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Frontal and rostral anterior cingulate (rACC) theta EEG in depression: Implications for treatment outcome?

Martijn Arns[a,b,*], Amit Etkin[c,d], Ulrich Hegerl[e], Leanne M. Williams[c,d], Charles DeBattista[d], Donna M. Palmer[f,g,h], Paul B. Fitzgerald[i], Anthony Harris[h,j], Roger deBeuss[k], Evian Gordon[f,g]

[a]*Department of Experimental Psychology, Utrecht University, Utrecht, The Netherlands*
[b]*Research Institute Brainclinics, Nijmegen, The Netherlands*
[c]*Veterans Affairs Palo Alto Healthcare System, and the Sierra Pacific Mental Illness, Research, Education, and Clinical Center (MIRECC), Palo Alto, CA, USA*
[d]*Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA*
[e]*Department of Psychiatry and Psychotherapy, University of Leipzig, Germany*
[f]*Brain Resource Ltd, Sydney, NSW, Australia*
[g]*Brain Resource Ltd, San Francisco, CA, USA*
[h]*Brain Dynamics Center, Westmead Millennium Institute for Medical Research and Sydney Medical School - Westmead, University of Sydney, Sydney, NSW, Australia*
[i]*Monash Alfred Psychiatry Research Centre, Monash University Central Clinical School and the Alfred, Melbourne, VIC, Australia*
[j]*Discipline of Psychiatry, Sydney Medical School, University of Sydney, Sydney, NSW, Australia*
[k]*Department of Psychology, University of North Carolina at Asheville, Asheville, NC, USA*

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Abstract
In major depressive disorder (MDD), elevated theta current density in the rostral anterior cingulate (rACC), as estimated by source localization of scalp-recorded electroencenphalogram (EEG), has been associated with response to antidepressant treatments, whereas elevated frontal theta has been linked to non-response. This study used source localization to attempt to integrate these apparently opposite results and test, whether antidepressant response is associated with elevated rACC theta and non-response with elevated frontal theta and whether theta activity is a differential predictor of response to different types of commonly used

*Correspondence to: Research Institute Brainclinics, Bijleveldsingel 34 6524 AD Nijmegen, The Netherlands. Tel.: +31 24 7503505; fax: +31 24 8901447.
E-mail address: martijn@brainclinics.com (M. Arns).

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antidepressants. In the international Study to Predict Optimized Treatment in Depression (iSPOT-D), a multi-center, international, randomized, prospective practical trial, 1008 MDD participants were randomized to escitalopram, sertraline or venlafaxine-XR. The study also recruited 336 healthy controls. Treatment response and remission were established after eight weeks using the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$). The resting-state EEG was assessed at baseline with eyes closed and source localization (eLORETA) was employed to extract theta from the rACC and frontal cortex. Patients with MDD had elevated theta in both frontal cortex and rACC, with small effect sizes. High frontal and rACC theta were associated with treatment non-response, but not with non-remission, and this effect was most pronounced in a subgroup with previous treatment failures. Low theta in frontal cortex and rACC are found in responders to antidepressant treatments with a small effect size. Future studies should investigate in more detail the role of previous treatment (failure) in the association between theta and treatment outcome.

Introduction

Fifteen years after the initial description of the alpha rhythm in the electroencephalogram (EEG) by Hans Berger, a new rhythm, namely the 'Theta' rhythm, was proposed by Walter and Dovey, as a rhythm of 4–7 cycles per second (Walter and Dovey, 1944). In this same first report on Theta they already described that this '*…6 c/s. is associated with involvement of sub-cortical structures…*' and this theta rhythm can also occur in the state just preceding sleep when the subject is on the verge of drowsiness (1944). To date these two types of theta are still the most well investigated oscillations in neuroscience, namely phasic frontal midline theta (FM), suggested to originate from the anterior cingulate (Asada et al., 1999; Ishii et al., 1999) and tonic drowsiness theta, found more widespread in cortical areas (for review see Arns and Kenemans (2012)).

Only few studies have reported differences in theta between patients with major depressive disorder (MDD) and healthy controls, and most commonly increased theta has been found in patients (for review see Olbrich and Arns (2013)). The few studies that have further investigated theta in MDD using source-localized or tomographic theta have found this increased theta to be localized to the Anterior Cingulate Cortex (ACC) (Jaworska et al., 2012; Korb et al., 2008), though decreased ACC activity in MDD has also been reported (Mientus et al., 2002) and other studies found no differences between MDD and controls (Lubar et al., 2003; Pizzagalli et al., 2002).

The majority of the literature on theta in MDD has focused on the association with antidepressant treatment outcome (see Table 1 for an overview of these studies). Most studies reported that increased scalp frontal theta was associated with non-response to antidepressant treatments (Arns et al., 2012; Iosifescu et al., 2009; Knott et al., 1996). On the other hand (Cook et al., 1999) found no differences and (Spronk et al., 2011) reported that increased theta at the frontal midline was associated with a favorable treatment outcome. Note that (Arns et al., 2012; Iosifescu et al., 2009; Knott et al., 1996) all reported on widespread frontal (not midline) theta, most likely a reflection of 'drowsiness' theta (Arns and Kenemans, 2012), whereas Spronk et al. (2011) found the opposite pattern for frontal midline theta, suggesting these two types of theta could have different implications. In line with the results from Spronk and colleagues, patients with increased ACC theta, as estimated by distributed source localization techniques, have consistently been found to respond better to antidepressant treatments (Korb et al., 2009; Mulert et al., 2007a; Narushima et al., 2010; Pizzagalli et al., 2001), which is in line with findings across imaging modalities demonstrating high rACC activity (a reflection of high rACC metabolic activity) associated with treatment response (for review and meta-analysis also see Pizzagalli (2011)). On the other hand several studies with a reversed finding have been published demonstrating *low* subgenual ACC or rACC activity associated with response (Brody et al., 1999; Dougherty et al., 2003; Konarski et al., 2009; McCormick et al., 2007; Mottaghy et al., 2002). Conversely, deep-brain stimulation (DBS) targeting the subgenual ACC in treatment resistant MDD patients has also been shown to result in clinical benefits (Mayberg et al., 2005), positing this area, most specifically the subgenual and rostral ACC, as a critical node in the depression network.

