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Rostral Anterior Cingulate Cortex Oscillatory Power Indexes Treatment-Resistance to Multiple Therapies in Major Depressive Disorder

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Abstract

Introduction: High rostral anterior cingulate cortex (rACC) activity is proposed as a nonspecific prognostic marker for treatment response in major depressive disorder, independent of treatment modality. However, other studies report a negative association between baseline high rACC activation and treatment response. Interestingly, these contradictory findings were also found when focusing on oscillatory markers, specifically rACC-theta power. An explanation could be that rACC-theta activity dynamically changes according to number of previous treatment attempts and thus is mediated by level of treatment-resistance. ***Methods:*** Primarily, we analyzed differences in rACC- and frontal-theta activity in large national cross-sectional samples representing various levels of treatment-resistance and resistance to multimodal treatments in depressed patients (psychotherapy [$n = 175$], antidepressant medication [AD; $n = 106$], repetitive transcranial magnetic stimulation [rTMS; $n = 196$], and electroconvulsive therapy [ECT; $n = 41$]), and the respective difference between remitters and non-remitters. For exploratory purposes, we also investigated other frequency bands (delta, alpha, beta, gamma). ***Results:*** rACC-theta activity was higher ($p < 0.001$) in the more resistant rTMS and ECT patients relative to the less resistant psychotherapy and AD patients (psychotherapy-rTMS: $d = 0.315$; AD-rTMS: $d = 0.320$; psychotherapy-ECT: $d = 1.031$; AD-ECT: $d = 1.034$), with no difference between psychotherapy and AD patients. This association was even more pronounced after controlling for frontal-theta. Post hoc analyses also yielded effects for delta, beta, and gamma bands. ***Conclusion:*** Our findings suggest that by factoring in degree of treatment-resistance during interpretation of the rACC-theta biomarker, its usefulness in treatment selection and prognosis could potentially be improved substantially in future real-world practice. Future research should however also investigate specificity of the theta band.

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Introduction

Major depressive disorder (MDD) is the leading cause of disability in the world, with symptoms ranging from mild anhedonia to social and occupational malfunctioning and death by suicide [1]. It is believed to be characterized by a disruption in the frontal-limbic circuitry [2], in which there is a deficit in switching between the default mode network and the central executive network [3]. Various therapies aim to modify the pathological network activity in depression using different modi operandi [4] and are usually delivered in a stepped-care model. This means that patients start with less invasive treatments (e.g., psychotherapy and/or antidepressant medication [AD]) and progress to more intensive treatments accompanied with higher costs and side effects (e.g., intranasal or intravenous ketamine, repetitive transcranial magnetic stimulation [rTMS], electroconvulsive therapy [ECT]) once prior treatments have failed [5]. Remission rates for treatments in the early stages are around 35% [6–10] and decrease to around 13–14% after 2–3 failed treatments [11], after which a patient's depression is categorized as treatment-resistant depression (TRD), also named "difficult-to-treat depression" [11]. To help treat MDD more efficiently, current research aims to identify biomarkers (i.e., prognostic metrics based on the brain network activity at baseline) that can identify likely TRD cases at an early stage, and predict which treatments are likely to be more effective in such cases.

One brain region of interest for biomarker discovery in depression is the rostral anterior cingulate cortex (rACC). High rACC activity has been proposed to be a nonspecific prognostic marker for treatment response [2, 12]. Studies using EEG, fMRI, or PET have found that patients with high rACC activity are more likely to achieve a positive treatment outcome, independent of modality (e.g., AD, sleep deprivation, rTMS) [2]. However, other studies using PET/SPECT have reported the opposite finding of a negative association between baseline rACC activation and treatment response [2]. These contrary findings were reported for treatments with paroxetine, venlafaxine, cognitive behavioral therapy (CBT), ECT, and rTMS [2, 13–16].

A similar apparent contradiction is seen in this region with theta power on EEG. A recently published follow-up to the large EMBARC biomarker study reported that patients with high baseline rACC-theta activity were more likely to improve with treatment in general, whether on sertraline or on placebo [12]. However, in contrast, the iSPOT-D biomarker study reported the opposite finding that patients with high baseline rACC-theta showed poorer response in general, to escitalopram, sertraline, or venlafaxine [17].

One proposal to reconcile these findings is that the predictive value of rACC-theta may depend on the degree of treatment-resistance. For example, Hunter et al. [18] found that antidepressant-naïve patients with high rACC-theta had greatest treatment improvement and that for antidepressant-experienced patients it was those with low rACC-theta that showed greatest treatment improvement. In keeping with this pattern, EMBARC patients (who were required to be fairly treatment-naïve, with no failed medication trials in the current episode) with high rACC-theta showed the greatest treatment improvement [12], while iSPOT-D patients with more treatment failures showed the strongest relationship between high rACC-theta and poor treatment response [17].

