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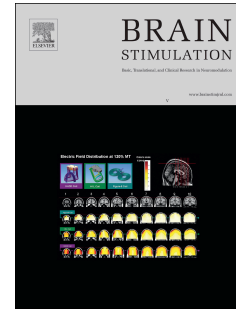
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PREDICTIVE VALUE OF DORSO-LATERAL PREFRONTAL CONNECTIVITY FOR
rTMS RESPONSE IN TREATMENT-RESISTANT DEPRESSION: A BRAIN PERFUSION
SPECT STUDY

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Abstract (222 words)

Background: Previous clinical trials have suggested that repetitive transcranial magnetic stimulation (rTMS) has a significant antidepressant effect in patients with treatment resistant depression (TRD). However, results remain heterogeneous with many patients without effective response.

Objective: The aim of this SPECT study was to determine before treatment the predictive value of the connectivity of the stimulated area on further rTMS response in patients with TRD.

Methods: Fifty-eight TRD patients performed a brain perfusion SPECT before high frequency rTMS of the left dorsolateral prefrontal cortex (DLPFC). A voxel based-analysis was achieved to compare connectivity of the left DLPFC in responders and non-responders using inter-regional correlations ($p < 0.005$, corrected for cluster volume). A multiple logistic regression model was thereafter used with the goal of establishing a predictive score.

Results: Before rTMS, responders exhibited increased SPECT connectivity between the left DLPFC and the right cerebellum in comparison to non-responders, independently of age, gender, severity of depression, and severity of treatment resistance. The area under the curve for the combination of these two SPECT clusters to predict rTMS response was 0.756 ($p < 0.005$).

Conclusions: SPECT connectivity of the left DLPFC predicts rTMS response before treatment.

Key words: Connectivity; SPECT; repetitive transcranial magnetic stimulation; treatment resistant depression; predictive value.

Highlights:

- SPECT connectivity predicts rTMS response before treatment in TRD patients
- This predictive value is independent of clinical known predictive factors
- Increased SPECT connectivity is observed before rTMS in responders patients
- This increased SPECT connectivity involves the left DLPFC and the right cerebellum
- A model of predictive score involving these 2 clusters and their interaction is proposed

1. Introduction

Approximately two-thirds of patients receiving initial antidepressant therapy do not achieve remission, and 20% have persistent resistance to conventional pharmacological treatments [1]. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive and well-tolerated method that may be an effective alternative therapeutic approach. Although previous clinical trials have suggested that rTMS has a significant antidepressant effect, results remain heterogeneous with many patients showing no response [2]. Regarding the medical cost of rTMS, which is time-consuming for both the physician and the patient, the identification of biomarkers of predictive response to rTMS seems necessary to optimize its effectiveness [3].

Using ^{99m}Tc -Ethyl-Cysteinate-Dimer (ECD) single photon emission computed tomography (SPECT), we previously reported that patients with Treatment-Resistant Depression (TRD) showed significant frontal and temporal hypoperfusion, with a left-side predominance [4,5]. Moreover, prior to treatment, non-responder patients showed greater hypoperfusion in the left medial and bilateral superior frontal cortices, in the left uncus/parahippocampal cortex, and in the right thalamus after rTMS of the dorso-lateral prefrontal cortex (DLPFC). These results suggest potential predictive value of ^{99m}Tc -ECD SPECT imaging involving remote regions from the stimulated area [4–6].

On the other hand, the study of connectivity in SPECT is gaining interest in depression and neurologic disorders [5,7–10]. Seed correlations or interregional correlation analysis (IRCA) is one of the main approaches proposed to study SPECT connectivity [10,11]. This approach involves picking a reference location and quantifying the correlation with perfusion for every other brain area, as previously described [5,8]. SPECT connectivity has been shown to be disturbed in TRD patients, who show higher connectivity between left frontal and left

cerebellar regions in comparison to healthy subjects [5]. Indeed, in addition to its role in motor coordination, the cerebellum may play an important role in cognitive processing and emotional control by modulating limbic regions [12]. Interestingly, also by using SPECT connectivity, we have recently reported that the clinical effects of rTMS were related to changes in connectivity between the stimulated area and remote medial temporal limbic areas [8], explaining perfusion changes within the left perirhinal cortex found after treatment [6]. In the current study, we hypothesize that differences in SPECT connectivity of the left DLPFC before rTMS may be related to later clinical response in patients with TRD.

