



## Neurophysiological predictors of non-response to rTMS in depression

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### ABSTRACT

**Background:** The application of rTMS in Depression has been very well investigated over the last few years. However, little is known about predictors of non-response associated with rTMS treatment.

**Objective:** This study examined neurophysiological parameters (EEG and ERP) in 90 depressed patients treated with rTMS and psychotherapy and sought to identify predictors of non-response.

**Methods:** This study is a multi-site open-label study assessing pre-treatment EEG and ERP measures associated with non-response to rTMS treatment.

**Results:** Non-responders were characterized by 1) Increased fronto-central theta EEG power, 2) a slower anterior individual alpha peak frequency, 3) a larger P300 amplitude, and 4) decreased pre-frontal delta and beta cordance. A discriminant analysis yielded a significant model, and subsequent ROC curve demonstrated an area under the curve of 0.814.

**Conclusions:** Several EEG variables demonstrated clear differences between R and NR such as the anterior iAPF, fronto-central Theta and pre-frontal cordance in the Delta and Beta band (representative of increased relative pre-frontal perfusion). The increased P300 amplitude as a predictor for non-response requires further study, since this was the opposite as hypothesized and there were no correlations of this measure with clinical improvement for the whole sample. Combining these biomarkers in a discriminant analysis resulted in a reliable identification of non-responders with low false positive rates. Future studies should prospectively replicate these findings and also further investigate appropriate treatments for the sub-groups of non-responders identified in this study, given that most of these biomarkers have also been found in antidepressant medication studies.

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### Introduction

The application of repetitive transcranial magnetic stimulation (rTMS) treatment in depression (MDD) has been investigated intensively over the last 15 years. Several meta-analyses have demonstrated that compared to placebo, the effects of high frequency (fast) rTMS (HF rTMS) applied to the left dorsolateral pre-frontal cortex (DLPFC) and low frequency (slow) rTMS (LF rTMS) over the right DLPFC both have antidepressant effects [1,2]. These and other results are suggesting that HF and LF rTMS in MDD yield similar clinical effects [1,3–5]. In depression, abnormal expression of BDNF has been observed [6] and is considered one of the most robust measures related to antidepressant response which also led to the ‘neurotrophin hypothesis of depression’ [7]. Both HF and LF

rTMS have been shown to upregulate BDNF [8,9], which is also found after antidepressant medication in MDD [6,10]. Furthermore, studies have found that responders to HF rTMS [11–14] and LF rTMS [15] are both characterized by increased metabolic activity in frontal regions and the anterior cingulate [16].

With the establishment of the efficacy of rTMS, there has been increased interest in finding potential predictors of clinical response. The value of clinical factors in predicting treatment outcome in MDD is very limited [17,18] and a shift towards biomarkers is noticeable. In the light of this ‘Personalized Medicine’ approach to depression, recently both genetic and neuroimaging biomarkers have been explored and both are showing promising results in aiding treatment prediction using pre-treatment measures [19,20].

Many studies have employed neurophysiological techniques such as electroencephalography (EEG), event-related potentials (ERP) and other neuroimaging techniques to investigate biomarkers for treatment response. Baseline neurophysiological and neuroimaging biomarkers for poor treatment outcome which have been replicated

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are: 1) Increased delta and theta EEG power at baseline [21–23]; 2) A slow individual alpha peak frequency (iAPF: [24–26]); 3) a reduced P300 amplitude [27–29] and a prolonged P300 latency [30,31]; and 4) decreased metabolic activity in frontal regions [11–15]. In addition, some groups have focused on treatment emergent biomarkers, that is, changes in activity in the early stages of treatment on measures such as EEG Cordance [32] which was shown to have potential in the prediction of treatment outcome to antidepressants. However, in these approaches patients need to be on medication for at least 7 days in order to obtain these treatment emergent biomarkers.

The primary aim of the current study was to explore potential neurophysiological predictors of non-response to rTMS treatment. We hypothesized that non-responders to rTMS would demonstrate increased theta EEG power, lower iAPF, lower P300 amplitudes and slower P300 latencies prior to treatment. Furthermore, since EEG Cordance has also been found to better reflect cortical perfusion as compared to absolute or relative EEG power [33] we hypothesized that non-responders to rTMS would demonstrate lower pre-frontal cordance, reflective of lower pre-frontal perfusion. In this study we only focussed on biomarkers obtained at baseline and their relation to treatment outcome rather than treatment emergent biomarkers.