Following these studies, we may question whether high rACC-theta should be considered a general (treatment nonspecific) marker of depressive symptom improvement (prognostic marker) [2], whether rACC-theta is a biological marker correlated to treatment-resistance (trait), or whether rACC-theta dynamically changes according to the number of previous treatment attempts and thus is mediated by the level of treatment-resistance [17, 18]. The aim of the present study was therefore to clarify this issue, by first determining whether the degree of treatment-resistance correlates with baseline rACC-theta activity, and second, whether rACC-theta activity can be used to predict treatment outcome more effectively when the degree of treatment-resistance is integrated in prediction analyses. We hypothesized that baseline rACC-theta activity would change with increasing levels of treatment-resistance and that patients with high treatment-resistance and co-occurring high baseline rACC-theta activity would show poorer treatment outcomes.

We set out to test this hypothesis in a new, large, naturalistic dataset comprising of four Dutch national open-label datasets, in which patients were allocated to treatment in a stepped-care model according to structured clinical guidelines [19–21]. The use of these datasets provided some assurance that patients were truly referred to treatments based on their level of depression severity and resistance level. The datasets covered a variety of treatment modalities: psychotherapy and AD for patients with low treatment-resistance, rTMS for patients with medium treatment-resistance, and ECT for patients with high treatment-resistance [22–24]. This study focused on rACC-theta and frontal-theta activity as this study was an a priori planned extension of the earlier 2015 iSPOT-D study [17]. Pretreatment EEG recordings and standardized clinical questionnaires obtained before and after treatment enabled assessment of rACC-theta at different

levels of treatment-resistance, as well as assessment of whether rACC-theta was associated with remission for any treatment modality.

Materials and Methods

Participants

Five hundred eighteen EEG recordings of participants from different clinics were collected for this study and were categorized into four datasets. These datasets were national open-label datasets, collected under naturalistic conditions, in which patients were allocated to treatment in a stepped-care-model according to structured clinical guidelines [19–21]. We also used the healthy control group from the iSPOT-D study [17] (n = 336) to visualize how rACC-theta activity compared to the following datasets in the remission section. All participants provided written informed consent.

Dataset 1: Psychotherapy

The psychotherapy dataset consisted of patients diagnosed with nonpsychotic MDD or dysthymia and a Beck Depression Inventory second edition (BDI-II) [25] score ≥14 at baseline, who received any form of psychotherapy as monotherapy (n = 175). Patients could further be divided in having received CBT (n = 94) or other types of psychotherapy (other; n = 81). BDI-II was recorded before and after treatment. Details about this sample are described elsewhere [26].

Dataset 2: Antidepressants

The AD dataset consisted of patients diagnosed with nonpsychotic MDD or dysthymia and a BDI-II score ≥14 at baseline, who received AD, either as monotherapy or in combination with psychotherapy (n = 106). This sample was taken from van der Vinne et al. [27]. BDI-II was recorded before and again after 8 weeks of medication (monotherapy) or at the end of psychotherapy if this preceded the 8 weeks of medication (combination).

Dataset 3: rTMS

The rTMS dataset consisted of 196 patients, diagnosed with nonpsychotic MDD or dysthymia and BDI-II ≥14 at baseline, who underwent protocolized rTMS treatment concurrent with psychotherapy. Patients received high-frequency TMS (10 Hz left dorsolateral prefrontal cortex, DLPFC), low-frequency TMS (1 Hz right DLPFC), or both 1 Hz and 10 Hz sequentially. All patients completed at least 10 sessions of treatment and filled in the BDI-II at baseline and at the last session (on average session 21). Details about this sample are described elsewhere [20, 26, 28], and data are part of the open access dataset TDBRAIN (https://brainclinics.com/resources/) [28].

Dataset 4: ECT

The fourth dataset consisted of 41 patients, treated with complete ECT-courses at the Rijnstate Hospital. Most patients suffered from TRD. Depression severity was scored with the Hamilton Rating Scale for Depression ($HRSD_{17}$), within 1 week before start of ECT and within 1 week after the course. ECT was administered according to Dutch standards, and right unilateral and bifrontotemporal electrode placements were applied according to the psychiatrists' discretion. The ECT course was terminated after reaching remission ($HRSD_{17}$ score ≤7), or when patients did not improve any further after 1 week, or if ten bilateral ECT-sessions did not show any change in depression.

EEG Data Collection and Preprocessing

EEG data were collected using a standardized methodology and platform (Brain Resource Ltd., Australia). The EEG platform and methodology used in this study were identical to the iSPOT-D study [17], and details and validations have been published elsewhere [29–31].

In summary, patients were seated in a sound and light attenuated room within a clinical setting. As a naturalistic dataset, recordings occurred either in the morning or in the afternoon based on patient and room availability. EEG data were acquired from 26 channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz, and O2 (ANT Waveguard-cap; NuAmps; 10–20 electrode international system). EEG was collected for 2 min with eyes open, with the patient asked to fixate on a red dot on the screen, and 2 min with eyes closed. The patient was instructed to remain relaxed for the duration of the recording. No intervention took place when drowsiness patterns were observed in the EEG. Data were referenced to averaged mastoids with a ground at AFz. Horizontal eye movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eyelid. Impedances were kept below 10 kΩ and the sampling rate was 500 Hz. A low pass filter with an attenuation of 40 dB per decade above 100 Hz was employed prior to digitization.