2. Materials and Methods

2.1. Subjects

This retrospective study, conducted in a public psychiatric university hospital, involved 58 right-handed TRD patients, treated with high-frequency (HF) rTMS, as described previously [8]. All participants met DSM-IV TR criteria for major depressive disorder (unipolar or bipolar depression) without psychotic features, and gave informed consent. TRD was defined as a non-response to at least two different classes of antidepressant medications for the current episode at the time of enrolment. All patients had maintained stable doses of antidepressant and/or mood stabilizer medications for at least 2 weeks before treatment and until completing the course of rTMS. Finally, a group of 55 healthy subjects was extracted from a local normal ^{99m}Tc -ECD SPECT database constituting a control population approved by our local ethics committee (Clinical Trials Ref: NCT00484523), with similar age and gender as those of the patients group ($p > 0.15$, 49.8 ± 16.6 years old, 32 women), to compare results of connectivity analysis with patients.

2.2 Data collection

The following data were recorded: demographic characteristics: gender and age; clinical characteristics: duration of illness, episode duration, depression severity using the 21-item Beck Depression Inventory (BDI-II) [13], and anxiety severity using the State Trait Anxiety Inventory (STAI-YA) [14]. The overall level of depression varies from minimal (score of 10) to severe (score > 29) depression. All patients were assessed twice with the BDI-II and STAI-YA: before rTMS, and after 20 rTMS sessions. RTMS response was defined as at least 50% reduction in the baseline BDI-II score. Level of treatment-resistant severity was assessed with the Maudsley Staging Method (MSM) which is a point-based staging method that measures level of treatment-resistant severity of the index episode by incorporating 3 factors: treatment, severity of illness, and duration of episode [15]. The overall level of treatment resistance varies from minimal (score of 3) to severe (score of 15) resistance.

2.3. rTMS treatment

Magnetic stimulation was performed using a Medtronic MagPro X100 stimulator and a figure eight-shaped water-cooled coil (Medtronic Inc., Minnesota). Twenty sessions of rTMS were delivered daily but not including weekends, to the left DLPFC, situated 6 cm anterior to the motor “hotspot” for the contralateral hand muscles, with a frequency of 10Hz with a 25-second inter-train interval (2,000 pulses/day) at 120% of the resting motor threshold.

2.4. SPECT protocol

Brain perfusion SPECT was performed after injection of 740 MBq of ^{99m}Tc-ECD in all patients and healthy subjects, with the same camera and under the same conditions, during the week before rTMS in patients as previously reported [8].

A voxel-by-voxel group study design was employed using SPM8 (Wellcome Department of

Cognitive Neurology, University College, London), running on Matlab (MathworksInc, Sherborn, MA), with normalization by proportional scaling. Based on the hypothesis that baseline connectivity of the stimulated area could explain further clinical response to the rTMS, we then studied SPECT connectivity of the left DLPFC. For this purpose, normalized perfusion values of the left BA46 volume-of-interest of PickAtlas® (ANSIR Laboratory, Department of Radiologic Sciences WFU School of Medicine, USA) used for the analysis of the left DLPFC and illustrated in Figure 1A, were individually extracted using Marsbar® (Marseille, France) software. Then a full factorial model of analysis was used with normalized perfusion of the left BA46 values as an interaction covariate to study inter-regional correlation, between responders and non-responders, with age, gender, depression severity (BDI) and therapeutic resistance (MSM) scores as covariates. The SPM (T) maps were obtained at a height threshold of $p < 0.005$ for the voxel, with clusters including at least 102 voxels (the expected threshold provided by SPM after simulation) to correct for volume, to avoid type II errors as recommended [16]. The normalized values of significant clusters from the full-factorial analysis were finally extracted using Marsbar® (Marseille, France) software, and used to calculate correlation coefficients with left DLPFC normalized values in responders, non-responders and healthy subjects. MNI coordinates were used to identify brain structures.