## Methods

### Design

This study was a multi-site open-label study. All files from patients enrolled in two clinics (Brainclinics Treatment and Psychologenpraktijk Timmers) between May 2007 and November 2009 were screened. Only data from patients with 1) a primary diagnosis of Depression or Dysthymic disorder according to the MINI (MINI Plus Dutch version 5.0.0) and 2) a Becks Depression Inventory (BDI) score of 14 or higher who were treated with left DLPFC HF rTMS (10 Hz) or right DLPFC LF rTMS (1 Hz) were included for this study. Exclusion criteria were: previously treated with ECT, epilepsy, wearing a cardiac pacemaker, metal parts in the head and pregnancy. All patients signed an informed consent form before treatment was initiated.

### Participants

The intake procedure consisted of a structured clinical interview (MINI), clinical questionnaires (BDI, Depression, Anxiety and Stress scale (DASS: [34]), 5 factor personality test NEO-FFI) and a neurophysiological assessment to record QEEG and ERP's. Patients were screened for major depression or dysthymic disorder by a clinical psychologist using a structured interview (MINI, sections Depressive episode, Dysthymia, Suicide, Manic episode, Alcohol Dependence & Abuse and Mixed Anxiety/Depressive disorder).

All participants were asked to refrain from caffeine or nicotine intake for at least 2 h prior to testing and all patients signed an informed consent form before treatment was initiated. When patients presented with alcohol dependence or abuse issues they were required to first tackle those issues before rTMS treatment could commence. Patients were not allowed to abuse alcohol and other drugs during the course of treatment.

### Pre-treatment QEEG and ERP's

EEG and ERP recordings were performed using a standardized methodology, details of this procedure have been published elsewhere [35–37] and details of reliability, validity and across site-consistency of this EEG and ERP procedure have been published here [35,38,39]. Patients' individual EEGs were screened for the

presence of focal beta spindles at F3 (beta spindles exceeding 20  $\mu$ V peak-to-peak amplitude [40]) or the presence of paroxysmal EEG activity, and this latter served as exclusion criterion for rTMS treatment.

### rTMS treatment

All patients were treated with left DLPFC HF rTMS (10 Hz) unless they demonstrated focal left frontal beta spindles in which case they were treated with right DLPFC LF TMS (1 Hz).

rTMS sessions were administered using a Magstim Rapid<sup>2</sup> (Magstim Company, Spring Gardens, UK) stimulator with a figure-of-8 coil (70 mm diameter). Patients received magnetic stimulation at 1) HF rTMS: 10 Hz over the left dorsolateral pre-frontal cortex 5 cm anterior to the motor cortex area of the musculus abductor pollicis brevis at 110% of the motor threshold (30 trains, 5 s duration ITI: 30 s: 1500 pulses per session) or 2) LF rTMS: 1 Hz over the right dorsolateral prefrontal cortex 5 cm anterior to the motor cortex area of the musculus abductor pollicis brevis at 110% of the motor threshold (120 trains, 10 s duration ITI 1 s: 1200 pulses per session). For some patients treated with LF rTMS, priming of 6 Hz was used before the 1 Hz rTMS (also see Ref [41]) consisting of 6 Hz stimulation at 90% MT (20 trains, 5 s. ITI 25 s). In patients older than 55 yrs of age the stimulation intensity was increased by 10% (in order to compensate for potential frontal atrophy, which seldom occurs before the age of 55 [42]). Furthermore, rTMS treatment was complemented by psychotherapy by a skilled psychologist for all patients. BDI and DASS scores were assessed during intake, outtake and after every fifth session, to track progress of treatment. For non-responders and drop-outs, the last BDI was used as outtake (last observation carried forward). The total number of sessions were determined by the therapeutic response of the patient and this was on average 20.7 sessions.

## Analysis

### Individual alpha peak frequency and theta power

For determination of the iAPF a method was used based on Doppelmayr and coworkers [43] and Lansbergen and coworkers [44] and in summary consisted of: EOG correction [45], a linked ears montage (for F3, Fz, F4, Cz, P3, Pz, P4, O1, Oz and O2), filtering (1–40 Hz), automatic artefact removal (threshold of 150  $\mu$ V), segmentation in 8 s segments, and an FFT power spectrum calculation. This pipeline was applied to both eyes open (EO) and eyes closed (EC) conditions.

The power spectrum from EO was subtracted from the FFT from EC and within the range of 7–13 Hz the maximum alpha suppression was determined across P3, Pz, P4, O1, Oz and O2. The site where the maximum alpha suppression occurred was chosen as the site where the iAPF was scored by establishing the exact frequency at which the alpha suppression was maximal (posterior iAPF). The iAPF at frontal sites (F3, Fz and F4) was scored by determining the maximum alpha suppression across these 3 sites and scoring the peak frequency where the highest alpha suppression took place between 6 and 13 Hz (anterior iAPF).

Furthermore, for the eyes closed data an FFT with a Hamming window was conducted to extract power in the Theta band (4–7 Hz), which was then log transformed.

