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ARTICLE

Predictors of antidepressant response in clinical trials of transcranial magnetic stimulation

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Abstract

Although previous clinical trials have suggested that repetitive transcranial magnetic stimulation (rTMS) has a significant antidepressant effect, the results of these trials are heterogeneous. We hypothesized that individual patients' characteristics might contribute to such heterogeneity. Our aim was to identify predictors of antidepressant response to rTMS. We pooled data from six separate clinical trials conducted independently, which evaluated the effects of rapid rTMS of the left dorsolateral prefrontal cortex in patients with major depression. We investigated 195 patients with regard to demographic, depression and treatment characteristics, psychiatric and drug history. Results showed that age and treatment refractoriness were significant negative predictors of depression improvement when adjusting these variables to other significant predictors and confounders. These findings were not confounded by methodological differences from the six studies, as the results were adjusted for the study site. In conclusion TMS antidepressant therapy in younger and less treatment-resistant patients is associated with better outcome.

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Key words: Age, Hamilton Depression Rating Scale, major depression, transcranial magnetic stimulation.

Introduction

Major depressive disorder (MDD) is a serious medical illness and a leading cause of disability worldwide (Ustun et al., 2004). The most used therapy for MDD is pharmacological treatment; however, this treatment is often associated with adverse events. A non-pharmacological option is electroconvulsive therapy (ECT). Although being the most efficacious treatment for MDD, ECT is associated with an anaesthetic risk, memory changes and social stigma (Fink, 2001). A non-invasive form of brain stimulation – repetitive transcranial magnetic stimulation (rTMS) – that is not associated with the adverse effects of ECT has been shown to be efficacious for the treatment of depression (see meta-analyses: Burt et al., 2002; Holtzheimer et al., 2001; Martin et al., 2003). Several studies have shown that this treatment can induce antidepressant effects with few, usually mild adverse effects (Conca et al., 1996; Eschweiler et al., 2000; George et al., 1997, 2000; Grunhaus et al., 2000; Holtzheimer et al., 2001; Pascual-Leone et al., 1996; Pridmore et al., 2000). However, other studies have failed to show clinical improvements in depressed patients after rTMS treatment (Hausmann et al., 2004; Padberg et al., 1999). Such variability could be explained by the random variability of the 'true' TMS effect, particularly because most published TMS studies to date are small and lack adequate statistical power; or alternatively by different patients' characteristics. In fact, Gershon et al. (2003), in a literature review, conclude that, although TMS shows promise

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Table 1. Baseline and demographic characteristics

Characteristics ($n=115$ patients)	All patients	Group 1 (Boston)	Group 2 (Innsbruck)	Group 3 (Sao Paulo 1)	Group 4 (Tel-Aviv)	Group 5 (Sao Paulo 2)	Group 6 (Ontario)	p value[d]
No. of patients	195	60	29	21	42	18	25	
Age (mean ± S.D.)	51.1 (15.1)	54.4 (13.0)	44.6 (12.4)	39.0 (13.0)	60.0 (14.6)	41.2 (10.6)	52.7 (15.4)	<0.001
Gender (M/F)	80/114	29/30	13/16	3/18	17/25	10/8	8/17	0.06
HAMD baseline (mean ± S.D.)	25.1 (6.1)	22.6 (5.8)	26.7 (6.2)	29.5 (5.3)	25.7 (4.9)	30.1 (4.9)	20.8 (3.9)	<0.001
Depression Improvement (mean % ± S.D.)	30.1 (27.5)	22.5 (26.2)	48.2 (24.1)	60.1 (22.2)	27.2 (24.5)	20.1 (19.8)	19.0 (21.5)	<0.001
Number of responders (% total)[a]	25.1	16.7	48.3	57.1	21.4	11.1	8.0	<0.001
Number of remissions (% total)[b]	11.8	8.3	17.2	38.1	7.1	0	8.0	0.002
Frequency	–	20	20	5	10	10	10	–
Number of pulses per session	–	1200	2000	1250	1200	2500	1800	–
TMS intensity[c]	–	120	100	120	90	110	110	–

HAMD, Hamilton Depression Rating Scale.

[a] HAMD reduction ⩾50%.

[b] Defined as HAMD post-treatment scores ⩽7.

[c] % of the motor threshold.

[d] Comparison between the three groups (ANOVA for the continuous variable – age, HAMD baseline and depression improvement and Fisher's exact test for categorical variables – gender, number of responders and remissions).

as a novel antidepressant treatment, 'large-scale studies are needed to identify patient populations most likely to benefit from rTMS treatment' (Gershon et al., 2003). We, therefore, pooled data from six clinical trials to investigate the predictors of the TMS antidepressant treatment based on patients' and treatment characteristics, such as the items of the Hamilton Depression Rating Scale (HAMD), age, gender, psychiatric and drug history and TMS parameters.