Data were filtered (0.3–100 Hz and notch of 50 Hz), EOG-corrected using a regression-based technique similar to that used by Gratton et al. [32], and automatic artifact-detection and -removal were performed. Artifact signals included EMG, sharp channel-jumps (up and down), kurtosis, extreme voltage swing, residual eyeblinks, electrode bridging, and extreme correlations. Automatic artifact rejection was performed using a custom-built Python package [28]. This package is based on the automated method employed in the iSPOT-D study [17], as it showed an agreement of 98.4% with "manual" artifact rejection by certified EEG expert [29] and was further validated by van Dijk et al. [28] [full python code available online (http://www.brainclinics.com/resources)].

Analysis

EEG eLORETA Analyses

EEG analysis was performed identical to the prior report by Arns and colleagues [17], but in short: based on the scalp-recorded electric potential distribution, the exact low-resolution brain electromagnetic tomography (eLORETA) software (http://www.uzh.ch/keyinst/loreta.htm) was used to compute the cortical three-dimensional (3D) distribution of current density (i.e., the amount of electrical current flowing through a solid; unit: amperes per square meter, $Å/m^2$).

Previous studies have demonstrated that eLORETA can outperform other linear inverse solutions (e.g., minimum norm estimate, dynamic statistical parametric mapping, weighted minimum norm, local autoregressive average, dynamic imaging of coherent sources, and linearly constrained minimum variance) under ideal, noise-free conditions [33–35]. It has also been reported that this linear inverse solution for the EEG has the unique

property of having exact (zero-error) localization for point test sources anywhere in the brain, albeit with low spatial resolution [33, 36–38].

Previous studies cross-validated the LORETA algorithm to ensure eLORETAs confidence estimates in the respective inverse solutions, using not only EEG but also independent techniques of higher anatomical precision such as fMRI and PET. These studies showed that the anatomical localization provided by eLORETAs intracortical EEG-source estimates showed good concordance with independent measures of neural activation obtained via BOLD signals on fMRI, and via glucose metabolism on PET imaging [39, 40]. eLORETA is an improvement over the original LORETA version [41] and the standardized version sLORETA [42]. The eLORETA method is described in detail by Pascual-Marqui [36].

As eLORETA is deemed a valid way of analyzing rACC-theta activity [43], we used it to extract EEG current source density from the rACC (using the voxels reported by Pizzagalli et al. [43]) and frontal cortex during resting state conditions with eyes closed. The regions of interest (ROI) did not overlap. The employed frequency band for theta was 6.5–8 Hz (for exploratory analyses also delta [1.5–3.5 Hz], alpha [8–13 Hz], beta [14.5–30 Hz], and gamma [31–49 Hz] bands were assessed). Participants were excluded if extraction was not possible.

Statistics

SPSS version 28 was used for statistical analyses. Remission was defined as a score ≤12 on the BDI-II posttreatment and ≤7 on the $HRSD_{17}$ (see Participants).

In accordance with the iSPOT-D study [17], the primary analysis consisted of assessing whether there was a significant difference in the ROI (rACC and frontal) in the theta frequency band between treatments (psychotherapy, AD, rTMS, ECT) at baseline. Normal distribution of EEG measures was inspected, and theta measures were log transformed before statistical analysis. Differences in age, sex, and baseline depressive severity were tested using One-Way ANOVA or nonparametric tests (sex). In case of group differences in one of these measures, these variables were added as a covariate. To determine whether there is a difference in activity between rACC- and frontal-theta and the level of TRD, a repeated measures ANOVA was conducted with dependent variable rACC-theta and frontal-theta during EC; fixed factors treatment and sex; and covariate age. When significant interactions were found, we followed up with univariate ANOVA-analyses.

For exploratory purposes, we repeated the analyses performed for theta band on the delta, alpha, beta, and gamma bands, and reported these in online supplementary Materials (for all online suppl. material, see https://doi.org/10.1159/000533853). As we are investigating an a priori defined analysis based on the 2015 iSPOT-D study [17], these exploratory analyses should be considered as post hoc and secondary to the main analysis, and therefore more strict corrections were used for multiple testing ($p = 0.05/61$).

The secondary analysis consisted of comparing rACC-theta activity between remitters and non-remitters. A univariate ANOVA was conducted with dependent variable rACC-theta during EC; fixed factors treatment (CBT, other, AD, rTMS, ECT), sex, and remission; and covariates age and baseline severity. When significant interactions were found, we followed up with univariate ANOVA-analyses. To test for protocol specific effects, we also performed a univariate ANOVA analysis comparing rACC-theta activity between remitters versus non-remitters across the 1 Hz versus 10 Hz protocol groups, with sex, age, and baseline BDI as covariates of noninterest (demographic features are presented in online suppl. Materials).

