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EEG alpha asymmetry as a gender-specific predictor of outcome to acute treatment with different antidepressant medications in the randomized iSPOT-D study

Martijn Arns^{a,b,*}, Gerard Bruder^c, Ulrich Hegerl^d, Chris Spooner^{e,f}, Donna M. Palmer^{e,f,g}, Amit Etkin^{h,i}, Kamran Fallahpour^{c,j}, Justine M Gatt^{g,k,l}, Laurence Hirshberg^m, Evian Gordon^{e,f}

^a Dept. of Experimental Psychology, Utrecht University, Utrecht, The Netherlands

^b Research Institute Brainclinics, Nijmegen, The Netherlands

^c Department of Psychiatry, Columbia University, New York, NY, USA

^d Dept. of Psychiatry and Psychotherapy, University of Leipzig, Germany

^e Brain Resource Ltd, Sydney, NSW, Australia

^f Brain Resource Ltd, San Francisco, CA, USA

^g Brain Dynamics Center, Sydney Medical School, The University of Sydney, Sydney, NSW and Westmead Millenium Institute, Westmead, NSW, Australia

^h Veterans Affairs Palo Alto Healthcare System, and the Sierra Pacific Mental Illness, Research, Education, and Clinical Center (MIRECC), Palo Alto, CA, USA

ⁱ Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA

^j Brain Resource Center, New York, USA

^k Neuroscience Research Australia, Randwick, NSW, Australia

^l School of Psychology, University of New South Wales, Sydney, NSW, Australia

^m Alpert Medical School, Brown University, The Neuro Development Center, Inc, Providence, RI, USA

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HIGHLIGHTS

- Patients with major depressive disorder do not differ from controls on frontal alpha asymmetry, occipital and frontal alpha.
- Tomographic differences in alpha between patients with major depressive disorder and controls are different for males and females.
- Right dominant frontal alpha asymmetry is associated with treatment response and remission to escitalopram and sertraline in females but not in males.

ABSTRACT

Objective: To determine whether EEG occipital alpha and frontal alpha asymmetry (FAA) distinguishes outpatients with major depression (MDD) from controls, predicts antidepressant treatment outcome, and to explore the role of gender.

Methods: In the international Study to Predict Optimized Treatment in Depression (iSPOT-D), a multi-center, randomized, prospective open-label trial, 1008 MDD participants were randomized to escitalopram, sertraline or venlafaxine-extended release. The study also recruited 336 healthy controls. Treatment response was established after eight weeks and resting EEG was measured at baseline (two minutes eyes open and eyes closed).

Results: No differences in EEG alpha for occipital and frontal cortex, or for FAA, were found in MDD participants compared to controls. Alpha in the occipital and frontal cortex was not associated with treatment outcome. However, a gender and drug-class interaction effect was found for FAA. Relatively greater right frontal alpha (less cortical activity) in women only was associated with a favorable response to the Selective Serotonin Reuptake Inhibitors escitalopram and sertraline. No such effect was found for venlafaxine-extended release.

* Corresponding author at: 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).

Conclusions: FAA does not differentiate between MDD and controls, but is associated with antidepressant treatment response and remission in a gender and drug-class specific manner.

Significance: Future studies investigating EEG alpha measures in depression should a-priori stratify by gender.

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1. Introduction

Since 1936, when Lemere first reported the capability to ‘... produce “good” alpha waves...’ to be associated with the ‘... affective capacity of the individual...’ (Lemere, 1936), there has been a broad interest in research on this resting state electroencephalographic (EEG) measure in major depressive disorder (MDD), both as an index of the disorder and as a predictor of treatment outcome. Heritability estimates of alpha EEG have been found to be among the highest for psychophysiological measures (e.g., 79% for alpha EEG power; van Beijsterveldt and van Baal, 2002). Compared to controls, participants with MDD are typically characterized by elevated resting state EEG alpha power across a broad range of individuals (Itil, 1983; Jaworska et al., 2012; Pollock and Schneider, 1990; Ulrich and Fürstenberg, 1999), including those in the early stages of depression (Grin-Yatsenko et al., 2009) and the elderly (Roemer et al., 1992). Some studies (Flor-Henry, 1979; Knott and Lapierre, 1987) have not found alpha power differences between MDD patients and healthy controls, and others (Pozzi et al., 1995; Price et al., 2008) have reported lower (relative) alpha activity in patients with MDD. Greater alpha is associated with a greater likelihood of response to a variety of antidepressant medications in MDD (Bruder et al., 2008; Tenke et al., 2011; Ulrich et al., 1986), but for the antidepressant treatment repetitive transcranial magnetic stimulation (rTMS), the opposite was reported (Micoulaud-Franchi et al., 2012; Price et al., 2008) maybe related to the higher level of treatment resistance in rTMS studies. However, it is not known how well alpha power differentially predicts outcome between different medication classes.

A substantial body of research on alpha power in MDD has been dedicated to ‘frontal alpha asymmetry’ (FAA) recorded during a resting state, originating with the pioneering work of Henriques and Davidson (1991). They reported relatively greater left frontal alpha power in MDD, indicative of left frontal hypoactivity (i.e. less left frontal cortical activity), which is interpreted as a deficit in the approach system. Hence, participants with this asymmetry are more prone to negative affective states (Henriques and Davidson, 1991). This measure has been extensively investigated in MDD and conflicting results have been published (for a review, see: Gordon et al., 2010; Olbrich and Arns, 2013). Some studies have looked at alpha asymmetry in relation to antidepressant treatment outcome and reported differences between responders and non-responders in mostly non-frontal areas (e.g., occipital sites: Bruder et al., 2008; Ulrich et al., 1986; right greater than left hemisphere alpha: Bruder et al., 2001, but differences were not specific to FAA). Tenke and colleagues conducted a larger study that used current source density measures (Tenke et al., 2011) and did not replicate their earlier alpha asymmetry findings in relation to treatment outcome (Bruder et al., 2008) and a similar null finding was reported by Li et al (2013), for response to rTMS. Interestingly, gender differences have been reported for this measure e.g. the association between alpha asymmetry and treatment outcome was only found in females (Bruder et al., 2001) and the association between perceptual asymmetry for dichotic words and alpha asymmetry was only found in depressed women, but not depressed men (Bruder et al., 2001). Therefore, we will in this

study also investigate gender differences and interactions with gender.

Our current report used data from the multi-center, randomized, prospective open-label international Study to Predict Optimized Treatment in Depression (iSPOT-D) (see Williams et al. (2011) for details). This study included 1008 MDD participants who were randomized to escitalopram, sertraline (Selective Serotonin Reuptake Inhibitors [SSRIs]) or venlafaxine-extended release (venlafaxine-XR) (Serotonin Norepinephrine Reuptake Inhibitor [SNRI]) and 336 healthy controls. This study therefore has sufficient statistical power to replicate previous findings, and a failure to replicate could thus question the veracity of previous findings. EEG and other metrics were recorded at baseline. Participants were re-evaluated after 8 weeks of treatment to verify whether they met response or remission status.

