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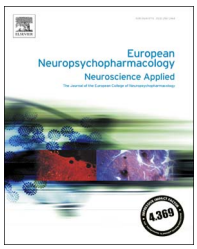

EEG connectivity between the subgenual anterior cingulate and prefrontal cortices in response to antidepressant medication

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Abstract
Antidepressant medication is the most common treatment for major depressive disorder (MDD), however, the precise working mechanism underlying these treatments remains unclear. Recent neuromodulation treatments demonstrate that direct stimulation of the dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex (DMPFC), and subgenual anterior cingulate (sgACC) relate to clinical improvement, suggesting connectivity alterations of the DLPFC-DMPFC-sgACC network to mediate antidepressant response. The international Study to Predict Optimized Treatment in Depression (iSPOT-D) is an international multicentre study that collected EEG data for 1008 MDD patients, randomized to 3 different antidepressant medications (N=447 MDD with complete pre- and post-treatment data and N=336 non-MDD). Treatment response was defined by a decline of >50% on the Hamilton Rating Score for Depression ($HRSD_{17}$). We investigated whether connectivity in alpha and theta frequencies of the DLPFC-DMPFC-sgACC network changed from pre- to post-treatment between: (i) patients and controls, and (ii) responders (R) and non-responders (NR). Women exhibited higher alpha

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and theta connectivity compared to males, both pre- and post-treatment. Furthermore, theta, but not alpha, hypo-connectivity was found for MDD patients. A decreased alpha connectivity after treatment was found only for male responders, while non-responders and females exhibited no changes in alpha connectivity. Decreasing alpha connectivity could potentially serve as a treatment emergent biomarker, in males only. Furthermore, it could be useful to *a priori* stratify by gender for future MDD studies.

1. Introduction

Major depressive disorder (MDD) is a chronic mental disease with a remitting and relapsing course. Despite the variety of available treatments, up to 40–50% of patients fail to respond (Kessler and Bromet, 2013). The use of antidepressant medication is a first-line treatment for MDD, in particular the use of selective serotonin reuptake inhibitors (SSRI's) and serotonin-norepinephrine reuptake inhibitor (SNRI's). Despite widespread use, the exact working mechanism behind these treatments is not clear. New treatments such as repetitive Transcranial Magnetic Stimulation (rTMS) and Deep Brain Stimulation (DBS) are emerging (Fox et al., 2012; Liston et al., 2014). These new treatments directly targeted key structures in depression such as the dorsolateral prefrontal cortex (DLPFC) (George et al., 2010; O'Reardon et al., 2007), the dorsomedial prefrontal cortex (DMPFC) (Downar and Daskalakis, 2013; Downar et al., 2014) and the subgenual cingulate cortex (sgACC) (Mayberg et al., 2005) and thereby have shown that direct stimulation of these regions is associated with clinical improvement. Recent insights into how these neuromodulation treatments work suggest network connectivity changes within a DLPFC-DMPFC-ACC network to mediate antidepressant response (Fox et al., 2012; Liston et al., 2014), and are also possibly implicated in pharmacological treatments.

The convergent evidence of involvement of these structures indicates that they are likely to be important hubs in the networks that modulate depression. The sgACC and sections of the DMPFC are components of the default mode network while the DLPFC is partly implicated in the central executive network (CEN). A deficit in switching between the DMN and CEN is well known in depression (Liston et al., 2014; Sridharan et al., 2008) and is considered to be one of the main reasons behind cognitive dysfunction in depression. The DLPFC has been described to be hypoactive in depression (Korgaonkar et al., 2013), and an increase in fMRI activity of this structure is associated with treatment response (Fitzgerald et al., 2006; Koenigs and Grafman, 2009). Contrary to the DLPFC, the sgACC has been described to be hyperactive in depression, along with hyperconnectivity to other parts of the DMN observed with PET scans and with fMRI (Liston et al., 2014; Mayberg et al., 2005), and a decrease in activity of the sgACC is associated with antidepressant response (Koenigs and Grafman, 2009; Mayberg et al., 2005). The DMPFC, or dorsal nexus, is a core region to multiple networks, including the DMN, CEN and salience network (SN), with increased fMRI connectivity to all three networks in depression (Sheline et al., 2010). The DMPFC has been observed to be abnormally activated during positive and negative affect processing in MDD, which normalizes after successful treatment (Bermpohl et al., 2009; Dunlop et al., 2016; Mayberg et al., 1999). As rTMS is limited to cortical surfaces, it is hypothesized that DLPFC-rTMS (and DMPFC-rTMS) might exert its antidepressant effect via trans-synaptic connectivity to deeper regions, such as the sgACC (Fox et al., 2012, 2014; George et al., 1995, 1997; Padberg and George, 2009). Serotonergic challenge has been observed to reduce intrinsic functional connectivity in brain regions implicated in mood regulation (Anand et al., 2005, 2007), such as the ventral anterior cingulate cortex (vACC, which includes the sgACC/Cg25 and the rACC/Cg24) and limbic structures such as the amygdala (Drevets et al., 2008; Gudayol-Ferré et al., 2015). However, the full scope of serotonergic and antidepressant action on functional connectivity in the human brain, especially with respect to the DLPFC-DMPFC-ACC network, has not been explored widely.

