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Alpha power, alpha asymmetry and anterior cingulate cortex activity in depressed males and females

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Left fronto-cortical hypoactivity, thought to reflect reduced activity in approach-related systems, and right parietal hypoactivity, associated with emotional under-arousal, have been noted in major depressive disorder (MDD). Altered theta activity in the anterior cingulate cortex (ACC) has also been associated with the disorder. We assessed resting frontal and parietal alpha asymmetry and power in non-medicated MDD ($N = 53$; 29 females) and control ($N = 43$; 23 females) individuals. Theta activity was examined using standardized low-resolution electromagnetic tomography (sLORETA) in the ACC [BA24ab and BA32 comprising the rostral ACC and BA25/subgenual (sg) ACC]. The MDD group, and particularly depressed males, displayed increased overall frontal and parietal alpha power and left midfrontal hypoactivity (alpha$_2$-indexed). They also exhibited increased sgACC theta$_2$ activity. MDD females had increased right parietal activity, suggesting increased emotive arousal. Thus, unmedicated depressed adults were characterized by lower activity in regions implicated in approach/positive affective tendencies as well as diffuse cortical hypoarousal, though sex specific modulations emerged. Altered theta in the sgACC may reflect emotion regulation abnormalities in MDD.

1. Background

Electroencephalographic (EEG) research has revealed that increased relative right fronto-cortical activity (probed with EEG alpha, which is inversely related to cortical activity; Neuper and Pfurtscheller, 2001) tends to emerge during the processing of negative information and emotions, while greater relative left fronto-cortical activity is associated with positive information/affective processing (Davidson, 1998). However, electrocortical asymmetry profiles accompanying the processing of anger or cognitive dissonance have also been associated with increased relative left fronto-cortical activity (Wacker et al., 2003; Harmon-Jones, 2004). To account for this, current frontal asymmetry models posit that approach tendencies and positive information/emotion processing are associated with greater left anterior activity while withdrawal tendencies and negative information/emotion processing are linked with right frontal activity. In support of this, individuals with greater relative left anterior activity report increased positive and decreased negative affect compared to those with the opposite asymmetry (Tomarken et al., 1992). Resting frontal alpha asymmetry has also been found to predict affective responses to emotive stimuli (Tomarken et al., 1990; Wheeler et al., 1993). As such, resting anterior asymmetry may be a trait-like feature biasing affective style (Jacobs and Snyder, 1996), though it is also plausible that these profiles may reflect a motivational abnormality rather than an affective disposition (Pizzagalli et al., 2005).

Individuals with major depressive disorder (MDD) tend to exhibit relative left frontal hypoactivity (Davidson and Slagter, 2000; Deldin and Chiu, 2005; Deslandes et al., 2008; Pössel et al., 2008; Kemp et al., 2010), which, along with right hyperactivity, has been associated with greater depression scores (Saletu et al., 2010). Remitted depressives also exhibit decreased relative left frontal activity (Henriques and Davidson, 1990). Thus, left frontal hypoactivity may be a risk marker for MDD. Although similar frontal asymmetry patterns have also been noted in other psychiatric disorders (e.g. anxiety, ADHD; Hale et al., 2010; Moscovitch

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et al., 2011), they have been most extensively studied and reliably altered in MDD.

Increased alpha power/amplitude over right parietotemporal regions has also been associated with MDD (Bruder et al., 2005, 2012; Kentgen et al., 2000). Right parietotemporal activity is thought to be involved in modulating emotion-related autonomic arousal (Heller and Nitschke, 1997), thus, decreased right parietotemporal activity may reflect diminished emotional arousal in the disorder. In support of this, depressed patients with co-morbid anxiety, characterized by a hyper-aroused state, were found to display right parietotemporal hyperactivity (Keller et al., 2000; Kentgen et al., 2000) while those without anxiety exhibit decreased activity in this region (Bruder et al., 1997). Accordingly, electrocortical asymmetry models have been expanded to include two dimensions: the valance/motivation dimension involving anterior regions and the arousal dimension involving right parietotemporal aspects.

However, certain caveats regarding the asymmetry model exist. First, when anterior asymmetry is examined in individuals without extreme or stable asymmetry, its relationship with dispositional affect weakens (Debener et al., 2000). Second, methodological differences (e.g. reference, sites assessed, alpha bands) influence the relationship between frontal asymmetry and affective style/motivation (Thibodeau et al., 2006). Factors such as age and sex have also been shown to modulate asymmetry, though the effects of the latter have been mixed and not extensively probed (Stewart et al., 2010). Lastly, several studies have noted no frontal asymmetry alterations in MDD, questioning its reliability as an endophenotype (Carvalho et al., 2011; Segrave et al., 2011).

In addition to alpha asymmetry alterations, enhanced alpha amplitude/power has been noted in MDD (Pollock and Schneider, 1990; Roemer et al., 1992; Baehr et al., 1998; Kemp et al., 2010, but see Knott and Lapierre, 1987; Bruder et al., 1997; Mientus et al., 2002). This increase tends to emerge posteriorly, though anterior alpha power increases have also been documented (Bauer and Hesselbrock, 2002; Ricardo-Garcell et al., 2009). Thus, depression may be associated with overall cortical hypoactivity. Evidence of altered delta, beta and gamma power in MDD is less consistent and sparse, though midfrontal theta modulations have been noted and are discussed below.

In humans, midfrontal theta power has been localized to the frontal lobes, specifically the anterior cingulate cortex (ACC; Ishii et al., 1999). Though tonic theta rhythms are evident across the scalp (but are maximal midfrontally), midfrontal theta tends to be phasic, as it emerges during working and episodic memory as well as during spatial navigation tasks, for instance. Thus, midfrontal theta has been linked with focused and sustained attention/concentration as well as mental effort. Though the functional correlates of resting midfrontal theta are less characterized, it is nevertheless thought to reflect ACC activity (Mitchell et al., 2008).