Therefore, the aim of this study was to further investigate the at face-value conflicting findings relating to frontal theta-EEG power and rACC theta, by using source localization to estimate rACC theta (phasic theta) and separately frontal theta (tonic theta), and investigate their relationship to antidepressant treatment outcome. We hypothesize that phasic theta (rACC) is associated with an improved treatment outcome, whereas tonic theta (frontal) is associated with non-response. In addition, in light of the large sample size, a further primary aim of this study was to test for differential treatment outcome to the three study medications (two Selective Serotonin Reuptake Inhibitors (SSRI's) escitalopram and sertraline and one Serotonin-Norepinephrine Reuptake Inhibitor (SNRI) venlafaxine-XR).

In addition to theta activity, many studies have also investigated the role of alpha EEG measures and the association to antidepressant treatment outcome, e.g. posterior alpha and alpha asymmetry (for review see Olbrich and Arns (2013)). Results for these alpha EEG metrics on this sample are reported in a separate manuscript (Arns et al., in preparation).

Experimental procedures

Design

This study was an international multi-center, randomized, prospective open-label trial (Phase-IV clinical trial) in which MDD participants were

Table 1 An overview of all findings related to antidepressant treatment outcome and theta EEG power in chronological order.

Reference	Treatment	*N*	Band (Hz)	Favorable treatment response associated with baseline		
				Increased theta (site)	Decreased theta (site)	Analyses
Knott et al. (1996)	Imipramine	40	4.5-8.0		*X* (all sites)	PSA
Knott et al. (2000)	Paroxetine	70[a]	3.5-7.5	*X* (Fpz, Fp1, Fp2, Fz, F3, F4)		PSA
Pizzagalli et al. (2001)	Nortriptyline	18	6.5-8.0	*X* (ACC)		LORETA
Mulert et al. (2007a)	Citalopram and reboxetine[b]	20	6.5-8.0	*X* (ACC)		LORETA
Korb et al. (2009)	Fluoxetine, venlafaxine and placebo	72	4.0-7.0	*X* (ACC)		LORETA
Iosifescu et al. (2009)	SSRI or venlafaxine	82	4.0-8.0		*X*[c]	PSA
Spronk et al. (2011)	Diverse antidepressants	25	4.0-7.5	*X* (Fz)		PSA
Arns et al. (2012)	rTMS & Psychotherapy	90	4.0-8.0		*X* (F7, F3, F4, F8, FC3, FCz, FC4, T3, Cz, C4, T4, CP4)	PSA
Rentzsch et al. (2013)	Diverse antidepressants	31	4.5-7.5	*X* (ACC)[d]		sLORETA

Notes:
PSA=Power Spectral Analysis.
[a]This sample consisted of males only.
[b]Subgroup analysis revealed the effect was only significant for reboxetine and not for citalopram.
[c]Iosifescu used a limited EEG design with only 4 EEG channels: F7-Fpz; F8-Fpz; A1-Fpz and A2-Fpz, and used relative theta.
[d]Main finding was rACC Delta activity in voxel-by-voxel analysis, theta only came out in a post-hoc analysis.

randomized to escitalopram, sertraline or venlafaxine-XR in a 1:1:1 ratio. The study protocol details including a power calculation have been published by (Williams et al., 2011). This design was deliberately chosen to mimic real-world practice—hence no placebo control was included—with the aim of improving the translatability of the findings and ecological validity.

Participants and treatment

This study included 1008 MDD patients and 336 healthy controls and this sample is independent form the sample reported by Spronk et al. (2011). The MDD sample is the first half of the total 2016 MDD participants that will be recruited into iSPOT-D. A complete description of the study assessments, inclusion/exclusion criteria, diagnostic procedures and treatment is available in Williams et al. (2011) and also see Saveanu et al. (2014) for complete sample characteristics. In summary, the primary diagnosis of nonpsychotic MDD was confirmed at the baseline visit (before randomization) using the Mini-International Neuropsychiatric Interview (MINI-Plus) (Sheehan et al., 1998), according to DSM-IV criteria, and a score ≥ 16 on the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$). MDD participants were also assessed on the 16-item Quick Inventory of Depressive Symptomatology - Self-Report ($QIDS\text{-}SR_{16}$). All MDD participants were either antidepressant medication-naive or, if previously prescribed an antidepressant medication, had undergone a washout period of at least five half-lives before the baseline visit clinical and EEG assessments. After the baseline visit, MDD participants were randomized to one of the three antidepressant medications. After eight weeks of treatment, participants were tested again using the $HRSD_{17}$, $QIDS\text{-}SR_{16}$ and an EEG assessment (Figure 1).

Ethics statement

This study was approved by the institutional review boards at all of the participating sites (Netherlands: Independent Review Board Nijmegen; US: Stanford Institutional IRB University, University of Missouri-St. Louis Institutional IRB, Western Institutional Review Board, Copernicus Group IRB; Australia: Sydney West Area Health Service Human Research Ethics, The Alfred Ethics Committee, Swinburne University Human Research Ethics Committee, Flinders Clinical Research Ethics, Human Research Ethics Committee (Tasmania) Network and Bellberry Human Research Ethics Committee; New Zealand: Northern X Regional Ethics Committee and South-Africa: Pharma-Ethics Independent Research Ethics Committee) and was conducted according to the principles of the Declaration of Helsinki 2008. After study procedures were fully explained in accordance with the ethical guidelines of the institutional review boards, participants provided written informed consent. This trial was registered with ClinicalTrials.gov. Registration number: NCT00693849; URL: http://clinicaltrials.gov/ct2/show/NCT00693849.

