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Predictors of remission after repetitive transcranial magnetic stimulation for the treatment of major depressive disorder: An analysis from the randomised non-inferiority THREE-D trial

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ABSTRACT

Background: Although repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for major depressive disorder (MDD), treatment selection is still mainly a process of trial-and-error. The present study aimed to identify clinical predictors of remission after a course of rTMS delivered to the left DLPFC to improve patient selection.

Methods: Data from a large randomised non-inferiority trial comparing standard 10 Hz and intermittent theta burst stimulation (iTBS) for the treatment of MDD were used for the exploratory analyses. Individual variables were assessed for their association with remission and then included in a logistic regression model to determine odds ratios (OR) and corresponding 95% confidence intervals. Model discrimination (internal validation) was carried out to assess model optimism using the c-index. ClinicalTrials.gov identifier: NCT01887782.

Findings: 388 subjects were included in the analysis (199-iTBS and 189-10 Hz, respectively). Higher baseline severity of both depressive and anxiety symptoms were associated with a lower chance of achieving remission (OR=0.64, 95% CI 0.46−0.88; and 0.78, 95% CI 0·60−0.98, respectively). Current employment was a positive predictor for remission (OR=1.69, 95% CI 1.06−2.7), while greater number of treatment failures was associated with lower odds of achieving remission (OR=0.51, 95% CI 0.27−0.98). A non-linear effect of age and remission was observed. An analysis to allow an estimate of the probability of remission using all variables was assessed. The c-index for the fitted model was 0.687.

Interpretation: Our results suggest that measuring depression symptom severity, employment status, and refractoriness are important in prognosticating outcome to a course of rTMS in MDD.

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1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) for major depressive disorder (MDD) has been extensively studied, demonstrating efficacy in large clinical trials and meta-analyses [1−4]. It is a recognised evidence-based treatment and integrated into clinical care for depression in the many countries [5−7]. However, the degree of response to treatment is quite variable across individuals, with previous studies showing a bimodal or trimodal distribution of outcomes [8,9].

Variations in the degree of response to rTMS have been attributed to several patient-specific, illness-specific, and treatment-modality-specific factors [10]. To increase the efficacy and effectiveness of rTMS for MDD, studies have attempted to identify replicable and

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Research in context

Evidence before this study

Repetitive transcranial magnetic stimulation (rTMS) is an evidence-based treatment for major depressive disorder (MDD). To enhance the efficacy and effectiveness of rTMS for MDD, studies have attempted to identify replicable and quantifiable predictors of therapeutic outcomes. We searched PubMed from 1996 to September Week 2 2019 with the terms depression, transcranial magnetic stimulation, theta burst stimulation, restricted to reviews and clinical trials in English, focusing on studies that assessed clinical and demographic predictors of response in rTMS for MDD.

Added value of this study

This exploratory study aimed at assessing the performance of a model for predicting remission after a course of rTMS based on pre-treatment clinical and demographic variables that are readily available to clinicians. We observed meaningful clinical effects of baseline severity of depressive and anxiety symptoms, employment status, failure of more than two antidepressant trials, and age on the odds of achieving remission after rTMS. The model had a modest predictive value.

Implications of all the available evidence

The identification of clinical and demographic predictors of remission of depression after rTMS is an important component in developing a personalised medicine approach. Our results suggest that there is utility in measuring baseline depression and anxiety severity, employment status, and quantifying the number of treatment failures in the current episode. The clinical variables identified in this study can help guide patient selection for rTMS delivered to the left DLPFC using either iTBS or 10 Hz, but improved prediction models will likely require the addition of other biological variables.

quantifiable predictors of therapeutic outcomes. However, most of the studies had small sample sizes or pooled data from previous trials and no baseline demographic variables have emerged as clear predictors of therapeutic outcome.

We previously reported the findings from a randomised, multicentre, non-inferiority trial that compared intermittent theta burst stimulation (iTBS) with conventional 10 Hz rTMS to the left dorsolateral prefrontal cortex (DLPFC) in subjects with MDD (N = 192 in the 10 Hz group and 193 in the iTBS group), the THREE-D study [11]. The 3 min iTBS sessions were non-inferior to the standard FDA-approved 37.5 min 10 Hz sessions. The observed response and remission rates (iTBS, 49% and 32%; 10 Hz, 47% and 27%, respectively) were encouraging, given that more than half of the sample met the criteria for treatment-resistant depression, having failed two or more adequate antidepressant trials [7,12]. rTMS requires patients to attend daily clinic visits over 6 weeks and only a third of the patients met criteria for remission. Identifying patient attributes that are associated with better outcomes could help improve outcomes and help with appropriate patient selection. Therefore, we aimed at identifying clinical and demographic predictors of remission after a course of rTMS using data from the THREE-D study. Secondarily, we aimed to assess the performance of a model for predicting of remission based only on pre-treatment clinical and demographic variables that are readily available to clinicians.