### EEG cordance

The EEG cordance method was initially developed by Andrew Leuchter and colleagues to provide a measure, which had face-validity for the detection of cortical deafferentation [46]. They

observed that often the EEG over a white-matter lesion exhibited decreased absolute theta power, but increased relative theta power, which they termed 'discordant'. Therefore the EEG Cordance method combines both absolute and relative EEG power and negative values of this measure (discordance) – specifically in theta or beta – are believed to reflect low perfusion or metabolism, whereas positive values (concordance) – specifically in alpha – are thought to reflect high perfusion or metabolism [46]. In a subsequent study they further confirmed this by comparing cordance EEG with simultaneously recorded PET scans reflecting perfusion [33].

For Cordance analysis eyes closed EEG data were filtered with a high-pass of 0.5 Hz and a low-pass of 40 Hz, resampled to 256 samples per second and segmented in 2 s segments. Data were manually de-artifacted and the first 30 artefact free data segments were used to calculate Cordance using the BVA history template obtained from Leuchter et al. in Brain Vision Analyzer 2.0. EEG Cordance for delta (0.5–4.0 Hz), theta (4.0–8.0 Hz), alpha (8.0–12.0) and beta (12.0–20.0 Hz) were averaged for left frontal (F3, FC3 and F7), right frontal (F4, FC4 and F8) and pre-frontal (Fp1, Fp2 and Fz) sites as a measure of cortical perfusion.

### P300

Conventional auditory ERP averages were calculated at Pz and Fz elicited by 60 high pitched (1000 Hz; 75 dB; 50 ms.) targets (oddball) intermixed with 280 background targets (500 Hz; 75 dB; 50 ms.). EOG correction was applied to remove EOG artefacts [45] and single-trial waveforms were filtered at 25 Hz with a Tukey (cosine) taper to 35 Hz. The peaks (amplitude and latency) of the P300 for the target waveforms of the ERP component were identified (relative to a pre-stimulus baseline average of –300 to 0 ms) in the 220–550 ms. window.

### Clinical outcome

The primary outcome measure is the response to treatment defined as reaching remission ( $BDI \leq 12$ ) or response (a more than 50% decrease in BDI) after treatment in agreement with the cut-offs as suggested by Riedel et al. [47]. Using this definition, patients were labelled as either a responder (R) or a non-responder (NR) to treatment. Furthermore, the effect size (ES: Hedges' D) was calculated (MetaWin 2.1) in order to compare these results to existing meta-analysis. In order to investigate possible differential treatment effects between HF and LF rTMS one way ANOVA's were used to test for differences in age, education, number of sessions, BDI at intake, outtake and percentage improvement on BDI, as well as Chi-Square tests for differences in gender and percentage responders.

### Response prediction

Differences between R and NR were analyzed using 1-way ANOVA's for 1) clinical baseline variables (age, education, gender, BDI intake, suicide risk (MINI), DASS Depression, Anxiety, Stress and Personality factors: NEO-FFI, neuroticism, extraversion, openness, agreeableness, conscientiousness); and 2) neurophysiological variables (anterior and posterior iAPF, P300 amplitude and latency at Pz and Fz and left, right and pre-frontal cordance). For EEG theta power a repeated measures ANOVA was used with factor electrode site (26 channels) and between subject factor responder status (R or NR).

Additionally, correlations were performed between the obtained predictors demonstrating a significant difference for R and NR and 1) clinical measures such as percentage improvement on the BDI, BDI at intake and outtake to investigate if the obtained markers are directly or indirectly related to treatment outcome and 2) among the obtained predictors of treatment outcome in order to investigate

**Table 1**

The clinical response to HF and LF rTMS and the effects for the total group.

Clinical response	LF rTMS	HF rTMS	P-value	Total group
Responders	78.8%	77.2%	0.997	77.8%
Number of sessions	19.3	21.4	0.168	20.66
BDI Intake	31.0 (SD 9.98)	29.9 (SD 9.03)	0.608	30.3 (SD 9.35)
BDI Outtake	12.6 (SD 11.73)	12.1 (SD 11.17)	0.847	12.3 (SD 11.31)
Percentage decrease BDI	60.8%	59.8%	0.889	60.2%
Hedges' d Intake – Outtake	ES = 1.67	ES = 1.74		ES = 1.73

how independent the predictors are. Using the significant biomarkers a discriminant analysis as performed and a Receiver Operator Characteristic (ROC) curve was plotted to investigate how well these measures could be used to predict treatment outcome. An ROC curve is a graph displaying the true positive rate vs. the false positive rate for responder status.