The international Study to Predict Optimized Treatment in Depression (iSPOT-D) is a multicentre study aimed at finding biomarkers for antidepressant treatment response (Williams et al., 2011). Preferably these biomarkers need to be cost-effective and EEG measurements represent an attractive modality due to the relatively low cost and burden imposed on patients, and informative about underlying brain circuits. To this goal, the study collected EEG data from 1008 MDD patients, randomized to 3 different antidepressant medications, prior to and after 8 weeks of treatment. 336 controls also completed EEG data collection at baseline and at 8 weeks. The aim of this manuscript is to investigate connectivity changes in the DLPFC-DMPFC-sgACC network across 8 weeks of treatment, not only for patients and controls, but also comparatively for antidepressant responders and non-responders, and thus to investigate whether these connectivity differences are state, trait or medication related. To this goal, we explored baseline to post-treatment connectivity changes between responders and non-responders to medication in alpha and theta EEG frequencies, as previous studies using the same sample as the current study have found the most relevant differences in alpha and theta (Arns et al., 2015a, 2015b, 2016). Gender was included as a factor because previous iSPOT-D studies have demonstrated clear qualitative gender differences in topographic distribution of EEG activity and gender-specific predictors of treatment response of alpha asymmetry (Arns et al., 2016) and Event Related Potentials (van Dinteren et al., 2015). Quantitative differences could be resolved by using gender as a covariate, however the clear qualitative differences warrant *a priori* stratification by gender rather

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than covariation, hence in this study Gender was included as a main factor rather than a covariate. Furthermore, it is well known that MDD is more prevalent in females as compared to males (Gorman, 2006; Martényi et al., 2001), further warranting *a priori* stratification by gender.

2. Experimental procedures

2.1. Design

In the international Study to Predict Optimized Treatment Response in Depression (iSPOT-D), a multi-centre, randomized, prospective open-label trial (Phase-IV clinical trial), 1008 MDD participants were randomized to escitalopram, sertraline or venlafaxine-XR in a 1:1:1 ratio. The 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. The complete study protocol and the consort diagram are available elsewhere (Williams et al., 2011; Arns et al., 2016).

2.2. Participants and treatment

This study included 1008 MDD patients and 336 matched healthy controls. A complete description of the study assessments, inclusion/exclusion criteria, diagnostic procedures and treatment is available elsewhere (Saveanu et al., 2015; Williams et al., 2011). In summary, the primary diagnosis of nonpsychotic MDD was confirmed at 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 three antidepressant medications. After eight weeks of treatment, participants were tested again, while still on treatment, using the $HRSD_{17}$, $QIDS\text{-}SR_{16}$ and an EEG assessment. This study was approved by the institutional review boards at all of the participating sites 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. Registry name: International Study to Predict Optimised Treatment - in Depression. Registration Number: NCT00693849; URL: http://clinicaltrials.gov/ct2/show/NCT00693849.

2.3. EEG acquisition

EEG recordings were performed using a standardized methodology and platform (Brain Resource Ltd., Australia). Details of this procedure have been published elsewhere (Williams et al., 2011) as well as details of the reliability and across-site consistency of this EEG procedure (Arns et al., 2016; Paul et al., 2007; Williams et al., 2005). In summary, 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 extended international system). EEG data was collected for two minutes with eyes closed (EC). Data were offline 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 lower eyelid. Impedance was $<5\ k\Omega$ for all electrodes. A continuous acquisition system was employed, with a sampling rate of all channels of 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

EEG pre-processing and validation has been described in more detail elsewhere (Arns et al., 2016; Paul et al., 2007; Williams et al., 2005, 2011). In brief, 1) A high pass filter of 0.3 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, Coles and Donchin (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 (Arns et al., 2016; Paul et al., 2007; Williams et al., 2005, 2011). In addition, an electrode-bridging check was carried out (Alschuler et al., 2014), and channels demonstrating bridging were rejected. 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).

2.4.2. EEG eLORETA analysis

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 connectivity values, for phase lags unequal to zero to rule out volume-conduction effects. The method of eLORETA is described in detail in (Pascual-Marqui, 2007). eLORETA is an improvement over the original LORETA version and the standardized version sLORETA. sLORETA (Pascual-Marqui, 2002) is an improve ment over the older LORETA (Pascual-Marqui et al., 1994), and has the ability to localize test point sources with zero localization error in the absence of noise, and is more accurate. eLORETA (Pascual-Marqui, 2007) is the newest version of LORETA and is a non-linear imaging method and a solution to the inverse problem, with exact and zero localization errors. In addition, eLORETA offers ways to assess functional brain connectivity between cortically defined regions of interest (ROIs), minimally affected by volume conduction and low spatial resolution.

2.4.3. ROI extraction

For the exact ROI coordinates see Table 1. The following ROIs were defined:

1) Right and left Dorsolateral Prefrontal Cortex (DLPFC) based on the coordinates published by (Fitzgerald et al., 2009; Fox et al., 2012) with a sphere of 20 mm, restricted to grey matter only (Figure 1c and d).

Table 1 ROI coordinates in MNI space.

	X	*Y*	*Z*	Sphere (mm)	BA
Left DLPFC	−46	45	38	20	46
Right DLPFC	46	45	38	20	46
DMPFC	0	30	30	20	24
sgACC	6	16	−10	10	25