2. Materials and methods

2.1. Design

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

2.2. Participants and treatment

This study included 1008 MDD patients and 336 healthy controls and these were recruited between October 2008 and January 2011. A complete description of the study assessments, inclusion/exclusion criteria, diagnostic procedures and treatment is available in Williams et al. (2011). 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 (HRSD₁₇). Comorbid anxiety disorders were allowed (present in 6.2% [specific phobia] to 10.5% [social phobia] of MDD participants). All MDD participants were either antidepressant medication-naïve 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 three antidepressant medications. After eight weeks of treatment, participants were tested again using the HRSD₁₇ and an EEG assessment (Fig. 1).

This study was approved by the institutional review boards at all of the participating sites and this trial was registered with ClinicalTrials.gov. Registration Number: NCT00693849; URL: <http://clinicaltrials.gov/ct2/show/NCT00693849>.

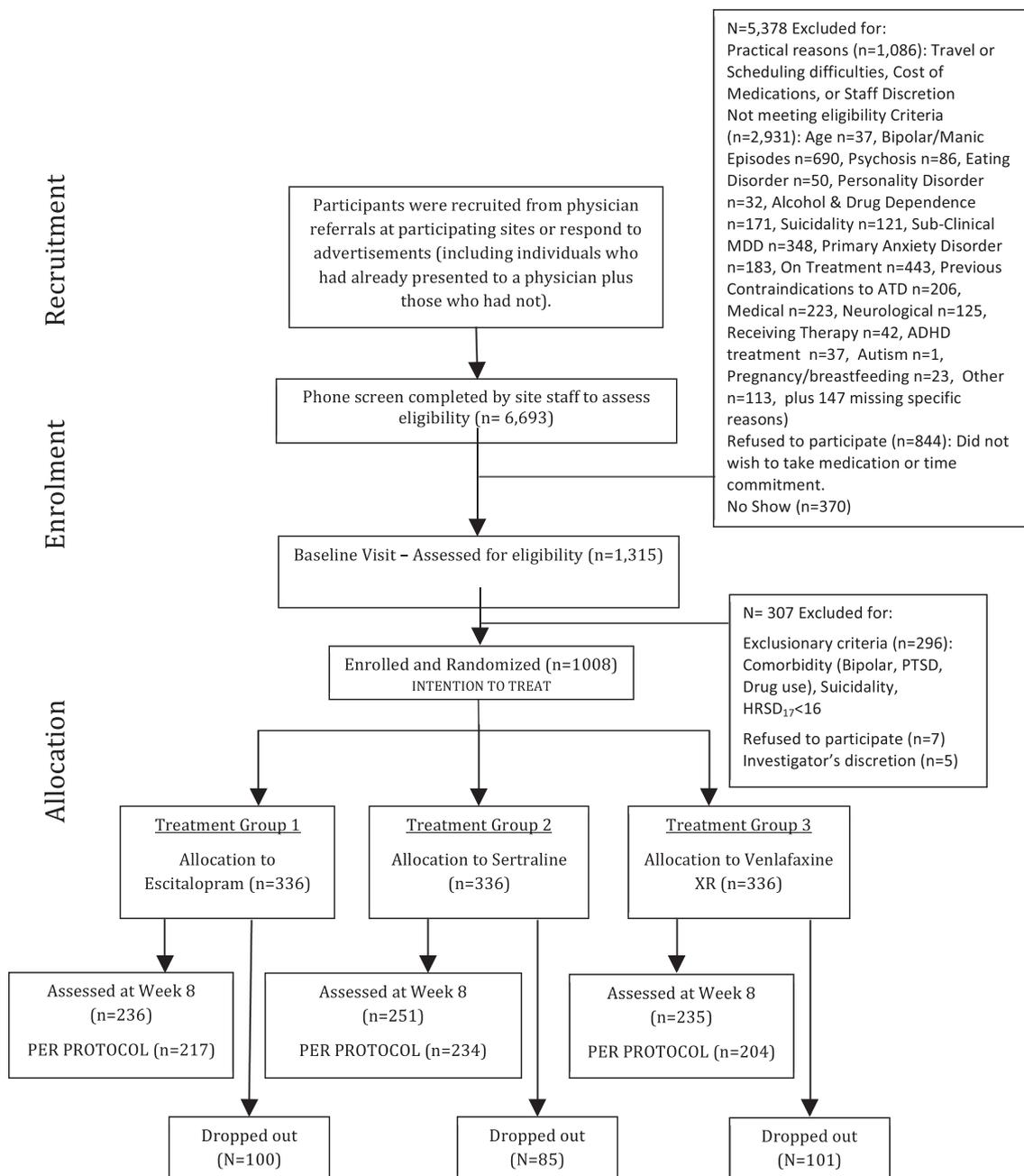


Fig. 1. Consort diagram of the iSPOT-D study. *Abbreviations:* ADHD, Attention deficit hyperactivity disorder; ADT, Antidepressant treatment; HRSD₁₇, 17-item Hamilton rating scale for depression; MDD, Major depressive disorder; PTSD, Post-traumatic stress disorder; XR, Extended release.

2.3. 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, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz and O2 (Quikcap; NuAmps; 10-20 electrode international system). EEG data was assessed 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) and 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 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. Skin resistance was <5 K Ohms for all electrodes. 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.

2.4. Analysis

2.4.1. EEG analysis

A detailed overview of the exact data-analysis procedure can be found in the [Supplementary Text S1](#). But in summary, data were (1) filtered (0.3–100 Hz and notch); (2) EOG-corrected using a regression-based technique similar to that used by [Gratton et al. \(1983\)](#); (3) segmented in 4-second epochs (50% overlapping) and an automatic deartifacting method was applied. This EEG processing pipeline was also validated against an independent manual-processing pipeline. See [Supplementary Text S1\(B\)](#) for these results and methods.

2.4.2. EEG eLORETA analyses

Based on the scalp-recorded electric potential distribution, the 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 by [Pascual-Marqui \(2007\)](#). eLORETA is an improvement over this LORETA version ([Pascual-Marqui et al., 1994](#)) and the standardized version sLORETA ([Pascual-Marqui, 2002](#)).

The following regions of interest (ROI) were defined (see [Fig. 2](#) for visualization of ROIs) and EEG current source density (Alpha [8–13 Hz]) was extracted from these ROIs: rACC (using the voxels as reported by [Pizzagalli et al. \(2001\)](#)), posterior cingulate (PCC), occipital, and frontal cortex. In addition, EEG power in Alpha was extracted from Oz and Fz to compare the results from source space to electrode space (the analyses using Oz and Fz are only intended to confirm eLORETA analysis and enable the comparison of our results to those of studies conducted in electrode space). Finally, FAA was calculated between F3 and F4 using an average reference with the formula $(F4 - F3)/(F4 + F3)$.