### Results

A total of 90 patients were enrolled meeting a primary diagnosis of MDD ( $N = 86$ ) or Dysthymia ( $N = 4$ ) (average age: 42.9 yrs, range 19–69 yrs; 49 females and 41 males).

### Clinical outcome

There were no differences in any of the clinical outcome measures and demographics between the HF and LF TMS groups. From the 70 responders, 58 (83%) achieved remission and the remainder demonstrated a more than 50% improvement on the BDI.

Table 1 summarizes the treatment effects of LF rTMS and HF rTMS. The response rate was on average 77.8% and patients on average had 20.66 sessions. The within subject Hedges' D effect size was 1.73 which can be considered a large ES.

### Response prediction

Given there were no baseline differences and differences in clinical response between LF and HF rTMS, both populations were grouped together in order to further investigate predictors of non-response to treatment.

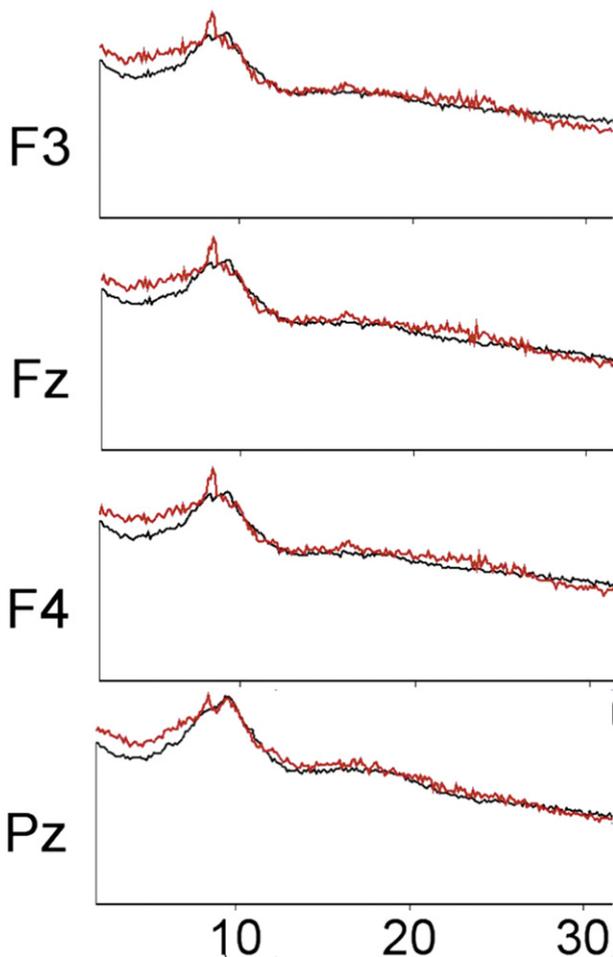
There were no significant differences between R and NR for any of the baseline clinical measures (Age, education, gender, BDI intake, DASS Depression, Anxiety, Stress, Personality factors (NEO-FFI, neuroticism, extraversion, openness, agreeableness, conscientiousness) and suicide risk (MINI)).

Fig. 1 shows the EEG power spectrum for eyes closed at frontal and parietal locations.

### EEG theta power

For Theta EEG power, there was a significant effect for site ( $P = 0.000$ ;  $F = 61.000$ ;  $DF = 25, 61$ ), responder status ( $P = 0.008$ ;  $F = 7.427$ ;  $DF = 1$ ) and a significant site X responder status interaction ( $P = 0.046$ ;  $F = 1.711$ ;  $DF = 25, 61$ ) reflecting that the R-NR difference was not equal across all sites. Hence 1-way ANOVA's were carried out. Only findings with  $P < 0.01$  were considered significant thereby adjusting for multiple comparisons. There was a significantly greater Theta in NR with  $P < 0.01$  for the following sites: F7 ( $P = 0.008$ ), F3 ( $P = 0.009$ ), F4 (0.004), F8 ( $P = 0.002$ ), FC3 ( $P = 0.006$ ), FCz ( $P = 0.009$ ), FC4 ( $P = 0.003$ ), T3 ( $P = 0.008$ ), Cz ( $P = 0.005$ ), C4 ( $P = 0.003$ ), T4 ( $P = 0.009$ ), CP4 ( $P = 0.008$ ) (see Fig. 2).

Baseline Theta at these sites also significantly correlated with percentage improvement on the BDI and BDI at outtake for all these



**Fig. 1.** The EEG power spectrum (FFT in Hz) for the eyes closed condition at F3, Fz, F4 and Pz for responders (black) and non-responders (red). Note the increased theta and the slower iAPF for non-responders, most prominent at frontal sites. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

sites except T4, with the strongest correlation for F7 and percentage improvement on BDI ( $P = 0.005$ ;  $r = -.296$ ;  $DF = 90$ ) and for F8 and BDI at outtake ( $P = 0.004$ ;  $r = .301$ ;  $DF = 90$ ). High theta was thus associated with a weaker decline in BDI score and, consistently, a higher BDI score at outtake.