Methods

Subjects

The data were collected for 195 patients diagnosed with MDD. The diagnosis of MDD was made using the Structured Clinical Interview for DSM-IV Axis I AQ2 Disorders (SCID) by a trained interviewer. These patients were pooled from six studies that evaluated the antidepressant effects of 10 d of high-frequency TMS applied to the left prefrontal cortex. In one of the studies (Ontario), the data presented were those related to the open-label treatment with real rTMS. The other five studies were randomized double-blind studies. These studies were done in Boston (Harvard Medical School), Innsbruck (Medical University Innsbruck), Tel Aviv (Tel Aviv University), Hamilton, Ontario (McMaster University) and Sao Paulo (two studies – University of Sao Paulo). The numbers and characteristics of patients in each study are summarized in Tables 1 and 2. All six studies were conducted on male or female patients older than 18 years. Study protocols had been reviewed and approved by the ethical review board at each centre, in accordance with the principles of the Declaration of Helsinki, and all patients provided written informed consent.

TMS clinical trials design

Five of these studies were randomized, double-blind clinical trials and one of them was an open-label study (Ontario site). Patients were scored on the HAMD by a rater who remained blinded to the

Table 2. Characteristics of each study design

Characteristics	Group 1 (Boston)	Group 2 (Innsbruck)	Group 3 (Sao Paulo 1)	Group 4 (Tel-Aviv)	Group 5 (Sao Paulo 2)	Group 6 (Ontario)
Study design	Randomized, double-blind, active-controlled study	Randomized, double-blind, placebo-controlled study	Randomized, double-blind, placebo-controlled study	Randomized, double-blind, active-controlled study	Randomized, double-blind, active-controlled study	Open-label study
Inclusion criteria	Unipolar depressive disorder, score at least 18 on HAMD	Medication free patients with major depression disorder. Score of at least 18 on HAMD	Unipolar depressive disorder, score of $\geqslant$22 on HAMD	Unipolar major depression, score of $\geqslant$18 in the HAMD	Medically refractory unipolar depressive disorder, score of $\geqslant$22 on HAMD	Unipolar major depression
Exclusion criteria	No active suicidality (score of $<$3 on item 3 of HAMD), other neuropsychiatric condition, inability to withdraw medications, altered neurological examination	Contra-indications to rTMS, major medical problems or suicidal ideation	Neurological disorders, personality disorders, suicide risk, alcohol or drug abuse, history of seizures	Contraindication to rTMS (safety guidelines), MD not secondary to a general medical condition, substance abuse, psychotic symptoms	Psychotic symptoms, contra-indications to rTMS	Contra-indications to rTMS
Criteria of refractoriness	Previous use of two or more antidepressants without response	Previous use of three or more antidepressants without response	Lack of response to at least two anti depressants of a different class	Failure to at least one course of antidepressant medications (at adequate levels for at least 4 wk)	Lack of response to at least two anti depressants of a different class	Failure to at least two courses of antidepressant
Sham type	Active rTMS control	Sham rTMS	Sham rTMS	ECT	ECT	Open study
Antidepressants use	Not allowed	Yes – chosen on naturalistic basis	Yes – amytriptiline 150 mg/d (adjusted for tolerability)	Not allowed	Yes – conform prescribed by treating physician	Some of the patients as prescribed by their physician
Age range (yr)	18–80	21–66	19–65	36–89	25–63	29–91
Publication	No	Yes	Yes	Yes	No	No
Reference[a]	Data not published	Hausmann et al. (2004)[a]	Rumi et al. (2005)	Grunhaus et al. (2003)[a]	Data not published	Data not published

HAMD, Hamilton Depression Rating Scale.

[a] Note that some patients from these centres were not included in this publication (this is the main publication from this dataset) – see References.

treatment type of the patient (except for the Ontario study). The 10 rTMS treatment sessions were given only on weekdays and were completed in a period of 2 wk. Patients were re-evaluated following the last session of rTMS (at the end of week 2). Repetitive TMS was administered using a figure-of-eight coil and applied over the left dorsolateral prefrontal cortex (5 cm anterior to the motor spot that elicited motor-evoked potentials in either the abductor pollicis brevis or the first interosseous dorsalis muscle of the right hand). However these studies used different parameters of stimulation (see Table 1). We addressed the influence of these parameters' difference in our final model.

Outcome measure

We used the HAMD as this instrument has been widely used in efficacy studies of antidepressant treatments (Endicott et al., 1981; Elkin et al., 1985; Williams, 1988). The version of the instrument utilized in these studies contains 17 items (depressed mood, feelings of guilt, suicide, insomnia early, insomnia middle, insomnia late, work and activities, retardation, agitation, anxiety/psychic, anxiety somatic, somatic symptoms/GI, somatic symptoms/general, genital symptoms, hypochondriasis, loss of weight, and insight).

Statistical methods

The following independent variables were selected from these studies: age, gender (M/F), study site (Boston, Innsbruck, Sao Paulo 1, Sao Paulo 2, Tel Aviv and Ontario), baseline scores for the Hamilton Depression Rating Scale (b-HAMD), post-treatment change in HAMD [δ-HAMD (%)], the scores of each HAMD baseline item, TMS frequency, number of pulses, TMS intensity, depression duration, medication use and treatment refractoriness. We treated all HAMD items as ordinal variables. Gender, medication (antidepressant use: yes/no) and treatment refractoriness (yes/no) were binary variables; location was categorical and age, TMS frequency, number of pulses, TMS intensity, baseline and HAMD changes (%) were treated as continuous variables. Our goal was to model the relationship between these predictors and the change in the Hamilton scores (δ-HAMD) using a linear regression analysis. Although the test for normality (Wilk–Shapiro) indicated that our outcome variable (HAMD change) was marginally significant (0.03), we considered this variable as normally distributed using the central limit theorem for large sample sizes as our sample had 195 patients. Therefore, the use of linear regression was adequate, and means and standard deviation are reported. Although the use of linear regression was adequate, we also performed a new analysis in which we considered treatment response as a categorical variable (responders and remission) and, therefore, used logistic regression.