2.5. Statistical analysis

Quantitative variables are expressed as means \pm standard deviations, and categorical variables as percentages. For patient's characteristics, t-tests were done for mean comparisons for quantitative variables while Chi-2 tests were done for categorical variables. Statistical parameters for SPM comparison between responders and non-responders at baseline are detailed above. Spearman coefficients were used to calculate correlations between normalized

values of significant clusters from the full-factorial analysis with clinical scores and left DLPFC normalized values in responders, non-responders and healthy subjects. Then, multiple logistic regression models including the normalized values of left DLPFC and of significant clusters from the SPM analysis, and their interaction, were used with the goal of establishing a predictive score to classify patients in the responder vs non-responder groups. For this purpose, we split the data into two samples: a training sample including 2/3 of the data and a test sample including the remaining 1/3. Multiple logistic regression was performed to predict response to treatment using the training dataset. Predictive scores were then calculated and an area under the receiver operation characteristics curve (AUC under ROC) was derived to evaluate the discriminative ability of this score between responders and non-responders. A binormal smoothing was performed for building ROC curves. The AUC ranges from 0.5 to 0.99 with higher values signifying higher model discrimination. In order to guarantee the robustness of our findings, the predictive score was applied on the test sample and we compared the AUC on the training and the testing datasets. Three different cutoff points were calculated by selecting the point on the ROC curve that maximized: (1) both sensitivity (Se) and specificity (Sp); (2) Se; and (3) Sp. The significance level p value for all statistical analyses was set at 0.05.

3. Results

3.1. Patient characteristics before rTMS

Before rTMS, the 58 patients (53.8 years \pm 14.0; 37 women) presented depression and anxiety with initial high severity (BDI-II=25.9 \pm 9.5, STAI-YA=63.2 \pm 10.9) and moderate treatment resistance (MSM=8.7 \pm 2.1). The episode duration was of 17.3 months \pm 8.1. Forty-four patients had unipolar depression, and 14 bipolar depression. After rTMS, 27 were responders (46.6%). Baseline characteristics of responder and non-responder groups are

presented in Table 1. There were no statistically significant differences in demographic and clinical characteristics ($p>0.10$), apart from a greater degree of treatment resistance ($p=0.033$) and a tendency for worse depression severity ($p=0.079$) in non-responders.

3.2 SPECT connectivity findings

Before rTMS, responders exhibited increased SPECT connectivity between the left DLPFC and the right cerebellum ($p<0.005$, $k=102$) compared to non-responders, even after controlling for age, gender, depression severity and treatment resistance (Figure 1B). No other difference in SPECT connectivity was found between responders and non-responders.

Correlation coefficients between left DLPFC and right cerebellum values were 0.559 in responders ($p<0.01$) whereas -0.123 ($p=0.51$) for non-responders, and -0.086 ($p=0.53$) for healthy subjects.

The two SPECT clusters (left DLPFC stimulated area and right cerebellum) and their interaction were selected for the multiple logistic regression models to predict the response to rTMS. From this analysis on the training sample, the following equation was obtained: predictive score = $\exp(292.622 + 0.063 \times \text{inter} - 3.397 \times \text{right cerebellum cluster} - 5.460 \times \text{left DLPFC cluster}) / (1 + \exp(292.622 + 0.063 \times \text{inter} - 3.397 \times \text{right cerebellum cluster} - 5.461 \times \text{left DLPFC cluster}))$. The AUC for the combination of SPECT clusters was 0.756 ($p<0.005$) (Fig. 2). The robustness of the predictive score was confirmed with similar AUC (0.808) for the test sample.

The cut-off points of the combination of SPECT clusters that maximized (1) both Se and Sp was > 0.36 (Se=90%, Sp=60%); (2) Se was > 0.16 (Se=100%, Sp=30%); and (3) Sp was >0.30 (Se=30%, Sp=100%).

4. Discussion

This perfusion SPECT study aimed to characterize left DLPFC connectivity in TRD patients who underwent rTMS to define neuroimaging biomarkers that discriminate non-responders from responders. Our findings, obtained in a large sample using SPECT, support the existence of increased connectivity between the stimulated left DLPFC area and the right cerebellum in responders before rTMS, independently of common clinical predictive factors such as age, gender, depression severity or therapeutic resistance.