#### Individual alpha peak frequency (iAPF)

There was no difference between R and NR in posterior iAPF ( $P = 0.258$ ;  $F = 1.295$ ;  $DF = 1, 85$ ) but there was a significant difference in anterior iAPF where the NR had an average anterior iAPF of 8.30 Hz ( $SD = 1.20$ ) and R had an average anterior iAPF of 9.16 Hz ( $SD = 1.14$ ) ( $P = 0.005$ ;  $F = 8.303$ ,  $DF = 1, 84$ ).

Baseline anterior iAPF also demonstrated a significant correlation with the percentage decrease on the BDI ( $P = 0.002$ ;  $r = 0.326$ ,  $DF = 86$ ) and BDI at outtake ( $P = 0.003$ ;  $r = -.312$ ,  $DF = 86$ ) but not with BDI at intake ( $P = 0.973$ ;  $r = -.004$ ;  $DF = 86$ ).

#### Cordance

R had a greater degree of pre-frontal Delta Cordance ( $P = 0.027$ ;  $F = 5.032$ ;  $DF = 1, 86$ ) and pre-frontal Beta cordance ( $P = 0.039$ ;  $F = 4.395$ ;  $DF = 1, 86$ ) than NR but no difference for right and left frontal cordance nor for alpha or theta cordance (visualized in Fig. 3). Pre-frontal beta cordance also correlated significantly with percentage improvement on the BDI ( $P = 0.044$ ;  $r = .215$ ;  $DF = 88$ ) but pre-frontal Delta cordance did not ( $P = 0.093$ ;  $r = .180$ ;  $DF = 88$ ).

#### P300

There was no difference between responders and non-responders with respect to P300 latency at Fz ( $P = 0.862$ ;  $F = 0.031$ ;  $DF = 1, 82$ ), Pz ( $P = 0.867$ ;  $F = 0.028$ ;  $DF = 1, 84$ ) and P300 amplitude frontal ( $P = 0.487$ ;  $F = 0.488$ ;  $DF = 1, 82$ ) but there was a marginally significant difference for P300 amplitude at Pz ( $P = 0.054$ ;  $F = 3.831$ ;  $DF = 1, 84$ ) where responders exhibited a lower P300 amplitude at Pz (11.2 uV;  $SD = 5.72$ ) as compared to non-responders (14.6 uV,  $SD = 8.68$ ), visualized in Fig. 4. There were no correlations between P300 amplitude and improvement on the BDI, nor with the BDI at intake or outtake.

#### Correlations between markers for treatment response

In order to assess if the obtained predictors were independent or might be a reflection of a shared underlying functional network, correlations were explored between P300 amplitude at Pz, anterior iAPF, Pre-frontal Delta and Beta cordance and Theta at F7 and F8.

**P300 amplitude:** There were no correlations between P300 amplitude and iAPF, pre-frontal cordance measures and Theta at F7 and F8.

**Anterior iAPF:** There were no correlations between anterior iAPF and P300 amplitude, pre-frontal cordance, but there was a negative correlation with Theta at F7 ( $P < 0.000$ ;  $r = -.426$ ;  $DF = 86$ ) and F8 ( $P < 0.000$ ;  $r = -.499$ ;  $DF = 86$ ).

For pre-frontal Delta and Beta cordance, there were no significant correlations with other variables.

These data suggest that the pre-frontal cordance and P300 amplitude are relatively independent measures, whereas Theta power at F7 and F8 and iAPF are highly correlated.