2.5. Statistics

Remission was defined as a score ≤ 7 on the HRSD₁₇ at 8 weeks, and response was defined as a >50% decrease in HRSD₁₇ score from baseline to 8 weeks. In this analysis, we primarily looked at remitters vs. non-remitters and responders vs. non-responders. Normal distribution of EEG measures was inspected and alpha measures were log transformed before statistical analysis. Non-log transformed alpha power¹ was used to calculate alpha asymmetry. Differences in age, gender, education and baseline depressive severity were tested using One-Way ANOVA or non-parametric tests (gender). When a difference between groups existed on one of these measures, the feature was added as a covariate.

The primary hypotheses tested in this study are

- (1) MDD patients compared to controls have greater occipital alpha power (outcome measure: eLORETA occipital alpha power)
- (2) MDD patients compared to controls have a left dominant alpha asymmetry (outcome measure: alpha asymmetry between F3–F4)
- (3) Responders and remitters to antidepressant treatment have greater occipital alpha power and lower frontal alpha power (outcome measure: eLORETA occipital and frontal alpha power)

- (4) Responders and remitters to antidepressant treatment demonstrate a right dominant alpha asymmetry (outcome measure: alpha asymmetry between F3–F4)

Given the large sample size we set the significance level for main effects found for group differences (MDD participants vs. controls) or main effects of response or remission to a conservative $p \leq 0.01$. When significant interactions were found prompting sub-group analysis per treatment arm, a conventional level of $p < .05$ was used. Effect sizes (ES) of main effects are reported in Cohen's *d*.

For the comparison of MDD participants vs. healthy controls and for investigating treatment prediction, a repeated-measures ANOVA was conducted with the within-subject factors Condition (Eyes Open and Eyes Closed EEG), between-subject factors group (MDD participants vs. controls, responders vs. non-responders, or remitters vs. non-remitters), treatment arm and gender (and age, or other factors that differed between groups, as identified from the preliminary analyses outlined above).

For treatment prediction, a within-subject factor *Site* (Alpha: Posterior vs. Anterior) was added to specifically test for interactions in alpha topography between frontal and occipital vs. rACC and posterior anterior cingulate. Analyses were performed for the 4 ROIs and electrodes Fz vs. Oz separately. When significant interactions were found, univariate analyses were performed.

A (partial) correlation was run between the percentage improvement on the HRSD₁₇ score between baseline and week 8, HRSD₁₇ score at baseline and HRSD₁₇ score at week 8, and the measures that were found to differ between responders and non-responders and between remitters and non-remitters.

All statistics for treatment prediction were performed on data from MDD participants who completed 8 weeks of treatment: participants who were dosed with their randomized medication for a minimum of 6 weeks and who returned for their week 8 visit and were still receiving their randomized medication at this visit ('per protocol' grouping, also see the Consort diagram in [Fig. 1](#)). Furthermore, when predictors of treatment outcome were found, linear repeated measure mixed models were employed to test the relationships between that predictor and outcome at week 8 in an intention-to-treat context. Since repeated measure mixed models estimate missing-data, data from participants with missing week 8 clinical data could be used and thus all subjects are included in this analysis (see [Supplementary Text S1\(C\)](#)).

3. 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 (overall remission and response rates were 46% and 64%, respectively) and 336 controls. Medications randomized were as follows: Escitalopram ($N = 217$), Sertraline ($N = 234$) and Venlafaxine-XR ($N = 204$). The remaining 341 MDD participants dropped out of the study, with the main reasons for drop-out being patients not starting the treatment, having less than 6 weeks of medication, or having no week 8 assessment. [Table 1](#) 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 (HRSD₁₇), remission and 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 artifacts for the MDD group during EC ($p < .001$; $Z = -4.314$: 1.7 (3.33) vs. 2.44 (3.90) epochs) and EO ($p < .001$; $Z = -1.399$: 2.04 (3.15) vs. 3.18 (4.237) epochs). MDD participants thus had 2% more rejected epochs compared to controls. In total, there were less than 5.3% rejected EEG epochs.

¹ Note that several equations have been used in the literature to calculate FAA. For example Bruder et al. used the log-transformed alpha difference $(\log(F4)) - (\log(F3))$, whereas we have used a non-log-transformed difference ratio $(F4 - F3)/(F4 + F3)$, since it had the closest to normal distribution. However, the results reported in this manuscript were identical when using either method.