2. Methods

2.1. Study design

Participants comprised the sample reported in detail elsewhere from the previously published multisite, randomised, non-inferiority trial of iTBS versus high-frequency 10 Hz rTMS over the left DLPFC in patients with depression (THREE-D) [11]. The current study follows the Consolidated Standards of Reporting Trials (CONSORT) statement.

2.2. Participants

In brief, participants were adult outpatients between 18 and 65 years old, diagnosed with MDD confirmed with the Mini-International Neuropsychiatric Interview. Subjects were considered ineligible if they presented with: (1) a positive history of substance abuse or dependence in the past 3 months, a personality disorder deemed to be the primary pathology, or any psychotic disorder or current psychotic symptoms; (2) active suicidal intent; (3) pregnancy; (4) a history of previous rTMS treatment; (5) a lifetime history of non-response to an adequate course of electroconvulsive therapy; (6) an unstable medical illness, substantial neurological illness, abnormal serology, or cardiac pacemaker; (7) a intracranial implant; (8) a current use of any anticonvulsant or more than 2 mg of lorazepam per day (or equivalent); (9) more than three adequate antidepressant trials failed during the current episode of depression. All participants had failed 1−3 antidepressant trials of adequate dose and duration or had been unable to tolerate at least two separate trials of antidepressant medications of inadequate dose or duration. The local research ethics boards approved the study at each site (Centre for Addiction and Mental Health, Toronto, ON; Toronto Western Hospital, Toronto, ON; University of British Columbia Hospital, Vancouver, BC), and each participant provided written informed consent for study participation.

2.3. Randomisation and masking

Participants were randomly assigned to receive treatment with iTBS (n = 209) or 10 Hz (n = 205) in a 1:1 ratio (see Fig. 1 for the CONSORT Diagram). Randomisation of participants was performed using a randomly permuted block method with a random number generator, stratified by site and degree of medication resistance (more than one versus one or fewer adequate medication trials without response). Before the recruitment phase, randomisation tables of a fixed size were made with a computer-based algorithm that generated randomly permuted blocks. Nontransparent, sealed envelopes with a randomisation ID on the outside and treatment allocation on the inside were managed by personnel external to the study team and accessed by the treatment technician only after participants received their MRI. Participants and treatment technicians were aware of the treatment condition, but raters were sequestered in a different clinic area and blinded to treatment condition. Participants were required to be on a stable antidepressant regimen for at least 4 weeks prior to, and throughout, the course of treatment, and were instructed not to discuss their treatment with raters or other subjects.

2.4. Procedures

During calibration, the resting motor threshold (RMT) for treatment was determined by visual observation and defined by the minimum stimulation intensity necessary to elicit a visible hand muscle contraction (i.e. abductor pollicis brevis) in a minimum of three out of five trials. rTMS treatments were delivered under real-time MRI-guided neuronavigation using a Visor2 system (ANT Neuro, Enschede, Netherlands) to optimise coil positioning. The left DLPFC was targeted using the stereotaxic coordinates [X-38 Y + 44 Z + 26] in the MNI-152