The first step of modelling was the selection of the covariates. We performed a univariate analysis for each one of our predictors using linear regression with only one variable and we obtained the values for the unadjusted β coefficients and 95% confidence intervals (CIs). We decided to include in our model-building process all variables that had a p value of <0.1 in order to include potential confounders that did not reach the 0.05 significance level in the univariate analysis.

As the site of the study is an important confounder, it was forced into the final model, although it was not a significant predictor of outcome. Furthermore, as this variable contains six categories that are not ordinal, the categories Sao Paulo 1, Sao Paulo 2, Tel Aviv, Ontario and Innsbruck were dummy coded and included into the model. Therefore, Boston was the reference group for this model since it contained the largest number of patients and provided the best power for the comparisons.

Since we anticipated the different HAMD-related variables to be correlated and thus potentially collinear, we used a forward selection process to build our model. This methodology is well-suited to exclude collinear terms, but risks excluding non-significant confounders. To correct for this caveat, we examined the potential confounding effect of each one of the excluded variables by adding them individually to the model. Confounding was defined by changes of $\pm 10\%$ or higher in the β coefficient of any variable from the forward selection model. Confounders were included in our final model.

Initially, we ran two models. In one of them (model 1), we used the 17 items of the HAMD and for the other model (model 2), we used the items of the HAMD collapsed in six categories as follows: anxiety (HAMD, items 10, 11), cognition (HAMD, items 6, 9, 10), mood (HAMD, item 1), motor function (HAMD, items 8, 9), social function (HAMD, item 7) and vegetative function (HAMD, items 4, 5, 6, 12, 13, 14, 16). We decided to pursue this second model as it would provide a more direct clinical interpretation, i.e. it would give a better notion whether symptoms related to anxiety, for instance, rather than item 10 only, would be associated with depression amelioration after 10 d of rTMS. Subsequently, as one of the

study sites was a significant predictor when compared to our reference group, we ran a new model without the patients of this group to test the external validity of our model, and also ran a model without the patients of the Ontario study as this was the only open study and included five elderly patients refractory to medication (5–14 antidepressant trials) who could not tolerate ECT (and therefore, could be an outlier for our results due to the severity of refractoriness and age).

Using the same method described for the linear regression model, we built two logistic regression models in which the outcome was either responders (HAMD decrease of $\geqslant 50\%$) or remissions (post-treatment HAMD baseline $\leqslant 7$). For the remissions model, we had to collapse the study sites to avoid non-convergence as the number of events were low (23) and one group (Sao Paulo 2) had no events, i.e. no remissions, and the other (Ontario) had just two events. We collapsed Sao Paulo 2 and Sao Paulo 1 (Sao Paulo); Ontario and Boston (Boston). The regression models were evaluated for goodness of fit using the Hosmer and Lemeshow test.

After defining our model, we checked whether the assumptions for these models were met, testing the normality and constant variance of the residuals. We plotted a graph of the residuals vs. the predicted values. In order to check for potential nonlinear effects of the predictors that could have improved our model, we plotted the residuals against each significant predictor and looked for nonlinear effects. We tested only the significant continuous variables.

To check for potential influential outliers that could have driven our results (as this test is based on normal distribution), the leverage of each subject was calculated using the Hat Diagonal test. Since we defined our model using multiple testing, we increased the risk of type II error and our model could have been overfitted. In order to determine if we had incurred this type of error, we performed the bootstrap test.

We decided to discard patients with missing data for the variables used in our final model. This elimination did not affect our analysis, as the patients that were discarded were small in number and uniformly distributed across the different studies. We eliminated a total of eight patients. The other variables also had few missing data, except for depression duration for which two centres (Ontario, Tel Aviv) could not provide this information. Nevertheless, we did not exclude all these patients, as this variable was not a significant predictor in either univariate or multivariate analysis.

Results

Table 1 presents the characteristics of all patients divided by treatment site. This analysis showed that these six groups were significantly different regarding age ($p<0.001$), b-HAMD ($p<0.001$), HAMD change ($p<0.001$), responders ($p<0.001$), and remissions ($p=0.002$). Although there was a trend, gender was not significantly different across these six studies ($p=0.06$). As can be observed in Table 2 (study characteristics), the differences across the studies might reflect the different designs and inclusion criteria of each study and they were addressed in our model as we forced study site into our final model.

Table 3 presents the results of the univariate analysis. Interestingly, this analysis demonstrated that TMS parameters investigated in this study, such as treatment frequency, intensity and number of pulses, were either marginally significant [TMS frequency, $p=0.05$; however, TMS frequency dichotomized ($\leqslant 10$ Hz or >10 Hz) was not significant, $p=0.96$] or not significant (TMS intensity, $p=0.54$, and number of pulses, $p=0.12$). Our threshold for inclusion in the model was $p<0.1$. According to this limit, some variables were excluded from further analysis. The following variables were selected for model 1: age, gender, depression duration, treatment refractoriness, medication, rTMS frequency, b-HAMD baseline and HAMD items 4, 7, 10, 11, 13, 17, and for model 2: age, gender, depression duration, treatment refractoriness, medication, rTMS frequency, b-HAMD and HAMD clusters: anxiety and work. The location, dummy coded into six categories – Sao Paulo 1, Sao Paulo 2, Boston, Tel Aviv, Ontario and Innsbruck – was forced into the models as discussed above.