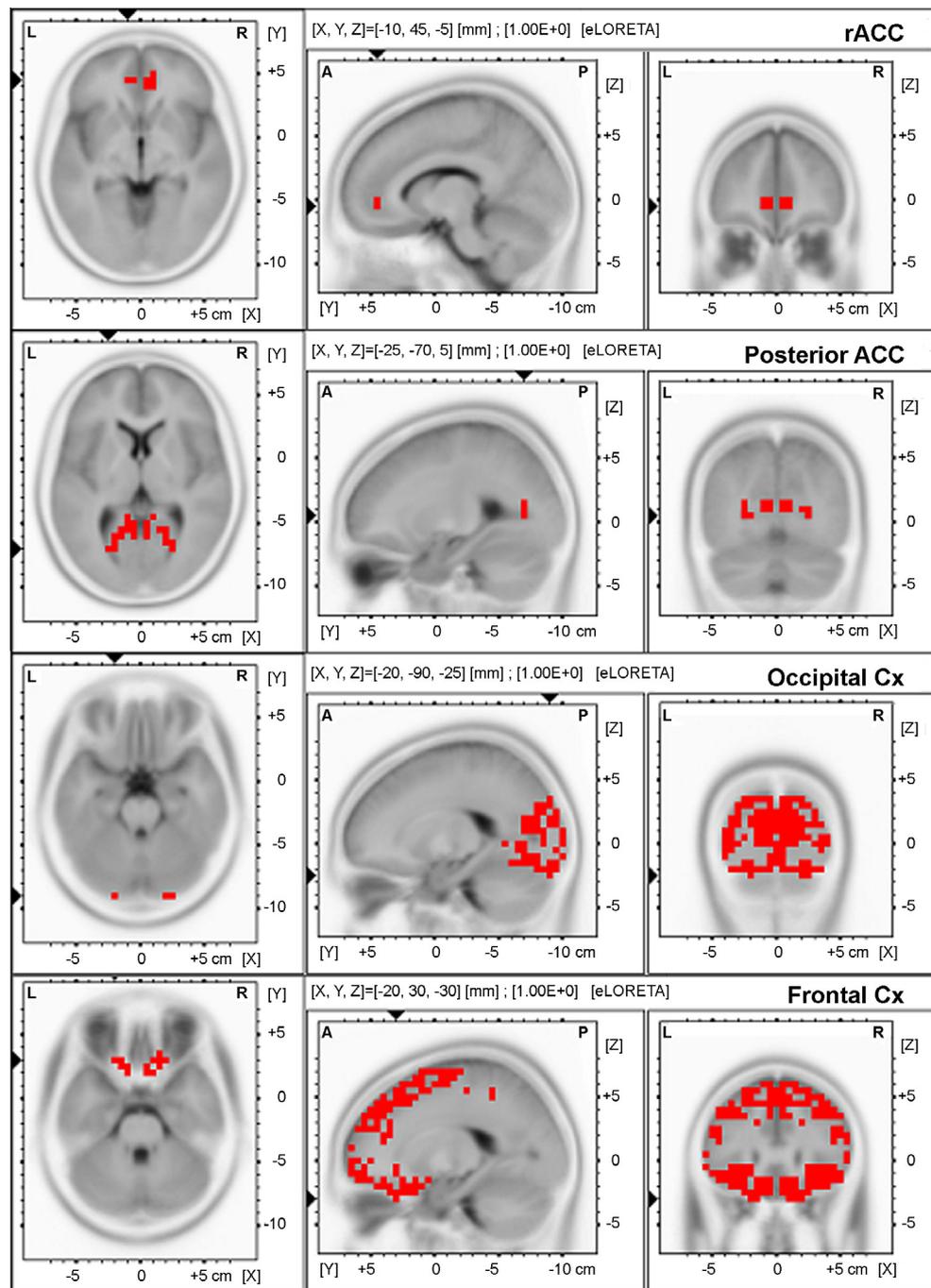


Fig. 2. The 4 regions of interest that were defined for this study. These regions of interest were used to extract alpha power (8–13 Hz) using eLORETA. *Abbreviations:* ACC, Anterior Cingulate Cortex; eLORETA, Exact low-resolution brain electromagnetic tomography analysis; rACC, rostral anterior cingulate.

3.1. MDD participants vs. controls

There were no differences between the MDD participants and controls regarding age ($p = .289$, $F(1,123) = 1.126$) or gender ($p = .949$, $Z = -.064$), but there was a difference in education ($p = .021$, $F(1,123) = 5.360$) with controls having a higher education (14.9 (SD = 2.5) vs. 14.5 (SD = 2.8) years of education).

3.1.1. eLORETA analysis: MDD participants vs. controls

Repeated-measures ANOVA, using education as a covariate, yielded the following results:

- (1) *Occipital alpha:* The study found an effect of Condition ($p < .001$; $F(1,1123) = 54.531$), a Condition \times Group interaction ($p = .004$; $F(1,1123) = 8.108$) and a Condition \times Gender

interaction ($p < .001$; $F(1,1123) = 27.575$). Separate univariate analyses for EO and EC demonstrated for EC a main effect for Gender ($p < .001$; $F(1) = 17.170$; $ES = 0.25$) in which females had higher occipital alpha and a trend for Group ($p = .052$: lower occipital alpha for the MDD group), and no effects for EO, thus no differences in occipital alpha between MDD participants and controls.

- (2) *Posterior cingulate:* The study found an effect of Condition ($p < .001$; $F(1,1123) = 65.829$), a Condition \times Group interaction ($p = .010$; $F(1,1123) = 6.729$), a Condition \times Gender interaction ($p < .001$; $F(1,1123) = 12.112$), a main effect of Gender ($p = .002$; $F(1) = 9.319$) and a trend for Group ($p = .032$). Separate univariate analyses for EO and EC demonstrated for EC a main effect for Group ($p = .004$;

Table 1
Demographic features of MDD patients and controls and treatment outcomes for patients who completed treatment.

Features	Escitalopram	Sertraline	Venlafaxine-XR	MDD	Controls
Number	217	234	204	1008	336
Females	119	139	120	571	191
Average age (years)	38.85	38.34	38.46	37.84	36.99
HRSD ₁₇ baseline	21.75	21.95	21.50	21.88	1.15
HRSD ₁₇ week 8	9.29	9.41	9.71	9.67	1.06
HRSD ₁₇ anxiety baseline	6.18	6.27	6.14	6.16	0.57
% Female	55	59	59	57	57
% Remission (HRSD ₁₇)	48	47	44	46	
% Response (HRSD ₁₇)	60	67	63	63	

Abbreviations: HRSD₁₇, 17-item Hamilton rating scale for depression; MDD, Major depressive disorder; XR, Extended release.

- $F(1) = 8.512$), for Gender ($p < .001$; $F(1) = 15.744$) in which females had higher posterior cingulate alpha ($ES = 0.24$), and MDD participants had lower posterior cingulate alpha during EC ($ES = -0.20$). No effects for EO were found.
- (3) rACC alpha: The study found a main effect of Group ($p < .001$; $F(1) = 17.756$) and Gender ($p < .001$; $F(1) = 15.954$) in which MDD participants and females had higher rACC alpha (MDD vs. Controls: $ES_{EC} = 0.25$; $ES_{EO} = 0.30$), and no interaction.
- (4) Frontal alpha: The study found an effect of Condition ($p = .020$; $F(1,1123) = 5.423$), a Condition \times Gender interaction ($p < .001$; $F(1,1123) = 15.978$) and no main effects, which indicates no differences in frontal alpha between MDD participants and controls.

Fig. 3 provides a further visualization of the above results from eLORETA (unthresholded) for MDD participants vs. controls (note that the overall eLORETA statistical analysis was not significant between groups, probably due to the correction for multiple measurements for all voxels). Fig. 3 further demonstrates the greater anterior alpha and lower posterior alpha in MDD participants vs. controls, and the gender interaction. eLORETA analyses suggested that females mainly had greater alpha in the medial frontal gyrus and males had lower alpha in the left lingual gyrus (occipital) and posterior cingulate, whereas eLORETA analyses suggested that both males and females demonstrated lower alpha in right posterior regions such as the cuneus, occipital lobe and posterior cingulate.

3.1.2. EEG analysis scalp potentials: MDD participants vs. controls

In electrode space for Oz and Fz the following results were found:

- (1) Alpha power at Oz: The study found a Condition effect ($p < .001$; $F(1,1190) = 23.983$), a Condition \times Group interaction ($p = .004$; $F(1,1190) = 8.335$), a Condition \times Gender interaction ($p < .001$; $F(1,1190) = 15.061$), a main effect for Gender ($p = .002$; $F(1) = 9.634$) and a trend for Group ($p = .014$; $F(1) = 6.100$). Separate univariate analyses for EO and EC only yielded a Group ($p = .006$; $F(1) = 7.477$) and Gender ($p < .001$; $F(1) = 14.529$) effect for EC, in which MDD participants had lower alpha power at Oz ($ES = 0.18$) and females had higher alpha than males ($ES = 0.23$).