#### Discriminant analysis

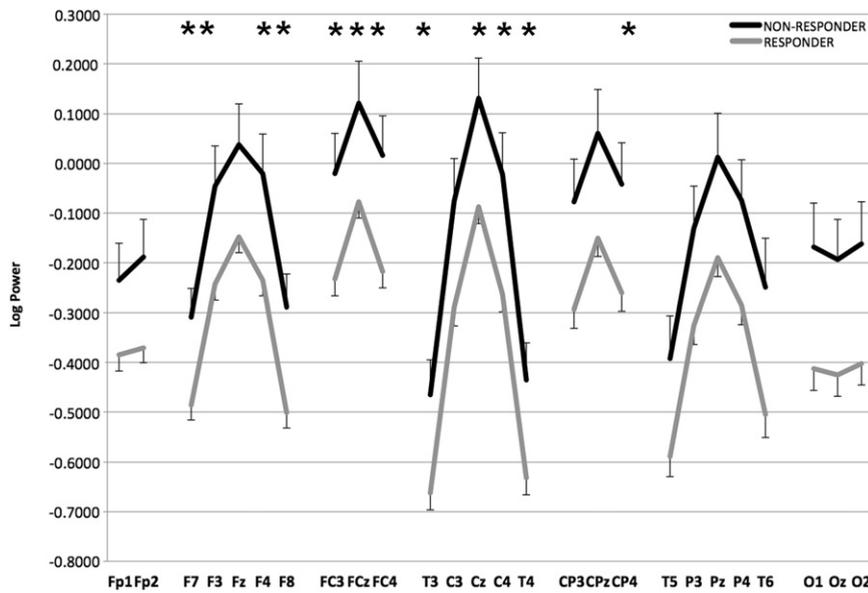
A discriminant analysis was performed using the following measures: P300 amplitude at Pz, pre-frontal Delta and Beta cordance and anterior iAPF. The grouping variable was responder status. The model resulted in a significant Wilks' Lambda ( $P = 0.001$ ; Wilks' Lambda = 0.781; Chi-square = 19.050;  $DF = 4$ ). The area under the ROC curve was 0.814. As can be seen in the ROC curve in Fig. 5 (showing the specificity and sensitivity for non-responders), when accepting a 10% false positive rate, 53% of the non-responders could be identified and when accepting a 5% false positive rate, 41% of the non-responders could be identified using the 4 biomarkers at baseline.

#### Medication status

From all patients, 32.2% ( $N = 29$ ) were unmedicated at the beginning of treatment. Twenty-one patients were medicated with a first-line antidepressant such as an SSRI or SNRI, and the remaining 40 patients took combined medication. There were no differences between the medicated and unmedicated patients for clinical outcome measures such as BDI at intake, outtake, improvement on BDI, number of sessions, responder status and also not for the significant predictors of treatment outcome described above (all  $P > 0.1$ ) demonstrating that medication status did not confound the results in this study.

#### Discussion

The primary aim of this study was to investigate predictors of non-response to rTMS treatment. Clinical measures at baseline such as anxiety, depression, stress, suicide risk, medication status etc. were not found to be related to treatment outcome. EEG and ERP



**Fig. 2.** Differences in theta power during eyes closed between responders (grey) and non-responders (black) to rTMS at baseline (\* indicate significant differences at  $p < .01$ , error bars are SEM).

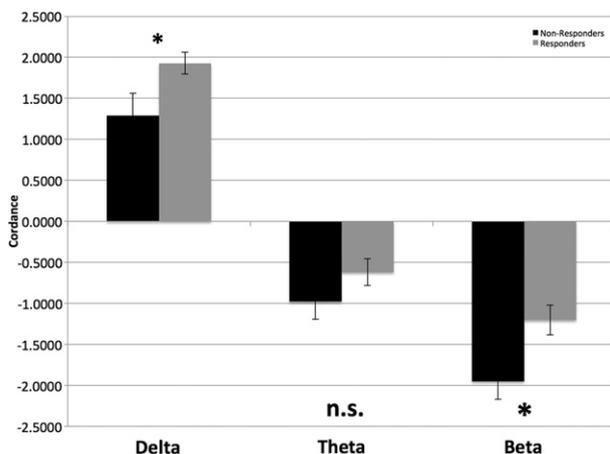
measures did demonstrate clear differences between responders (R) and non-responders (NR).

The increased theta for NR is in line with previous studies demonstrating non-response to antidepressant medication to be associated with increased theta [21–23]. As can be seen in Fig. 2 the increased theta is most specifically increased in right and left fronto-central locations and not limited to frontal midline sites. Frontal midline theta has been localized to the medial pre-frontal cortex and anterior cingulate [48,49] and a recent meta-analysis has demonstrated that theta in the rostral anterior cingulate is associated with improved response to antidepressant treatment [16]. Hence, our findings point rather to a generalized increased theta in non-responders as opposed to frontal midline theta originating from the anterior cingulate. The studies from Knott et al. [21,22] as well as Iosifescu et al. [23] also reported a generalized increase in theta in NR. These results might hence be interpreted as a sub-group characterized by a decreased EEG vigilance regulation [50,51] characterized by frontal theta, whereas typically in depression higher EEG vigilance regulation – expressed as hyperstable or rigid parietal alpha or A1 stages – is reported [52,53].