Our previous SPECT study showed higher connectivity in TRD patients in comparison to healthy subjects [5]. We now show that increased connectivity is particularly associated with subsequent therapeutic response to left DLPFC rTMS in TRD. It could thus mean that responders are those who exhibit especially high SPECT connectivity between the DLPFC and certain remote areas of the brain [6]. In line with this, increased connectivity between the DLPFC stimulated area and the cerebellum has already been reported in resting-state functional MRI studies in patients with depression [17,18]. Interestingly in a recent FDG-PET study, higher cerebellar metabolism has been found to be indicative of beneficial response to high frequency-rTMS treatment [17]. These results suggest the novel role of the cerebellum in the pathophysiology of depression, particularly in the clinical outcome [17].

Changes in connectivity of the stimulated area are also predictive of the response after rTMS for TRD according to fMRI studies. Indeed, by targeting the dorso-medial prefrontal cortex (DMPFC), responders to rTMS also showed increased resting state connectivity, but mainly between the DMPFC and the ventromedial prefrontal cortex [18,19]. However, this contrasts with other studies that have shown that changes in functional connectivity to remote areas are rather predictive of better response to treatment of rTMS of left DLPFC, such as subgenual cortex [9,20] or cingular cortex [21].

The present study brings a predictive model for assessing rTMS response in TRD including SPECT normalized values of the left DLPFC stimulated area and the right cerebellum with good performances (AUC of 0.808 in the test sub-group). Thus, several cut-offs of normalized perfusion values for left DLPFC and the right cerebellum could be proposed (Figure 2). One option would be to offer rTMS only to those patients in whom the model would predict a good response with high specificity. On the other hand, by choosing normalized perfusion values with good sensitivity for predicting treatment response, a high number of TRD patients could be treated.

Otherwise, our study reports that patients with higher degree of treatment resistant and depression severity presented a statistical trend for lower response to rTMS. Even if these predictive factors did not influence our SPECT results, this confirms previous research which has identified the main predictive clinical characteristics as longer duration of the episode, treatment refractoriness or age [17,22].

Several limitations have to be carefully considered. Interpretation of these data should be performed in the context of the study design, namely, an observational study in which treatment was offered to all participants in an open label fashion. Second, our sample included patients with unipolar and bipolar depression; however, previous studies have reported that patterns of SPECT perfusion were similar in these two groups of patients [5,9,17-21,23]. Third, as in previous studies, our participants were treated with rTMS as add-on therapy.

To conclude, SPECT connectivity of the to-be-stimulated left DLPFC area before rTMS has an independent predictive value in terms of treatment response, even after taking into account clinical known prognostic factors such as age, gender, depression severity or therapeutic resistance. Patients with higher SPECT connectivity between the stimulated area and the cerebellum can be expected to have a better response to rTMS. Therefore, it seems that connectivity of the target before rTMS is linked mechanistically to the successful response.

Future studies should be aimed exploring other target areas for rTMS in non-responders.

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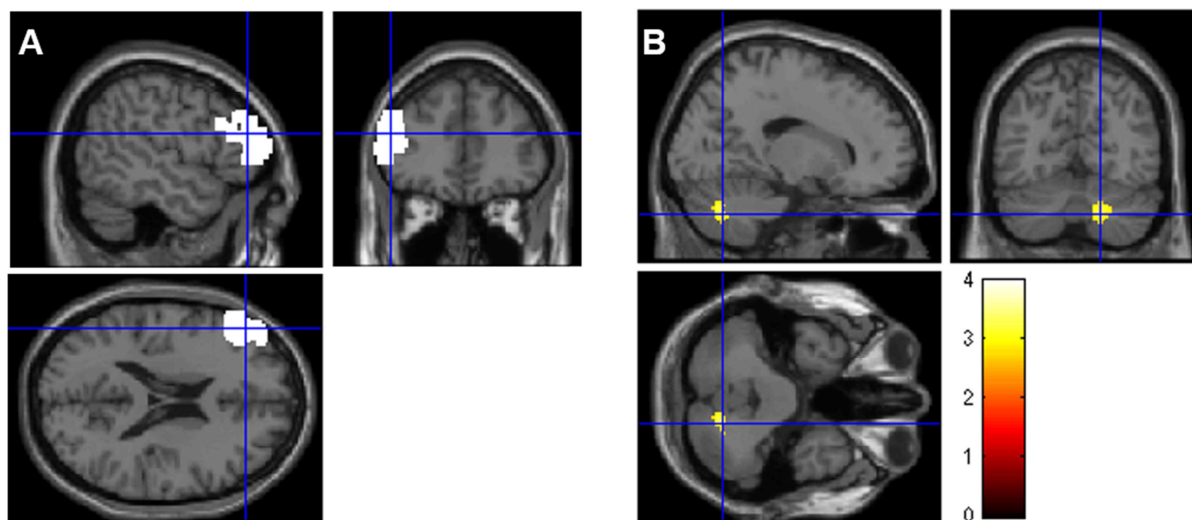