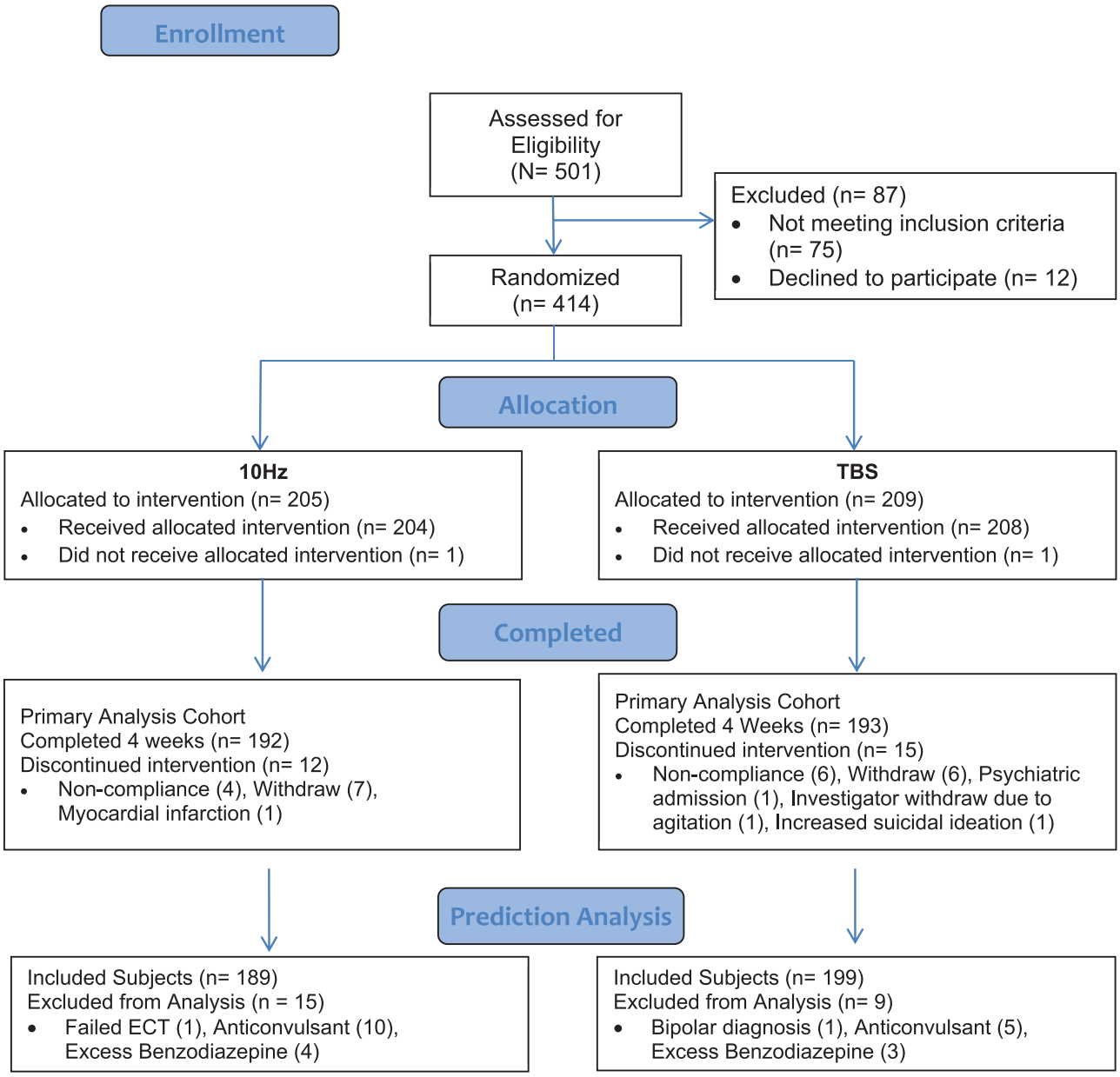

Fig. 1. CONSORT flow diagram.

stereotaxic atlas. The device used was a MagPro X100/R30 stimulator equipped with a B70 fluid-cooled coil (MagVenture, Farum, Denmark). The 10 Hz treatment condition aimed for treatment at 120% resting motor threshold (4 s on, 26 s off, 3000 pulses/session over 37.5 min); iTBS was delivered to the same site with the same intensity, but with a different stimulation pattern (triplet 50-Hz bursts, repeated at 5 Hz, 2 s on, 8 s off, 600 pulses per session over 3 min). Further details are provided in the original THREE-D report [11].

Treatments were administered five days/week over four to six weeks for 20 to 30 treatments. All participants received an initial course of 20 daily treatments (four weeks), and participants who achieved a reduction of at least 30% from baseline in the HAM-D score, but not remission, received an additional ten treatments over two weeks to try to achieve remission.

Participants were withdrawn if they reported a worsening in the depressive symptoms higher than 25% (measured by the HAM-D) in two consecutive assessments; developed significant suicidal ideation; attempted suicide; or missed four consecutive treatments.

2.5. Outcomes

All demographic characteristics potentially associated with remission were measured at baseline. The primary outcome measure for the THREE-D study was the 17-item Hamilton Depression Rating Scale (HAM-D) [13]. Anxiety symptom severity was also assessed via the 5 anxiety items from the Brief Symptom Inventory (BSI-A) [12]. These outcome measures were obtained at baseline, then weekly (after each five sessions) during treatment, then at 1, 4, and 12 weeks after the final session of treatment.

2.6. Statistical analysis

For analytical purposes, participants from both treatment groups (iTBS and 10 Hz) were designated as remitters (28·6%, n = 111) or non-remitters (71.4%, n = 277). Remission was defined based on a HAM-D score <8 at the first time point following completion of all treatment sessions (either 20 or 30) for each participant.