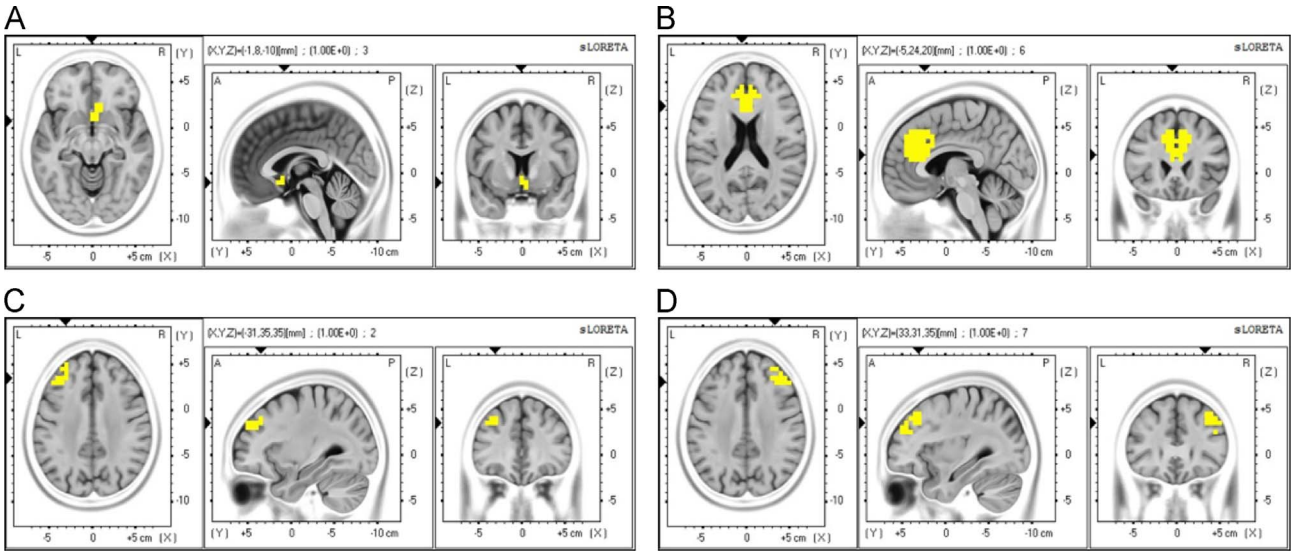

Figure 1 Regions of interest. The four regions of interest (ROI) used in this study; **(A)** sgACC; **(B)** DMPFC (medial) **(C)** DLPFC (left); **(D)** DLPFC (right).

2) The dorsomedial prefrontal cortex (DMPFC) was defined by a seed coordinate (Salomons et al., 2014), with a sphere of 20 mm (Figure 1b).
3) The subgenual ACC (sgACC) was defined based on the averaged coordinates obtained from a meta-analysis (Fox et al., 2012), that included studies that showed reductions in subgenual activity as a result of antidepressant response (Figure 1a).

2.4.4. Connectivity

Using this region of interest (ROI) approach, linear-lagged connectivity measures were computed. In general, this linear-lagged connectivity represents the linear covariation between fluctuations in activity recorded from distinct neural networks, that were measured in preselected ROI's. These connectivity measures were obtained for theta (4–7.5 hz) and alpha (8–13 hz) frequencies with LORETA, as previous studies using the same sample as the current study have found the most relevant differences in these frequency bands (Arns et al., 2015a, 2015b, 2016). It should be noted that the specific frequencies chosen to measure theta differs from the earlier iSPOT-D manuscript on theta in which the 6.5–8.0 Hz theta band was used since that band was specifically used in rACC studies. However, normally the standard theta band of 4–7.5 Hz is used in studies that employ data from iSPOT, thus were also used in the current study. These values were then log-transformed prior to analysis, to meet statistical assumptions of normal distribution. (Table 2).

2.5. Statistics

Response was defined as a $>50\%$ decrease in $HRSD_{17}$ score from baseline to 8 weeks. Based on the literature, as summarized in the introduction, our primary analysis focused on sgACC-rDLPFC (right); sgACC-lDLPFC (left) and sgACC-DMPFC (medial) connectivity. These combinations are in the analysis referred to as Connectivity-pair. Gender was included as a factor because gender differences have now been reported in several manuscripts using the iSPOT-D sample (Arns et al., 2016; van Dinteren et al., 2015).

The primary hypotheses tested in this study are:

(1) MDD patients exhibit abnormal baseline connectivity values within these Connectivity-pairs, compared to healthy controls.
(2) Baseline connectivity within these Connectivity-pairs in responders, but not non-responders, will normalize over time.
(3) Baseline connectivity within these Connectivity-pairs differs between men and women, as a consequence of distinct brain network connectivity, and may lead to different antidepressant medication outcomes.

State effects will show-up as connectivity changes across time for responders but not for non-responders to treatment, medication effects will show-up as changed connectivity for both responders and non-responders, while trait effects would show no time-differences for responders or non-responders, but merely a difference between MDD patients and healthy controls that remains stable across time.

The analysis was divided into multiple parts. First, we examined baseline differences between MDD patients and healthy controls (HC). A repeated measures design was conducted, with baseline Connectivity-pair as within-subject factor. Gender and Group (HC or MDD) were included as between-subject factors in the MDD-HC analysis. When a significant interaction between Group or Gender and Connectivity-pair was observed, analysis was run separately for Group or Gender, or per Connectivity-pair using univariate models.

Secondly, we focused on differences over time between responders (R), non-responders (NR) and healthy controls. Repeated measures ANOVA with Connectivity-pair and Time (pre and post-treatment) were used as within-subject factors. Gender and Group (R, NR or HC) were used as between-subject factors. In a separate analysis we added medication as additional between-subjects factor and evaluated whether medication type (escitalopram, sertraline or venlafaxine-XR) led to significant differences with respect to connectivity changes. *F* ratios were evaluated using degrees of freedom computed using the Greenhouse-Geisser ε correction where appropriate to counteract heterogeneity of variance matrices associated with repeated measures. When Gender or Connectivity-pair had significant interactions with Group, Time or combinations of those, analyses were run separately per Gender, Group, Time or Connectivity-pair. When post-treatment connectivity values were analyzed separately from baseline values, the latter were included as a covariate to correct for baseline differences in connectivity values. Furthermore, Group means were used to calculate the effect-size (Cohen's *d*), where needed. The Group means and standard deviations were directly adapted from SPSS. Correlation analysis with these difference scores was conducted to confirm whether a change in

Table 2 Sample characteristics.