Since the rTMS parameters are not independent variables as they depend on the study, we also performed a meta-analysis of these data in which we compared the difference in the depression intensity indexed by HAMD between the post- and pre-treatment rTMS. In the next step, we performed a meta-regression to analyse if these variables (TMS parameters) were significantly associated with mood improvement and found that none of them were significant predictors of the outcome (TMS intensity, $p=0.985$; number of pulses, $p=0.225$; frequency of stimulation, $p=0.813$).

We used these variables in our forward selection (the results are presented in Table 4). This process resulted in a model with nine variables for model 1 (age, treatment refractoriness, HAMD item 17, gender,

Table 3. Unadjusted predictors of antidepressant response (indexed by HAMD) to TMS treatment

Predictor	β coefficient	95% CI	Unadjusted p value
Age	−0.47	−0.72 to −0.22	0.0002
Gender	8.70	0.87 to 16.5	0.030
Depression severity	0.43	−0.20 to 1.01	0.18
Treatment refractoriness	29.42	22.50 to 36.35	<0.0001
Medication	−18.17	−25.74 to −10.60	<0.0001
Depression duration	−1.1	−2.30 to 0.054	0.06
TMS intensity (continuous)	−0.11	−0.46 to 0.24	0.54
TMS intensity (dichotomized: ⩽10 or >10 Hz)	0.22	−7.59 to 8.04	0.96
TMS frequency	−0.73	−1.46 to −0.0053	0.05
TMS number of pulses	0.0049	−0.0014 to 0.011	0.12
HAMD-17			
1. Depressed Mood	2.19	−2.46 to 6.84	0.35
2. Feelings of Guilt	1.26	−2.43 to 4.94	0.50
3. Suicide	−2.08	−5.83 to 1.66	0.27
4. Insomnia early	−4.11	−7.61 to −0.62	0.02
5. Insomnia middle	1.84	−3.17 to 6.84	0.47
6. Insomnia late	1.97	−3.06 to 7.01	0.44
7. Work activities	3.47	0.67 to 6.27	0.02
8. Retardation to stupor	1.46	−3.15 to 6.06	0.53
9. Agitation	−2.24	−5.72 to 1.24	0.21
10. Fear (0–4)	2.99	−0.52 to 6.50	0.09
11. Anxiety	4.03	0.42 to 7.64	0.03
12. Gastrointestinal symptoms	0.40	−5.39 to 6.19	0.89
13. Systemic somatic symptoms	4.86	0.15 to 9.56	0.04
14. Decreased libido or menstrual disturbance	1.89	−2.19 to 5.98	0.36
15. Hypochondriasis	1.90	−1.71 to 5.51	0.30
16. Weight loss	−0.30	−3.60 to 3.00	0.86
17. Diminished insight	−4.87	−9.48 to −0.26	0.04
Clusters			
Mood (1)[a]	2.19	−2.45 to 6.84	0.35
Vegetative symptoms (4, 5, 6, 12, 13, 14, 16)[a]	0.034	−1.61 to 1.68	0.97
Motor (8, 9)[a]	−0.76	−3.34 to 1.81	0.56
Work (7)[a]	3.47	0.67 to 6.27	0.015
Anxiety (10, 11)[a]	2.44	0.37 to 4.50	0.021
Cognition (6, 9, 10)[a]	0.49	−1.49 to 2.47	0.62

HAMD, Hamilton Depression Rating Scale.
[a] HAMD items.

Sao Paulo 1, Sao Paulo 2, Innsbruck, Tel Aviv and Ontario). Among these variables, age ($p=0.0002$), treatment refractoriness ($p<0.0001$) and Tel Aviv ($p=0.0004$) were the only significant predictors and the other variables were included because they were either confounders (gender and HAMD item 17) or forced into the model (Sao Paulo 1, Sao Paulo 2, Innsbruck and Ontario) (Table 4). For model 2, age, treatment refractoriness, work, gender, Sao Paulo 1, Sao Paulo 2, Innsbruck, Tel Aviv and Ontario were included into the final model. Similarly to the model 1, age ($p=0.0001$), treatment refractoriness ($p<0.0001$) and Tel Aviv ($p=0.003$) were the only significant predictors and the other variables were included because they were either confounders (gender and work) or forced into the model

Table 4. Adjusted predictors of antidepressant response (indexed by HAMD) to TMS treatment