For the predictive model, we assessed variables that have been previously associated with response and remission after pharmacotherapy or after a course of rTMS for MDD. We only considered variables with a plausible theoretical reason to be important as well as variables consistently demonstrated as important in the literature, and the chosen variables were defined as the ones most likely to effect the relationship of rTMS treatment with the probability of remission [14]. The chosen variables were age, employment status (as a measure of functionality), baseline HAM-D score (as a measure of severity), baseline BSI for anxiety, and degree of resistance to pharmacotherapy based on the antidepressant treatment history form (ATHF) [12]. Even though sex is a consistently assessed variable in rTMS trials, we chose not to include it as a variable due to the inconsistency on the predictive value of sex for response after rTMS for MDD [10,15–18].

Moreover, the relationship between sex and the effect of rTMS seems to be related, at least in part, to hormonal changes, with greater neuroplastic response to rTMS reported in women when oestrogen is at its highest, compared to men, suggesting that endogenous oestrogen levels contribute to the variability in response to HF-rTMS [19]. Unfortunately, we did not assess menstrual status or hormonal changes during treatment in the female participants.

All statistical analyses were conducted using R (version 3.5.2) [20]. The age variable was modelled with a restricted cubic spline with three knots. The rms package for R was used to construct the spline function and fit the models [20]. Treatment resistance was dichotomised by number of prior treatment failures (2 or fewer treatment failures or more than two treatment failures) as a previous report found lower remission rates in the sample that had more than two treatment failures [43]. Furthermore, because this trial used two different rTMS treatment techniques, we included the treatment allocation in the model (iTBS and 10 Hz) as a covariate, even though the original THREE-D study demonstrated non-inferiority of outcomes for iTBS versus 10 Hz treatment.

Next, the candidate clinical predictor variables were included in a logistic regression model to determine their association with remission as measured by odds ratios (OR) and the corresponding 95% confidence intervals. Statistical tests were two-tailed, with the alpha (Type I error rate) set to 0.05. Model discrimination (internal validation) was carried out to assess for optimal model fit using the c-index, which corresponds to the area under the ROC curve constructed from the model-predicted probabilities of remission in comparison with the actual observed outcome. A bootstrap procedure with 100 iterations was then applied for a more robust estimate of the c-index.

Finally, given that some studies have suggested that worse rTMS treatment outcomes may be associated with a greater length of the current episode of depression [15] and with the use of benzodiazepines during treatment [21,22], we performed a supplementary analysis to assess the impact of adding these two additional predictors (current depression episode length, and presence/absence of benzodiazepines in the medication regimen) to the initial model. In light of previous reports of differences in response to neurostimulation between males and females, we performed a sensitivity analysis that included sex as an interaction term for each variable in the model. Another sensitivity analysis on potential stimulation parameter (10 Hz or iTBS)-specific predictors was also conducted whereby stimulation parameter was built as an interaction term for each variable in the model. The interaction term between each variable was included in the model and tested using a likelihood ratio test for an interaction.

We've chosen to investigate these variables in a prespecified prediction model rather than the classic approach that begins with univariate pre-screening for variables where $P < .05$ and then carrying those variables forward, with backward elimination, to arrive at a final set of statistically significant variables. The additional models that we tested were reported only to assess changes in the exposure effect as a result of ignoring a potential confounder while adjusting for other variables, to answer whether a potential confounder is still a confounder after adjustment [14]. Five independent variables based on the smallest sample size of the smallest group of remitters in either the iTBS or 10 Hz arm of the original study were chosen to guard against overfitting (50 remitters in the 10 Hz group and 61 in the iTBS group).

2.7. Role of the funding source

The device manufacturer (Magventure) that provided partial equipment support and the funding sources of the study had no role in the study design, data collection, analysis and interpretation, writing of the manuscript or the decision to submit. The corresponding author (DMB) and statistician (KET) had full access to all the data and the corresponding author (DMB) had final responsibility for the decision to submit the manuscript.

3. Results

A total of 414 participants were randomised into the study, with 26 excluded: two before receiving treatment and 24 who received treatment but were subsequently found to have violated study inclusion criteria (Fig. 1). Therefore, the analytic cohort for this study consisted of 388 participants who received at least one rTMS treatment session (Table 1). For further baseline characteristics by treatment group allocation, please refer to the THREE-D study report [11].

Table 1
Baseline characteristics of the included subjects by remitters and non-remitters.