For main effects, significance level was set at $\alpha = 0.05$, and for post hoc comparisons a Bonferroni-corrected p value was used (determined by the number of comparisons). Effect sizes of main effects are reported in Cohen's d.

Results

The final demographic features and depression severity of participants included in the analyses following exclusion criteria (e.g., no EEG data) are presented in Table 1.

Primary Analyses: ROI Activity and TRD Levels

No significant correlation was found between baseline BDI-II and rACC-theta and frontal-theta activity when grouping the psychotherapy, AD and rTMS datasets ($p = 0.826$ and $p = 0.929$), nor between baseline $HRSD_{17}$ and rACC-theta and frontal-theta activity for the ECT dataset ($p = 0.231$ and $p = 0.160$). As one dataset used $HRSD_{17}$ and the other three datasets used BDI-II, we removed baseline severity as covariate from further analyses in this section.

Repeated measures ANOVA, using age as a covariate, yielded for frontal and rACC-theta a significant effect of treatment ($F(3, 449) = 7.607$; $p < 0.001$), ROI ($F(1, 449) = 53.809$; $p < 0.001$), age ($F(1, 449) = 17.437$; $p < 0.001$), an interaction effect of ROI X treatment ($F(3, 449) = 4.949$; $p = 0.002$), and of ROI X sex ($F(1, 449) = 6.298$; $p = 0.012$). Post hoc analyses revealed a significant difference between the two ROIs across treatments ($p < 0.001$).

Following up on the interaction ROI X treatment, a univariate ANOVA, using age as covariate, was conducted for rACC-theta and yielded a significant main effect of treatment ($F(3, 449) = 10.186$; $p < 0.001$) and of age ($F(1, 449) = 16.382$; $p < 0.001$). Pairwise comparisons revealed a significant difference in rACC-theta activity between all types of treatments [ECT patients had higher rACC-theta activity than psychotherapy, AD, and rTMS patients (psychotherapy-ECT: $p < 0.001$, $d = 1.031$; AD-ECT: $p < 0.001$, $d = 1.034$; rTMS-ECT: $p = 0.005$, $d = 0.480$); rTMS patients had higher rACC-theta activity than psychotherapy and AD patients (psychotherapy-rTMS: $p < 0.001$, $d = 0.315$; AD-rTMS: $p = 0.004$, $d = 0.320$)], except between psychotherapy and AD ($p = 726$, $d = 0.008$; shown in Fig. 1a).

Table 1. Key demographic features and depression severity of the patient sample

	Datasets				
	psychotherapy		AD	rTMS	ECT
	CBT	other			
Full datasets					
Sample size, *n*	175 94	 81	106	196	41
Included in analysis					
Sample size, *n*	140 74	 66	97	193	28
Males, *n* (%)	50 (36) 32 (43)	 18 (27)	41 (42)	95 (49)	11 (39)
Age, mean (SD), years	37 (14.1) 35 (14.1)	 40 (14.1)	40 (14.2)	43 (13.4)	50 (14.2)
Baseline BDI-II/$HRSD_{17}$	31.6 30.2	 33.0	32.5	31.2	20.9
Posttreatment BDI-II/$HRSD_{17}$	20.1 20.1	 20.1	22.9	14.1	13.28

Sample size included in analysis reflects the number of people with complete baseline data who finished treatment and with successful eLORETA extraction. Dataset psychotherapy was divided into participants having received cognitive behavioral therapy (CBT) and other types of psychotherapy (other). AD, antidepressant medication; rTMS, repetitive transcranial magnetic stimulation; ECT, electroconvulsive therapy; CBT, cognitive behavioral therapy; SD, standard deviation; BDI-II, Beck Depression Inventory; $HRSD_{17}$, Hamilton Rating Scale for Depression.

Furthermore, a univariate ANOVA for frontal-theta, using age as covariate, yielded a significant main effect of treatment ($F(3, 449) = 5.071$; $p = 0.002$), and of age ($F(1, 449) = 15.783$; $p < 0.001$). Pairwise comparisons revealed only a significant difference in frontal-theta activity between ECT and the other types of treatments [ECT patients had higher rACC-theta activity than psychotherapy, AD, and rTMS patients (psychotherapy-ECT: $p < 0.001$, $d = 1.769$; AD-ECT: $p < 0.001$, $d = 0.913$; rTMS-ECT: $p = 0.003$, $d = 546$; shown in Fig. 1b)].

Due to the ROI X treatment interaction found in the repeated measures ANOVA, a mediation analysis was performed to rule out that rACC-theta effects were mediated by frontal-theta [44]. Univariate ANOVA, using age and frontal-theta as covariate, yielded for rACC-theta a significant main effect of treatment ($F(3, 448) = 8.901$; $p < 0.001$), frontal-theta ($F(1, 448) = 1{,}095.624$; $p < 0.001$), and of sex ($F(1, 448) = 5.128$; $p = 0.024$). Pairwise comparisons revealed rACC-theta activity to be significantly higher in rTMS and ECT patients compared to psychotherapy patients (psychotherapy – rTMS: $p < 0.001$, $d = 0.541$; psychotherapy – ECT: $p = 0.003$, $d = 0.628$) and in rTMS patients compared to AD patients ($p = 0.003$, $d = 0.374$; shown in Fig. 1c).