Significant predictors	β coefficient	95% CI	p value
Model 1. Age, Gender, Treatment refractoriness, Medication, Depression duration, TMS frequency and HAMD (items 4, 7, 8, 10, 11, 13, 17) – study site (Sao Paulo 1, Innsbruck, Sao Paulo 2, Tel Aviv and Ontario) was forced into this model			
Innsbruck[a]	−4.40	−18.30 to 9.49	0.53
Sao Paulo 1[a]	3.90	−11.57 to 19.38	0.62
Sao Paulo 2[a]	5.36	−8.03 to 18.75	0.43
Tel Aviv[a]	24.24	11.02 to 37.47	0.0004
Ontario[a]	13.87	−2.07 to 29.81	0.09
Age	−0.52	−0.79 to −0.25	0.0002
Refractoriness	38.45	24.69 to 52.20	<0.0001
Gender[b]	5.12	−1.67 to 11.90	0.14
HAMD item 17 (Insight)[b]	3.28	−8.83 to 2.28	0.25
Model 1 ($R^2 = 0.39$)			
Model 2. Age, Gender, Treatment refractoriness, Medication, Depression duration, TMS frequency and HAM *clusters* (anxiety and work) – study site (Sao Paulo 1, Innsbruck, Sao Paulo 2, Tel Aviv and Ontario) was forced into this model			
Innsbruck[a]	−2.46	−16.56 to 11.65	0.73
Sao Paulo 1[a]	5.18	−10.25 to 20.60	0.51
Sao Paulo 2[a]	3.41	−9.24 to 16.06	0.60
Tel Aviv[a]	18.45	6.27 to 30.62	0.003
Ontario[a]	5.92	−8.65 to 20.49	0.42
Age	−0.50	−0.75 to −0.25	0.0001
Refractoriness	35.28	22.56 to 48.00	<0.0001
Gender[b]	6.10	−0.45 to 12.65	0.07
Work[b]	−0.32	−3.94 to 3.30	0.86
Model 2 ($R^2 = 0.38$)			
Model 3. Linear regression model without patients from Tel-Aviv site (significant predictor) – the same predictors as used in model 1 was adopted to build this model			
Innsbruck[a]	−0.67	−14.80 to 13.46	0.93
Sao Paulo 1[a]	5.76	−9.88 to 21.40	0.47
Sao Paulo 2[a]	3.95	−8.51 to 16.42	0.53
Ontario[a]	8.27	−3.04 to 19.58	0.15
Age	−0.51	−0.80 to −0.21	0.0009
Refractoriness	33.81	20.89 to 46.73	<0.0001
Gender[b]	−3.10	−7.63 to 1.44	0.18
HAMD item 4 (Sleep)[b]	5.65	−1.66 to 12.95	0.13
Model 3 ($R^2 = 0.44$)			

The other variables that were not included into the final model where neither significant nor confounders.
HAMD, Hamilton Depression Rating Scale.
[a] Forced into the model.
[b] Included into the model as confounders.

(Sao Paulo 1, Sao Paulo 2, Innsbruck and Ontario) (Table 4). The exclusion of such a high number of variables could have been due to the anticipated collinearity. Our final model with the nine variables for model 1 had a $R^2 = 0.39$ and for model 2 had a $R^2 = 0.38$. Therefore, these models could explain 38–39% of the data variability respectively.

Since refractoriness was strongly correlated to depression improvement after 2 wk of rTMS treatment and the criteria of refractoriness varied among different study sites, we tested if other variables such as number of unsuccessful antidepressant trials (as a continuous variable), previous sessions of ECT [as a continuous and categorical (yes/no) variable] and previous hospitalizations [as a continuous and categorical (yes/no) variable] were associated with mood amelioration (induced by rTMS) as indexed by HAMD. The results are summarized in Table 5. On the univariate analysis, only previous hospitalizations and ECT (both as categorical variables)

Table 5. Univariate and multivariate analysis of refractoriness based on different criteria

Predictor	β coefficient	95% CI	Unadjusted p value
	Univariate analysis		
Number of antidepressant trials	0.17	−1.36 to 1.70	0.82
Number of previous hospitalizations	−1.29	−3.87 to 1.29	0.32
Previous hospitalizations – dichotomized (yes/no)	13.92	2.28 to 25.55	0.02
Number of previous ECT	−0.25	−0.93 to 0.42	0.454
Previous ECT – dichotomized (yes/no)	10.17	−1.40 to 22.76	0.08
	Multivariate analysis		
Previous hospitalizations – dichotomized (yes/no)	13.79	1.86 to 25.72	0.024
Previous ECT – dichotomized (yes/no)	11.64	−0.46 to 23.74	0.059

Table 6. Adjusted predictors of antidepressant response (indexed by HAMD) to TMS treatment – model without Ontario study

Significant predictors	β coefficient	95% CI	p value
Model 4. Linear regression model without patients from Ontario site (only open study) – the same predictors of model 1 were adopted to build this model			
Innsbruck[a]	1.12	−13.17 to 15.42	0.88
Sao Paulo 1[a]	10.06	−5.99 to 26.10	0.22
Sao Paulo 2[a]	3.18	−9.81 to 16.17	0.63
Tel Aviv[a]	15.22	3.16 to 27.28	0.0137
Age (yr)	−0.41	−0.70 to −0.13	0.0046
Refractoriness	31.88	19.35 to 44.42	<0.0001
Gender[b]	4.91	−2.31 to 12.13	0.18
HAMD item 17 (Insight)[b]	−1.00	−4.81 to 2.82	0.61
$R^2 = 0.37$			

The other variables that were not included into the final model where neither significant nor confounders.
HAMD, Hamilton Depression Rating Scale.
[a] Forced into the model.
[b] Included into the model as confounders.

reached our threshold of $p < 0.1$ ($p = 0.02$ and $p = 0.08$ respectively) in the univariate analysis and were marginally significant in the multivariate analysis ($p = 0.024$ and $p = 0.059$ respectively). It is interesting to note, however, that the β coefficient for these two variables had a small magnitude compared to the original variable refractoriness included in our original model [13.8 and 11.7 vs. 38.4 respectively for hospitalization, ECT and refractoriness (original variable)]. One of the reasons for such a difference might be the power of these analyses as the information of previous hospitalizations and ECT was not present for all the studies.