The ACC is involved in a range of cognitive and emotive functions such as conflict monitoring, error detection and in evaluating the emotional significance of stimuli (i.e., operations that evoke theta activity; Pizzagalli, 2011). It is a heterogeneous structure that is subdivided into ventral and dorsal aspects. The subgenual (sgACC; BA25) and rostral aspects (BA32 and BA24ab) comprise the ventral ACC; dorsally, the ACC includes BA24′ and BA32′ (Pizzagalli, 2011). The latter constitute the dorsal 'cognitive' ACC as it is intimately connected with the dorsolateral prefrontal cortex (DLPFC). The ventral ACC comprises the 'affective' region as it is connected with limbic and subcortical structures as well as the orbital PFC (Ongür and Price, 2000). The sgACC, in particular, has been implicated in visceral responses to emotive processing, in emotive memory formation and in regulating reward contingencies (Drevets et al., 2008).

A handful of studies have indicated that MDD is associated with increased anterior and right hemisphere scalp theta amplitude/power (Kwon et al., 1996; Knott et al., 2000; Ricardo-Garcell et al., 2009). However, decreased frontal theta activity in MDD has been noted using source localization techniques [magnetoencephalography, low-resolution brain electromagnetic tomography (LORETA); Wienbruch et al., 2003; Coutin-Churchman and Moreno, 2008; Saletu et al., 2010]. Methodological differences may underlie these discrepancies, whereby frontal scalp theta amplitude/power likely stems from several neural generators, while source localization/neuroimaging approaches enable activity assessment in specific regions. Sex may also account for some of the variability, though its influence on theta activity has been underexplored (Morgan et al., 2005). Altered theta may reflect disrupted functional connectivity in fronto-cingulate pathways mediating emotive regulation in MDD (Pizzagalli et al., 2003). This idea is strengthened by evidence that ACC-localized theta is useful in predicting antidepressant treatment response (Pizzagalli et al., 2001, 2005; Mulert et al., 2007; Korb et al., 2011) and is modulated with treatment (Knott et al., 1996; Landolt and Gillin, 2002).

This study assessed resting frontal and parietal alpha power and asymmetry in MDD and control males and females. Alpha power and asymmetry were assessed using three reference montages, which have been shown to influence asymmetry (Stewart et al., 2010; Hagemann, 2004). Given evidence that alpha$_2$ has been linked with memory retrieval while alpha$_1$ is broadly associated with attentive processes (Klimesch et al., 2007), and that individual variability characterizes alpha$_{Total}$ (Segrave et al., 2011), power in alpha sub-bands was assessed. We expected greater relative left frontal alpha power in MDD. Given that past work suggests decreased ACC-localized theta activity in MDD, we probed this and expected similar findings. Theta sub-bands were assessed as previous work suggests somewhat different profiles of theta sub-bands in MDD (Fingelkurts et al., 2006). Finally, correlations were carried out between the electrophysiological indices and clinical scores. To our knowledge, very few studies have assessed alpha asymmetry and power as well as ACC-theta in the same (large) sample of depressed males and females despite known alterations in these indices in MDD.

2. Methods

2.1. Participants

Resting EEG activity was obtained from 53 adults with a primary diagnosis of MDD (Table 1). Patients were diagnosed by

Table 1
Major depressive disorder (MDD) and control group characteristics & demographics (Means ± S.D.).

	MDD females ($N = 29$)	MDD males ($N = 24$)	Control females ($N = 23$)	Control males ($N = 20$)
Age	43.2 ± 11.6*	37.7 ± 11.6	37.2 ± 7.8	35.8 ± 11.9
Education (Years)	15.6 ± 2.4	16.5 ± 2.5	16.4 ± 2.0	16.4 ± 1.9
HAMD$_{17}$	22.4 ± 5.1*	19.1 ± 4.7	–	–
HAMD$_{29}$	32.5 ± 5.4	29.5 ± 6.7	–	–
MADRS	30.8 ± 5.1	30.8 ± 5.4	–	–
BDI-II	–	–	4.4 ± 5.0	3.1 ± 4.8
Ethnicity	27 Caucasian; 1 Asian; 1 South Asian;	21 Caucasian; 2 Asian; 1 African	20 Caucasian; 2 South Asian; 1 African	19 Caucasian; 1 Asian

HAMD$_{17/29}$: Hamilton Rating Scale for Depression, 29 & 17 item versions.
MADRS: Montgomery–Åsberg Depression Rating Scale; BDI-II: Beck Depression Inventory-II.
*$p < .05$, MDD females had higher HAMD$_{17}$ versus MDD males; MDD females were older than control females.

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psychiatrists using the Structured Clinical Interview for DSM (Diagnostic and Statistical Manual of Mental Disorders) IV-TR Diagnoses, Axis I, Patient Version (SCID-IV-I/P; First et al., 1997); most patients have had previous major depressive episodes. The 17 and 29 item versions of the Hamilton Rating Scale for Depression ($HAMD_{17/29}$; Hamilton, 1960) and Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) were used to assess symptom severity; MADRS scores were $\geq$22 (moderate depression) at enrollment. Exclusion criteria included: Bipolar Disorder (BP-I/II or NOS), psychosis history, current (<6 months) drug/alcohol abuse or dependence, history of seizures or known increased seizure risk, unstable ($\geq$3 months) medical condition and history of anorexia/bulimia. Patients at a significant risk for suicide were also excluded. Patients with a secondary diagnosis of some anxiety disorder were included ($N = 33$: no anxiety co-morbidity; $N = 12$: sub-threshold anxiety; $N = 8$: secondary diagnosis of some form of anxiety). At the time of testing, patients were not taking any psychoactive drugs; appropriate drug washout periods were employed prior to testing for any previously medicated patients.

Forty-three adults with no psychiatric, alcohol/drug abuse or dependence history (assessed with non-patient version of the SCID [SCID-IV-I/NP]), and no history of seizures or brain trauma were tested (Table 1). Controls were included only if they scored $\leq$13 on the Beck Depression Inventory-II (BDI-II; Beck et al., 1996) and if they had no psychiatric history in first-degree relatives (Family Interview for Genetic Studies [FIGS]-assessed; Maxwell, 1992).

2.2. Session procedures

Prior to testing, participants abstained for >3 h from caffeine and/or nicotine, as well as alcohol and drugs (other than medication for a physical condition) beginning at midnight. Upon arrival, mood evaluations were carried out using the Profile of Mood States (POMS; McNair et al., 1992) questionnaire from which values are aggregated to form seven mood dimensions (tension–anxiety, depression–dejection, anger–hostility, vigor–activity, fatigue–inertia, confusion–bewilderment and total mood disturbance, which is computed from the other dimensions). Electrodes were applied and EEG was recorded. All participants were compensated $30.00 CDN/session (patients participated in multiple sessions as part of a larger study). This study was approved by the Royal Ottawa Health Care Group and the University of Ottawa Social Sciences and Humanities Research Ethics Boards; informed consent was obtained from all participants.