Finally, univariate ANOVA, using age and rACC-theta as covariate, yielded for frontal-theta a significant main effect of treatment ($F(3, 448) = 3.837$; $p = 0.010$), rACC-theta ($F(1, 448) = 1{,}095.624$; $p < 0.001$), and of sex ($F(1, 448) = 6.179$; $p = 0.013$). Pairwise comparisons only revealed frontal-theta activity to be significantly lower in rTMS patients compared to psychotherapy patients ($p < 0.001$, $d = 0.380$; shown in Fig. 1d).

For the other frequency bands, an exploratory analysis found that a significant interaction between ROIs and treatment groups was evident for delta (rACC), beta and gamma (rACC and frontal) bands, but not for the alpha band. The results remained significant when mediated by the respective frequency band in the frontal region (online suppl. Materials).

Secondary Analyses: rACC-Theta and Remission

When investigating whether rACC-theta activity was associated with remission, we divided the data further into five treatments: CBT, other psychotherapy forms (Other), AD, rTMS, and ECT. A one-way ANOVA with remission as factor determined that baseline severity was significant for each treatment, except for ECT (CBT $p = 0.006$; other $p = 0.006$; AD $p < 0.001$; rTMS $p < 0.001$;

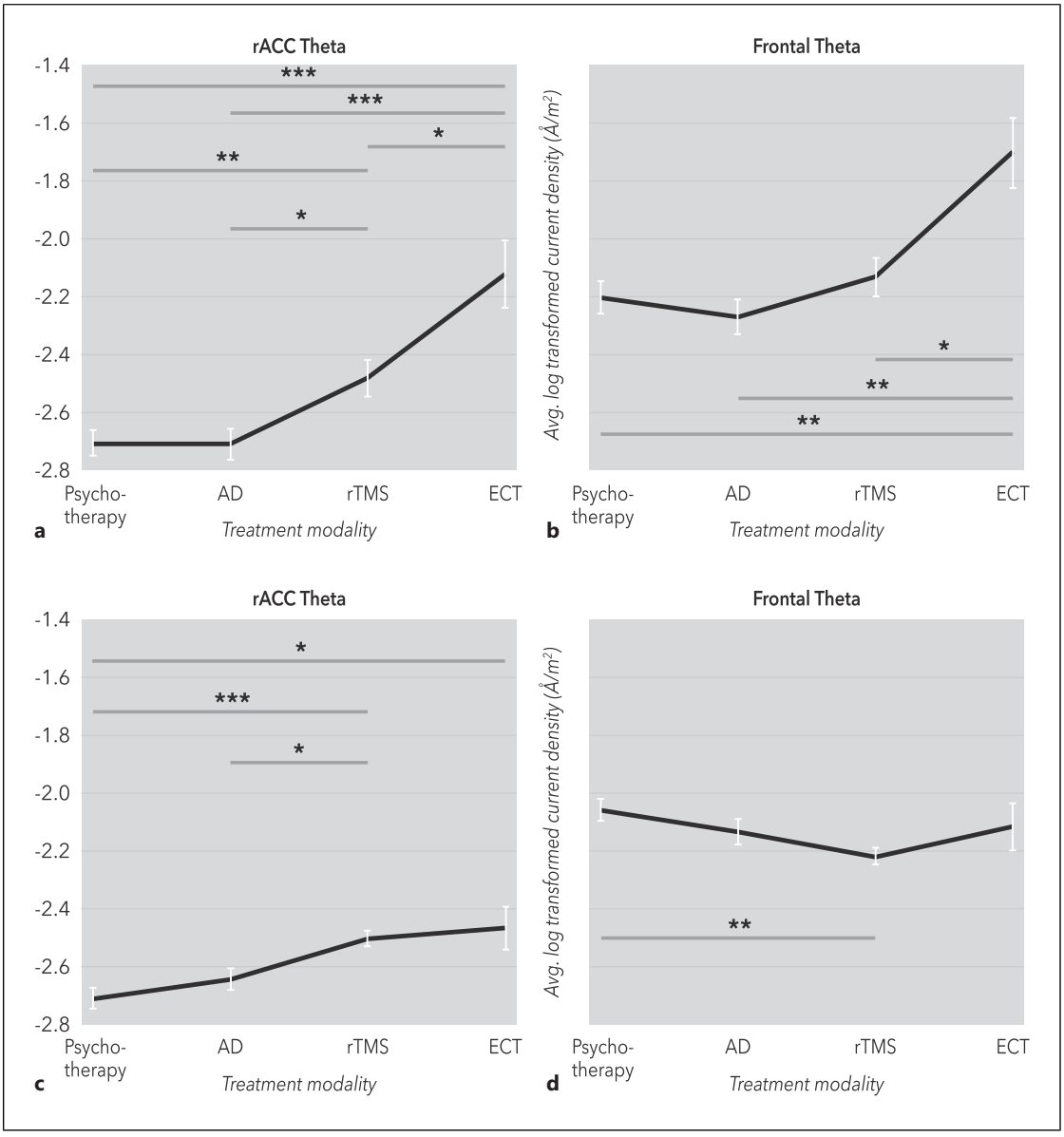

Fig. 1. rACC-theta and frontal-theta power levels across treatment modalities. **a** Illustrates rACC-theta activity being higher as treatment-resistance level increases, with no significant difference found between psychotherapy and AD. **b** Illustrates frontal-theta activity being higher in ECT compared to the other treatments. **c** Illustrates rACC-theta activity covaried by frontal-theta activity, and shows higher rACC-theta activity in rTMS compared to psychotherapy and AD, and in ECT compared to psychotherapy. **d** Illustrates frontal-theta activity covaried by rACC-theta activity, and shows lower frontal-theta activity in rTMS compared to psychotherapy. Significance level was Bonferroni-corrected. Error bars represent standard error of the mean. *$p < 0.008$, **$p < 0.0017$, ***$p < 0.00017$.

