorder; GAD = Generalised Anxiety Disorder; ECT = Electroconvulsive therapy.

**Table 2**  
Change in Bayesian information criterion (BIC) with number of response trajectories using cubic trajectories.

| Number of Groups | BIC             | 2xΔBIC <sup>a</sup> |
|------------------|-----------------|---------------------|
| 1                | –3163.65        | NA                  |
| 2                | –2964.12        | 399.06              |
| 3                | –2868.73        | 190.78              |
| <b>4</b>         | <b>–2852.32</b> | <b>32.82</b>        |
| 5                | –2849.9         | 4.84                |

BIC = Bayesian information criterion.

<sup>a</sup> A log Bayes factor approximation with a value greater than 10 was used as the criterion for selecting a more complex model. The bolded value indicates the optimal number of response trajectories.

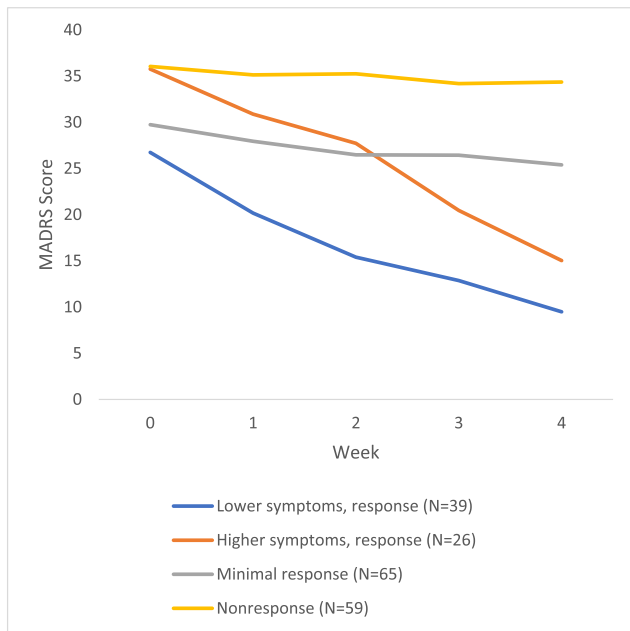
severity but significant symptom reduction with treatment; and “lower symptoms, response” (N = 39; 20.6%) in which there was a relatively low baseline symptom severity with further symptom reduction with treatment. The response and remission rates for each trajectory are presented in Table 3. Due to small cell sizes, we were unable to conduct statistical analyses for the initial 2–3 weeks of treatment; however, descriptively there are clear differences in the proportion of participants in each response trajectory achieving

response and remission as early as after two weeks of treatment. These differences were statistically significant at week 3 for response and week 4 for remission.

For our primary analysis, we failed to find an association of accelerated vs standard rTMS protocols on response trajectory membership, even after adjusting for baseline depressive symptom severity, though confidence intervals were wide (Table 4). Baseline depressive symptom severity itself was significantly associated with response trajectory membership. We failed to find an association between treatment protocol and response trajectory (p > 0.05). Furthermore, visual inspection of the response trajectories for individuals randomized to accelerated or standard rTMS protocols yielded nearly identical trajectories (Supplemental Fig. S2).

#### Additional analyses

In additional analyses examining only individuals with unipolar depression, we identified 3 response trajectories as resulting in the optimal fit to the observed data with a combination of quadratic



**Fig. 1.** Longitudinal depressive symptom response trajectory with four weeks of rTMS treatment with no adjustment for baseline depressive symptom severity.

and linear categories. Qualitatively, the trajectories appeared to be similar with the primary analysis with the exception of the ‘Higher symptoms, response’ trajectory, which was not identified in the unipolar-only group (Supplemental Fig. S3). Consistent with this, we found there were significant differences in the response trajectory groups for individuals with unipolar vs bipolar depression in our primary analysis ( $p = 0.0214$ ). Specifically, there were more individuals with bipolar depression (vs unipolar depression) belonging to the “higher symptoms, response” group (33.3% vs 11.1%). Due to small cell size, we were unable to conduct this additional analysis for individuals with psychosis.