2.3. Electrophysiological recordings

While participants were seated in a sound- and light-attenuated chamber, EEG recordings were obtained during 3 min vigilance-controlled eyes-closed (EC) and 3 min eyes-open (EO) conditions (counterbalanced). EEG was recorded (500 Hz; mastoid referenced) using a cap with 32 Ag/AgCl electrodes (EasyCap, Herrsching–Breitbrunn, Germany) positioned according to the 10-10 system (Chatrian et al., 1985); electrooculographic (EOG) activity was also obtained. An AFz electrode served as the ground. Impedance was maintained at $\leq$5 kΩ and EEG was recorded with amplifier filters set at .1–80 Hz (BrainVision Recorder, Richardson, TX, USA). Acquired signals were stored for subsequent analyses (BrainVision Analyzer, Richardson, TX, USA).

Off-line, EEG data were re-referenced and analyzed using three references: average mastoids ($TP_{9/10}$), Cz and average references. Signals were filtered (.1–30 Hz), ocular-corrected (Gratton et al., 1983) and segmented into 2 s epochs (50% overlap). This was followed by artifact rejection, which excluded epochs with EEG activity exceeding $\pm$75 μV; data were also visually inspected for artifacts and faulty channels. Subsequently, >100 s artifact-free data for each EO/EC condition were subjected to a Fast Fourier Transform algorithm (Hanning window with 5% cosine taper) for computation of absolute, ln-transformed power (μV^2) at $alpha_1$ (8–10.5 Hz), $alpha_2$ (10.5–13 Hz), $alpha_{Total}$ (8–13 Hz), $theta_1$ (4–6 Hz), $theta_2$ (6–8 Hz) and $theta_{Total}$ (4–8 Hz). Alpha power was assessed at $F_{4/3}$, $F_{8/7}$, $P_{4/3}$ and $P_{7/8}$. Asymmetry indices were calculated for each alpha band by subtracting power at left electrodes from homologous right electrodes (i.e., $F_4 - F_3$, $F_8 - F_7$, $P_4 - P_3$; positive values reflect greater right hemisphere alpha power, and thus decreased relative right hemisphere activity; negative values reflect the opposite). Only right-handers (Oldfield, 1971) were examined in the alpha asymmetry analyses (MDD females = 27, males = 22; control females = 23, males = 18).

2.4. Source localization

EC $theta_1$, $theta_2$ and $theta_{Total}$ EEG was re-referenced to the average (as in Pizzagalli et al., 2001) and subjected to analysis with standardized low-resolution electromagnetic tomography (sLORETA) software (Pascual-Marqui, 2002; artifact- and ocular-corrected epochs, 60 s of data from 28 electrodes). Practical considerations dictated the use of 60 s of data for sLORETA analyses; others have used substantially shorter recording periods (e.g. Korb et al., 2011). sLORETA analysis estimates neuronal activity as current density based on the Montreal Neurological Institute 152 template creating a low-resolution activation image. The sLORETA solution space consists of 6239 voxels (5 × 5 × 5 mm/voxel) restricted to gray matter. Current source density is calculated from a linear, weighted sum of scalp potentials; this value is then squared for each voxel yielding current density power measures (A/m^2). Validation of the previous version of sLORETA (i.e., LORETA) has been independently replicated (Phillips et al., 2002) and cross-validated (Pizzagalli et al., 2004; Mulert et al., 2005); cross-validation of sLORETA also exists (Olbrich et al., 2009). sLORETA was used to estimate theta current source density at specific ACC regions of interest (ROIs). Consistent with precedent work (Mulert et al., 2007), ROIs (including both hemispheres) were: BA24ab (16 voxels) and BA32 [54 voxels], comprising the rostral ACC, as well as BA25 [subgenual (sg) ACC; 12 voxels; Supplementary Table 1; Fig. 1]. Due to faulty channels, several participants were excluded from the sLORETA analysis ($N = 50$ MDD; 28 females and $N = 39$ controls; 23 females). As hemispheric effects were not assessed, 6 left-handed or ambidextrous individuals (4 MDD; 2 controls) were included in the sLORETA analysis (their inclusion did not alter results, data not shown).

2.5. Statistical analyses

Analyses of variances (ANOVAs) were carried out (SPSS Inc., Chicago, IL, USA) on each POMS dimension with group (MDD; controls) and sex (males; females) as between-subject factors. Repeated-measures ANOVAs (rmANOVAs) were carried out on ln-transformed frontal absolute power in each alpha band with four within-subject factors: regional aspect (medial: $F_{3/4}$; lateral: $F_{7/8}$), condition (EC, EO), reference (average, Cz, mastoid) and hemisphere [left (L), right (R)]. Sex and group were between-subject factors. Similarly, rmANOVAs were carried out on absolute parietal alpha power in each band, with hemisphere (L: average $P_{3/7}$ power; R: average $P_{4/8}$ power), condition and reference as within- and sex and group as between-subject factors; parietal aspects (medial/lateral) were not assessed as there was little rationale for doing so. rmANOVAs were carried out on each alpha asymmetry index ($F_4 - F_3$, $F_8 - F_7$, $P_4 - P_3$; $P_8 - P_7$ asymmetry is not typically