Figure 1. Anatomical localization of Region Of Interest (ROI) of left Dorso-Lateral Prefrontal Cortex (DLPFC) (in A) and of area of increased left DLPFC connectivity in responders in comparison to non-responders (in B) projected onto sections of a normal MRI set spatially normalized and smoothed into the standard SPM8 template ($p < 0.005$, uncorrected, $k > 102$). Before rTMS, responders exhibited increased SPECT connectivity between left DLPFC and right cerebellum (in B) compared to non-responders.

Figure 2. Receiver-operating characteristic (ROC) curve for prediction of response to rTMS according to the combination of SPECT connectivity clusters on a training sample including 2/3 of the data.

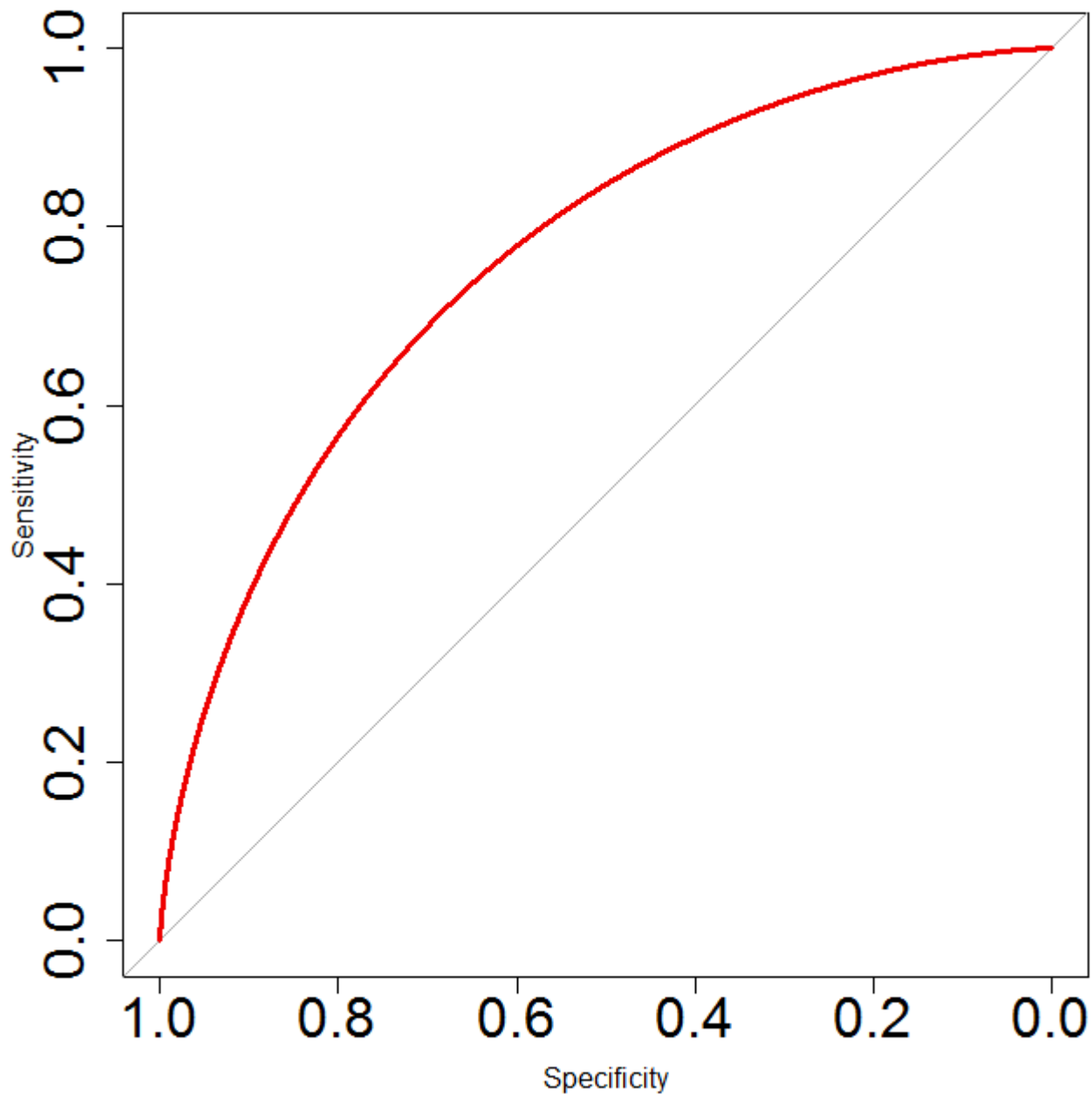


Table 1. Baseline characteristics of responders and non-responders (n=58)

	Responders (n=27)	Non-responders (n=31)	
	Mean (SD)	Mean (SD)	<i>p-value</i>
Demographic characteristics			
Gender (male), n (%)	11 (40.7%)	10 (32.3%)	0.346
Age	54.4 (12.0)	53.6 (15.4)	0.829
Clinical characteristics			
Depression			
Unipolar, n (%)	18 (66.7%)	26 (83.9%)	0.111
Bipolar, n (%)	9 (33.3%)	5 (16.1%)	0.111