## Discussion

In this work combining data from two recent randomized controlled trials comparing accelerated with standard rTMS

treatment protocols, we failed to find an association between treatment protocol and response trajectory membership. Despite using analytical techniques that account for non-linear response trajectories, our findings are consistent with the primary analyses from the original publications, which used linear mixed model analyses to examine the impact of treatment allocation on symptom change over time. Our findings pertaining to depressive symptom trajectories were consistent with findings of previous similar studies [13], though with several notable differences as outlined below.

Enthusiasm about accelerated rTMS protocols came from early pilot studies in which multiple rTMS treatments were provided daily that were tolerable and also resulted in a rapid reduction of depressive symptoms [7,8,24]. The hope of these accelerated protocols, in addition to faster onset of efficacy, was that the ultimate clinical effect would be greater with “intensified” treatment [25]. However the results of this study using group-based trajectory modelling (and statistical methods from the original trials [11,12]) did not support either of these hypotheses. Therefore, the primary advantage of accelerated rTMS protocols (as designed in the current protocols) is that multiple treatment sessions may be safely delivered in a single day, thereby reducing the number of days required of patients to travel to a treatment centre and the logistical burden associated with rTMS therapy.

While we failed to find an impact of rTMS protocol on the proportion of respondents belonging to each treatment trajectory, the identified response trajectories themselves are of clinical interest. To date, there has been one published analysis of longitudinal rTMS response trajectories, which identified 4 distinct trajectories: a rapid response group, two linear response groups, and a non-response group [13]. In the current work, at the most simplistic level, we confirmed that there are, in fact, distinct response trajectories to rTMS. Furthermore, we found an identical number of trajectories (four) optimally fit the observed data, though with different patterns of response. The most relevant finding in the present work is the lack of a subgroup of individuals rapidly responding to rTMS, which was found in prior work [13]. In the current study it appears that all individuals who responded did so in an approximately linear fashion – with the majority of participants in two subgroups achieving response by the end of the trial. This may potentially be due to the fact that individuals in these trials were required to have failed two antidepressant trials (rather

**Table 3**  
MADRS response and remission rates for each of the four depressive symptom trajectories.

|                  | Total Sample<br>(N = 189) | Lower symptoms, response<br>(N = 39) | Higher symptoms, response<br>(N = 26) | Minimal response<br>(N = 65) | Nonresponse<br>(N = 59) | $\chi^2$ | p      |
|------------------|---------------------------|--------------------------------------|---------------------------------------|------------------------------|-------------------------|----------|--------|
| <b>Response</b>  |                           |                                      |                                       |                              |                         |          |        |
| Week 1           | 4 (2.1%)                  | 3 (7.7%)                             | 1 (3.9%)                              | 0 (0%)                       | 0 (0%)                  | N/A      | N/A    |
| Week 2           | 15 (7.9%)                 | 14 (35.9%)                           | 1 (3.9%)                              | 0 (0%)                       | 0 (0%)                  | N/A      | N/A    |
| Week 3           | 30 (15.9%)                | 20 (51.3%)                           | 10 (38.5%)                            | 0 (0%)                       | 0 (0%)                  | 69.9492  | <.0001 |
| Week 4           | 52 (27.5%)                | 31 (79.5%)                           | 20 (76.9%)                            | 1 (1.5%)                     | 0 (0%)                  | 129.0356 | <.0001 |
| <b>Remission</b> |                           |                                      |                                       |                              |                         |          |        |
| Week 1           | 0 (0%)                    | 0 (0%)                               | 0 (0%)                                | 0 (0%)                       | 0 (0%)                  | N/A      | N/A    |
| Week 2           | 7 (3.7%)                  | 7 (18.0%)                            | 0 (0%)                                | 0 (0%)                       | 0 (0%)                  | N/A      | N/A    |
| Week 3           | 12 (6.4%)                 | 11 (28.2%)                           | 1 (3.9%)                              | 0 (0%)                       | 0 (0%)                  | N/A      | N/A    |
| Week 4           | 26 (13.8%)                | 24 (61.5%)                           | 2 (7.7%)                              | 0 (0%)                       | 0 (0%)                  | 95.6355  | <.0001 |

N/A indicates that statistical testing was not conducted because 50% of the cells have expected counts <5, and the chi-square test may not be valid.