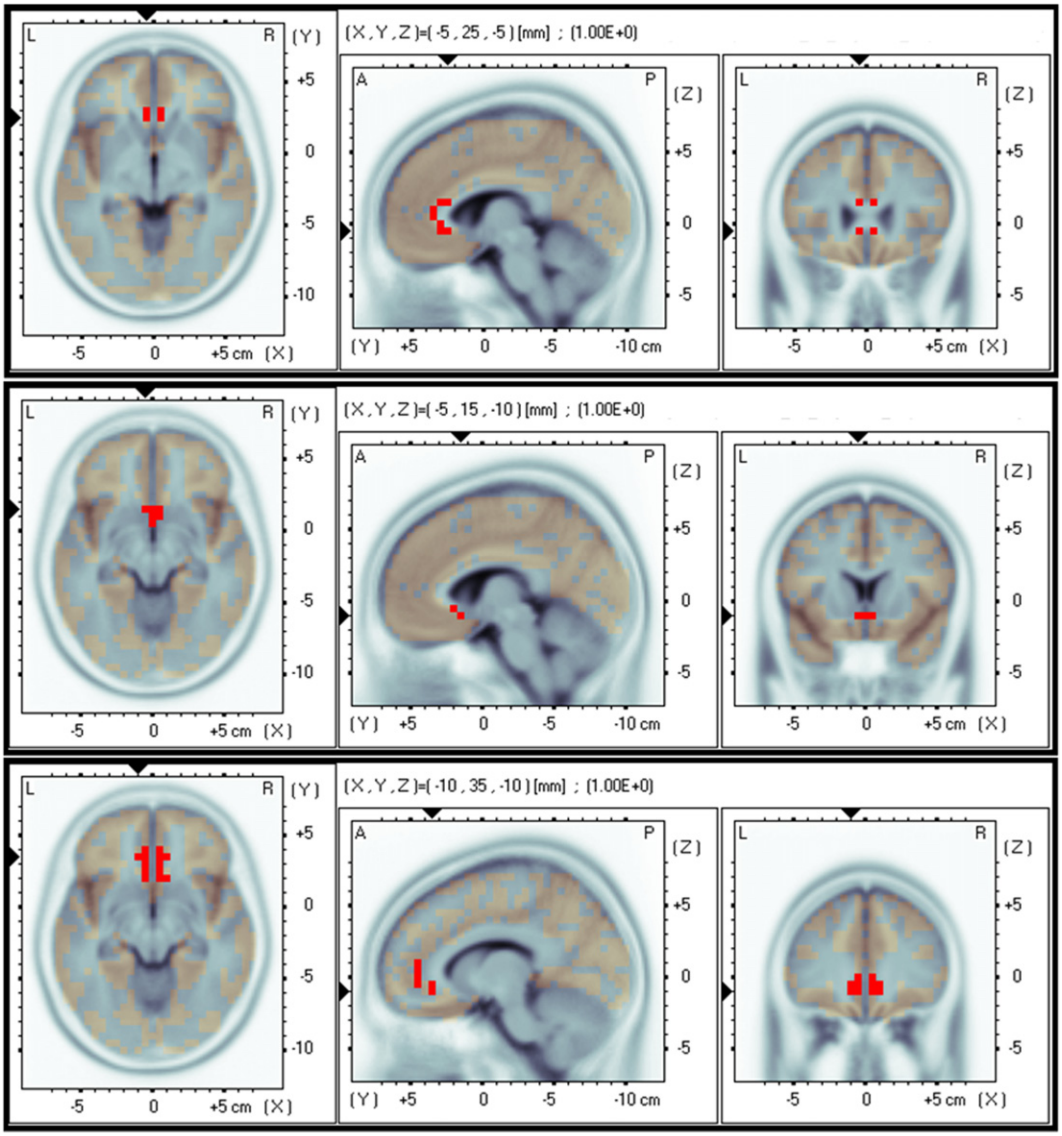

Fig. 1. Anterior cingulate cortex (ACC) regions of interest (ROIs). Top panel: ROI consisting of voxels from BA24. Middle panel: ROI consisting of voxels from BA25 (subgenual ACC). Bottom panel: ROI consisting of voxels in BA32.

probed and was not assessed in the current study) with reference and condition as within- and group and sex as between-subjects factors. Given the known influence of anxiety on parietal alpha asymmetry, its presence/absence (secondary clinical diagnosis, $N = 8$ patients) was used as a covariate in $P_4 - P_3$ alpha asymmetry assessments. Only significant ($p < .05$) main effects are reported as well as interactions wherein direct group or sex comparisons revealed significant differences. For the ROI analyses, rmANOVAs were applied for each theta band, with ROI (BA24ab, BA25, BA32) as within- and group and sex as between-subject factors; main effects are reported as are interactions indicating direct group or sex differences. Greenhouse–Geisser corrections were applied to all significant results. To account for multiple comparisons, Bonferroni adjustments (built into SPSS) were applied to all pairwise comparisons. Correlations were carried out between EC $F_4 - F_3$ asymmetry in the MDD group (sex collapsed; maximal group differences have been reported for $F_4 - F_3$ alpha; Pössel et al., 2008) for each alpha band at all three reference montages and MADRS, $HAMD_{17/29}$ and POMS depression–dejection scores (sex collapsed) for the MDD group. Similar correlations were carried out with EC theta activity at the three ROIs (BA25, BA24ab, BA32). To adjust for multiple comparisons, significance was set at $p < .005$ for the correlations. Unless specified, means ± SEMs (standard error of the mean) are reported.

3. Results

3.1. Profile of mood states (POMS)

Scores were unavailable for one patient ($N = 52$; controls: $N = 43$). A main group effect was noted for tension [$F(1,91) = 110.59$, $p < .001$; MDD: 18.2 ± .8, control: 5.2 ± .9], depression [$F(1,91) = 243.47$, $p < .001$; MDD: 35.4 ± 1.4, control: 3.4 ± 1.5], anger [$F(1,91) = 71.36$, $p < .001$; MDD: 16.9 ± 1.0; control: 3.9 ± 1.1], fatigue [$F(1,91) = 216.76$, $p < .001$; MDD: 20.2 ± .7; control: 4.4 ± .8], confusion [$F(1,91) = 155.18$, $p < .001$; MDD: 16.5 ± .7, control: 4.1 ± .7] and total mood disturbance [$F(1,91) = 300.20$, $p < .001$; MDD: 102.5 ± 3.9, control: 1.6 ± 4.3];

scores were greater for the MDD versus control group. Vigor [$F(1,91) = 169.29$, $p < .001$] scores were lower for the MDD (5.0 ± .7) versus control group (19.4 ± .8).