ECT $p = 0.568$). We therefore took baseline severity into account for the following analyses of this section. We accounted for the difference between questionnaires (BDI-II and $HRSD_{17}$) by performing a Z-score transform.

Univariate ANOVA, using age and baseline severity as covariates, yielded for rACC-theta in relation to remission a significant main effect of treatment ($F(4, 432) = 5.793$; $p < 0.001$), age ($F(1, 432) = 17.456$; $p < 0.001$), and an interaction effect of treatment X remission ($F(4, 432) = 4.591$; $p = 0.001$). Repeating the analysis for every treatment independently only revealed a significant difference in rACC-theta activity

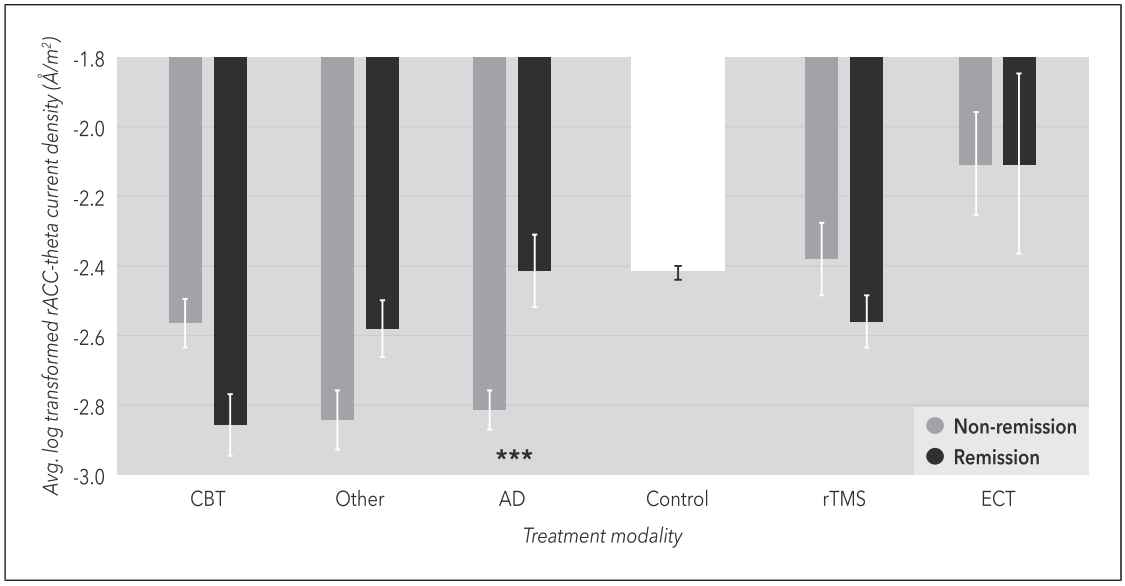

Fig. 2. rACC-theta and frontal-theta power levels across treatment modalities, and healthy controls (n = 336, from the iSPOT-D study [17]), in relation to remission. Graph shows higher rACC-theta activity in rTMS and ECT compared to psychotherapy and AD, with healthy controls in between these two levels of treatment-resistance. A significant difference in rACC-theta activity between remitters and non-remitters was only found in the AD dataset, with rACC-theta activity being higher in remitters. Significance level was Bonferroni-corrected. Error bars represent standard error of the mean. *p < 0.01, **p < 0.002, ***p < 0.0002.

between remitters and non-remitters for AD (remitters had higher rACC-theta activity than non-remitters: p < 0.001, d = 0.781), but not for CBT, other, rTMS or for ECT (p = 0.014; p = 0.019; p = 0.089; p = 0.820; respectively, shown in Fig. 2, in which the reader can also visually compare the results to a healthy control group extracted from the iSPOT-D study [17]). The exploratory analysis, testing for protocol specific effects, revealed no significant interaction between remission and rTMS protocol groups (p = 0.900).