		Non-remitters (n = 277, 71.4%)	Remitters (n = 111, 28.6%)
Treatment Allocation, n (%)	*iTBS*	138 (69.4)	61 (30.6)
	10 Hz	139 (73.5)	50 (26.5)
Age, mean (SD)		41.6 (11.6)	44.2 (10.9)
Sex, n (%)	*Male*	118 (42.6)	41 (36.9)
	Female	159 (57.4)	70 (63.1)
Years of education, mean (SD)		16.2 (3.2)	16.5 (2.7)
Working status, n (%)	*Not working*	184 (75.7)	59 (24.3)
	Working	93(64.1)	52(35.9)
>2 Medication trials, n (%)	*≤2*	217 (69.1)	97 (30.9)
	>2	60 (81.1)	14 (18.9)
Episode Length, mean (SD)		23.2 (26.6)	24.0 (29.4)
Age of onset, mean (SD)		20.6 (10.9)	21.6 (11.0)
Receiving pharmacotherapy during treatment, n (%)			
Benzodiazepine		94 (33.9)	29 (26.1)
Antidepressant		208 (75.1)	87 (78.4)
Antidepressant combination		63 (22.7)	21 (18.9)
Antipsychotic augmentation		51 (18.4)	20 (18.0)
Lithium augmentation		10 (3.6)	3 (2.7)
Previous electroconvulsive therapy, n (%)		16 (5.8)	2 (1.8)
Baseline HDRS, mean (SD)		24.1 (4.4)	22.2 (3.7)
Baseline BSI, mean (SD)		10.6 (5.2)	8.5 (5.1)

iTBS= intermittent theta burst stimulation; 10 Hz=10 Hz rTMS over the left DLPFC; SD=standard deviation.

Table 2
Estimated effect sizes for the independent variables included in the model.

	Odds Ratio	95% Confidence Interval	*p*-value
Age (per 5 year)			0.056 (overall)
30–35 years	1.248	1.003–1.554	0.280 (non-linearity)
45–50 years	1.036	0.866–1.241	
Baseline HAM-D (per 5 unit)	0.64	0.464–0.884	0.0067
Baseline BSI-A (per 5 unit)	0.764	0.596–0.98	0.0342
Treatment allocation (reference 10 Hz)	1.194	0.746–1.911	0.4603
Working status (ref. Not Working)	1.691	1.056–2.706	0.0287
>2 Medication Trials (ref. ≤2 Trials)	0.513	0.268–0.984	0.0445

For age and baseline HAM-D and BSI-A, we have chosen to express the effect for a 5-unit difference based on one standard deviation. HAM-D = 17-item Hamilton Depression Rating Scale; BSI-A = Brief Symptom Inventory for anxiety; 10 Hz = 10 Hz rTMS over the left DLPFC.

For the effect of baseline HAM-D and BSI-A, we have chosen to express the effect with a five-unit difference based on one standard deviation of change in both treatment groups (Table 2). Higher baseline severity of both the depressive and anxiety symptoms were associated with a lower chance of achieving remission after rTMS (HAM-D OR=0.64, 95% CI 0.46–0.88; and BSI-A OR=0.76, 95% CI 0.60–0.98, respectively). Current employment was a positive predictor of remission (OR=1.69, 95% CI 1.06–2.7), while failure of more than two antidepressant trials was also associated with lower odds of achieving remission (OR=0.51, 95% CI 0·27–0·98).

We observed a non-linear effect of age on the odds of achieving remission, demonstrated by the shape of the relationship on the log-odds scale (please see Fig. 2). Due to the non-linear relationship, the effect of age was expressed for a five-year difference at two representative points (places where the relationship is approximately linear based on visual inspection of the graph): ages 30–35 and 45–50. The negative relationship between age and remission is stronger for younger individuals (e.g. OR 1.25, 95% CI 1.003–1.55 for between 30 and 35 years) and lessens as subjects age (e.g. OR 1.04, 95% CI 0.87–1·24 for between 40 and 45 years).

We found no significant effect of group allocation to iTBS or 10 Hz (OR 1.19; 95% CI 0.75–1.91) on the odds of achieving remission when controlled for the variable included in the model.

The sensitivity analysis with length of current depressive episode, use of benzodiazepines, sex, and parameter-specific effects showed no significant effect on the likelihood of remission when these factors were added separately to the model (Wald test for significance, p = 0.28, 0.80, 0.39, and 0.122, respectively). These variables were therefore not included in the final predictive model.