3.2. EEG results

3.2.1. Alpha power: effects of regional aspect, hemisphere, condition and reference

A main effect of condition existed for alpha$_1$ [$F(1,86) = 130.57$ (frontal), 190.01 (parietal), $p < .001$], alpha$_2$ [$F(1,86) = 199.61$ (frontal), 194.08 (parietal) $p < .001$] and alpha$_{Total}$ [$F(1,86) = 213.40$ (frontal), 276.44 (parietal), $p < .001$], with greater power in the EC condition. A main effect of reference was found for alpha$_1$ [$F(2,86) = 170.97$ (frontal), 343.03 (parietal), $p < .001$], alpha$_2$ [$F(2,86) = 24.82$ (frontal), 24.68 (parietal), $p < .001$] and alpha$_{Total}$ [$F(2,86) = 142.55$ (frontal), 379.86 (parietal), $p < .001$]. For frontal and parietal alpha$_1$, power was different in all reference montages ($p < .05$), with smallest power in the average and greatest in the mastoid reference montage; the same was true for frontal alpha$_{Total}$ ($p < .001$). For frontal alpha$_2$ and parietal alpha$_{2/Total}$, smaller power values existed in the average versus both the Cz and mastoid references ($p < .001$). A main effect of regional aspect was found for frontal alpha$_2$ [$F(1,86) = 31.50$, $p < .001$] and alpha$_{Total}$ [$F(1,86) = 11.35$, $p = .001$], with greater power in the lateral ($F_{7/8}$) versus medial ($F_{3/4}$) aspect; a similar trend existed for frontal alpha$_1$ [$F(1,86) = 3.71$, $p = .056$]. A main effect of hemisphere existed for parietal alpha$_2$ [$F(1,86) = 5.45$, $p = .022$] and alpha$_{Total}$ [$F(1,86) = 4.20$, $p = .043$], with greater power in the right hemisphere.

3.2.2. Frontal alpha power: effects of group and sex

Alpha$_1$: A main effect of group existed [$F(1,86) = 5.44$, $p = .022$] with greater alpha$_1$ power in the MDD (1.70 ± .12 μV^2) versus control (1.29 ± .13 μV^2) group.

Alpha$_2$: A main effect of group [$F(1,86) = 6.80$, $p = .011$], with greater alpha$_2$ power in the MDD (1.19 ± .08 μV^2) versus control (.88 ± .09 μV^2) group, was found. A reference × hemisphere × group × sex interaction [$F(2,172) = 8.36$, $p = .003$] existed. Follow-up comparisons indicated group differences (Cz reference) in the left frontal hemisphere between MDD versus control males ($p = .047$; same trend in right frontal hemisphere, $p = .055$). For the mastoid reference, the same difference was found in the left frontal hemisphere ($p = .010$; same trend in right hemisphere, $p = .051$). In both cases, greater alpha$_2$ power existed in MDD versus control males.

Alpha$_{Total}$: A main group effect existed [$F(1,86) = 6.68$, $p = .011$], with greater power in the MDD (2.33 ± .11 μV^2) versus control (1.92 ± .12 μV^2) group. A reference × aspect × group × sex interaction [$F(2,86) = 3.99$, $p = .025$] existed, with follow-up comparisons indicating greater alpha$_{total}$ in MDD versus control females in the lateral aspect ($F_{7/8}$) in the mastoid reference montage ($p = .046$). For all references, in both regional aspects, MDD males had greater alpha$_{total}$ than control males ($p < .05$).

3.2.3. Frontal alpha power asymmetry ($F_4 - F_3$)

Alpha$_1$ and *Alpha*$_{Total}$: No main effects or interactions with group or sex were noted.

Alpha$_2$: A main effect of group existed [$F(1,86) = 4.87$, $p = .030$], with a positive index in the control (.055 ± .025 μV^2) and a negative one in the MDD group (−.020 ± .023 μV^2; Fig. 2). A positive index reflects greater right frontal alpha power, thus, relatively decreased right fronto-cortical activity; a negative index reflects greater left frontal alpha power, thus, decreased relative left fronto-cortical activity. A condition × group interaction was noted [$F(1,86) = 6.14$, $p = .015$], with a group difference in the EO condition ($p = .007$), with a positive index in controls (.091 ± .031 μV^2) and a negative one in the MDD group (−.025 ± .028 μV^2). A reference × group × sex interaction existed [$F(2,172) = 6.58$, $p = .006$], with a group difference in females in the Cz reference montage ($p = .010$). In males, a group difference was noted in the mastoid reference montage ($p = .009$). In both cases, the index was negative for the MDD and positive for the control group. In controls, a sex difference was noted in the mastoid reference montage ($p = .015$), with a positive index in males (.12 ± .041 μV^2) and a negative one in females (−.013 ± .036 μV^2).

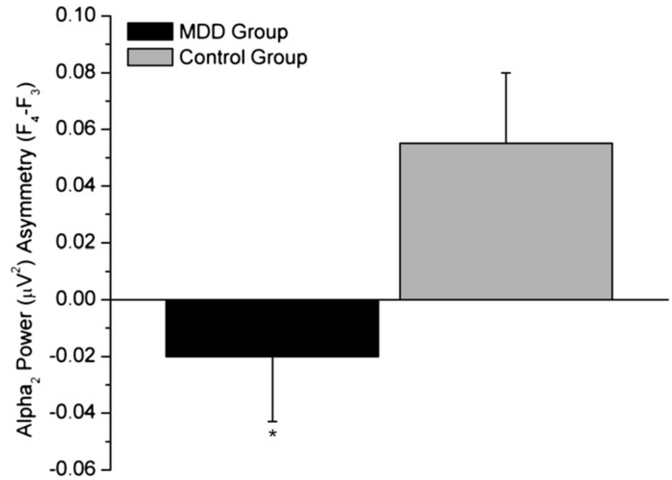

Fig. 2. Midfrontal alpha$_2$ asymmetry in the major depressive disorder (MDD) and control groups (sex collapsed; *$p < .05$). Negative values reflect greater left alpha$_2$ power (i.e., decreased relative left cortical activity); positive values reflect greater right alpha$_2$ power (i.e., decreased relative right cortical activity).

3.2.4. Frontal alpha power asymmetry ($F_8 - F_7$)

Alpha$_1$: Only a main effect of reference existed for alpha$_1$ $F_8 - F_7$ asymmetry [$F(2,172) = 5.55$, $p = .012$], with a difference between the average (−.077 ± .023 μV^2) versus the mastoid (−.008 ± .021 μV^2) reference montage ($p = .012$).