- (2) Alpha power at Fz: The study found a Condition effect ($p < .001$; $F(1,1191) = 26.965$), a Condition \times Gender interaction ($p < .001$; $F(1,1191) = 15.084$), a main effect of Gender ($p < .001$; $F(1) = 19.680$) and a trend for Group \times Gender interaction ($p = .055$; $F(1) = 3.687$) in which female MDD participants tended to have lower alpha at Fz and male MDD participants tended to have higher alpha at Fz compared to controls.
- (3) FAA: For FAA (F4–F3), only a Condition \times Gender interaction was found ($p = .008$; $F(1,1173) = 7.074$) and no group effect was found ($p = .819$). Post-hoc analysis also showed no difference for P3–P4 asymmetry, and also no differences when analyses were performed for males and females separately or when participants with a comorbid anxiety disorder were excluded. Re-analyzing these findings in a subgroup with severe MDD ($HRSD_{17} \geq 24$) also did not result in any significant Group effect.

3.1.3. Correlations: MDD severity and EEG

There were no significant correlations between HRSD₁₇ severity at intake and the above metrics within the MDD and control groups.

3.2. Response vs. non-response (HRSD₁₇)

For the entire group, there were significant differences between responders and non-responders, in which responders were younger ($p = .002$; $F(654) = 9274$), and there were no differences for baseline HRSD₁₇ MDD severity and anxiety severity, education, gender or rejected epochs.

3.2.1. eLORETA analysis: response vs. non-response

For response and alpha in the four ROIs, repeated-measures ANOVA demonstrated many significant interactions involving Group and Condition (EC/EO); therefore, only results for EC are reported.

For EC occipital and frontal alpha, a repeated-measures ANOVA with covariate age yielded a within-subject effect of Site ($p < .001$; $F(1,598) = 108.981$), a Site \times Age interaction ($p < .001$; $F(1,598) = 17.702$) and a between-subject effect of age ($p < .001$; $F(1,598) = 16.790$) and gender ($p = .015$; $F(1,598) = 5.910$). Response type was not significant ($p = .179$).

Repeating the analysis using posterior cingulate and rACC also did not yield significant main effects for Response.

3.2.2. FAA (F4–F3)

For FAA, a repeated-measures ANOVA with the covariate age yielded a significant Treatment Arm \times Gender ($p = .027$; $F(2,564) = 3.638$) and Treatment Arm \times Response \times Gender interaction ($p = .027$; $F(2,564) = 3.617$). Repeating the analysis for males and females separately only yielded an effect for females, with a significant Treatment Arm \times Response interaction ($p = .008$; $F(2,320) = 4.933$). This interaction was mainly driven by significant treatment response effects for the SSRI's escitalopram and sertraline but not for the SNRI Venlafaxine. Repeating the analysis for the SSRIs escitalopram and sertraline alone resulted in a main effect of response ($p = .001$; $F(1,219) = 10.391$; $ES_{EO} = 0.37$; $ES_{EC} = 0.44$). The same analysis for venlafaxine resulted in a trend for a main effect of response ($p = .070$; $F(1,102) = 3.343$). This indicates that female responders showed greater alpha (less cortical activity) over the right frontal site, whereas non-remitters showed the opposite asymmetry. These effects were also significant after controlling for research center, and adding research center as a between-subject factor still yielded a main effect of response ($p = .003$) in females prescribed SSRI's and no significant interactions involving research center. Repeating this same analysis on

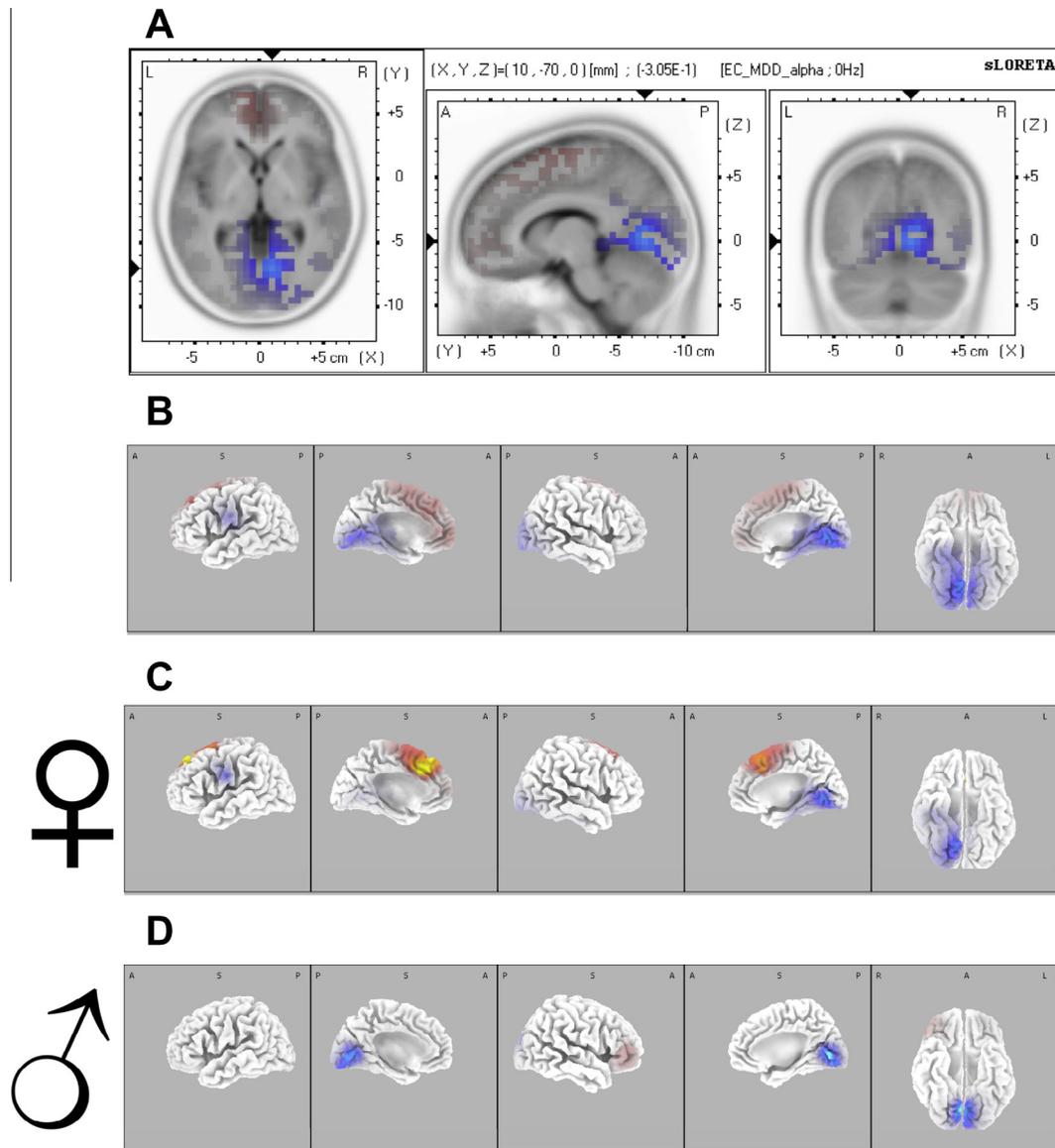


Fig. 3. Differences in eyes closed alpha CSD between MDD participants and controls assessed using eLORETA. This figure further visualizes the effects of lower posterior cingulate and higher rACC alpha in MDD participants. In the bottom half of the figure, results for males and females are shown separately, where the gender-specific effects become apparent. (A) The differences in eyes closed alpha CSD between MDD Participants and Controls. (B) Male and female data shown together. (C) Female-only data. (D) Male-only data. Abbreviations: A, Anterior; P, Posterior, CSD, Current source density; eLORETA, Exact low-resolution brain electromagnetic tomography analysis; L, Left; R, Right; MDD, Major depressive disorder.

an MDD subgroup in which participants with comorbid anxiety were excluded yielded the same interactions and results, which further suggests that these effects are not mediated by a comorbid anxiety disorder.