Following the individual evaluation of the five clinical predictor variables, an equation to allow an estimate of the probability of remission using a combination of the five variables was constructed (Supplementary Fig. 1) and its performance assessed via c-index as described above (the receiver operating characteristic (ROC) curve can be found in Supplementary Fig. 2). The c-index for the fitted model was 0·687, with the bootstrap-corrected c-index falling slightly to 0·661. Using the equation, we estimate the probability of remission for a subject who is unemployed, has tried more than 2 medications, with a baseline HAM-D of 30 and a baseline BSI-A of 20 to be 0.022 (95% CI 0.007–0.071) when receiving 10 Hz. Using the same equation, a subject who is employed, has not tried more than 2 medications, with a baseline HAM-D of 20 and a baseline BSI-A of 5 has an estimated probability of remission of 0.58 (95% CI 0.46–0.70) when receiving iTBS.

4. Discussion

This study was an exploratory analysis of clinical and demographic variables associated with the clinically important outcome of remission in a large sample of patients with depression treated with excitatory rTMS delivered to the left DLPFC. We observed meaningful clinical effects of baseline severity of depressive and anxiety symptoms, employment status, failure of more than two antidepressant trials, and age on the odds of achieving remission after rTMS. A unified predictive model constructed from these clinical variables achieved a modest overall performance with a c-index of 0.687, but falling short of the degree of individual-patient prediction accuracy that would likely be required in a real-world clinical setting.

Baseline severity has been found to be a negative predictor of response after rTMS, with mild to moderate episodes of depression predicting better treatment outcome [23]. In fact, pooled data from 11 different trials of rTMS in depression showed that less severe depression at baseline was associated with higher odds of responding to rTMS [9]. Our data corroborate these findings, with baseline depression severity found to be strong factor in the odds of achieving remission.

Baseline anxiety has also emerged as an important predictor of response in antidepressants use in depression. Importantly, when anxiety was analysed as a predictor of remission in the STAR*D data, remission rates were significantly lower in patients with anxious depression, at level 1 (citalopram) and 2 (switching antidepressants or augmentation) of the study [24]. In a study that looked at patients treated with rTMS (n = 70), responders had less anxiety at baseline in comparison to non-responders, and higher response rates have been observed in patients receiving rTMS with no comorbid anxiety disorder (54.1%) in comparison to patients with comorbid panic disorder or generalised anxiety disorder (35% and 47.3%, respectively; p<.005) [15]. We observed that baseline anxiety negatively impacted the odds of achieving remission. To our knowledge, this is the first large scale trial to report on the impact of baseline anxiety symptoms on the odds of achieving remission of depression symptoms after iTBS and 10 Hz. A strength of the analysis includes the use of a separate anxiety scale (BSI-A) rather solely the anxiety sub-items from the HAM-D.

One possible explanation of the negative impact of baseline anxiety may be related to the use of benzodiazepines during the trial. Previous reports have suggested that medications that interfere with cortical plasticity, such as benzodiazepines or antiepileptic medications, can impact outcomes of brain stimulation treatments, including electroconvulsive therapy [21,25]. In fact, Hunter et al. performed a retrospective chart review (N = 181) and reported that the response rates at week 6 of rTMS (10 Hz rTMS administered to left DLPFC and 1 Hz to the right DLPFC if inadequate response or intolerance of left-sided stimulation) were significantly lower in benzodiazepine users versus non-users (16.4% vs. 35.5%) [21].

Even though a maximum daily dosage of benzodiazepines was set to minimise the impact of the benzodiazepines in the outcome (maximum daily dosage of 2 mg of lorazepam or equivalent) and those on anticonvulsants were excluded in the THREE-D study, the absence of benzodiazepine use during rTMS has been shown to be associated with rapid response trajectory (near-maximal improvement by week 2–3), with higher total daily benzodiazepine doses associated with reduced odds of a rapid response [22]. In addition, the use of benzodiazepines during rTMS has not been consistently reported to be associated with a reduced remission rate. We didn't observe any meaningful impact of benzodiazepine use in the model, and the variable was not included in the final prediction model of remission.