Alpha$_2$: Follow-up comparisons of the reference × group × sex interaction [$F(2,172) = 6.69$, $p = .006$] indicated a group difference in alpha$_2$ $F_8 - F_7$ asymmetry in females in the Cz reference ($p = .045$). MDD females had a more negative asymmetry index (−.095 ± .031 μV^2), reflecting greater relative left hypoactivity, than control females (−.001 ± .034 μV^2). In the MDD group, a sex difference existed in the Cz reference ($p = .036$), with a more negative index for females versus males (.004 ± .034 μV^2).

Alpha$_{Total}$: No main effects of group or sex or interactions were found.

3.2.5. Parietal alpha power: effects of group and sex

Alpha$_1$: No effects of group, sex or interactions existed for parietal alpha$_1$ power.

Alpha$_2$: A main effect of group existed [$F(1,86) = 5.33$, $p = .023$], with greater parietal alpha$_2$ power in the MDD (1.64 ± .10 μV^2) versus control (1.31 ± .11 μV^2) group. A hemisphere × sex × group interaction [$F(1,86) = 4.32$, $p = .041$] was noted. Greater parietal alpha$_2$ power exited in MDD (L: 1.67 ± .15 μV^2; R: 1.77 ± .15 μV^2) versus control (L: 1.15 ± .16 μV^2; R: 1.16 ± .16 μV^2) males in both hemispheres (L: $p = .02$; R: $p = .007$).

Alpha$_{Total}$: A main effect of group was found [$F(1,86) = 4.22$, $p = .043$], with greater parietal power in MDD (2.76 ± .14 μV^2) versus controls (2.34 ± .15 μV^2).

3.2.6. Parietal alpha power asymmetry ($P_4 - P_3$)

Alpha$_1$ and *Alpha*$_{Total}$: No effects of interest were noted for parietal asymmetry.

Alpha$_2$: A group × sex interaction existed [$F(1,85) = 7.06$, $p = .009$], follow-up comparisons indicated a group differences in females ($p = .038$). MDD females exhibited a negative index ($-.053 \pm .040$), reflecting relative left parietotemporal hypoactivity or relative right parietotemporal hyperactivity, while control females exhibited a positive one ($.070 \pm .041$ μV^2), reflecting the opposite. A sex difference existed in the MDD group ($p = .032$), with a negative parietal asymmetry in MDD females ($-.053 \pm .04$ μV^2) and a positive one in males ($.074 \pm .041$ μV^2; Fig. 3).

3.2.7. Anterior cingulate cortex theta activity

For each theta band, a main effect of region was noted [theta$_1$: $F(2,170) = 220.36$, $p < .001$; theta$_2$: $F(2,170) = 58.53$, $p < .001$; theta$_{Total}$: $F(2,170) = 119.22$, $p < .001$], in all cases theta activity was greatest in BA32, intermediate in BA24ab and smallest in BA25.

Theta$_1$ and *Theta*$_{Total}$: No sex or group effects or interactions were noted.

Theta$_2$: A trend for group effect existed [$F(1,85) = 3.48$, $p = .066$], with greater theta$_2$ activity in the MDD ($5.42 \pm .076$ A/m^2) versus control group ($5.20 \pm .09$ A/m^2). A region × group interaction existed [$F(2,170) = 3.22$, $p = .042$], with greater BA25 theta$_2$ activity in MDD ($5.36 \pm .09$ A/m^2) versus controls ($5.07 \pm .1$ A/m^2, $p = .03$; Fig. 4).

3.2.8. Correlations

$F_4 - F_3$ alpha$_1$ asymmetry (mastoid reference) tended to correlate negatively with POMS depression-dejection scores [$r = -.37$, $N = 53$, $p = .006$].

4. Discussion

This study assessed frontal and parietal alpha power and asymmetry as well as ACC theta activity in MDD versus control individuals. Depressed individuals were characterized by disturbances in all mood dimensions (POMS-assessed). These findings indicate that while MDD is primarily characterized by depressed affect, it is also associated with disturbances in several mood dimensions, which may contribute to the specific resting electrocortical and neuroimagaing profiles that have been associated with the disorder. Greater anterior alpha power (i.e. frontal hypoactivity) existed in MDD, which was especially evident in males; similar findings were noted for parietal alpha power. Group differences emerged in midfrontal alpha$_2$ asymmetry indicating left frontal hypoactivity in MDD. MDD females were characterized by right parietal hyperactivity relative to MDD males. Finally, greater sgACC theta$_2$ activity existed in MDD. These results and their significance are discussed below.

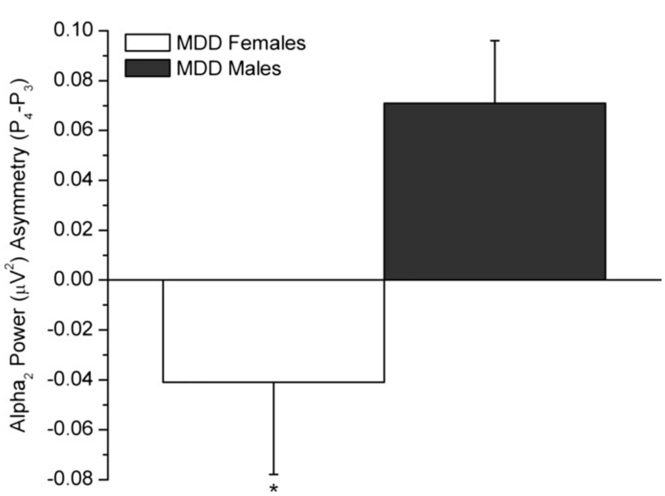

Fig. 3. Parietal alpha$_2$ asymmetry in the females and males with major depressive disorder (MDD) (*$p < .05$). Negative values reflect greater left alpha$_2$ power (i.e., decreased relative left cortical activity or, conversely, increased relative right cortical activity); positive values reflect greater right alpha$_2$ power (i.e., decreased relative right cortical activity).