**Table 4**

Impact of accelerated protocol on odds of response trajectory membership after adjustment for baseline depressive symptoms.

| Characteristic       | Lower symptoms, response (N = 39) | Higher symptoms, response (N = 26) | Minimal response (N = 65) | Nonresponse (N = 59) |
|----------------------|-----------------------------------|------------------------------------|---------------------------|----------------------|
| Primary Covariate    |                                   |                                    |                           |                      |
| Accelerated Protocol | 0.83 (0.35–1.98)                  | 0.926 (0.30–2.82)                  | (Reference)               | 1.12 (0.44–2.85)     |
| Adjustment Covariate |                                   |                                    |                           |                      |
| Baseline MADRS       | 0.84 (0.75–0.94)                  | 1.55 (1.31–1.83)                   | (Reference)               | 1.57 (1.35–1.83)     |

than at least one adequate trial in prior work [13]) as well as the inclusion in these trials, individuals with bipolar depression (excluded in prior work), both of which may result in a more treatment resistant population [26]. This is supported by our additional analyses, which found that individuals with bipolar disorder more frequently belonged to the “higher symptoms, response” subgroup compared to unipolar depression. Of note, participants in this subgroup (“higher symptoms, response”) started with baseline depressive symptoms similar to the “non-response” subgroup; however, the depressive symptoms between the groups appeared to diverge as early as after two weeks of treatment. Furthermore, the mean depressive symptoms in the subgroups that achieved response, did not appear to reach a stable plateau by the end of 4 weeks of treatment. This suggests that for individuals who are benefitting from rTMS treatment, and who have not yet achieved remission, it may be of value to persist with treatment until achieving remission, as opposed to *a priori* specified treatment durations for all individuals.

The depressive symptom trajectories to rTMS treatment identified in this work are similar to what has previously been observed with pharmacotherapy. For example, previous work examining depressive symptom trajectories with venlafaxine treatment for late-life depression found that participants with non-response trajectories tended to have higher baseline depressive symptoms, while lower baseline symptoms were associated with more rapid improvement in depressive symptoms [22]. Furthermore, this previous work found that individuals with higher baseline symptoms who ultimately responded required longer to achieve this [22]. This similarity between depressive symptom trajectories with pharmacotherapy and rTMS suggests that symptom improvement in depression is an incremental process and may involve a common final pathway – for example through normalization of the default mode network which has been demonstrated in both rTMS [3] and antidepressant [27] treatment. To our knowledge, depressive symptom trajectories have not been identified with other brain stimulation treatment (e.g. electroconvulsive therapy), which will be an important area for further study.

In terms of characteristics associated with response trajectories, as previously indicated, we failed to find an association between rTMS protocol (accelerated vs standard) and membership in a particular response trajectory. However, we did find a significant association between baseline depressive symptom score and response trajectory membership, which is consistent with previous work [13]. We found that, relative to the “minimal response” response trajectory, higher baseline depressive symptoms increased the odds of membership in “nonresponse” or “higher symptoms, response” and decreased the odds of membership in the “lower symptoms, response” group. Given that this was an *a priori* specified analysis based on the findings of an independent sample, it provides confirmatory evidence that one of the most important characteristics influencing the trajectory of response with rTMS treatment is an individual’s baseline depressive severity. In particular, this suggests that individuals with lower baseline levels of symptom severity are both more likely to respond to rTMS and to respond more quickly, which is consistent with our previous work [13]. With respect to other covariates potentially associated with

response trajectories, this will require additional studies with large sample sizes to enable including multiple other covariates into the multinomial regression model.