Pre-treatment assessments

EEG recordings were performed using a standardized methodology and platform (Brain Resource Ltd., Australia). Details of this procedure have been published elsewhere (Arns et al., 2008; Williams et al., 2011) and details of the reliability and across-site consistency of this EEG procedure have been published (Paul et al., 2007; Williams et al., 2005). In summary, participants were seated in a sound and light attenuated room that was controlled at an ambient temperature of 22 °C. EEG data were acquired from 26 channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz,

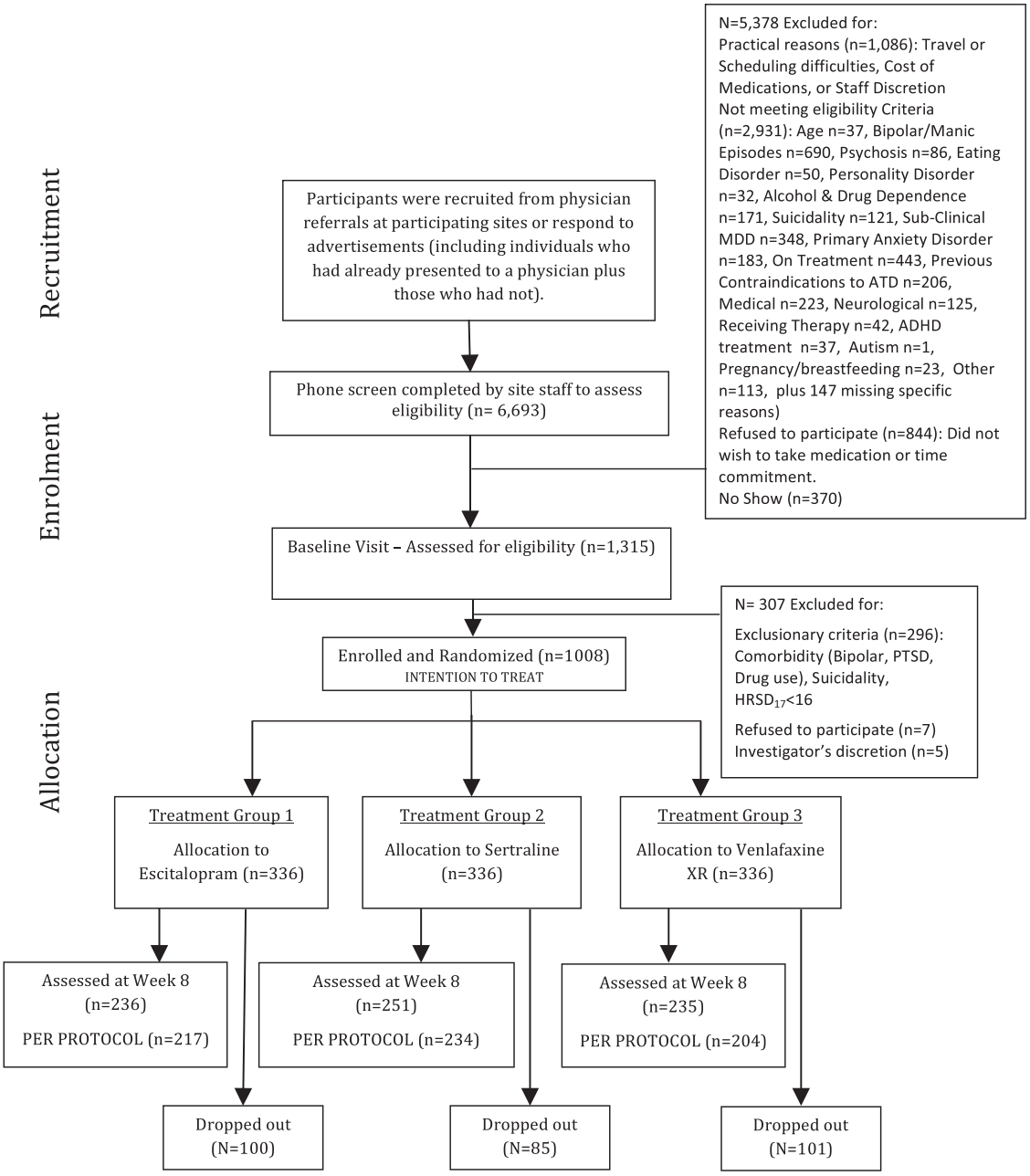

Figure 1 Consort diagram of the iSPOT-D study. Abbreviations: ADHD, attention deficit hyperactivity disorder; ADT, antidepressant treatment; $HRSD_{17}$, 17-item Hamilton Rating Scale for Depression; MDD, major depressive disorder; PTSD, post-traumatic stress disorder; XR, extended release.

C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz and O2 (Quikcap; NuAmps; 10–20 electrode extended international system). EEG data were collected for two minutes with eyes open (EO) (with the participant asked to fixate on a red dot on the screen) and two minutes with eyes closed (EC) (with the participant instructed to remain relaxed for the duration of the recording). The full two minutes of EEG were recorded and the operator did not intervene when drowsiness patterns were observed in the EEG. Data were referenced to averaged mastoids with a ground at FPz. 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. Skin resistance was $<5\ k\Omega$ for all electrodes. A continuous acquisition system was employed and EEG data were electrooculogram (EOG)-corrected offline. The sampling rate of all channels was 500 Hz. A low pass filter with an attenuation of 40 dB per decade above 100 Hz was employed prior to digitization.