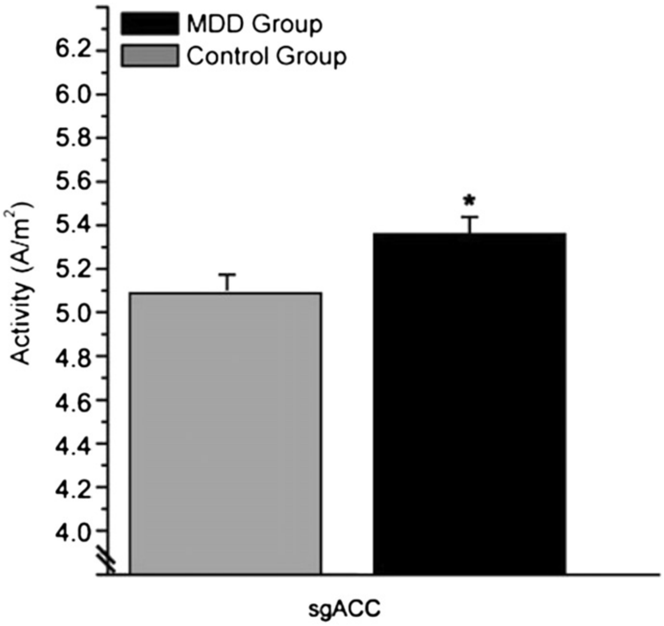

Fig. 4. Theta$_2$ activity in BA25/subgenual anterior cingulate cortex (sgACC) in the major depressive disorder (MDD) and control groups (sex collapsed; *$p < .05$).

A main effect of reference was noted for alpha power, but had a less substantial influence on alpha asymmetry. Nevertheless, group effects on alpha power and asymmetry indices emerged only with certain reference montages, highlighting the utility of assessing several montages in comparable future work (Stewart et al., 2010; Hagemann, 2004). Specifically, group differences in alpha asymmetry and power differences emerged with the Cz, and to a lesser extent, mastoid reference montages; none emerged with the average reference. However, the 32 channels used in the current study likely lacked the spatial sampling recommended for average referencing (Junghöfer et al., 1999). Given that the Cz is cephalically active, its use as a reference has been discouraged, thought it has been frequently used in frontal asymmetry research. Although the mastoid reference is also problematic (Hagemann, 2004), out of the three reference montages used in the current study, it may represent the least biased EEG asymmetry measures.

A main effect of regional aspect existed for alpha$_{2/Total}$, with a similar trend for alpha$_1$, with greater power in lateral versus medial aspects, which differs from what others have found (Deslandes et al., 2008). Nevertheless, these results suggest that different generators likely contribute to alpha power measured at various frontal sites. Future work, perhaps combining EEG and fMRI, which has superior spatial resolution than sLORETA, should also explore the neurofunctional correlates of scalp-localized frontal alpha asymmetry, as research on this is sparse.

Our finding of increased alpha power in MDD (i.e., cortical hypoactivity) is consistent with precedent work (Pollock and Schneider, 1990; Roemer et al., 1992; Baehr et al., 1998; Kemp et al., 2010; Grin-Yatsenko et al., 2010; Köhler et al., 2011), though notable exceptions exist (Knott and Lapierre, 1987; Bruder et al., 1997; Mientus et al., 2002). Given that enhanced alpha existed in both frontal and parietal regions, this points toward generalized cortical hypoactivity in MDD, which did not appear to be directly related to increased fatigue (POMS-indexed; exploratory correlations, data not shown).

When alpha power results was broken down by sex, we found that although MDD males exhibited increased anterior $alpha_2$, this was more pronounced in the left frontal region, consistent with reports of left frontal hypoactivity in depression (Davidson and Slagter, 2000; Deldin and Chiu, 2005; Kemp et al., 2010). The enhanced posterior $alpha_2$ and frontal $alpha_{total}$ power in MDD appeared to be driven largely by depressed males, though no direct sex differences emerged. However, the significance and reliability of these sex-sensitive results is unknown, as limited work has explored the influence of sex on resting EEG in MDD adults.

Alpha sub-bands (i.e., $alpha_1$ and $alpha_2$) were examined because $alpha_{total}$ is susceptible to inter-individual variations due to factors such as genotype and age (Segrave et al., 2011) and alpha sub-bands have been associated with varying cognitive processes (Klimesch et al., 2007). Though the functional correlates of power in alpha sub-bands at rest are unclear, and both are thought to reflect decreased cortical activity, their inspection enables greater specification regarding the electrocortical correlates of MDD. We noted that anterior power in both alpha sub-bands was greater in MDD. However, only $alpha_2$ power was specifically increased in the left frontal hemisphere and enhanced parietally in MDD versus control males, consistent with precedent work also documenting specific $alpha_2$ modulations in MDD (Lubar et al., 2003).

No anterior $alpha_1$ or $alpha_{total}$ asymmetry differences were noted between the groups, in line with others' findings (Mathersul et al., 2008; Carvalho et al., 2011; Segrave et al., 2011). However, a tendency for a negative correlation between $F_4 - F_3$ $alpha_1$ asymmetry and POMS depression-dejection scores in MDD was observed, suggesting that left frontal hypoactivity is associated with greater state depression. A group difference, regardless of reference, existed for midfrontal $alpha_2$ asymmetry. Consistent with the purported involvement of left fronto-cortical activity in approach-related tendencies/motives and positive processing, a positive index was noted in controls indicating increased relative left frontal activity; a negative index existed in the MDD group indicating the opposite. Further breakdown by sex indicated a group difference in midfrontal $alpha_2$ asymmetry in females (Cz reference); in males, a group difference in midfrontal asymmetry emerged (mastoid reference), with the expected asymmetry in both cases. These findings further highlight the influential role of reference in frontal alpha asymmetry assessments and strengthen the idea that altered $alpha_2$ power may be most pronounced in MDD.

Consistent with precedent work (Pössel et al., 2008), mid ($F_4 - F_3$) versus lateral ($F_8 - F_7$) frontal asymmetry better differentiated MDD and control individuals. By extension, this suggests that frontolateral asymmetry may be the less reliable index in the valence/motivation frontal alpha asymmetry model. Few main effects, in general, emerged for frontolateral alpha asymmetry, with the exception of a more negative $alpha_2$ asymmetry index (Cz reference) in MDD females versus males (i.e., greater left frontal hypoactivity in MDD females), consistent with precedent work (Stewart et al., 2010). However, this finding failed to reach statistical significance ($p = .09$) when $HAMD_{17}$ scores were controlled for (data not shown). In general, little evidence for direct sex differences in frontal alpha asymmetry emerged.