Due to their recent development, there continue to be important unanswered questions regarding optimal design of both iTBS stimulation patterns and accelerated rTMS protocols. With respect to the iTBS pattern used in the current trials, we acknowledge that previous studies of accelerated iTBS used a significantly higher number of pulses per session ranging from 1,620 [28] to 1,800 [29]. However, given that neurophysiological studies found reduced cortical excitability with prolonged iTBS stimulation patterns [30,31], and that the landmark THREE-D study used this same iTBS pattern to demonstrate non-inferiority of once daily iTBS with HF-rTMS [4], the iTBS pattern used in the current study was felt to be appropriate for the initial studies. For the design of the accelerated protocol in the current trial it was designed to balance characteristics such as the number of days traveling to the clinic, total clinic time, safety (e.g. potential risk of seizure), and efficacy. Based on the success of the current trials it appears that a more “intensified” could have been feasible, which would have enabled for assessment of a delayed response to the accelerated protocol as has previously been demonstrated [28]. The protocols were also structured to reduce the risk of early relapse that we have seen in protocols conducted only over 3–4 days in extensive pilot work prior to these trials. Furthermore, a key component of accelerated protocols is the inter-session interval, which in these studies was 15 min; however, recent work has questioned whether this is the optimal inter-session interval. A recent review identified that theta-burst stimulation applied at intervals of 60–90 min enhanced long-term potentiation, while shorter intervals did not [32]. However, longer inter-session intervals would necessitate longer treatment days that could potentially impede the number of treatment sessions provided. Ultimately, the concept of ‘dose’ in rTMS is complex and extends beyond the number of pulses [33], and is further complicated by the parameters required by the accelerated protocol.

#### Limitations

Despite the importance of these findings, there are limitations to be considered. First, this analysis used data from two separate trials using different stimulation parameters (HF-rTMS and iTBS) delivered in an accelerated protocol compared to standard HF-rTMS. As a result, one possibility for the failure to detect a difference in response trajectories between accelerated and standard rTMS protocols is due to confounding by the differing stimulation parameters applied. However, this is likely to be small as previous work has suggested that the difference in clinical efficacy between HF-rTMS and iTBS (when delivered according to a standard protocol) is small [4]. Second, similar to previous work, we used a data-driven analytic approach which may result in overfitting of data. However, the fact that our work closely replicates several aspects of previous works lends greater credence to our findings. Third, the accelerated protocol used in both trials was still delivered over a period of several weeks, and it is possible that a more intensely accelerated protocol (e.g. over 1 week) might have increased the speed of response. Similarly, as treatment was delivered over a

maximum of four weeks, it is possible that a prolonged treatment course (e.g. 6 weeks or longer) could have improved the overall response rates. Fourth, the generalizability of the results from this study are limited by the fact that this is a highly resistant sample of individuals with a substantial number of failed medication trials (e.g. 90% have failed 3 or more trials of antidepressant medications) with a median duration of illness of nearly two decades. As such, the trajectories we have identified may differ in a less treatment-resistant population. Last, an important limitation in the current study was that no biomarkers (such as baseline anatomical/functional MRI or neurophysiological markers) were included that could provide additional information on the biological mechanisms for the distinct response trajectories.

## Conclusion

In this work using two large prospective clinical trials and group-based trajectory modelling, we did not find differences in the patterns of response trajectories between accelerated and standard rTMS protocols. By applying the same statistical methods as previous work, we were able to identify four similar depressive symptom response trajectories to rTMS treatment. Further, we found, based on an *a priori* hypothesis, that baseline depressive symptom severity was a characteristic significantly associated with response trajectory membership which provides confirmatory evidence regarding its importance for determining depressive symptom response trajectory. This work highlights the heterogeneity of depression with differing response trajectories to treatment, and emphasizes the need for development of biomarkers to predict treatment outcomes. It also suggests that optimizing treatment outcomes with rTMS will require more than simply increasing the intensity of treatment – such as increasing the number of pulses or number of daily treatment sessions – and will likely require novel approaches incorporating an individual's unique biological characteristics into treatment planning. This biologically-driven approach will enable for personalized treatment in order to ultimately improve the outcomes for individuals suffering from depression.

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## CRedit authorship contribution statement

**Tyler S. Kaster:** Conceptualization, Formal analysis, Methodology, Resources, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **Leo Chen:** Data curation, Investigation, Project administration, Resources, Writing - review & editing. **Zafiris J. Daskalakis:** Resources, Supervision, Writing - review & editing. **Kate E. Hoy:** Data curation, Investigation, Project administration, Resources, Writing - review & editing. **Daniel M. Blumberger:** Conceptualization, Formal analysis, Methodology, Resources, Software, Writing - review & editing. **Paul B. Fitzgerald:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Resources, Supervision, Validation, Writing - review & editing.

## Appendix A. Supplementary data

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