Analysis

EEG analysis

EEG data analysis and validation have been described in more detail elsewhere (Arns et al., in preparation). In brief, 1) A high pass filter of .3 Hz, a low pass filter of 100 Hz and notch filters of 50 or 60 Hz (depending on the country in which the data were recorded) were applied; 2) data were EOG corrected using a regression-based

technique similar to (Gratton et al., 1983), 3) data were segmented in 4 s epochs (50% overlapping), 4) and individual epochs per channel were marked as artefact based on the following criteria: a) EMG detection, b) pulse and baseline shift detection, c) crosstalk detection, d) high kurtosis, e) extreme power level detection, f) residual eye blink detection and g) extreme voltage swing detection. Detailed methodology information for these 7 artefact detection criteria can be found in Arns et al. (in preparation) and validating this automated EEG processing pipeline to a manual EEG processing pipeline resulted in high agreements (r^2=97–98%: see Arns et al. (in preparation) for more details).

For eLORETA analysis, rejected channels were replaced using a spherical spline interpolation (only when at least 3 surrounding channels were present, otherwise the data were rejected).

EEG eLORETA analyses

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 distribution of current density. The method of LORETA is described in detail in (Pascual-Marqui, 2007). eLORETA is an improvement over the original LORETA version (Pascual-Marqui et al., 1994) and the standardized version sLORETA (Pascual-Marqui, 2002).

EEG current source density (Theta (6.5–8 Hz)) was extracted from the rostral anterior cingulate (rACC; using the voxels reported by Pizzagalli and colleagues (Pizzagalli et al., 2001)) and frontal cortex (FR) (also see Figure 2 for visualization of ROIs) during resting state conditions with eyes closed (EC). These ROIs did not overlap. In addition EEG power in theta was extracted from Fz and Oz in order to compare the results from source space to electrode space (the analyses using Fz and Oz are only intended to further evaluate the eLORETA analysis and allow comparison of results to studies conducted in electrode space, and are thus secondary analyses).

Statistics

Remission was defined as a score $\leq$7 on the $HRSD_{17}$ at 8 weeks, and response was defined as a $>$50% decrease in $HRSD_{17}$ score from baseline to week 8. In this analysis, we primarily assessed remitters vs. non-remitters and responders vs. non-responders. Normal distribution of EEG measures was inspected and theta measures were log transformed before statistical analysis. Differences in age, gender, education and baseline depressive severity were tested using One-Way ANOVA or non-parametric tests (gender). In case of group differences in one of these measures, these variables were added as a covariate.

For comparison of MDD vs. healthy controls as well as investigating treatment prediction a repeated measures ANOVA was conducted with within-subject factors site (Frontal and rACC), between-subject factors group (MDD vs. controls or response vs. non-response or remission vs non-remission), treatment arm (For response and remission analyses only: ESC, SER and VEN) and gender, [and age (or other factors differing between groups, as identified from preliminary analyses outlined above) as covariates]. When significant interactions were found, univariate analyses were performed.

A partial correlation (correcting for age) was run between the percentage improvement on the $HRSD_{17}$ between baseline and week 8, $HRSD_{17}$ at intake and $HRSD_{17}$ at week 8 and frontal and rACC theta.

All statistics for treatment prediction were performed on data from MDD participants who completed 8 weeks of treatment per protocol: participants who were dosed with their randomized medication for a minimum of 6 weeks and who returned for their