Assessments of parietal $alpha_2$ power asymmetry indicated greater relative right parietal activity in MDD females versus both control females and MDD males. Activity in the right parietotemporal cortex has been linked with emotional arousal, suggesting emotional hyperarousal in depressed females (Kentgen et al., 2000; Manna et al., 2010). While it is tempting to associate increased emotional arousal with anxiety (i.e., excessive emotive and physiological arousal) in MDD females (7 MDD females and 1 MDD male had a secondary anxiety diagnosis), this linear relationship is too simplistic as the incidence of anxiety was co-varied for in the analyses. Including sub-threshold anxiety as a covariate also did not alter the results, though it diminished significance (data not shown). Nevertheless, it is feasible that right parietal hyperactivity may be related to specific features of anxiety (e.g. somatic features; Heller and Nitschke, 1997) rather than anxiety in general, which were not specifically probed. Though our findings of relative right parietal hyperactivity in MDD females contradict some reports (Bruder et al., 2005, 2012; Kentgen et al., 2000), no associations between right parietal hypoactivity and MDD have also been noted (Debener et al., 2000; Deslandes et al., 2008; Mathersul et al., 2008) while others, consistent with our results, have reported the opposite (Pössel et al., 2008). Stewart et al. (2011) also found that currently depressed females exhibited greater right parietal activity than those with an MDD history. This was moderated by caffeine consumption, which may have induced greater anxious arousal in currently depressed females. However, this explanation is unlikely in our study given that participants were asked to refrain from caffeine prior to testing, though compliance cannot be assured.

Few studies have examined baseline ACC theta activity in depressed non-medicated individuals versus controls, though some groups have probed frontal scalp-derived theta, and noted both theta power/amplitude reductions (Ohashi, 1994; Wienbruch et al., 2003; Saletu et al., 2010) and increases (Roemer et al., 1992; Knott et al., 2000; Köhler et al., 2011) in MDD. In the current study, greater sgACC $theta_2$ activity was found in the MDD group; a similar trend was noted in BA25, part of the rostral ACC ($p = .11$). Though this runs counter to some findings (Mientus et al., 2002; Coutin-Churchman and Moreno, 2008), our results are consistent with the idea that the ACC, particularly the rostral ACC, is implicated in emotive processing and cognitive control, and that elevated rostral ACC theta in MDD may reflect compensatory activity in fronto-cingulate networks in the disorder (Pizzagalli, 2011). In support of this, elevated baseline sgACC theta (Narushima et al., 2010) and rostral ACC theta has been shown to predict a positive antidepressant response (Pizzagalli et al., 2001; Mulert et al., 2007; Korb et al., 2011).

Our findings of increased ACC theta in MDD were confined to $theta_2$ activity, somewhat consistent with previous work indicating that antidepressant-associated modulations emerged only in theta sub-bands (Pizzagalli et al., 2001; Narushima et al., 2010), thus, alterations in specific theta bands in MDD seem feasible. However, the functional significance of resting activity in theta sub-bands should be further explored. Additionally, though the spatial limitations of sLORETA are acknowledged, significant differences existed in theta activity in the examined ROIs suggesting that theta activity was likely elicited by various aspects ACC aspects (though regional overlap is feasible). The sgACC, where theta activity group differences emerged, and midline brain structures have been implicated in regulating emotional behaviors and the stress response, which tend to be disturbed in MDD (Northoff et al., 2011). Previous research has noted glial loss (Drevets et al., 2008) in the sgACC and metabolic activity alterations (Drevets, 2007; Monkul et al., 2012) in this region in MDD; these alterations could be associated with increased theta activity. However, given that no correlations between depression scores and sgACC theta activity were noted, the increased theta does not appear to be directly related to illness severity.

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5. Limitations & conclusions

Certain study limitations must be pointed out. First, current source density (CSD) analysis was not used, though recent work has highlighted its purported superiority given that it is a "reference-independent measure of the strength of extracellular current generators" underlying the EEG (Tenke and Kayser, 2005) and seems the least likely to bias asymmetry measures. Second, alpha activity source localization should be carried out in future investigations, as relatively scant literature exists on the generators of anterior alpha power and asymmetry (Lubar et al., 2003). Third, it is feasible that assessment of electrocortical activity during an emotional challenge may have resulted in more pronounced group differences (Stewart et al., 2011). However, the utility of assessing resting brain activity is advantageous from a clinical/diagnostic perspective. Additionally, theta activity in the dorsal ACC (BA 25′/32′) should be examined in comparable future work as previous neuroimaging research suggests that MDD is associated with decreased activity in this region (Pizzagalli, 2011). Finally, though exploratory covariate analyses did not indicate that smoking status/abstinence may have influenced the alpha asymmetry results (data not shown), this, along with factors such as depression severity, co-morbid anxiety and age, should be more carefully controlled for in comparable research.

In confirmation and extension of previous literature, MDD was characterized by a general reduction in cortical activity. Midfrontal $alpha_2$ power asymmetry indices, regardless of sex or reference, indicated increased relative left frontal hypoactivity in MDD, consistent with indications that left frontal hypoactivity is associated with decreased approach-related motivations and positive affective dispositions. MDD females exhibited right parietal hyperactivity perhaps reflecting enhanced baseline emotive arousal states. Finally, the MDD group had increased theta activity in the sgACC, a region implicated in emotion and stress response regulation and which has been also associated with morphological and functional alterations in the disorder.

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Contributors

N Jaworska assisted with conceptualizing the study, collected the data, analyzed it and wrote the manuscript.

W Fusee assisted with collecting the clinical data, in patient assessments and recruitment.

P Blier is the PI on the clinical trial from which the patients were recruited. He also carried out patient assessments and edited drafts of the manuscript.

V Knott is the PI on the current study. He oversaw the work of N Jaworska and assisted in data analyses and in editing drafts of the manuscript.

Conflict of interest

Dr. Pierre Blier has been a speaker for, on the advisory boards of, and has received grants/honoraria from Biovail, Eli Lilly, Lundbeck, Organon, Pfizer, and Wyeth; and has a financial interest in Medical Multimedia Inc. None of these companies had any association with the work presented in this manuscript. None of the other authors have any conflicts of interest to disclose.

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Appendix A. Supplementary material

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2012.08.003.

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