	Intention to treat (N)	Per protocol (N)	Gender	N	Response type	N	Treatment	N	Age	HDRS pre	HDRS post	MDD duration	Number of episodes
MDD	1008	655	Male	277	Responders	172	Escitalopram	61	37.16 (11.60)	21.85 (3.92)	4.66 (3.05)	14.03 (11.48)	3.95 (1.51)
							Sertraline	63	38.29 (12.58)	21.57 (4.28)	6.19 (3.08)	13.63 (11.98)	3.98 (1.42)
							Venlafaxine-XR	48	38.95 (12.65)	21.31 (3.66)	5.83 (3.27)	12.02 (11.18)	3.85 (1.58)
					Non-responders	105	Escitalopram	37	43.56 (11.30)	21.62 (3.49)	16.08 (4.19)	16.25 (12.21)	4.25 (1.38)
							Sertraline	32	43.04 (13.14)	22.28 (4.42)	16.75 (4.89)	16.90 (14.43)	3.74 (1.59)
							Venlafaxine-XR	36	38.36 (12.30)	22.17 (4.27)	15.31 (3.85)	16.91 (12.01)	4.09 (1.22)
			Female	378	Responders	243	Escitalopram	70	38.44 (12.58)	21.63 (3.90)	5.10 (3.10)	14.38 (13.00)	3.96 (1.44)
							Sertraline	92	35.79 (11.42)	22.27 (4.06)	5.87 (3.29)	14.54 (12.43)	4.20 (1.30)
							Venlafaxine-XR	81	37.13 (12.73)	20.72 (3.55)	5.80 (3.14)	15.78 (12.14)	4.14 (1.09)
					Non-responders	134	Escitalopram	49	38.04 (13.65)	21.90 (4.60)	15.94 (4.87)	15.73 (12.70)	4.10 (1.31)
							Sertraline	46	40.45 (12.65)	21.61 (4.12)	15.85 (4.35)	13.49 (11.66)	3.75 (1.51)
							Venlafaxine-XR	39	40.73 (14.06)	22.77 (4.17)	17.44 (4.07)	17.84 (14.76)	3.89 (1.49)
HC	336		Male	145					37.16 (12.77)	0.95 (0.14)	0.95 (0.12)		
			Female	191					36.87 (13.35)	1.30 (0.12)	1.15 (0.11)		

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connectivity was associated with symptom severity or improvement. In addition, in case of finding significant differences between R and NR, discriminant analysis was performed and a Receiver Operator Characteristic (ROC) curve was plotted to investigate how well these measures could be used to predict treatment outcome. An ROC curve is a graph displaying the true positive rate vs. the false positive rate for R and NR status.

3. Results

Of 336 controls, 279 subjects (157 females, 122 males) had useable baseline EEG data and were included in the baseline analysis. 222 of them also had complete week 8 data, and were included in part two of the analysis. Of the 1008 MDD patients, 807 patients had useable baseline EEG data and were used in the baseline analysis (434 females, 373 males). 655 patients (378 females, 277 males) had completed the study according to the protocol. Of these, there were 447 subjects with useable resting EEG and $HRSD_{17}$ data at baseline and post-treatment (244 females, 203 males) and were used for the second part of the EEG analysis. The log-transformed data were normal distributed. Within the MDD sample, there was a significant age difference between responders and non-responders ($F(1,637)=7.884$, $p<0.005$). Therefore, age was entered as a covariate in all analyses.

3.1. Alpha

3.1.1. MDD-HC (baseline)

Women had higher baseline alpha connectivity in all three connectivity pairs, compared to men, indicated by a main

