Non-replication of neurophysiological predictors of non-response to rTMS in depression and neurophysiological data-sharing proposal

Dear Editor,

The application of repetitive transcranial magnetic stimulation (rTMS) as a treatment for Major Depressive Disorder (MDD) has been shown to be effective when applied to either the right or left dorsolateral prefrontal cortex (DLPFC) in placebo controlled studies [1,2] as well as open-label studies [3]. Given the effectiveness of rTMS as a treatment for MDD, the interest for finding clinical or (neuro)physiological predictors has been increasing. In 2012, we [4] reported neurophysiological predictors of non-response (NR) for rTMS treatment in MDD. These predictors included the EEG metrics: increased fronto-central theta, a low individual alpha peak frequency (iAPF), and a large P300 amplitude at site location Pz in a sample of 90 MDD patients, however these biomarkers still require replication. The aim of the current study is to investigate the replicability of these findings in a newly collected sample, and also to make our EEG and ERP data available to scientific use for replication analyses that have specific formulated hypotheses, and thus facilitating future replication studies.

Methods and materials

Design

This study was an open-label study (details published recently in this journal [3]. In summary, data for this replication cohort were collected in two clinics (Brainclinics Treatment/neuroCare Nijmegen and The Hague, The Netherlands) between November 2009 and March 2016. 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. Response was defined by achieving response (>50% decrease on BDI) or remission (BDI≤12), like in the earlier study. EEG and ERP acquisition and analysis were identical to the methods used in the earlier 2012 study.

Analysis

Given the confirmatory nature of this data analysis where we specifically aimed to replicate earlier reported measures, we initially only ran One-Way ANOVA's to test differences between responders and non-responders in iAPF, P300 amplitude, and fronto-central theta (for exact processing details see Ref. [4].

Results

A total of 106 patients were included in this study (average age: 43.92 yrs, range 18—78 years; 50 females and 56 males; 63 responders). No differences between responders (R) and non-responders (NR) were found for age, gender, or rTMS protocol (each p > .236). BDI baseline scores were significantly lower for responders than for non-responders (p = .018, F = 5.761, DF = 1).

EEG biomarkers

No significant differences were found between R and NR for frontal theta (F7, F3, F4; Fig. 1a); P300 amplitude at electrode site Fz and Pz (Fig. 1b), nor for iAPF (Fig. 1c). The patterns of results were in the same direction as the original study for P300 and iAPF albeit not significant and with small effect sizes.

Exploratory analysis

Additional analyses were performed to test for subgroup interactions. One-Way ANOVA's for males and females separately also yielded no significant differences between responders and non-responders for fronto-central theta, P300 amplitude at Pz, and iAPF. We also performed a univariate analysis with age as a covariate, but this too did not yield significant differences between responders and non-responders on the targeted variables.

Discussion

The aim of the current study was to replicate the findings from our earlier study [4], however, we were unable to replicate the earlier obtained findings for fronto-central theta, P300 amplitude and iAPF: Numerically the trends and direction of the results were the same for iAPF and P300, however non-significant and with small effect sizes. The results for theta are in line with rather opposite findings throughout the literature where sometimes increased frontal midline theta — with a putative generator in the rostral anterior cingulate cortex — versus decreased frontocentral theta has been found to be related to antidepressant treatment response including rTMS (also see Refs. [5,6] for reviews and data). In a previous paper combining our earlier sample and this

Figure 1a. ANOVA outcomes for frontal theta, iAPF, and P300.