3.3. Remission vs. non-remission (HRSD₁₇)

For the whole group, there were significant differences between remitters and non-remitters, with remitters being younger ($p = .004$; $F(654) = 8.497$), having lower baseline MDD severity (HRSD₁₇: $p < .001$; $F(654) = 25.678$) and lower Anxiety severity (HRSD₁₇: $p < .001$; $F(654) = 14.899$). There were no differences in gender, education or rejected epochs.

3.3.1. eLORETA analysis: remission vs. non-remission

For remission and alpha in the four ROIs, repeated-measures ANOVA demonstrated many significant interactions involving

Group and Condition (EC/EO); therefore, only results for EC are reported.

For frontal and occipital alpha, repeated-measures ANOVA with the covariates of age, baseline HRSD₁₇ MDD severity and Anxiety severity yielded a within-subject effect of Site ($p < .001$, $F(1,596) = 59.827$), a Site \times Age interaction ($p < .001$; $F(1,596) = 17.993$), a site \times MDD severity interaction ($p = .003$; $F(1,596) = 9.001$) and between-subject effects of age ($p < .001$; $F(1,596) = 25.276$) and gender ($p = .013$; $F(1,596) = 6.273$), but no effect of remission.

Repeating the analysis using posterior cingulate and rACC did not yield any significant effects, thus there are no differences in alpha power between remitters and non-remitters.

3.3.2. EEG analysis scalp potentials: remission vs. non-remission

Repeating this analysis in electrode space on alpha power at Fz and Oz yielded similar non-significant results in the same direction.

3.3.3. FAA (F4–F3)

For FAA, a repeated-measures ANOVA with the covariates of age, baseline HRSD₁₇ MDD and Anxiety severity yielded a Condition \times Gender interaction ($p = .024$; $F(1,562) = 5.153$) and a Remission \times Gender interaction ($p = .050$; $F(1,562) = 3.847$). Running this analysis separately for females yielded a between-subject effect of MDD severity ($p = .040$; $F(1,318) = 4.242$), Remission ($p = .001$; $F(1,318) = 10.360$) and a trend for a Treatment Arm \times Remission interaction ($p = .054$; $F(2,318) = 2.946$). As can be seen in Fig. 4 and similar to the analysis on response, this effect was mainly driven by sertraline and escitalopram showing a response effect different to that of venlafaxine-XR. Repeating the analysis in females only using SSRI vs. SNRI as a factor instead of Treatment Arm yielded a main effect of MDD severity ($p = .040$; $F(1,320) = 4.250$), Remission ($p = .021$; $F(1,320) = 5.399$) and a significant Treatment Arm \times Remission interaction ($p = .022$; $F(2,320) = 5.273$). Including only the SSRI's escitalopram and sertraline yielded a between-subject effect of Remission ($p < .001$; $F(1,217) = 16.999$), suggesting that SSRI remitters have a positive alpha asymmetry ($ES_{EO} = 0.42$; $ES_{EC} = 0.55$). These effects were also significant after controlling for research center, and adding research center as a between-subject factor still yielded a main effect of remission ($p < .001$) in females prescribed SSRI's and no significant interactions involving research center. This indicates that female SSRI remitters showed greater alpha (less cortical activity) over the right frontal site compared to the left frontal site, whereas non-remitters showed the opposite asymmetry. Repeating this analysis in males only or for venlafaxine-XR only, yielded no significant effects.

Partial correlations in this subset of data (females only and SSRI only, using baseline MDD, anxiety and age as covariates) resulted in significant correlations between alpha asymmetry (F4–F3) and HRSD₁₇ score at week 8 (EO: $p = .005$; $r(217) = -.187$; EC: $p < .001$; $r(217) = -.238$) and percentage improvement in HRSD₁₇ score (EO: $p = .004$; $r(217) = -.192$; EC: $p < .001$; $r(217) = -.236$), which implicates that more right frontal alpha is associated with a lower MDD severity at week 8 and a larger decrease in MDD symptoms between baseline and week 8. Interestingly, when calculating bivariate correlations in this subgroup, no correlation was found between FAA (F4–F3) and HRSD₁₇ score at baseline ($p > .18$), or between FAA and anxiety at baseline ($p > .88$). The only correlations found were between FAA and HRSD₁₇ score at week 8 (all $p < .011$) and between FAA and percentage improvement on

HRSD₁₇ score (all $p < .003$), which further demonstrates that this measure is specifically related to treatment outcome and is not mediated by MDD and anxiety severity.

3.4. Intention-to-treat analysis

The above findings related to alpha asymmetry were also analyzed in an intention-to-treat analysis using a mixed models approach including all subjects, which corroborated the findings (see Supplementary Text S1(C)). This further demonstrates the strength of this effect. Also, repeating the repeated-measures analyses above for FAA and controlling for research center did not change the results.

3.5. Response prediction

Based on the results for alpha asymmetry as visualized in Fig. 4, we also conducted a simulation in which we established the percentage of remitters using a simple decision rule of $FAA \geq 0$, or $FAA < 0$. Table 2 shows the results of this simulation. We specifically tested the hypothesis derived from the results and Fig. 4 on what the effect would have been if participants with greater left alpha (< 0) had been prescribed with the SNRI venlafaxine-XR, and conversely if participants with greater right alpha (≥ 0) had been prescribed with the SSRI escitalopram or sertraline. The bold data in Table 2 demonstrates these results. Given the overall remission rate of 46% in this study based on randomized treatment allocation, an improvement of 7% for venlafaxine-XR and 14% for SSRI treatment could have been achieved by assigning female MDD participants to treatment based on their FAA (eyes closed alpha asymmetry between F4 and F3: ECAAF43) at baseline.