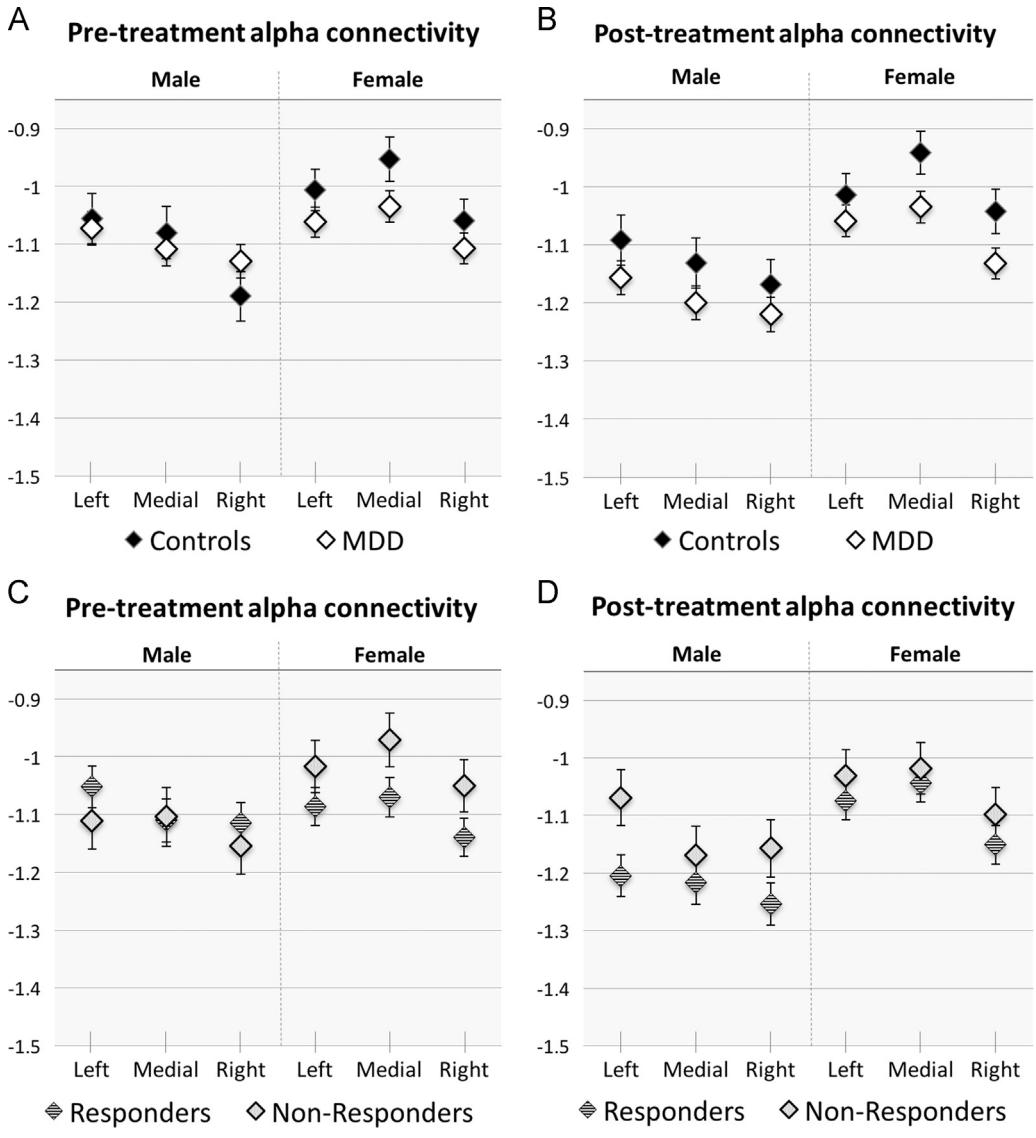

Figure 2 Pre- and post-treatment alpha connectivity. A) Pre-and B) post treatment alpha connectivity levels for sgACC-lDLPFC (left), sgACC-DMPFC (medial) and sgACC-rDLPFC (right) connectivity, separated for males and females, between controls and MDD patients. C) Pre-and D) post-treatment alpha connectivity levels for sgACC-lDLPFC (left), sgACC-DMPFC (medial) and sgACC-rDLPFC (righ) connectivity, separated for males and females, between responders and non-responders. Error bars represent the standard error of the mean (SEM). *The results shown are based on the age-covaried analysis, including only subjects used in the second part of the analysis.

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effect of Gender ($F(1,1081)=6.956$, $p<0.008$; ES$=-0.156$) (Figure 2A and B). There was no effect of Group, nor interactions involving Group, suggesting there were no baseline differences between MDD patients and controls (Figure 2A and B).

3.1.2. R-NR-HC (baseline-week 8)

For alpha connectivity, a main effect of Gender was observed ($F(1, 662)=11.690$, $p<0.001$, ES$=0.266$), and of Connectivity-pair $F(2, 661)=3.633$, $p<0.027$). Women exhibited in general higher connectivity with the sgACC then men, and the sgACC has higher connectivity with the DMPFC, than with the left or right DLPFC (Figure 2C and D).

A significant Time*Group*Gender ($F(2, 662)=3.346$, $p<0.036$) interaction, Connectivity-pair*Gender ($F(2,661)=9.947$, $p<0.001$) and a Connectivity-pair*Time*Group ($F(4,1324)=2.777$, $p<0.026$) interaction were found. Separate analysis per gender revealed a significant Group*Time effect ($F(2,292)=4.105$, $p<0.017$) for males only, not for females. This was driven by a decreasing connectivity over time only for responders ($F(1,130)=19.439$, $p<0.001$, ES$=0.369$), while non-responders and controls remained stable (Figure 3). Subsequent analysis within the male group revealed that the group differences were negligible on baseline, but significantly different after 8 weeks of treatment, when covaried for baseline connectivity ($F(2,291)=4.4$, $p<0.013$). Pooled across connectivity pairs, responders differed from non-responders ($p<0.013$, ES$=-0.363$) and healthy controls ($p<0.016$, ES$=-0.327$). Non-responders did not differ from healthy controls ($p<0.797$). These results will be further explored in the discriminant analysis. A positive correlation between $HRSD_{17}$ difference scores and connectivity difference scores ($r=0.189$; $p<0.007$) was found within the male MDD group, but not separately for responders or non-responders, confirming only the results from the ANOVA.

As reported above, there was also a significant Connectivity-pair*Time*Group and Connectivity-pair*Gender interaction. Separate analyses for each Connectivity-pair investigating the Time*Group effect only revealed a main effect of Group for sgACC-DMPFC connectivity ($F(2,665)=3.746$, $p<0.024$), but no Time*Group effects. Analyzing the Time*Connectivity-pair interaction for each Group revealed a main effect of Time ($F(1,287)=7.183$, $p<0.008$) in the responders group, but no Time*Connectivity-pair interaction. It should be noted that the apparent difference between males and females with respect to the pattern of results as visible in Figure 2, in where a larger post-treatment difference is seen within male responders for sgACC-lDLPFC and sgACC-rDLPFC connectivity compared to sgACC-DMPFC connectivity, could not be confirmed statistically. With respect to medication-type effects, no apparent interactions nor main effects were found.

3.2. Theta

3.2.1. MDD-HC (baseline)

A baseline gender difference ($F(1,1082)=11.421$; $p<0.001$; ES$=0.205$) was found for theta connectivity, which was higher in woman (Figure 4). A main effect of Group was found ($F(1,1082)=5.135$; $p<0.024$; ES$=0.157$), discriminating MDD patients from healthy controls, but a Group*Connectivity-pair interaction ($F(2,1080)=6.374$, $p<0.002$) was observed as well, indicating that the group difference varied across Connectivity-Pairs. Subsequent analysis showed that the group difference was only significant for sgACC-lDLPFC ($p<0.003$) and sgACC-DMPFC ($p<0.010$). In general, MDD patients had lower connectivity then controls (Figure 4). A Connectivity-pair*Gender interaction ($F(2,1080)=3.225$, $p<0.040$) was found, but Gender remained significantly different in all Connectivity-pairs: sgACC-lDLPFC ($p<0.004$), sgACC-DMPFC ($p<0.001$) and sgACC-rDLPFC ($p<0.001$).