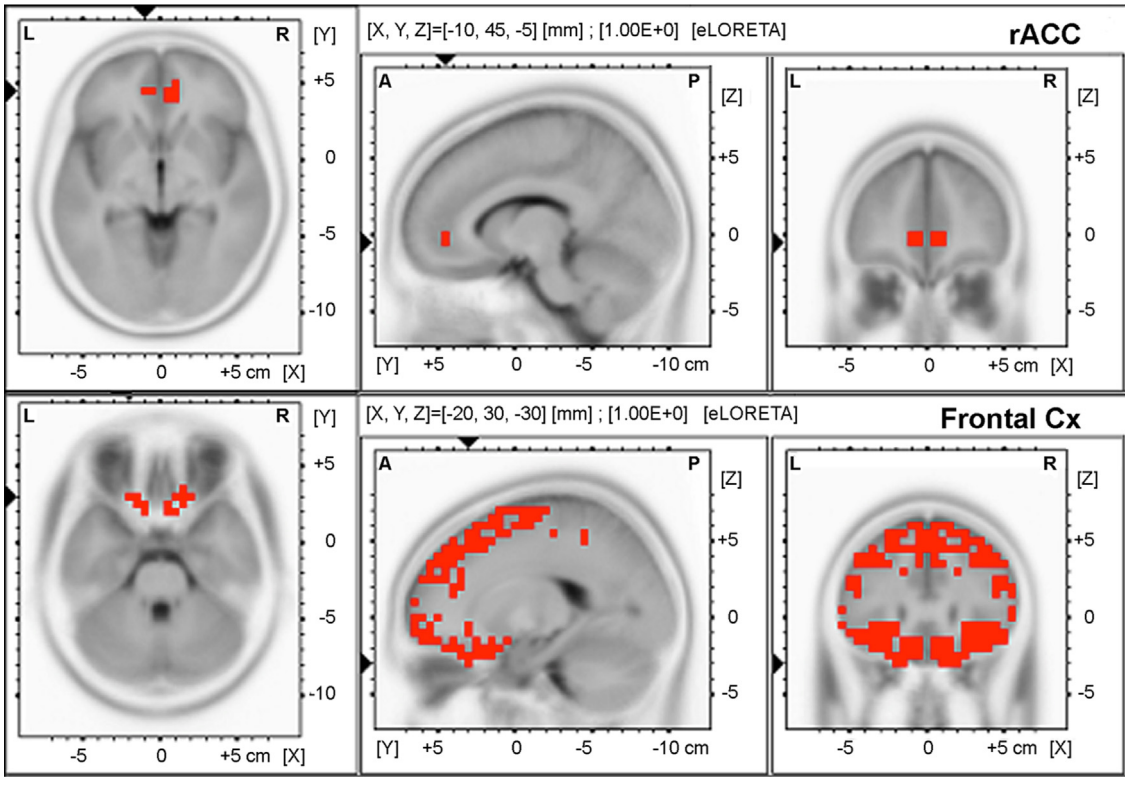

Figure 2 The 2 regions of interest (ROI) used in the present study. The rACC and frontal cortex regions used to extract resting state theta power (6.5–8 Hz) using eLORETA. Abbreviations: eLORETA, exact low-resolution brain electromagnetic tomography analysis; rACC, rostral anterior cingulate.

week 8 visit and were still receiving their randomized medication at this visit ('per protocol' grouping, also see the Consort diagram in Figure 1). Significance level was set at $p \leq .05$ and effect sizes (ES) of main effects are reported in Cohen's *d*.

Results

Of the 1008 MDD participants and 336 healthy controls enrolled, the final MDD sample for the treatment prediction analyses consisted of 667 MDD participants (per protocol grouping, also see Figure 1) with overall remission and response rates being 46% and 64%, respectively and 336 controls. Medications group sizes for per protocol completers, were as follows: escitalopram ($N=217$), sertraline ($N=234$) and venlafaxine-XR ($N=204$). The remaining MDD participants dropped out of the study or had protocol violations. Table 2 shows the demographic information and response and remission rates for these groups. There were no differences between the three treatment groups regarding age, gender, baseline MDD, anxiety severity ($HRSD_{17}$), remission or response rates, or number of rejected EEG epochs. For the total sample of 1008 MDD participants and 336 controls, more epochs were rejected due to artefacts for the MDD group during EC ($p<.001$; $Z=-4.314$: 1.7 (3.33) vs. 2.44 (3.90) epochs). MDD participants thus had 2% more rejected epochs compared to controls. In total, there were less than 5.3% rejected EEG epochs.

MDD participants vs. controls

There were no differences between the MDD participants and controls regarding age ($p=.289$, $F=1.126$; DF=1343) or gender ($p=.949$, $Z=-.064$), but there was a difference in education ($p=.021$, $F=5.360$, DF=1343) with controls having a higher education (14.9 (SD=2.5) vs. 14.5 (SD=2.8) years of education).

eLORETA analysis: MDD participants vs. controls

Repeated-measures ANOVA, using education as a covariate, yielded the following results for Frontal and rACC theta: an effect of site ($p<.001$; $F=61, 348$; DF=1, 1234), a Site X gender ($p=.050$; $F=3.857$; DF=1, 1234) and a main effect of group ($p=.004$; $F=8.437$; DF=1, 1234), but no group X Site interaction ($p=.100$). MDD patients thus had increased theta in both frontal cortex (ES=.13) and rACC (ES=.25).

Correlations: MDD severity and EEG

Partial correlations between $HRSD_{17}$ MDD severity and the above metrics, corrected for education, were significant for rACC Theta ($p<.001$; $r=.102$; DF=1236), and for frontal theta ($p=.031$; $r=.061$; DF=1236), for the whole group only, but no significant correlations were found within the MDD and control group separately suggesting this correlation was mainly driven by the group difference.

Response vs. non-response ($HRSD_{17}$)

For the entire group, there were significant differences between responders and non-responders on demographics, in which responders were younger ($p=.002$; $F=9$, 274, DF=654), but there were no differences for baseline $HRSD_{17}$ MDD severity and anxiety severity, education, gender or rejected epochs.

A repeated measures ANOVA with covariates age yielded a within subject effect of site ($p<.001$, $F=23.390$; DF=1, 598), Site X age ($p=.001$; $F=12.056$; DF=1, 598) and a between subject effect of age ($p<.001$; $F=14.110$; DF=1, 598) and response ($p=.035$; $F=4.448$; DF=1, 598), where responders had less theta in both the rACC (ES=−.14) and frontal cortex (ES=−.17) compared to non-responders and no Site X response interaction ($p=.507$). Including research-center as a covariate did not change these results.

A post-hoc eLORETA voxel-by-voxel, between group comparison yielded a non-significant effect for responders compared to non-responders ($p>.10$), see Figure 3A. Repeating this eLORETA voxel-by-voxel analysis per drug-class resulted only in a significant effect for venlafaxine-XR ($p<.05$) where responders had low theta activity, mainly involving BA 6 (Middle and Medial Frontal Gyrus), BA 24 (Cingulate Gyrus) and BA 31 (Paracentral Lobule), also see Figure 3B. For sertraline and escitalopram there were no

Table 2 Demographic features of MDD patients and controls and treatment outcomes for patients who completed treatment per protocol. The demographics for the MDD vs. controls comparison can be found on the left, whereas the demographics for the treatment prediction analyses are summarized on the right.

Features	Full sample		Per protocol sample		
	MDD	Controls	Escitalopram	Sertraline	Venlafaxine-XR
Number	1008	336	217	234	204
Females	571	191	119	139	120
Average age (years)	37.84	36.99	38.85	38.34	38.46
$HRSD_{17}$ baseline	21.88	1.15	21.75	21.95	21.50
$HRSD_{17}$ week 8	9.67	1.06	9.29	9.41	9.71
$HRSD_{17}$ anxiety baseline	6.16	.57	6.18	6.27	6.14
	%	%	%	%	%
% Female	57	57	55	59	59
% Remission ($HRSD_{17}$)	46		48	47	44
% Response ($HRSD_{17}$)	63		60	67	63

Abbreviations: $HRSD_{17}$, 17-item Hamilton Rating Scale for Depression; MDD, major depressive disorder; XR, extended release.