Illness duration (years)	15.3 (10.9)	18.0 (12.4)	0.397
Episode duration (months)			
< 24 months, n (%)	12 (44.4%)	13 (41.9%)	0.529
> 24 months n (%)	15 (55.6%)	18 (58.1%)	0.529
Failed antidepressant trials			
current episode	3.5 (2.0)	4.3 (1.8)	0.143
BDI-II score	23.6 (10.0)	28.0 (8.6)	0.079
STAI score	64.0 (9.5)	65.2 (8.9)	0.622
MSM score	8.1 (2.0)	9.2 (2.0)	0.033*

SD: standart deviation; BDI-II : Beck Depression Inventory 21 items; STAI-YA: State Anxiety Inventory-State; MSM : Maudsley Staging Method

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Clinical characteristics			
Depression			
Unipolar, n (%)	18 (66.7%)	26 (83.9%)	0.111
Bipolar, n (%)	9 (33.3%)	5 (16.1%)	0.111
Illness duration (years)	15.3 (10.9)	18.0 (12.4)	0.397
Episode duration (months)			
< 24 months, n (%)	12 (44.4%)	13 (41.9%)	0.529
> 24 months n (%)	15 (55.6%)	18 (58.1%)	0.529
Failed antidepressant trials current episode			
BDI-II score	23.6 (10.0)	28.0 (8.6)	0.079
STAI score	64.0 (9.5)	65.2 (8.9)	0.622
MSM score	8.1 (2.0)	9.2 (2.0)	0.033*

SD: standard deviation; BDI-II : Beck Depression Inventory 21 items; STAI : State Anxiety Inventory-State; MSM : Maudsley Staging Method