3.2.2. R-NR-HC (baseline-week 8)

Woman exhibited higher connectivity values then men ($F(1,662)=18.635$, $p<0.000$, ES$=0.341$). Furthermore, a main effect of Group was found ($F(2, 662)=6.068$, $p<0.002$), which was driven by controls being different from responders ($p<0.001$) and non-responders ($p<0.027$), thus only

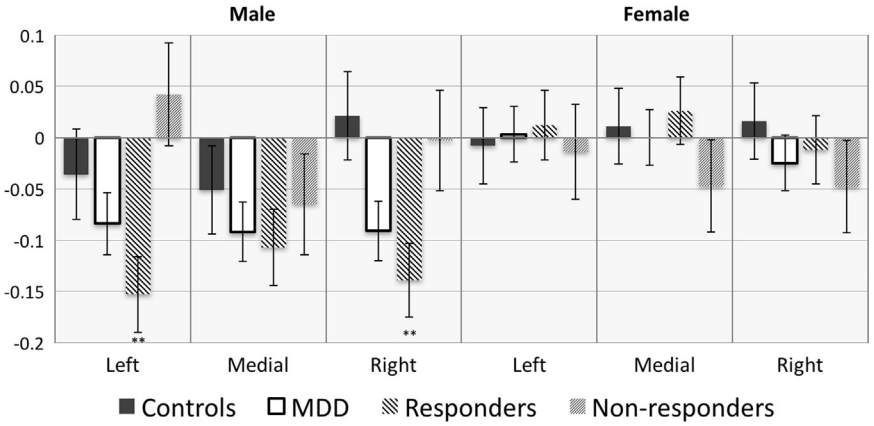

Figure 3 Change in alpha connectivity from pre- to post treatment. Alpha connectivity changes over time (post minus pre-treatment) for sgACC-lDLPFC (left), sgACC-DMPFC (medial) and sgACC-rDLPFC (right), separated for males and females, MDD patients and controls, and responders and non-responders. Error bars represent the standard error of the mean (SEM). *The results shown are based on the age-covaried analysis, including only subjects used in the second part of the analysis. Significant changes over time are observed only in male responders.

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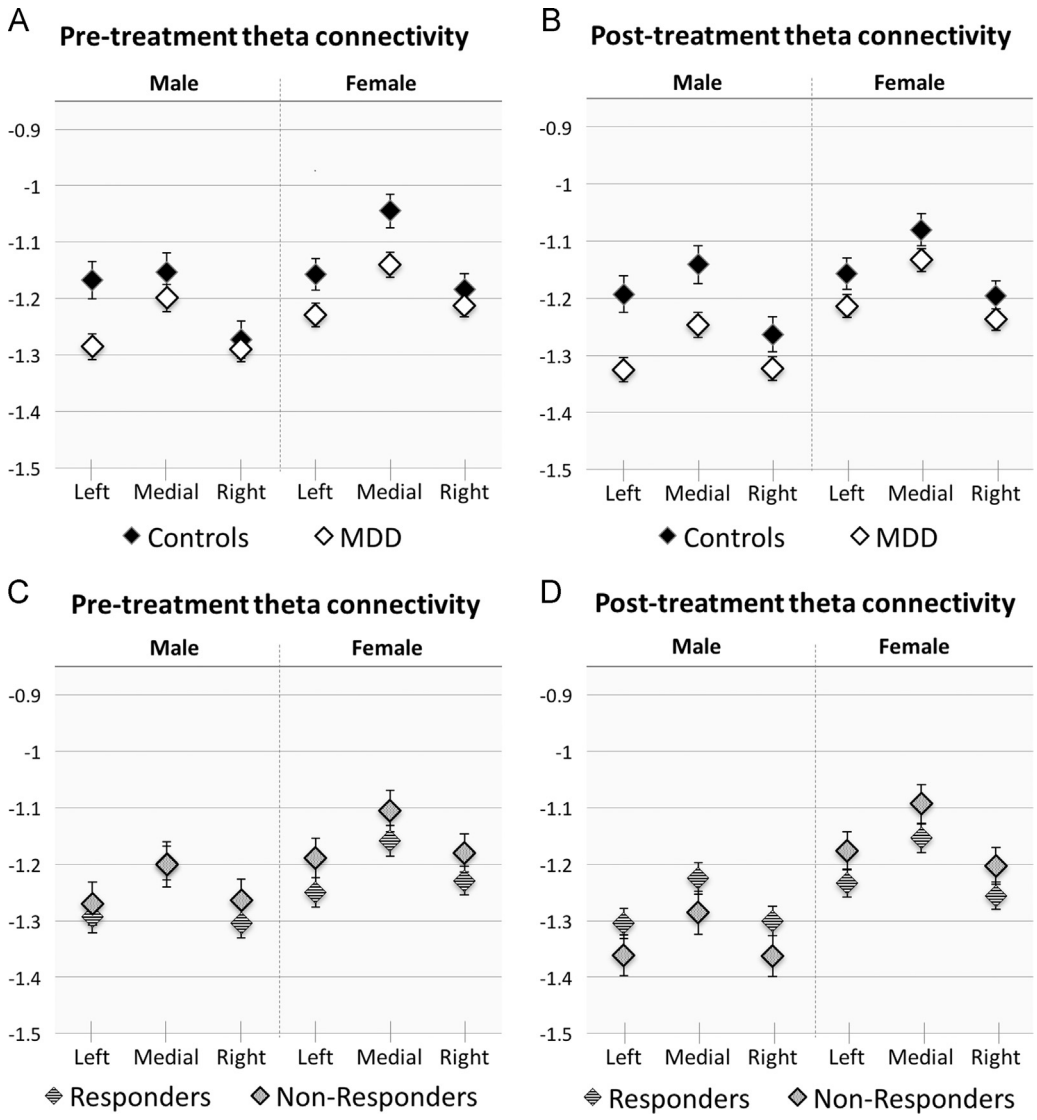