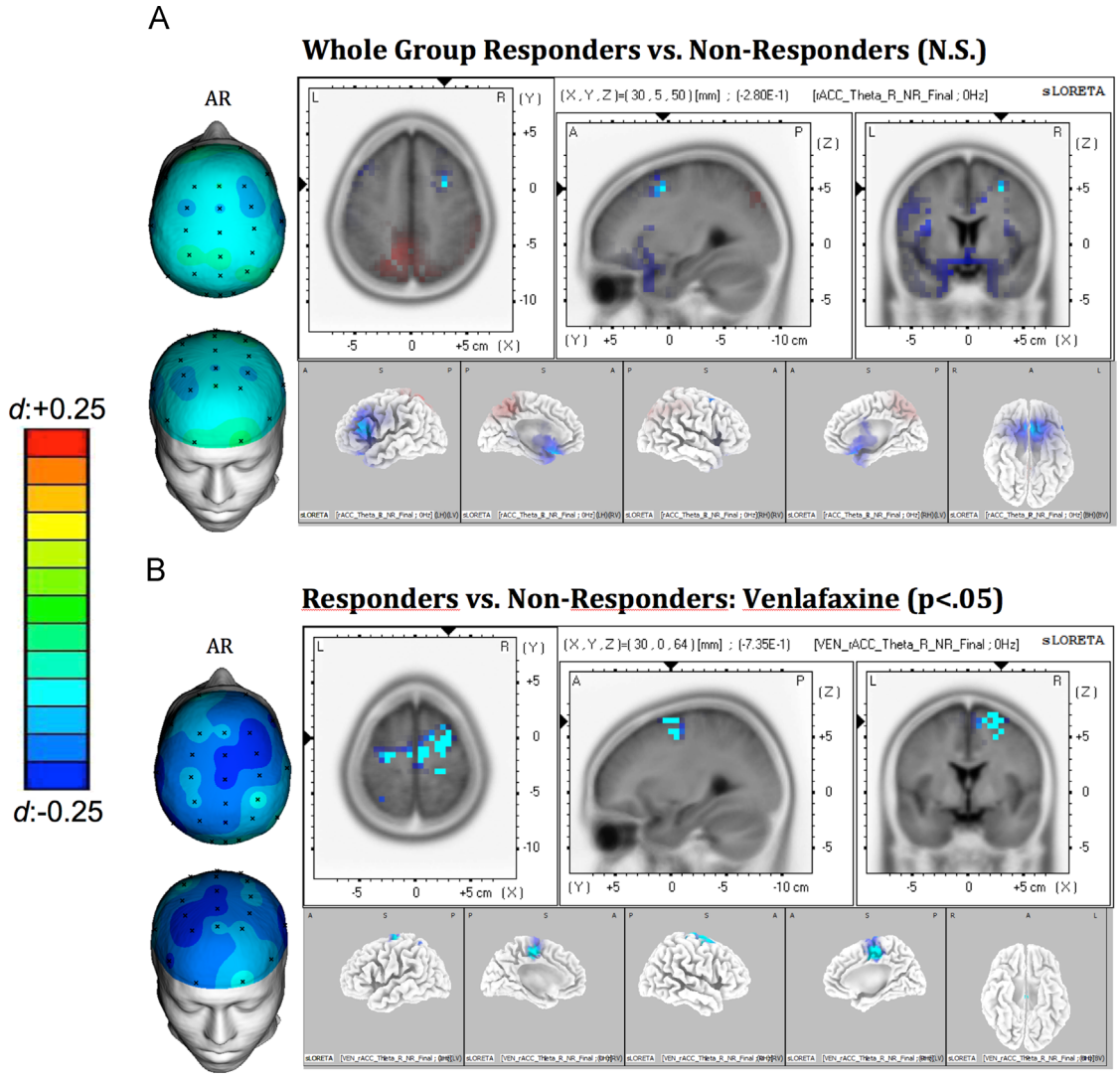

Figure 3 Post-hoc eLORETA voxel-by-voxel analysis visualizing the differences between MDD non-responders and responders in Theta CSD (eLORETA, right) and in topographical plots (in Cohen's *d* ($d = \pm .25$, left), based on an average reference (AR)) for 3A: the whole group and for 3B: venlafaxine-XR only. In line with the statistics for the whole group based on ROIs, indeed responders exhibit decreased rACC theta, but the same is also found for the left frontal cortex. Middle frontal gyrus, Inferior Frontal Gyrus and Rectal Gyrus were the structures that deviated most clearly. Note that the voxel-by-voxel test for the whole group was not significant. Post-hoc analyses for the SNRI venlafaxine-XR demonstrated a significantly decreased theta mainly involving BA 6 (Middle and Medial Frontal Gyrus), BA 24 (Cingulate Gyrus) and BA 31 (Paracentral Lobule). Also note the similarities for cortical sites between eLORETA and the topographical headplots based on an average montage. Note that the scale on the left only applies to the average reference (AR) headmaps and not to the LORETA images on the right. Blue indicates decreased theta for responders. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

differences between responders and non-responders, also not when combined into an SSRI group.

Remission vs. non-remission ($HRSD_{17}$)

For the whole group there were significant differences between remitters and non-remitters where remitters were younger ($p = .005$; $F = ,7.914$ DF = 666), had lower baseline MDD severity ($HRSD_{17}$: $p < .001$; $F = 28.301$; DF = 666) and anxiety severity ($HRSD_{17}$: $p < .001$; $F = 16.337$; DF = 666) but no differences in gender and education.