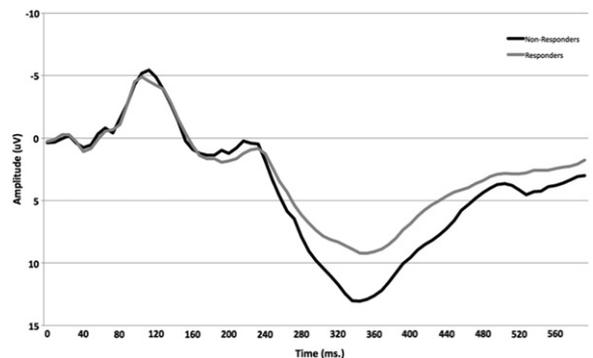
Given that patients with a decreased EEG vigilance regulation respond better to stimulant medication (Manic Depression: [50,54,55]; ADHD: [36,56]) it is tempting to speculate if this sub-group of non-responders might respond better to stimulant medication. Suffin and Emory [57], did report that this sub-group of depressed patients does respond to stimulant medication, recently replicated by DeBattista et al. [58]. However further research is required to investigate this speculation.

The finding of a slower (anterior) iAPF in NR is in line with previous work on rTMS [25,26] and medication [24]. A slow iAPF has also been shown to be a predictor for non-response to stimulant medication in ADHD [36] and to antipsychotics [59]. Hence this sub-group of non-responders might represent a non-specific sub-group of patients who fail to respond to treatment. In a previous study we have investigated if personalizing the rTMS frequency based on the anterior iAPF would improve clinical efficacy, which was not found to be the case [26], whereas this was found to result in more specific clinical effects in rTMS treatment for Schizophrenia [60]. Future research should investigate further to which treatment this sub-group could be most responsive.

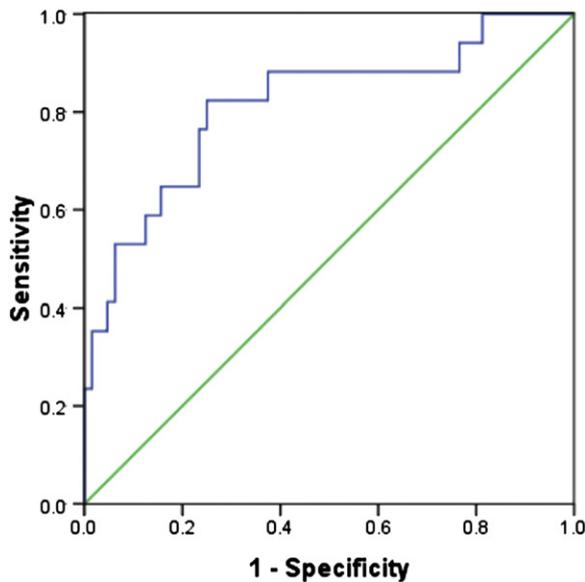
The slow anterior iAPF and frontal theta demonstrated a high correlation. This is in line with several earlier studies demonstrating a slow iAPF can confound theta EEG power constrained to



**Fig. 3.** The increased delta and beta cordance for R at pre-frontal regions, suggesting more ‘concordant’ delta and beta activity representative of increased relative pre-frontal perfusion for R (\* indicate  $p < .05$ ; error bars are SEM).



**Fig. 4.** The oddball ERP grand average waveforms for non-responders (black) and responders (grey) to rTMS treatment at Pz. Note the larger P300 amplitude for non-responders.



**Fig. 5.** Receiver Operating Characteristic (ROC) curve of the obtained discriminant function predicting non-response to rTMS combining the following biomarkers: P300 amplitude, Pre-frontal delta and beta cordance and anterior iAPF. ROC area is 0.814.

a fixed frequency band [45,46]. In this study the main aim was to replicate earlier findings hence a fixed theta-frequency band was chosen, and as can be seen in Fig. 1, NR exhibited both a slowed iAPF and increased theta. Future studies should hence more clearly dissociate these 2 measures, may be by using personalized frequency bandwidths similar to those used by Doppelmayr and coworkers [45] and also by investigating the localization of these activities using techniques such as LORETA.

Decreased pre-frontal cordance in the delta and beta band was found for NR – indicative of a less ‘concordant’ EEG state possibly reflective of lower relative perfusion in the underlying cortex [33]. This finding of decreased concordance over pre-frontal areas for NR is in line with previous studies (HF rTMS: [11–14]; LF rTMS: [15]) and hence lower concordance of frontal areas can be considered a predictor for non-response.

Finally, NR exhibited a higher P300 amplitude at Pz as compared to NR, contrary to previous studies (Medication: [27,28]; ECT [29]). Bruder and coworkers [61] found that patients with anxiety demonstrated larger P300 amplitudes whereas patients with a depression and no comorbid anxiety demonstrated a reduced P300 amplitude as compared to healthy controls. Hence, it might be speculated that the NR with a larger P300 amplitude represent a sub-group with more comorbid anxiety. However, post-hoc analysis did not demonstrate a correlation between anxiety and P300 amplitude failing to support this notion.