Figure 4 Pre- and post-treatment theta connectivity. A) Pre-and B) post-treatment theta connectivity levels for sgACC-lDLPFC (left), sgACC-DMPFC (medial) and sgACC-rDLPFC (right) connectivity, separated for males and females, between controls and MDD patients. C) Pre-and D) post-treatment theta connectivity levels for sgACC-lDLPFC (left), sgACC-DMPFC (medial) and sgACC-rDLPFC (righ) connectivity, separated for males and females, between responders and non-responders. Error bars represent the standard error of the mean (SEM). *The results shown are based on the age-covaried analysis, including only subjects used in the second part of the analysis.

emphasizing the difference between patients and controls. A main effect of Connectivity-pair was observed ($F(2,662) = 15.926$, $p < 0.001$). Higher connectivity is observed for sgACC-DMPFC, in both male and female subjects, when compared to sgACC-lDLPFC or sgACC-rDLPFC connectivity, similar to findings for alpha (Figure 4).

Furthermore, Connectivity-pair interacted with Group ($F(4, 1324) = 3.227$, $p < 0.012$). Subsequent analysis per Connectivity-pair indicated a significant Group difference for sgACC-lDLPFC ($F(2, 662) = 9.761$, $p < 0.000$), and for sgACC-DMPFC ($F(2, 662) = 5.101$, $p < 0.006$) but both were due to a difference between patients and controls (respectively sgACC-lDLPFC and sgACC-DMPFC connectivity: R-HC ($p < 0.001$;$p < 0.001$); NR-HC ($p < 0.006$;$p < 0.027$)), and not between R-NR ($p < 0.337$;$p < 0.553$). No apparent time effects were found. Additional analysis of the differential effects across treatment-types did not reveal interaction with treatment-type nor any main effects. (Figure 5).

3.3. Discriminant analysis

A discriminant analysis was performed using alpha sgACC-lDLPFC, sgACC-rDLPFC and sgACC-DMPFC connectivity difference scores. The grouping variable was responder status. The model resulted in a significant Wilks' Lambda ($P < 0.004$; Wilks' Lambda = 0.936; Chi-square(3) = 13.204). Figure 6 shows the specificity (18%) and sensitivity (91%) for responders (dotted line) and non-responders (striped line), with an area under the curve of 0.664. 65,5% of the subjects

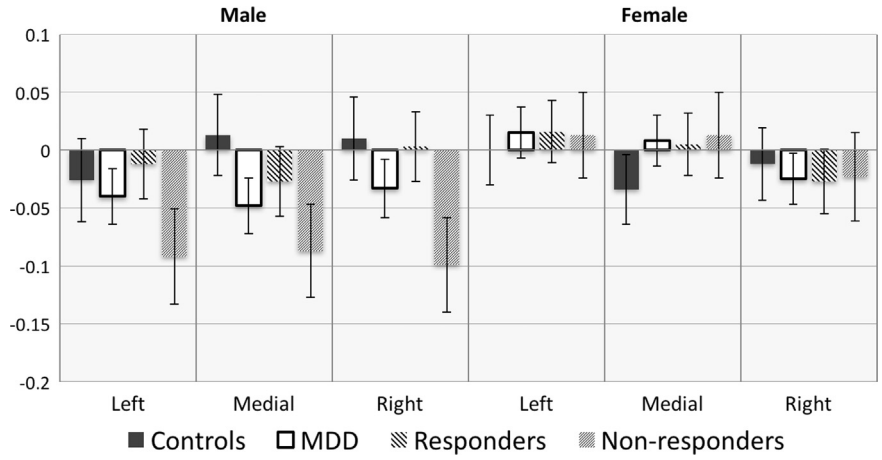

Figure 5 Change in theta connectivity from pre- to post-treatment. Theta connectivity changes over time (post minus pre-treatment) for sgACC-lDLPFC (left), sgACC-DMPFC (medial) and sgACC-rDLPFC(right), separated for males and females, MDD patients and controls, and responders and non-responders. Error bars represent the standard error of the mean (SEM). *The results shown are based on the age-covaried analysis, including only subjects used in the second part of the analysis.

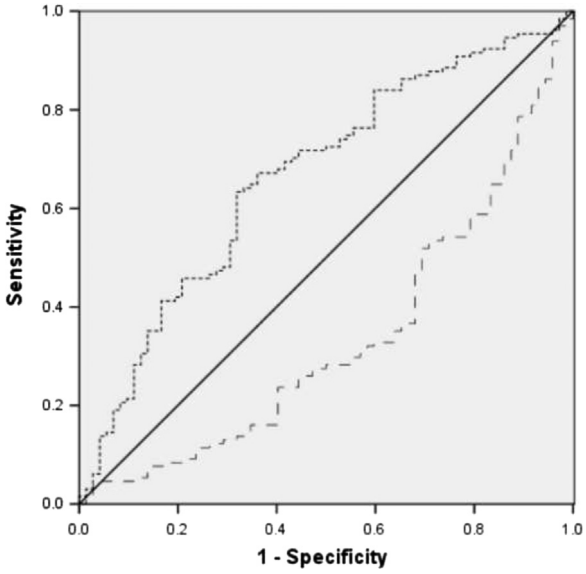

Figure 6 Receiver Operator Curve (ROC) for the results of a discriminant analysis on response. Receiver Operator Curve (ROC) for the results of a discriminant analysis on response, with an area under the curve of 0.664. The ROC shows the specificity (18%) and sensitivity (91%) for responders (dotted line) and non-responders (striped line).

could be classified correctly. Running the same analysis including the baseline characteristics of age, MDD severity and anxiety severity resulted in a significant Wilks' Lambda ($p<0.011$; Wilk's Lambda=0.897; Chi-Square(8)=19.934), with an area under the curve of 0.698, showing a slight improvement of the model.