Because one of the groups (Tel Aviv) was a significant predictor ($p = 0.0004$) when compared to the reference group (Boston), we built another model excluding the patients of this group to test the validity of our model. This new model (model 3 in Table 4) yielded the same significant predictors (age, $p = 0.0009$; treatment refractoriness, $p < 0.0001$), but one different confounder (item 4 instead item 17 of HAMD). Gender was still a confounder in this model. Indeed, the Tel Aviv group was increasing the variability of our models (1 and 2) as the R^2 of the model 3, without Tel Aviv, was higher than model 1 and 2 (0.44 vs. 0.39 and 0.38 respectively). Using a similar rationale, we built another model excluding the patients from the Ontario site as this was the only open study included in this analysis. We wanted to test if the results of our study were being confounded by the inclusion of this study. This new model (model 4 in Table 6) yielded the same

Table 7. Model 1 with the interaction term (age vs. refractoriness)

Significant predictors	β coefficient	95% CI	p value
Model 1. Age, depression severity, gender and HAMD (items 1, 10, 11, 12, 13, 16) – local of origin (Sao Paulo, Innsbruck) was forced into this model			
Innsbruck	−5.65	−21.51 to 10.22	0.48
Sao Paulo 1	2.30	−16.02 to 20.63	0.80
Sao Paulo 2	5.59	−7.91 to 19.09	0.41
Tel Aviv	23.84	10.36 to 37.33	0.0006
Ontario	13.65	2.39 to 29.69	0.09
Age	−0.40	−1.19 to 0.39	0.32
Refractoriness	43.93	7.77 to 80.10	0.017
Gender	5.11	−1.70 to 11.91	0.14
HAMD item 17 (Insight)	−3.21	−8.79 to 2.38	0.26
Interaction term (age vs. refractoriness)	−0.09	−0.65 to 0.47	0.75
$R^2 = 0.39$			

HAMD, Hamilton Depression Rating Scale.

significant predictors: age ($p = 0.005$), treatment refractoriness ($p < 0.0001$), and same confounders (HAMD item 17 and gender). Furthermore, this new model could explain similar data variability compared to models 1 and 2 as the R^2 of this model without Ontario was 0.37 (vs. 0.39 and 0.38 of models 1 and 2 respectively). Furthermore, the residuals for the Ontario site were similar to the other sites, indicating that data from this study behaved similarly to the other sites.

The β coefficient for the significant predictors was −0.52 (95% CI −0.79 to −0.25) for age and 38.45 (95% CI 24.69–52.20) for treatment refractoriness. This suggests that an increase in age by 1 yr decreases HAMD response by 0.52%, when adjusting for the other variables. Likewise patients with treatment refractoriness have a HAMD response 38.45% smaller than non-refractory patients when adjusting for the other variables.

To test if there was a synergistic effect between age and treatment refractoriness, i.e. age could be a significant predictor only in treatment-refractory patients, we forced the interaction term into the model. The new model (Table 7) with the interaction term disclosed that this variable was not a significant predictor ($p = 0.75$). Therefore, we concluded that there was no synergistic effect between age and treatment refractoriness and did not include the interaction term into the final model (Table 7).

Finally, we built two logistic regression models in which the outcome was either responders (HAMD decrease of $\geqslant 50\%$) or remissions (post-treatment b-HAMD of $\leqslant 7$). Using the same process as the linear regression and forcing the study sites into the final model, the significant variables in these two models were the same as in the linear regression models: age and treatment refractoriness ($p = 0.0042$ and $p = 0.0009$ respectively, for responders and $p = 0.0058$ and $p = 0.0001$ respectively, for remissions). The goodness of fit for both models (Hosmer and Lemeshow test) indicate good fit ($\chi^2 = 5.26$, d.f. = 8, $p = 0.72$ for the responders model and $\chi^2 = 4.25$, d.f. = 8, $p = 0.83$ for the remissions model) (Table 8).

As sedatives, such as benzodiazepines, might interfere with the effect of rTMS treatment and thus be a significant predictor, we included the variable sedatives in our analysis. We initially tested the use of sedatives (benzodiazepines or non-benzodiazepines with similar effects, such as zolpidem and zopiclone) during rTMS treatment as a categorical variable (yes/no). The univariate analysis showed a significant correlation ($p = 0.02$); however, in the multivariate analysis, this variable was no longer significant ($p = 0.37$). Similar results were obtained with this variable treated as a continuous variable (dosage of these drugs using a table of equivalent oral dosages by Ashton et al., 2002); the univariate analysis showed a significant correlation ($p = 0.005$), whereas the multivariate analysis showed that this variable was not significant when adjusting it for other confounders ($p = 0.77$).