A discriminant analysis for remission using FAA from EO and EC for females only who were randomized to an SSRI resulted in a significant Wilks' Lambda ($p < .001$; Wilk's Lambda = .930; Chi-Square(2) = 16.000). The Receiver Operator Curve can be found in Fig. 5 with an Area Under the Curve of .641. Running the same analysis including the baseline characteristics of age, MDD severity and anxiety severity resulted in a significant Wilks' Lambda ($p < .001$; Wilk's Lambda = .915; Chi-Square(5) = 30.909). The Receiver Operator Curve for this analysis can be found in Fig. 5 with an Area Under the Curve of .721, which suggests that adding additional baseline characteristics further improved the prediction of remission. Repeating this model for the whole group (including

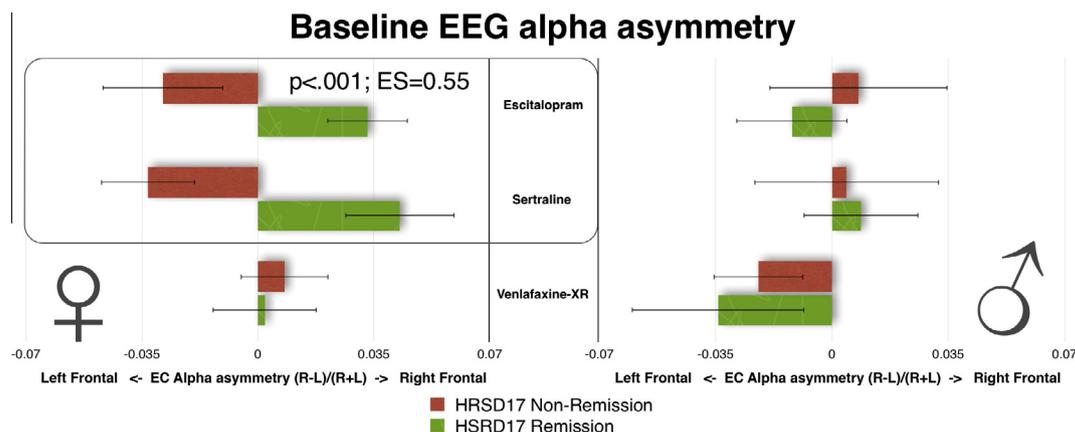


Fig. 4. Baseline EEG alpha asymmetry during eyes closed: Females (left) and Males (right) at frontal sites (F4–F3). This figure shows the clear interaction between the SNRI Venlafaxine-XR and the SSRIs Escitalopram and Sertraline and its relation to remission (Green) and non-remission (Red; the results for remission and eyes open were similar). A greater right frontal alpha at baseline is associated with remission/response to an SSRI and greater left frontal alpha is associated to non-remission/non-response to an SSRI. There is no such relation for the SNRI Venlafaxine-XR. Abbreviations: EC, Eyes closed; ES, Effect size; ESC, Escitalopram; HRSD₁₇, 17-item Hamilton rating scale for depression; SER, Sertraline; SNRI, Serotonin norepinephrine reuptake inhibitor, SSRI; Selective serotonin reuptake inhibitor; VEN, Venlafaxine-XR; XR, Extended release. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2

The results of a simulation analysis on remission rates if patients are prescribed a given treatment based on their alpha asymmetry at baseline (eyes open: EOAAF43 or eyes closed: ECAAF43), for males, females and all separately.

Measure	Gender	Escitalopram		Sertraline		Venlafaxine-XR		SSRI (ESC + SER)	
		≥0 (%)	<0 (%)	≥0 (%)	<0 (%)	≥0 (%)	<0 (%)	≥0 (%)	<0 (%)
EOAAF43	ALL	51	46	55	37	39	48	53	42
ECAAF43	ALL	55	44	59	36	41	45	57	40
EOAAF43	Male	54	47	46	37	33	44	50	42
ECAAF43	Male	56	49	51	39	43	35	54	44
EOAAF43	Female	48	46	61	37	43	52	55	41
ECAAF43	Female	54	38	64	35	40	53	60	36

The data in **bold** demonstrates the simulated outcomes if patients with left dominant alpha (<0) are prescribed the SNRI Venlafaxine-XR and if patients with right dominant alpha (≥0) are prescribed an SSRI. Note that overall remission rate was 46%, suggesting this selection procedure potentially improves the remission rates with 9–14% for SSRI and 6–7% for SNRI. SSRI includes escitalopram and sertraline.

Abbreviations: SSRI, Selective serotonin reuptake inhibitor; XR, Extended release.

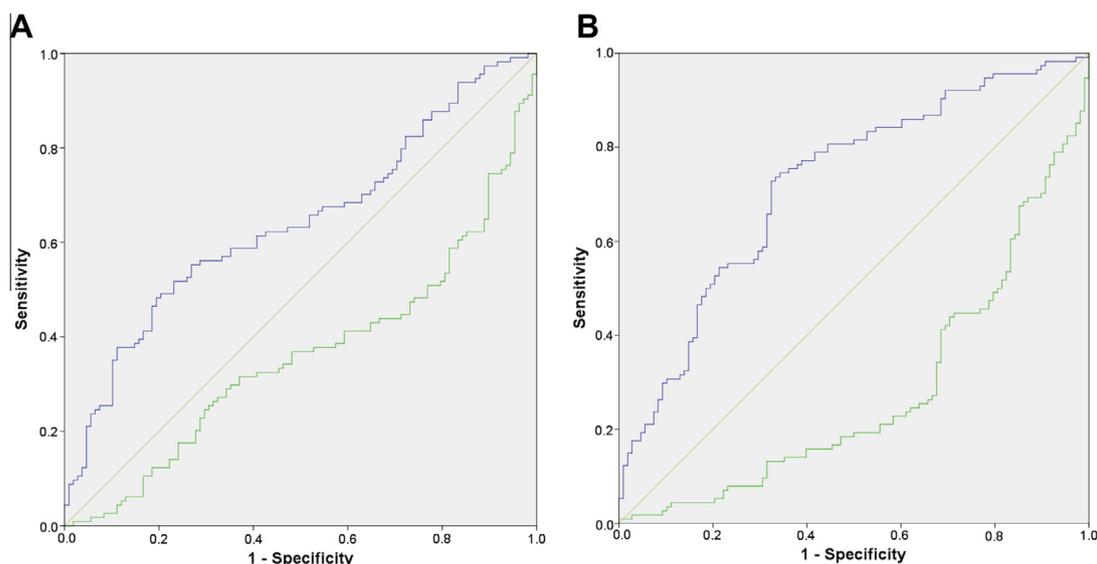


Fig. 5. Receiver Operator Curves (ROCs) for the results of a discriminant analysis on Remission. (A) Baseline FAA from eyes closed and eyes open EEG with an area under the curve of .641. (B) Baseline FAA from eyes open and eyes closed, and age, baseline depression severity (HRSD₁₇) and anxiety severity with an area under the curve of .721. These ROCs suggest that adding clinical baseline measures into the model substantially improves the prediction of remission. The blue line represents the prediction for non-remission, and green for remission. Abbreviations: EEG, Electroencephalogram; HRSD₁₇, 17-item Hamilton rating scale for depression. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

males, females, SSRI responders and SNRI responders) also resulted in a significant model and an Area Under the Curve of .651.