Several lines of evidence suggest that medication resistance is a predictor of poor response to both ECT [26,27] and rTMS [18]. Brakemeier et al. reported a lower number of previous treatment trials to be amongst the main predictors of response to rTMS for MDD, in

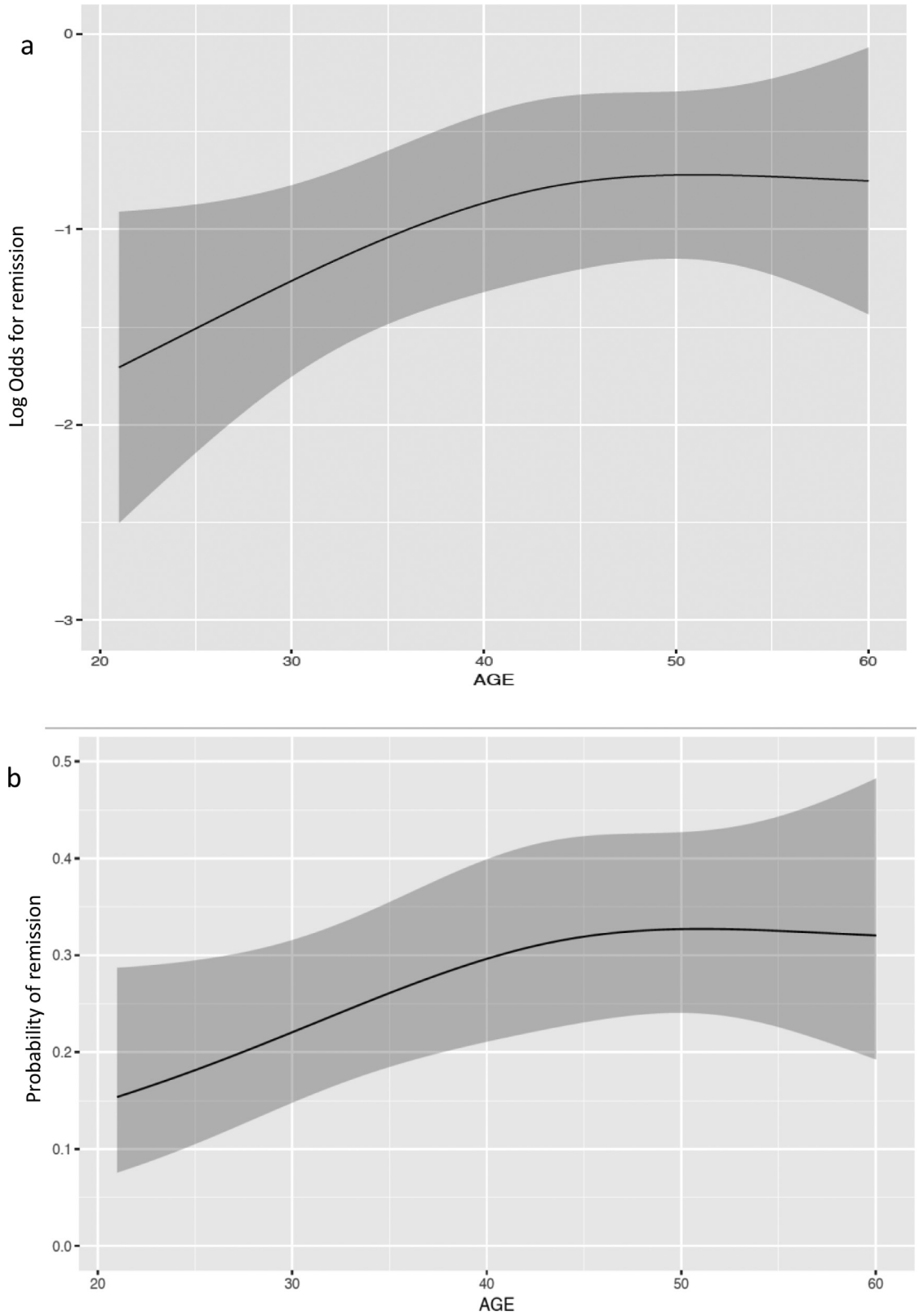

Fig. 2. Non-linear age effect demonstrated by the shape of the relationship on the log-odds (a) and probability (b) scales.

addition to a short duration of episode, and a high level of sleep disturbances [15]. Patients with chronic depression may represent a distinct sub-group who are less likely to respond to rTMS [15]. However, we observed no impact in adding the duration of the current episode of depression on the odds of achieving remission, and the variable was not included in the final model. Levkovitz et al. reported that the mean number of antidepressants used in the current episode (before dTMS treatment) was 2.6 medications in subjects who responded and 3·6 in subjects who did not respond [28]. Fregni et al. analysed the pooled data from six separate clinical trials

(n = 195) and reported that, in addition to age, refractoriness was a significant negative predictor for a response after rTMS [29]. Our results are consistent with previous findings that greater number of medication failures in the current episode is an important negative predictor of remission after rTMS.