Because we were limited to analysing the active rTMS group, the predictors of the antidepressant response to rTMS might be in part due to a placebo

Table 8. Logistic regression models (responders and remissions)

Significant predictors	Odds ratio	95% CI	*p* value
Model 1. Responders (HAMD decrease of $\geqslant$50%)			
Innsbruck[a]	0.47	0.12–1.79	0.27
Sao Paulo 1[a]	0.53	0.12–2.35	0.40
Sao Paulo 2[a]	3.54	0.29–42.71	0.32
Tel Aviv[a]	17.94	2.05–157.46	0.01
Ontario[a]	3.84	0.32–45.60	0.29
Age	0.95	0.92–0.99	0.0042
Refractoriness	71.76	7.23–712.63	0.0009
Model Goodness of Fit – Hosmer and Lemeshow test ($\chi^2 = 5.26$, d.f. $= 8$, $p = 0.72$)			
Model 2. Remissions (HAMD post-treatment $\leqslant$7)[b]			
Sao Paulo (1 and 2)[a]	0.35	0.07–1.87	0.22
Innsbruck[a]	0.16	0.03–0.89	0.04
Tel Aviv[a]	4.71	0.72–30.86	0.11
Age	0.94	0.90–0.98	0.0058
Refractoriness	37.09	5.97–230.63	0.0001
Model Goodness of Fit – Hosmer and Lemeshow test ($\chi^2 = 4.25$, d.f. $= 8$, $p = 0.83$)			

HAMD, Hamilton Depression Rating Scale.

[a] Forced into the model.

[b] Because this model had a non-convergence problem, as two predictors (study site) had low or zero events, the study sites had to be collapsed – Boston and Ontario were collapsed to Boston and Sao Paulo 1 + Sao Paulo 2 were collapsed to Sao Paulo.

effect. Since, in two studies, there was a group of patients that received placebo rTMS, we performed a model including only these patients. Using a forward selection we could not find any significant predictor of the depression improvement after 2 wk of placebo treatment. Indeed, age and refractoriness (highly significant predictors of antidepressant response after active rTMS) were not even close to significance in this model ($p = 0.91$ for age and $p = 0.48$ for refractoriness). A lack of power, however, might account for part of these results as this analysis included 44 patients only.

Another method to determine whether the results of our study are due to a general, rather, than a specific effect of rTMS is to build a model including the placebo and active rTMS groups in order to evaluate whether the interaction term between the significant predictors (age and refractoriness) and treatment is significant. We attempted to perform this analysis, however, because only two studies were placebo-controlled; this analysis did not have enough power. Indeed, the only significant variable in this model was treatment ($p = 0.0069$), therefore, the study of the interaction term is not adequate for our dataset.

In order to rule out that dropouts could be influencing our results, we included the dropouts in our analysis and used an intention-to-treat analysis in which the last evaluation carried out was used for the subsequent evaluations. Only three of these studies reported dropouts (Sao Paulo 2, two patients; Innsbruck, two patients; Boston, four patients). The new model revealed the same significant variables (age, $p = 0.0003$; refractoriness, $p < 0.0001$) with a slight change in the β coefficient (from -0.52 to -0.51 for age and from 38.4 to 37.3 for refractoriness) (the number of dropouts per study site is given in Table 9).

The diagnostic tests for the linear regression showed that the residuals of models 1 and 2 were normally distributed (p value of the Wilk–Shapiro test 0.17 and 0.10 respectively). The plot of the predicted values against the residuals for each model shows no special pattern, therefore, we assumed equal variance.

As one of our main predictors (age) for depression improvement following rTMS is continuous, we checked whether the best relationship of this variable and the outcome was linear. Therefore, we performed the plots of age against the outcome and against the residuals. These plots suggest that the linear relationship was the best approach for age in either models 1 or 2.

When looking for potential outliers, we found five patients having large leverage as detected by the Hat

Table 9. Dropouts and adverse events

Characteristics	Group 1 (Boston)	Group 2 (Innsbruck)	Group 3 (Sao Paulo 1)	Group 4 (Tel-Aviv)	Group 5 (Sao Paulo 2)	Group 6 (Ontario)
Adverse events (number)	34	n.a.	20	n.a.	2	n.a.
Dropouts	4	2	0	0	2	0

n.a., Data not available.
The most common adverse effects were headache, neck pain and scalp burn. There was no report of seizures.

Diagonal test. We excluded these patients from our database and ran the model again. The new model without the outliers showed a slight increase in the R^2 from 0.39 to 0.41 for model 1 and from 0.38 to 0.39 for model 2. There was a slight change in the β coefficient: age changed from -0.52 to -0.49 (model 1) and from -0.50 to -0.47 (model 2); treatment refractoriness changed from 38.45 to 38.50 (model 1) and from 35.28 to 34.85 (model 2). There was no change in the significance of the predictors. These results suggest that our model was stable and the results are not due to outliers. Finally, the bootstrap test showed that the significant variables remained significant after performing this test for both models.

Discussion

Our results show that age and medication refractoriness are the two most important predictors of rapid antidepressant response following 2 wk of rTMS treatment. These two variables were significant in all models and remained significant after adjusting for all potential confounders. Therefore, younger and non-refractory patients seem to respond better to rTMS antidepressant treatment. Importantly, the significant variables remained significant after adjusting for the study site. This is particularly important as heterogeneity from different studies is expected and it cannot be entirely accounted for by including only the studied variables.