A repeated measures ANOVA with covariates age, baseline $HRSD_{17}$ MDD and anxiety severity yielded a within subject effect of site ($p = .025$, $F = 5.041$; DF = 1, 596), Site X age ($p < .001$; $F = 12.348$; DF = 1, 596) and a between subject effect of age ($p < .001$; $F = 13.062$; DF = 1, 596), a trend for treatment arm (p = .055) and no effect of remission ($p = .521$).

Theta and treatment response

Partial correlations within the per protocol MDD group correcting for age yielded no correlations between $HRSD_{17}$ baseline severity and rACC theta ($p = .174$; $r = .055$; DF = 608) and

frontal theta ($p=.158$; $r=.057$; DF=608). However, significant correlations were found between $HRSD_{17}$ at week 8 and rACC theta ($p=.021$; $r=.093$; DF=608) and frontal theta ($p=.014$; $r=.100$; DF=608) as well as between percentage improvement on $HRSD_{17}$ and rACC theta ($p=.049$; $r=.080$; DF=608) and frontal theta ($p=.026$; $r=.090$; DF=608).

When dividing the MDD sample into two groups based on baseline theta (high vs. low theta) in rACC or Frontal yielded no differences between groups on baseline anxiety severity, number of MDD episodes and duration of current MDD episode.

Post-hoc verifications

Given we were unable to replicate the often reported association between elevated rACC theta and treatment response, we also performed several post-hoc verifications to rule out methodological issues. None of these approaches resulted in a change from low rACC theta to elevated rACC theta in responders:

- All EEG data have been processed in 2 ways for verification purposes. 1) The reported data in this manuscript are based on an automated de-artifacting method (for details and validation see Arns et al. (in preparation)) and eLORETA. 2) In addition the same data have also been processed with manual de-artifacting and the older version of LORETA in Brain Vision Analyzer (Brainproducts GMBH) by MA.
- Repeating the analyses in a subgroup of severe MDD patients with baseline $HRSD_{17} \geq 24$ to partly restrict the analysis to an MDD subgroup less susceptible to placebo effects (Kirsch et al., 2008).
- Repeating analyses in males vs. females or controlling for comorbidities/subtypes such as GAD, panic disorder, melancholia etc.
- When dividing the group into patients with ($N=174$) and without ($n=437$) previous treatment failures (as a means to separate into a more and less treatment resistant subgroup) and repeating the main analysis, the trends are the same for both groups, albeit for patients with no previous treatment failures the main effect for response was not significant ($p=.216$; $F=1.538$; DF=1,424) with a small ES for frontal theta (ES=.10) and rACC (ES=.09) and for patients with previous treatment failures there was a trend effect for response ($p=.061$; F=3.563; DF=1,161) with substantially larger ES for frontal (ES=.35) and rACC (ES=.27) suggesting that treatment resistance could be an important factor in the association between theta and treatment response.

Discussion

We found that MDD patients compared to controls have increased theta in frontal cortex and rACC, and this increase was strongest for the rACC (ES=.25) as compared to the frontal cortex (ES=.13). This finding of increased rACC theta in MDD patients is in line with earlier findings (Jaworska et al., 2012; Korb et al., 2008). Given theta has good test–retest reliability (76–87%: (Williams et al., 2005)), has an estimated heritability of 89% (van Beijsterveldt et al., 1996) makes this measure a potential endophenotype for MDD (Hasler and Northoff, 2011) albeit its genetic underpinnings are largely unknown. Future studies could perform genetic analyses in MDD subgroups with high vs. low theta to investigate its value as an endophenotype further. Given the small ES and the fact that this measure did not correlate with MDD severity within the MDD population makes this measure unlikely to be of diagnostic value.

Regarding treatment response we found that low frontal and low rACC theta were associated with response, where the frontal finding is in line with previous studies (Arns et al., 2012; Iosifescu et al., 2009; Knott et al., 1996), albeit with a small ES ($d=.14$–$.17$) and this was not found for remission. Our analysis did not result in a response X Site interaction and thus no evidence for our initial hypothesis of a differential association of tonic vs. phasic theta to treatment response was found. We were thus unable to replicate previous reports of high frontal theta (Spronk et al., 2011) and high rACC theta to be associated with response (Korb et al., 2009; Mulert et al., 2007a; Narushima et al., 2010; Pizzagalli et al., 2001). In this study we only used three types of medication (escitalopram, sertraline or venlafaxine-XR), and these results might thus be specific to these types of medications. Previous studies that did find high rACC theta was associated with treatment response have used tricyclic antidepressants (Pizzagalli et al., 2001), rTMS (Narushima et al., 2010), or other types of SSRI/SNRI's such as citalopram and reboxetine (Mulert et al., 2007b) or fluoxetine (Korb et al., 2009). Our results are in agreement with several PET and SPECT imaging studies that reported *low* subgenual ACC activity associated with response (Brody et al., 1999; Dougherty et al., 2003; Konarski et al., 2009; McCormick et al., 2007; Mottaghy et al., 2002).