Discussion

Following up on the iSPOT-D study [17], we investigated whether there are differences in pretreatment frontal- and rACC-theta activity across treatments with various levels of TRD. We found that rACC-theta activity differed between the first-line care (i.e., psychotherapy and AD; low activity) and the second/third line care (i.e., rTMS and ECT; high activity), and these effects were not mediated by frontal-theta activity. Therefore, the data suggest that these results are specifically associated with TRD level and rACC-theta, which is in favor of our hypothesis that baseline rACC-theta activity changes with increasing levels of treatment-resistance.

Furthermore, we only found a significant difference in rACC-theta between remitters and non-remitters for the patients treated with AD, with higher rACC-theta found in remitters compared to non-remitters. We believe that this result shows an interesting consistency with the previously reported findings in the fairly treatment-naïve patients of the EMBARC study: those with high rACC-theta activity likewise showed greater improvement on ADs than those with lower rACC-theta activity [12]. Intriguingly, resemblance to the iSPOT-D study finding that patients with high rACC-theta activity and higher levels of treatment-resistance showed poorer response to treatment [17], can be found in the current rTMS group. Close inspection of Figure 2 reveals a similar trend in the rTMS group (who had relatively higher levels of treatment-resistance): higher rACC-theta activity in non-remitters compared to remitters. However, this finding is not significant. Summarized, the present findings offer some suggestive evidence towards a reconciliation of the EMBARC and the iSPOT-D findings regarding rACC-theta and remission.

We also found that rACC-theta for healthy controls is situated in between the first-line care (lower rACC-theta) and the second/third-line care (higher rACC-theta). Based on these large sample sizes (n = 518 MDD, n = 336 healthy controls), it is interesting to find this scattered pattern as it further demonstrates that high rACC-theta activity is not a

nonspecific prognostic biomarker for patients with depression [2], with overall more variable effects and lower effect sizes relative to the primary analysis focused on treatment-resistance level, lending more support for an association with treatment-resistance. It is recommended that studies do follow-up EEGs in depressed patients (longitudinal studies) using a within-subject design.

Our finding that rACC-theta differed across TRD levels lends support to the suggestion that rACC-theta is not simply mediated by placebo response (since lower placebo response is expected with higher TRD level). Furthermore, as the EMBARC study determined that rACC-theta activity remained stable between baseline and week 1 for patients given either sertraline or placebo, rACC-theta is most likely not mediated by acute pharmacological effects nor placebo effects [12]. We must therefore question whether the difference in rACC-theta across TRD levels is a preexisting biomarker for resistance to first-line treatments, or whether it is instead associated with prior (pharmacological) treatment exposures. The results however are in line with our earlier iSPOT-D report [17] where the MDD population as a whole had higher rACC-theta compared to the control group – a finding which we can now interpret as a consequence of enrolling an MDD population with a fairly high TRD level, relative to our psychotherapy and AD samples.

It is also possible that the baseline differences in rACC-theta between the patient groups in our study reflect a process of neuroplasticity in response to illness progression and successive treatment failures. rACC-theta has been found to change in an individual over time within a single episode of MDD, meaning rACC-theta may capture some state-related aspect of brain functioning that is associated with subsequent response to medication [17, 18]. An MRI study reported that MDD patients with larger ACC volumes had fewer previous hospitalizations than patients with smaller ACC volumes [45]. Duman et al. [46] further associated the extent of ACC volume reduction with severity of depression, duration of illness, and time length of treatment. The process of neuroplasticity in response to illness progression and successive treatment failures would be an interesting issue for further studies to pursue.

The understanding of the pathophysiology of MDD has shifted to a model based on dysfunctional connectivity between neural networks, rather than abnormalities in the activity of a single neuroanatomical location [47]. In this view, we should consider the activity of the rACC as a node integrated in more complex neural brain networks with different patterns of connectivity and predictive capacities between different levels of response or resistance to treatments. We suggest an enhancement of our current analyses by incorporating connectivity with rACC and its association with treatments with levels of TRD, and also by comparing connectivity pre- and posttreatment.

Of note, the exploratory analyses for the other frequency bands in the ROIs also revealed significant differences between treatment groups in the delta (rACC), beta, and gamma (rACC and frontal) bands. The relatively treatment-resistant ECT patients had significantly higher power in beta and gamma bands in both rACC and frontal regions compared to the other, less treatment-resistant, patient samples. For the delta band, the rTMS patients had significantly higher power in the rACC compared to the psychotherapy and AD patients. In addition, when mediated by the respective frontal band, rTMS patients had significantly higher (delta, beta, gamma) power in the rACC compared to psychotherapy patients. These results could suggest that the effects of treatment-resistance are more specific to the theta band. However, since the literature on the role of these frequency bands in treatment-resistance is currently limited, and the focus of this paper is on rACC-theta, it falls beyond the scope of the present work to examine these findings in comprehensive detail. However, based on our results, we do suggest further exploration of frequency bands other than theta, and whether they may also play an important role in treatment selection or outcome prediction in TRD, or instead, whether they reflect other potential cofounding factors such as medication effects, sleep disturbance, or other factors yet to be determined.