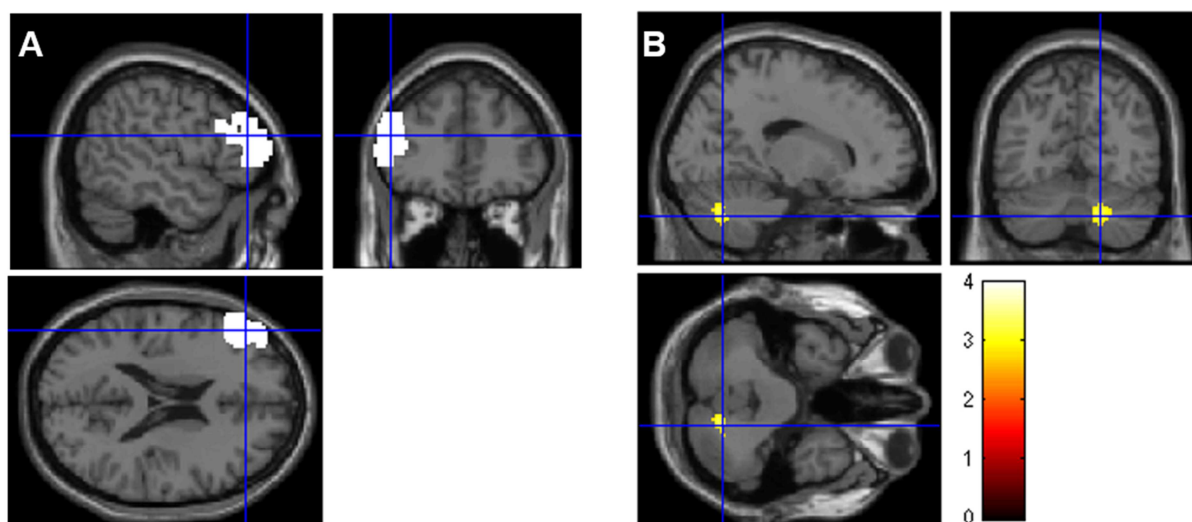
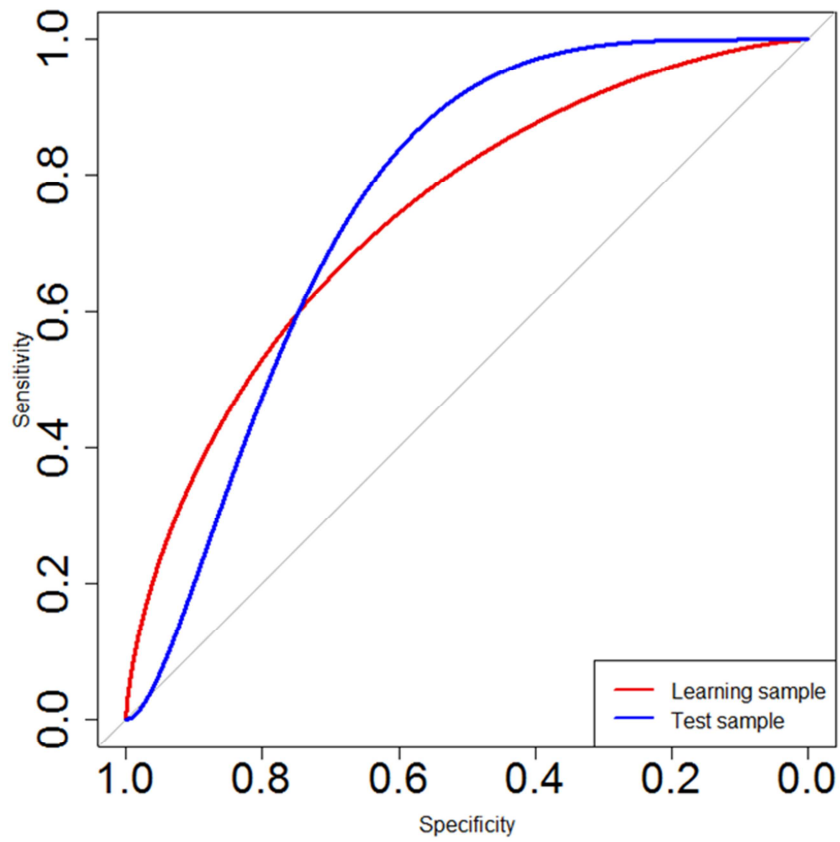


Figure 1. Anatomical localization of Region Of Interest (ROI) of left Dorso-Lateral Prefrontal Cortex (DLPFC) (in A) and of area of increased left DLPFC connectivity in responders in comparison to non-responders (in B) projected onto sections of a normal MRI set spatially normalized and smoothed into the standard SPM8 template ($p < 0.005$, uncorrected, $k > 102$). Before rTMS, responders exhibited increased SPECT connectivity between left DLPFC and right cerebellum (in B) compared to non-responders.

Figure 2. Receiver-operating characteristic (ROC) curve for prediction of response to rTMS according to the combination of SPECT connectivity clusters on training and test samples



Highlights:

- Pretherapeutic SPECT connectivity of the DLPFC predicts antidepressant effect of TMS.
- Responders show increased connectivity between the targeted area and the cerebellum.
- A mathematical model of predictive score involving these two regions is proposed.