4. Discussion

In this study, we found that compared to healthy controls, participants with MDD demonstrated lower alpha in the posterior cingulate and higher alpha in the rACC (with a small ES), whereas no differences were found for occipital and frontal cortex, or for frontal alpha asymmetry (FAA). Furthermore, gender differences emerged for alpha between MDD participants and controls.

For treatment response, we failed to replicate the earlier reports of occipital and frontal alpha, both in standard scalp potentials and using eLORETA source localization as an inverse solution. However, the strongest finding in this study was the gender-specific effect for FAA (F4–F3), in which relatively greater right frontal alpha (less cortical activity) was associated with response and remission to an SSRI (escitalopram or sertraline) in females only. This effect was not found for the SNRI venlafaxine-XR and was also not found for males. Furthermore, the effects were found for both eyes open and eyes closed condition, with slightly stronger effect sizes for

the eyes closed condition. A simulation suggested that using the direction of FAA alone to prescribe an SSRI or SNRI would have improved the overall remission rate from 46% to 55–60% for an SSRI. Discriminant analyses further suggested that including other clinical variables such as age, baseline HRSD₁₇ and baseline anxiety severity further improved the prediction of remission.

Based on the Approach-Withdrawal model of MDD, relatively greater left frontal alpha (less activity or hypoactivity) would be expected in MDD. However, several studies have been unable to find this (see Olbrich and Arns (2013) for review) or have even observed less activity over right frontal sites in MDD participants (Gordon et al., 2010). Interestingly, in this study FAA did not differ between MDD participants and controls on the group level, and there were also no correlations between FAA and depressive and anxiety complaints at baseline. Therefore, these results are not in line with the original Approach-Withdrawal model of Davidson (Henriques and Davidson, 1991). Interestingly, less right frontal activity (greater right frontal alpha) was found in female SSRI responders, and in this subgroup alpha asymmetry only correlated significantly with MDD severity at week 8 and percentage improvement on the HRSD₁₇, but not with anxiety or MDD severity

at baseline. Also, the same results were obtained when participants with comorbid anxiety disorders were excluded, which rules out mediation of this effect by comorbid anxiety. These data and the study's large sample size clearly demonstrate the lack of 'diagnostic' value for FAA in MDD; however, this FAA does have prognostic value for predicting outcome to treatment (see Arns and Gordon (2014), this journal, for further discussion), with a medium effect size for eyes closed alpha asymmetry ($d = 0.41–0.55$) for both HRSD₁₇ response and remission.

Bruder et al. (2001) reported a similar gender-specific effect of alpha asymmetry in females related to treatment outcome with the SSRI fluoxetine, albeit for averaged alpha asymmetry at anterior, central and posterior regions. In our study, we only found the effects for F4–F3 asymmetry (and not for P4–P3). Furthermore, Jaworska et al. (2012) also found suggestions for gender-specific effects for alpha measures in MDD. What could account for this gender-specific difference in FAA between female responders and nonresponders? One possibility is gender differences in cognitive function and hemispheric organization among depressed patients (Heller, 1993). One form of depression among women that responds to an SSRI may be characterized by relatively greater activation of left compared to right frontal regions. Bruder et al. (2004) found that responders to an SSRI had a heightened left hemisphere advantage for processing dichotic words, but this was evident among depressed women and not depressed men. Bruder et al. (2001) also found that perceptual asymmetry for dichotic words was significantly correlated with resting alpha asymmetry in depressed women ($r = .51$), but not depressed men. Future studies should further investigate the underpinnings of this gender-specific and drug-class-specific effect (e.g., investigate differences in serotonergic genotypes and alpha asymmetry as well as differences in right and left frontal connectivity).

Compared to healthy controls, MDD participants were found to have greater anterior alpha (rACC) and lower posterior alpha at Oz, which seemed to originate more from the posterior cingulate, which is also in agreement with an earlier report of Pizzagalli et al. (2002). The gender interactions observed in the statistical results suggested mainly higher alpha in the medial frontal gyrus for females and mainly lower alpha in the left lingual gyrus (occipital) and posterior cingulate for males, whereas both males and females demonstrated lower alpha in right posterior regions such as the cuneus, occipital lobe and posterior cingulate. However, no significant correlations were found within the MDD and control groups, suggesting the groups differ on these measures, but do not support a direct association with MDD symptoms.

For alpha power, no specific effects were found to be related to treatment response and remission, hence we were unable to replicate the previous reports of greater posterior alpha power in responders than in non-responders (Bruder et al., 2008; Tenke et al., 2011; Ulrich et al., 1986). It has to be noted that the earlier study by Tenke et al. (2011) used frequency principal components analysis of spectra derived from reference-free current source density, which is different from the eLORETA method used in this study. Future studies should further investigate whether a specific method would be more likely to yield differences in alpha between antidepressant responders and non-responders. Finally, no support was found for greater posterior alpha and lower frontal alpha in MDD, as predicted by the EEG Vigilance theory of affective disorders (according to this model MDD symptoms such as withdrawal and sensation avoidance are autoregulatory reactions to a hyperstable vigilance regulation, indexed as a persistent posterior alpha; Hegerl et al., 2012). This is most likely related to the limited use of 2 min of eyes closed EEG in the present study, which might have been too short of a recording time to reliably pick-up differences in alpha power found during the 4 minutes of recording used in the studies of Bruder et al. (2001, 2008) or the expected changes

in EEG vigilance between groups (Hegerl et al., 2012). In contrast, the difference in vigilance regulation for the alpha stage became evident after 1 min, and became stronger with time.

An important strength of this multi-site study was the large sample size, but this could also account for differences in results between this study and others that were conducted at only one research site. Weaknesses of the study include the relatively high response and remission rates obtained and the relatively low venlafaxine-XR doses used, which call into question whether the actions of venlafaxine were really typical of an SNRI. Also, EEG as compared to fMRI has relatively less spatial resolution, and a further limitation is that eLORETA estimates in a specific ROI are based on an inverse model and thus yield estimates of neuronal sites that are inferred and not directly quantified.

In conclusion, alpha EEG power in relation to MDD and antidepressant treatment outcome seems to be regulated differently in males compared to females. Therefore, future studies should report EEG alpha findings for male vs. female subgroups separately. Our FAA finding warrants replication to establish its utility as a biomarker for the prediction of treatment outcome to SSRIs.

Disclosures

MA reports research grants and options from Brain Resource Ltd. (Sydney, Australia). GB, UH reports no conflicting interests and no financial disclosure to declare relating to Brain Resource Ltd. or any other companies; CS has received income and stock options with the role of software engineer as an employee with Brain Resource Ltd. DP has received income and stock options with the role of science and data processing manager as an employee with Brain Resource Ltd. AE reports research funds from Brain Resource Ltd. Related to this study; KF reports research grants, options and shares from Brain Resource Ltd. JMG has previously received fees from Brain Resource for consultancies unrelated to this study (Sydney, Australia), and is a stock-holder in Freedomway Corp Pte. Ltd. LH reports 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.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at <http://dx.doi.org/10.1016/j.clinph.2015.05.032>.

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