In our post-hoc analysis we found indications that the association between high rACC theta and treatment response was mostly driven by a higher degree of treatment resistance (previous treatment failures). This is in line with the observation by Mayberg in her ground-breaking deep-brain stimulation (DBS) study for treatment-resistant MDD, where she found that her patients at baseline – pre-DBS – had high subgenual activity which decreased with chronic DBS stimulation in responders (Mayberg et al., 2005). In addition, some of the studies where the opposite was found (high rACC theta associated with non-response) as described by Pizzagalli (Pizzagalli 2011), used ECT (McCormick et al., 2007), anterior cingulotomy (Dougherty et al., 2003) or rTMS (Mottaghy et al., 2002), all treatments aimed at patients with high levels of treatment resistance. In addition, Hunter et al. (2013) also described an inverse association between rACC theta and treatment outcome for treatment naïve vs. treatment-experienced patients, where in treatment-experienced patients low rACC theta was associated with a better response to treatment. Therefore, prior exposure to, or failure to respond to antidepressant treatment could influence the association between rACC theta and treatment outcome, which needs to be further investigated in future studies.

Interestingly, exploratory analysis using eLORETA revealed a specific effect for the SNRI venlafaxine-XR of low theta in right frontal and medial-frontal areas in responders (also see Figure 3B: BA 6: Middle and Medial Frontal Gyrus, BA 24: Cingulate Gyrus and BA 31: Paracentral Lobule), suggesting the frontal theta effect reported above could be mainly driven by

the SNRI venlafaxine-XR. Future studies should replicate and extend this finding further.

Korb et al. (2009) previously demonstrated that the rACC-treatment response association is specific to antidepressant treatment response but does not generalize to placebo response. Since the current study has a relatively high remission/response rates (46/63%) and was not placebo controlled it cannot be ruled out that these effects are due to a substantial placebo response thereby masking the real effects of these measures. In order to partly control for this this we conducted a seperate anlayses in a subgroup with severe MDD complaints as characterized by a $HRSD_{17}$ score ≥ 24, since in a previous meta-analysis it was found that placebo response is lower in patients with severe MDD complaints at baseline (Kirsch et al., 2008). However, this did not change the results either. Furthermore, differences in electrode montages and numbers of electrodes could play a role. Korb et al. (2008) found that specifically Fpz was important in localizing ACC activity, and this site was included in the studies by Pizzagalli et al. (2001, 2002) and Korb et al. (2009), but not in this study. In addition, future studies might consider to include AFz as a recording site as well, rather then a ground, since this site is important in adequately characterizing frontal midline theta (D. Brandeis, personal communication and see Maurer et al. (2014)).

As demonstrated by Hunter et al. (2013) rACC theta may represent a 'state' rather than a 'trait' marker of antidepressant responsiveness, and they suggest augmentation of rACC theta might improve antidepressant treatment outcome by for example cognitive-behavioral therapy or specific tasks activating the rACC, which was recently confirmed by Li et al. (2014) who demonstrated that adding a task that activates rACC activity before rTMS sessions improved treatment outcome compared to rTMS-monotherapy, also in congruence with the clinical results reported by Arns et al. (2012) who demonstrated that combining rTMS with simultanous psychotherapy (augmenting rACC activity) resulted in response rates of 78% which is more than double the response rate of most rTMS studies. Furthermore, Li et al. (2014) also demonstrated that baseline frontal theta predicted treatment outcome better when it was quantified after an ACC activating task, relative to resting state theta, suggesting that potentially the resting state is not the best state to quantify rACC theta for treatment prediction, and future studies should consider using activation tasks.

Summarizing, in this study we found that patients with MDD have high frontal and rACC theta and responders to antidepressant medication have low frontal and low rACC theta, whereas no effects were found for remission. The obtained effect sizes were small, suggesting that it is unlikely that these measures alone will be of diagnostic or prognostic utility in practice, and future studies should more systematically investigate the role of prior treatment (failure) on the association between rACC theta and treatment outcome. This effect was probably driven by the SNRI venlafaxine-XR, which requires replication. The effects observed are likely too small to be of clinical value in guiding treatment outcome.

Author contributions

MA initiated the proposal for this manuscript which was approved by the iSPOT-D publication committee, conducted the statistical analyses and the independent EEG processing validation, and initiated the manuscript. DMP and AE were involved in data processing and data analysis, and development of the manuscript. MA, AE, CD, PF, AH and RB were also principal investigators of the iSPOT-D study and AE, UH, LW, CD. DMP, PBF, AH, RD and EG read and contributed to the manuscript.

Conflicts of interest

MA reports research grants and options from Brain Resource Ltd. (Sydney, Australia), acted as a paid consultant for the United BioSource Corporation (UBC), Bracket and Vivatech and is a co-inventor on 3 patent applications (A61B5/0402; US2007/0299323, A1; WO2010/139361 A1) related to EEG, neuromodulation and psychophysiology, but does not own these nor receives any proceeds related to these patents. AE reports research funds from Brain Resource Ltd. related to this study; UH was an advisory board member for Lilly, Lundbeck, Takeda Pharmaceuticals, Servier and Otsuka Pharma; a consultant for Nycomed; and a speaker for Bristol-Myers Squibb, Medice Arzneimittel, Novartis and Roche Pharma in the last 3 years; CD has received support from Brain Resource, CNS response, St. Jude, Astra Zeneca, Takeda, Assurex and is a consultant for Pfizer and Genentech; DMP has received income and stock options with the role of science and data processing manager as an employee with Brain Resource Ltd. AH has received consultancy fees from Janssen Australia and Lundbeck Australia. He has received payments for educational sessions run for Janssen Australia and the Lundbeck Institute. He has recently been an investigator on industry-sponsored trials by Hoffman-La Roche, Janssen-Cilag Australia and Brain Resource Ltd. RD has received research grants from Brain Resource Ltd.; EG is founder and receives income as Chief Executive Officer and Chairman for Brain Resource Ltd. He has stock options in Brain Resource Ltd. PBF is supported by a NHMRC Practitioner Fellowship (606907). PBF has received equipment for research from MagVenture A/S, Medtronic Ltd., Cervel Neurotech and Brainsway Ltd. and funding for research from Cervel Neurotech.

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