4. Discussion

We explored the sgACC-DLPFC-DMPFC network in relation to depression and treatment response and found a significant treatment-related change over time for male responders in the alpha band for connectivity of the sgACC with the DLPFC and DMPFC, whereas non-responders and control subjects remained stable over time. Based on these results, there was not enough evidence to determine whether decreasing alpha connectivity could be state-related. However, the decreasing alpha connectivity in male responders, suggests that, for males only, decreasing alpha might serve as a treatment emergent biomarker.

Males classified as responders based on the $HRSD_{17}$ change, displayed a significant decrease in alpha connectivity, with a significant post-treatment difference, while non-responders and control subjects exhibited stable connectivity patterns over the 8-week time course. Interestingly, male responders thus become less like healthy controls for alpha connectivity, which is not in line with previous literature on treatment response in MDD patients, in which multiple studies have described a normalization of the existing hyper-connectivity (Koenigs and Grafman, 2009; Liston et al., 2014; Mayberg et al., 2005). In some studies differences in ACC or DLPFC connectivity after treatment have been reported, therefore it was hypothesized that connectivity tends to normalize or resemble the connectivity pattern of healthy controls, but could still be incomplete (Liston et al., 2014). However, this is also not the case within this sample, where the opposite is seen in male responders: they become less like healthy controls. This could be due to the type of treatment (antidepressant medication rather than neuromodulation), the use of EEG recording rather than fMRI, or due to gender differences not picked up in previous studies that were not statistically powered to tests such gender differences. Decreasing alpha connectivity might serve as a treatment emergent biomarker, as supported by the discriminant analysis and ROC curve, and needs to be investigated in a gender controlled design, on earlier time points within 8 weeks of treatment to evaluate the potential as treatment emergent biomarker for a more clinically relevant usage, for example, similar to the work on treatment emergent biomarkers at 5–7 days such as EEG Cordance (Leuchter et al., 1994) and ATR (Leuchter et al., 2009a, 2009b).

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Secondly, strong gender differences in connectivity patterns were found in MDD patients as well as in healthy controls. In general, we observed higher connectivity in females for both alpha and theta activity. This is in line with previous research on network connectivity where especially the frontal parts exhibits more (inter-hemispheric) connections in females, while males had more (intra-hemispheric) connections throughout the whole brain (Ingalhalikar et al., 2014). The higher functional connectivity in females could be due to the frontal locations of our regions of interest e.g. the DLPFC and DMPFC. To rule out that these gender differences would be driven by weight or length, we included these factors as covariate in a post-hoc analysis, which did not change the results. Gender differences have not been widely explored in depression research, particularly for treatment response. Clinically however, depression is found to be more common in female patients (Kessler and Bromet, 2013). The cause for this is not clear, but it could be due to differences in emotional processing between men and women (Gorman, 2006).

Thirdly, we found theta hypoconnectivity in MDD patients, both in male and females, in contrast to healthy controls, while previous research has described hyperconnectivity of the sgACC with the CEN (which includes right and left DLPFC) (Liston et al., 2014; Mayberg et al., 2005). However, it is worth noting that these studies performed analysis using fMRI connectivity measurements and it is not yet understood how these relate to EEG measurements of connectivity. While both methods are usually based on the covariation in fluctuations of the signal, the source of the signal differs. fMRI connectivity more often relates to slower fluctuations in blood oxygenation responses (<1 Hz), whereas in our analysis we looked at faster oscillations in the theta and alpha bands (3.5–13 Hz). EEG reflects the cortical electrical activity of the brain produced by waxing and waning postsynaptic potentials, and the waveforms produced can be classified according to frequency. In contrast, fMRI is usually based on the Blood Oxygen Level Dependent (BOLD) signal, in where the amount of oxygen in the blood is a reflection of activity in an area, and is a result of a long chain of neural and hemodynamic processes (Sato et al., 2010). When there is high covariation between two regions, one could assume that there is a functional connection between the two regions. It should be noted that our analysis addressed only non-zero phase-lag connectivity so that contamination by volume conduction effects can be ruled out (Pascual-Marqui et al., 2011).

Limitations of this study are in the design, which was not placebo-controlled, while the placebo-response rates are about 31–45%, compared to 50% responses to antidepressants (Peciña et al., 2015) Signal-to-noise ratio is lower in EEG compared to fMRI, however, due to the large sample size available in this study provides improved sensitivity to these effects. EEG is marked by a high temporal but a low spatial resolution. The EEG picks up post-synaptic potentials from cortical layers, but is hardly or not at all sensitive to post-synaptic potentials from deeper structures such as the hippocampus and amygdala. The sgACC is a relatively small structure lying deeper in the brain, and while it is still valid to use as an EEG target in LORETA analysis, the measured EEG signal might not be an exact reflection of this precise region of interest and may also reflect activity derived from adjacent areas due to the relatively low spatial resolution of EEG at this depth.

In conclusion, we found strong evidence that alpha connectivity decreases in male responders in response to antidepressant medication, while non-responders and healthy controls remained stable, suggesting that decreased alpha might serve as a treatment emergent biomarker, but, more research is needed to evaluate connectivity on multiple time points within these 8 weeks of treatment. Furthermore, we found gender differences in the DLPFC-sgACC-DMPFC network in a large sample of MDD patients and healthy controls, similar to gender differences reported in other analysis of the iSPOT-D study (Arns et al., 2016; van Dinteren et al., 2015). These data suggest that future EEG and imaging studies in MDD could benefit by *a priori* stratifying their analysis by gender (rather than co-vary for gender) to rule out such gender differences that could results in spurious findings or mask real effects.

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Contributors

TI managed the literature searches, performed the analyses and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

TI has no disclosures. MA reports research grants and options from Brain Resource (Sydney, Australia) and shares from neuroCare Group (Munich, Germany), acted as a paid consultant for neuroCare Group, Vivatech and is a co-inventor on 4 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; The other authors report no disclosures or conflicts of interest.

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