When the 4 biomarkers (anterior iAPF, P300 amplitude at Pz, pre-frontal delta and beta cordance) were combined in a discriminant analysis they yielded a moderate predictive power to identify non-responders using these baseline measures, as can be judged from the ROC curve in Fig. 5. When a false positive rate of 10% is acceptable (i.e. from the patients classified as a non-responder, 10% would have been a responder), 53% of the non-responders could have been selected a-priori, resulting in a higher efficacy by excluding these non-responders a-priori. In comparison, Leuchter et al. [62] using the ATR (an EEG based ‘treatment-emergent biomarker’) obtained an ROC of 0.77 and Cook et al. [32] using theta cordance obtained an ROC area of 0.76. Compared to these ROC areas, the obtained area of 0.814 can be considered high, especially taking into account that this study only investigated measures assessed at baseline instead of a treatment-emergent biomarker

such as cordance or ATR. Therefore, these results show promise for future applications of neurophysiological biomarkers to be applied in practice and select the appropriate patients for rTMS treatment. However, these results first need to be replicated prospectively in an independent sample before use is warranted in practice.

#### Clinical effects

In this study we found that HF and LF rTMS combined with psychotherapy resulted in an overall response rate of 77.8%. If only remission is considered, the response rate in this study was 64%. In comparison to previous rTMS studies these efficacy rates tend to be rather high, however these results reflect the efficacy of combined rTMS with psychotherapy. Keller et al. [63] demonstrated in a large study that psychotherapy combined with medication also resulted in a large response rate of 73% whereas either treatment as a monotherapy had a response rate of 48%. Furthermore, most previous rTMS studies consisted of samples with high rates of treatment resistance, which is known to result in lower response rates [64–66]. In this study we did not systematically track treatment resistance but 32.2% of patients were not on medication when the treatment was initiated and 23.3% of patients (21 out of 61 medicated patients) were medicated with a ‘first-choice’ type of antidepressant medication such as an SSRI or SNRI, suggesting the majority of patients (55.5%) had a low ‘treatment resistance’. Therefore, these results tend to be in line with results from combined psychotherapy and antidepressant medication and further demonstrate the feasibility of combining psychotherapy and rTMS treatment in clinical practice.

#### Limitations

This study did not employ a double blind placebo controlled design, hence it cannot be ruled out that the results are partly explained by placebo effects. Furthermore, in this study we combined psychotherapy with rTMS making it difficult to disentangle whether the obtained predictors reflect generic predictors for non-response, or a predictor for non-response to either rTMS or psychotherapy. In any case non-responders did not respond to treatment, hence did not respond to rTMS nor psychotherapy nor to the placebo aspect. Hence, the combination measures may be useful as generic predictors of non-response in clinical practice. The fact that these same predictors have also been found in medication studies, further supports this notion.

The P300 amplitude finding was marginally significant and opposite the hypothesized direction. Furthermore, the P300 amplitude and pre-frontal Delta Cordance did not demonstrate a correlation with ‘percentage improvement’ or ‘BDI at outcome’ in the whole sample, thereby questioning whether these are real effects or represent a type-I error. Additionally, for the general measures (Theta power, iAPF, P300 amplitude and P300 latency and pre-frontal cordance) no correction for multiple measurements was performed. Both P300 amplitude and pre-frontal Delta cordance would not survive such a correction, further cautioning these findings. Therefore, future studies should investigate the P300 amplitude and Delta cordance measures further with independent replication in a larger sample.

The open-label nature of this study is another weakness combined with the fact that most patients were medicated. Medications have effects on their own on the EEG. For example benzodiazepines have the most marked effects on the EEG by increases in beta and slowing of the iAPF. If the iAPF slows down due to a benzodiazepine with more than 0.5 Hz, that drug is often discontinued in clinical practice, due to the severity of the cognitive side-effects [67]. The non-responders in this study exhibited an

average iAPF of 8.3 Hz, almost 1 Hz slower than responders, therefore this is unlikely to be an effect of medication though future studies are required to investigate that. Finally, prospective replication of these results is required to investigate the value of these measures in practice.

## Conclusion

Several EEG variables demonstrated clear differences between R and NR such as the anterior iAPF, fronto-central Theta, P300 amplitude and pre-frontal cordance in the Delta and Beta band (representative of increased relative pre-frontal perfusion). Combining these biomarkers in a discriminant analysis resulted in a reliable identification of non-responders with low false positive rates.

More studies are required to replicate these findings and also focus on explaining these predictors for non-response (since these have also been found to be related to non-response after antidepressant medication) and investigate to what treatments these subgroups might respond. These results also demonstrate the feasibility of combining rTMS treatment with psychotherapy, and suggest this may result in improved efficacy of the combined treatment as reflected in a large effect size.

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