The influence of socioeconomic status has been investigated in the outcomes after treatment with citalopram using data from the STAR*D with higher remission rates associated with working employment status [30,31]. In the current study, we included working status as potential clinical predictor variable (self-employed, part-time employed, and full-time employed as currently working versus unemployed or retired, as not currently working), not only as a measure of baseline functionality, but also because working status has been shown to be a positive predictor of achieving remission with other treatments. Our findings suggest that currently working status positively impacts the odds for remission. Given the time commitment needed to attend rTMS this finding was somewhat unexpected but may be associated with overall functional status and severity.

The relationship between age and rTMS treatment response is not consistently apparent in the literature, with initial studies reporting higher age as a predictor of worse outcome for rTMS, not observed in recent trials [29,32–36]. We observed that age had a non-linear relationship with the odds of remission (Fig. 2), with age having a negative effect on remission in younger subjects (Fig. 2 and Table 2). However, the observed effect was modest.

With baseline depressive and anxiety symptom burden, failure of more than two antidepressants, employment status, and age, the model estimated the odds of achieving remission after rTMS with significant accuracy at the group level (Supplementary Fig. 1). However, the model should be viewed as a candidate that requires verification in a separate sample. Furthermore, the accuracy of the present model remains fairly modest for predicting remissions at the individual-patient level, from clinical factors alone. Further optimisation would be required to meet the substantially higher bar of individual-level rTMS outcome prediction in the clinical setting; for such purposes, biological markers such as functional MRI or heart rate variability have shown some recent promise [37,38].

Our findings should be considered in light of some potential limitations. First, the selection criteria prevent the generalisation of our results to individuals over age 65. Second, two different treatments were used in the study, even though non-inferiority was reported in the original research. To minimise the impact of the rTMS modality allocation in the final model, we included the group allocation as a possible confounder. We observed no difference in predictors of remission for 10 Hz versus iTBS, further substantiating the similarity in clinical effectiveness between the two treatments. Third, our analysis was exploratory and data-driven. While we applied conservative significance thresholds to mitigate this issue, the characteristics identified could still be a result of model overfitting and therefore would require replication in independent cohorts to develop clinically useful predictive models. Another possible limitation is the wide variability in concomitant antidepressant use during the trial. However, to minimise potential confounding effects of concomitant pharmacological treatment at least four weeks of medication stability was present prior to enrolment and the pharmacological regime was not changed during rTMS therapy. In addition, the relationship between the effect of rTMS and menstrual status or hormonal changes during treatment in female participants has been previously reported and was not addressed in the present study [19]. Recently, higher baseline anhedonia has also been reported to be a negative predictor of response in rTMS for MDD [39,40] and was not assessed in the current study given that no tools for the assessment of anhedonia were applied in the THREE-D study. The lack of external validation is an additional limitation to the study findings and a potential obstacle to the translation of research evidence into clinical practice, thus further warranting the replication of our findings in future studies.

Finally, this analysis only considered clinical and demographic characteristics associated with remission after rTMS and did not use any neurobiological markers. On the other hand, the objective of the current study was not only to assess baseline predictors of remission, but also to explore a model comprised of simple clinical variables on the odds of achieving remission with rTMS targeted to the left DLPFC. Thus, while neuroimaging and neurophysiological biomarkers may increase the accuracy of the prediction of remission in MDD, they potentially increase costs in the real-world setting, and may not be easily available in smaller centres. However, complementary models with biomarkers and clinical and demographic variables have shown to provide more accurate predictive models of response, and may improve prediction overall [10,41]. Our findings of higher baseline depression and anxiety severity associated with low likelihood of remission and current employment status having a higher likelihood of remission converge with a recent exploratory analysis from the large scale U.S. Department of Veterans Affairs Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) study of medication switch vs. augmentation strategies in depressed patients with one prior medication failure [42]. These variables suggest that there may be common clinical variables that predict response in patients with treatment-resistant depression across different treatment modalities rTMS.

In summary, the identification of clinical and demographic predictors of remission of depression after rTMS represents a critical step in developing personalised medicine in MDD. Our results suggest that there is clinical utility in measuring baseline depression and anxiety severity, employment status, and quantifying the number of treatment failures in the current episode to help guide patient selection for rTMS delivered to the left DLPFC using either iTBS or 10 Hz. Sham-controlled studies are necessary to better understand the relationship between potential predictors of remission and the treatment-specific effects of the rTMS interventions. Complementary biological and clinical variables are likely to aid in the development of better predictive models

Data statement

Data collected from the study, including individual participant data and a data dictionary, may be made available upon request to the corresponding author.

Declaration Competing of Interest

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100349.

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