	Responder	Non-responder	*F*	*p*	Cohen's d
Theta per electrode site					
F7	.7941 (.25923)	.7641 (.28731)	.305	.582	.110
F3	1.0795 (.27429)	1.0310 (.28521)	.753	.388	.173
F4	1.0749 (.27767)	1.0550 (.30055)	.120	.730	.069
P300 amplitude					
Frontal	7.414 (7.333)	5.106 (6.911)	2.315	.132	.324
Parietal	11.824 (7.964)	11.969 (7.087)	.008	.929	.019
iAPF					
Frontal	9.048 (1.227)	8.891 (1.048)	.449	.504	.138
Parietal	9.522 (1.337)	9.597 (.960)	.094	.760	.064

Figure 1b. P300 amplitude at Pz.
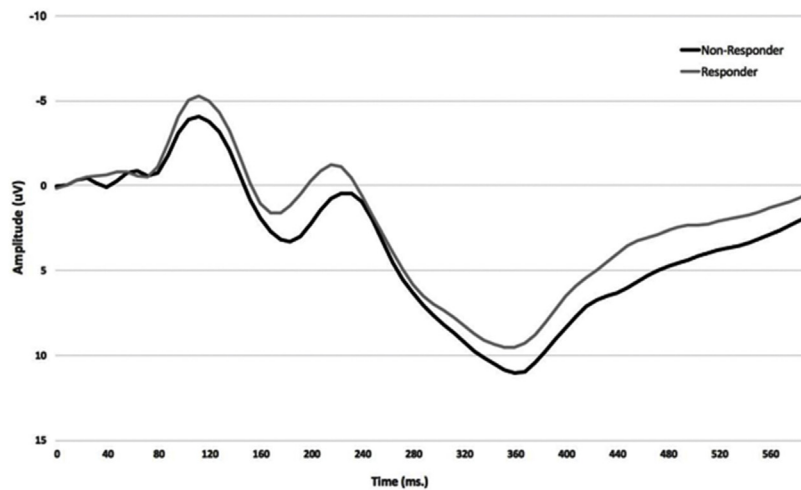
Figure 1c. Power spectrum of iAPF at F3, Fz, F4, and Pz.
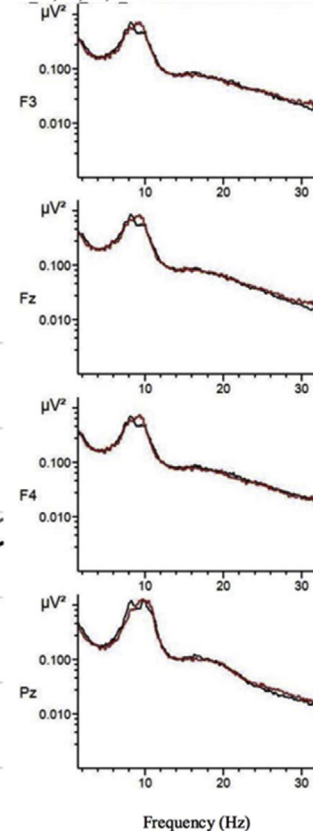
Fig. 1. a—c. Fig. 1a shows the ANOVA outcomes for the tested parameters demonstrating that there were no significant differences between R and NR for the tested parameters. Fig. 1b visualizes the P300 amplitude at Pz, for which a difference between R and NR was found in Ref. [4], lacking such a statistical significant difference between groups in the current sample. Fig. 1c shows the visualization of the power spectral content for R (black) and NR (red), demonstrating no differences between R and NR. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

new sample we were unable to find meaningful clinical predictors for treatment response to rTMS treatment in MDD, the predictors including depression severity (rated with BDI), comorbid depression, anxiety and stress (using DASS scales) [3] as well as personality traits (NEO FFI; unpublished findings). These findings demonstrate that future treatment prediction studies should be adequately powered with sample sizes preferably larger than 100, and furthermore should aim to include replication analyses in order to more reliably report on biomarkers for treatment response. For our future EEG biomarker studies, we have implemented this by a priori dividing our current database into a discovery and replication dataset, which enables us to prospectively verify findings found in the discovery dataset. In addition, to reduce the likelihood of future non-replication, we hereby offer our full sample of EEG and ERP data (N = 196) for scientific use in replication analyses employing specifically formulated hypotheses.

References

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