The use of a large naturalistic dataset in this study offers benefits in terms of generalization to real-world practice. However, it also engenders a number of limitations that should be acknowledged. Demographic differences (e.g., premorbid IQ, social and economic status, ethnicity, smoking and drinking status, the history of drug abuse, and other psychiatric and neurological diseases) may affect a person's resistance to treatment, and therefore may have influenced our results. However, such data were not systematically collected for all datasets. Furthermore, in selecting confounds for our model, we were as comprehensive as possible given the available data in this large naturalistic community sample. Future research could consider collecting a wider array of variables to address other potential confounding factors. Regarding ROI, as the present work was an a priori planned follow-up study drawing upon the findings of the earlier 2015 iSPOT-D study [17], in which the effects

of interest were seen specifically in theta activity of the rACC and frontal regions, we here exclusively focused on these regions as a measure to limit type-I error. Exploring other regions may be of interest to future studies. In this study, the datasets were collected with the intention to identify predictors of treatment response; thus, posttreatment EEG was not systematically collected. Future studies could investigate the longitudinal development of the rACC-TRD association through within-subject designs, by comparing pre- and posttreatment EEGs. Since this dataset was collected under naturalistic conditions, standardized therapy regimens were sometimes influenced by clinical judgement. Although the lack of treatment standardization conform RCTs is a limitation to be acknowledged, it also offers the advantage of representing real-world clinical practice. As such, the findings are likewise more likely to translate successfully to real-world settings. While it would have been interesting to analyze the differences between specific ADs in relation to rACC-theta and levels of treatment-resistance, the number of participants for each AD was too small to perform a meaningful statistical analysis (there were a total of 24 different AD combinations, comprising of seven major group classes, for 106 subjects), reflecting the naturalistic research setting. Future research could focus on AD-specific markers. Although it is theoretically possible that MDD patients starting with different ADs have different levels of baseline rACC-theta activity, we consider this less likely due to previously reported results from the EMBARC study showing no differences in rACC-theta between unmedicated (baseline) and medicated (week 1) patients [12].

In conclusion, our study found that rACC-theta differs across treatments for MDD, with higher rACC-theta activity found in the second/third-line care (i.e., rTMS and ECT), and lower activity in the first-line care (i.e., psychotherapy and AD). Furthermore, our study found AD remitters to have higher rACC-theta activity compared with AD non-remitters, which is consistent with the EMBARC findings [12]. Our study also found suggestive evidence that other frequency bands outside of theta could potentially be useful in treatment selection or outcome prediction – an interesting topic for future study. Overall, the findings of the present study provide a new perspective on a known biomarker, by refining upon the older theory that high rACC activity is a nonspecific prognostic biomarker for patients with depression [2]. By factoring in the degree of treatment-resistance during interpretation of the rACC-theta biomarker, its usefulness in treatment selection and prognosis could potentially be improved substantially in future real-world practice.

Statement of Ethics

All subjects provided written informed consent that their data could be used for research purposes. Samples used all underwent open labeled treatment as usual and were treated in various clinics. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

M.A. holds equity/stock in neurocare, serves as consultant to Synaeda and Sama Therapeutics, and is named inventor on several patents related to EEG, ECG, and TMS, but receives no royalties; Research Institute Brainclinics received equipment support from neuroConn and Deymed. All the other authors have no conflict of interests to declare. A.T.S. is chief scientific advisor of PlatoScience Medical, scientific advisor of Alpha Brain Technologies, Founder and CEO of Neurowear Medical, Director of the International Clinical TMS Certification Course (www.tmscourse.eu), and he received equipment support from MagVenture, MagStim, and Deymed.

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Author Contributions

Amourie Prentice and Martijn Arns designed the study. Nikita van der Vinne, Sven Stuiver, and Jeroen Antonius van Waarde contributed to the acquisition of data. Amourie Prentice, Nikita van der Vinne, Hanneke van Dijk, and Martijn Arns conducted the data analysis and interpretation. Amourie Prentice wrote the first draft of the manuscript. Amourie Prentice, Ana Rita Barreiros, Nikita van der Vinne, Sven Stuiver, Hanneke van Dijk, Jeroen Antonius van Waarde, Mayuresh Korgaonkar, Alexander T. Sack, and Martijn Arns revised and approved the final version.

Data Availability Statement

Data from the TMS sample can be obtained from the TDBRAIN open access EEG database at: https://brainclinics.com/resources/ and other data are available from Martijn Arns upon reasonable request.

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