The effect of age

Age was a highly significant predictor of the antidepressant response to rTMS. This finding is consistent with previous research. In an open study with 56 patients, Figiel et al. (1998) showed that the antidepressant response rate was higher for younger (<65 yr) compared to older patients (56% vs. 23%) (Figiel et al., 1998; see also Epstein et al., 1998). In addition, two other studies have reported that elderly patients have no significant antidepressant response to TMS compared to placebo (Manes et al., 2001; Mosimann et al., 2004). Nahas et al. (2004) hypothesized that this lack of effect in the elderly is due to frontal atrophy and conducted a pilot study that showed that TMS treatment adjusted for the prefrontal atrophy is more effective than TMS treatment without adjusting for atrophy. This finding would explain why younger patients responded more than older patients as the TMS intensity in these past studies was not adjusted for prefrontal atrophy.

Another potential explanation to account for the decreased response in elderly patients is a general refractoriness of these patients to any type of antidepressant treatment. However, elderly patients may have a good response to ECT, although ECT clinical trials tend to have a relatively low number of elderly patients (UK ECT Review Group, 2003). There are few studies comparing the effects of antidepressants between older and younger patients, and these show mixed results. Whereas some studies show that antidepressants are equally effective in older compared to younger depressed patients (Gildengers et al., 2002; Zanardi et al., 2003), others have reported decreased efficacy of these drugs in the older population (Martin et al., 1987; Mulsant and Pollock, 1998). One of the reasons for the different antidepressant response rate, based on the age of the patient, may be due to the atypical features that depression may display in the elderly and the association with other brain organic disorders. Furthermore, late-life depression has been associated with a chronic course that may be less responsive to medical treatment. However, this fact seems unlikely to explain our findings as we controlled for treatment refractoriness and tested for depression duration in our model as well.

Finally, the lower antidepressant response of older patients to TMS could be due to a slower response of older patients compared to younger patients as we only evaluated the acute response (after 2 wk

of treatment) and did not include the follow-up evaluation in our model. Indeed, past research has shown that depressive symptoms continue to decrease after the cessation of rTMS (Koerselman et al., 2004) and the effects of antidepressants may be slower in elderly patients (Zanardi et al., 2003). If this is the case, future rTMS trials should have a long-term follow-up to evaluate this possible delayed antidepressant effect in elderly patients.

The effect of treatment refractoriness

Treatment refractoriness was another significant predictor in our model after adjusting for the other significant variables and potential confounders. This finding seems to be intuitive, as patients refractory to antidepressants might have a more severe form of depression and be also resistant to the antidepressant effects of rTMS. In fact, medication resistance can also decrease ECT antidepressant effect magnitude (UK ECT Review Group, 2003). However, the mechanisms of action of rTMS may differ from those of antidepressant medications. Despite the fact that past research suggests that rTMS may act on neurotransmitter levels, similarly to antidepressants (Ben-Shachar et al., 1997), this is not the only rTMS mechanism of action that has been proposed as it has been shown that this therapy can increase the metabolism of the cortical stimulated area (Mottaghy et al., 2003) and exert network-specific effects in cortical and subcortical structures bihemispherically. Therefore, the poor response of refractory depressed patients to rTMS might be due to similar pathophysiological mechanisms of rTMS and drugs or other TMS-specific effects not yet known.

This result yields two important implications for future clinical trials of rTMS treatment for depression. First, because rTMS has a greater effect in patients that are not refractory to medications, it should be further investigated in these patients (e.g. non-refractory patients who are not willing to take antidepressant medications or have contraindications to these drugs). Second, the smaller effect of rTMS in refractory patients might indicate that the rTMS treatment for these patients needs to be prolonged, i.e. 'higher rTMS dosage', thus, future clinical trials should address this issue, adjusting rTMS dosage according to patients' status (refractory vs. non-refractory).

Some methodological considerations

This study has some methodological issues that should be addressed. Some potential important predictors and unmeasured confounders for antidepressant response might not have been included in our model. Our models, however, had a satisfactory R^2 (0.44, 0.39 and 0.38) and hence could predict up to 44% of the data variability. Furthermore, the patients enrolled into each of these six studies consented to participate in a clinical trial evaluating a new tool for depression treatment, therefore, this sample may not be representative of the general population of depressive patients, and thus our findings may not be externally generalized to other patients with depression.

The effects of the predictors of age and refractoriness might not be specific for rTMS as our model did not evaluate the effects of other treatments such as antidepressants or placebo. Another potential limitation is that these six studies were slightly different regarding the criteria of refractoriness. Whereas some of these studies classified patients as refractory if they failed to respond to three antidepressants, others defined this threshold as failing to respond to only two antidepressants. We do not believe that these criteria biased our results as the number of failed medications might not be correlated to the degree of refractoriness and most of the patients that were refractory to at least one drug were refractory to several drugs.

Finally, the six studies that were included in our analysis had different methodologies, such as differences in rTMS parameters and population sample. In order to account for this confounder, we controlled for study site. These differences, however, might not have been fully accounted for and, therefore, the results of this study have to be interpreted with caution.

Conclusions

Based on the finding that rTMS can cause a greater antidepressant effect in younger and non-refractory patients, further clinical trials should study the effects of rTMS early in antidepressant treatment and in young patients who are unwilling to take antidepressants or have contraindications to these drugs. These findings, therefore, might assist in designing future studies using rTMS for the treatment of depression.

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Statement of Interest

None.

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