

Resting Frontal EEG Asymmetry as an Endophenotype for Depression Risk: Sex-Specific Patterns of Frontal Brain Asymmetry

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Resting frontal electroencephalographic (EEG) asymmetry has been hypothesized as a marker of risk for major depressive disorder (MDD), but the extant literature is based predominately on female samples. Resting frontal asymmetry was assessed on 4 occasions within a 2-week period in 306 individuals aged 18–34 (31% male) with ($n = 143$) and without ($n = 163$) lifetime MDD as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (American Psychiatric Association, 1994). Lifetime MDD was linked to relatively less left frontal activity for both sexes using a current source density (CSD) reference, findings that were not accounted for solely by current MDD status or current depression severity, suggesting that CSD-referenced EEG asymmetry is a possible endophenotype for depression. In contrast, results for average and linked mastoid references were less consistent but demonstrated a link between less left frontal activity and current depression severity in women.

Keywords: EEG asymmetry, depression, sex differences, endophenotype

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The economic and personal burden of depression is overwhelming, contributing to pervasive and chronic disability in occupational and interpersonal functioning (e.g., Greenberg et al., 2003; Judd et al., 2000) and substantially increased risk for suicide (Kessler, DuPont, Berglund, & Wittchen, 1999). In the quest to reduce this burden, *endophenotypes* (Gottesman & Gould, 2003; Iacono, 1998), measurable endogenous characteristics of an individual that are related to underlying mechanisms conferring risk, may prove useful in identifying a subset of the population at risk for developing depression, and may ultimately assist in identifying functional mechanisms that may point to new treatments and preventions. A potential promising endophenotype is resting frontal electroencephalographic (EEG) asymmetry.

Depressed individuals appear to be characterized by a pattern of relatively less left than right resting frontal activity (inferred by

relatively greater left than right alpha band activity; see Allen, Coan, & Nazarian, 2004), which is thought to reflect reduced approach motivation and decreased responsiveness to reward. Moreover, this pattern distinguishes both symptomatic and remitted depressed individuals from never-depressed individuals, suggesting that frontal EEG asymmetry may be a traitlike liability marker for development of depression (e.g., Allen, Urry, Hitt, & Coan, 2004; Coan & Allen, 2003; Gotlib, Ranganath, & Rosenfeld, 1998; Henriques & Davidson, 1990, 1991). Consistent with this hypothesis, research has also demonstrated relatively less left frontal activity in children of depressed mothers (e.g., Dawson, Frey, Panagiotides, Osterling, & Hessl, 1997). Studies examining the heritability of frontal EEG asymmetry have determined that this pattern of frontal regional brain activity has a significant genetic component (Anokhin, Heath, & Myers, 2006; Smit, Posthuma, Boomsma, & de Geus, 2007), but EEG asymmetry may only relate to anxiety and depression risk in young women, not men (Smit et al., 2007), suggesting that further research is needed to explore sex differences in this potential endophenotype for depression.

Psychometric characteristics of resting frontal EEG asymmetry also support a trait-level individual difference, with excellent internal consistency (Towers & Allen, 2009) and modest test–retest reliability in both depressed and nonpsychiatric samples (Allen, Urry, et al., 2004; Hagemann, Naumann, Thayer, & Bartussek, 2002; Tomarken, Davidson, Wheeler, & Kinney, 1992), and approximately 60% of the variance representing stable trait variance (e.g., Hagemann et al., 2002). Several EEG studies, however, have failed to confirm an association between left frontal hypoactivity and depression (e.g., Bruder et al., 1997; Pizzagalli et al., 2002; Reid, Duke, & Allen, 1998), and although some evidence suggests

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that this pattern of asymmetrical frontal activity remains stable in the midst of fluctuating symptom severity (Allen, Urry, et al., 2004), there exists some evidence to the contrary (Debener et al., 2000). Before resting frontal EEG asymmetry can be considered a viable endophenotype for depression risk in a particular subset of individuals, these inconsistencies must be addressed.

Several methodological and sample-specific factors might explain the inconsistent findings, including small patient samples, diagnostic heterogeneity and comorbidity, sexual dimorphism in EEG asymmetry and/or depressive illness, choice of EEG reference, the measure of depression used (e.g., MDD diagnosis vs. questionnaire indexing current symptom severity), and the reliability and stability of EEG asymmetry within and across sessions (e.g., Allen, Coan, & Nazarian, 2004; Allen, Urry, et al., 2004; Coan, Allen, & McKnight, 2006; Davidson, 1998; Hagemann, 2004). To date, however, the role of these factors has not been systematically examined due primarily to relatively small patient samples. In the present study, a large sample of depressed and nondepressed individuals was recruited to address these and other factors in order to evaluate the utility of frontal EEG asymmetry as an endophenotype of risk for depression.

Although a recent meta-analysis suggests a moderately robust association exists between depression (and related constructs) and relatively less left frontal activity (Thibodeau, Jorgensen, & Kim, 2006), participants in EEG asymmetry investigations have been predominantly female (Coan & Allen, 2004; Thibodeau et al., 2006). It thus remains to be determined how reliable and stable this pattern is for depressed men, especially given that studies including substantial male samples (not included in the meta-analysis) are inconsistent, one indicating that male depression is associated with relatively more left frontal activity (Miller et al., 2002), and one demonstrating the opposite pattern (Jacobs & Snyder, 1996). Small patient samples have also prevented within-study comparisons of EEG activity between currently depressed individuals and euthymic individuals with a history of depression (with the exception of Gotlib et al., 1998), a contrast needed to test the assertion that EEG asymmetry is a traitlike marker of depression risk. Conflicting results across studies may also be due to heterogeneity of depressed samples, potentially attributable to types of comorbid anxiety that are associated with different patterns of brain asymmetry than those displayed by nonanxious depressed individuals (e.g., Heller & Nitschke, 1998).

In addition to differences in sample selection and recruitment, EEG-specific methodological issues, such as choice of electrode reference, may account for differences across studies. Cz has been the most-often utilized reference for asymmetry studies (Coan & Allen, 2003), particularly in infant and child samples, but data from the Cz reference do not correlate highly with data from other references thought to be better suited to capturing regionally specific brain activity (cf. Reid et al., 1998; see also Allen, Coan, & Nazarian, 2004; Hagemann, Naumann, & Thayer, 2001, and Hagemann, 2004, for discussion of additional reference issues). A current source density (CSD) derivation has more recently been advocated as an alternative that reduces the influence of cross-hemisphere and distal volume conduction on the asymmetry score with greater specificity for local electrical sources and sinks (Hagemann, 2004). In simpler terms, the CSD algorithm for a particular electrode location estimates the amount of the brain's electrical current flowing in and out of superficial scalp regions

adjacent to that electrode. The CSD reference might thus be preferred as the reference most likely to link surface-recorded frontal EEG asymmetry to activity generated in frontal systems (as opposed to activity from distal nonfrontal sources that can be reflected at frontal recording sites under other reference montages such as average or linked mastoids). No EEG asymmetry studies of clinical depression that utilize a CSD reference appear in the literature.

We addressed these methodological issues in the present study with a substantially larger sample than previous EEG asymmetry studies of depression, obtaining adequate power to examine whether relatively less left frontal activity would characterize individuals with any history of depression and whether this effect might vary for men versus women. To reduce potential heterogeneity of depression, depressed participants included in the study met *DSM-IV* criteria for lifetime major depressive disorder (MDD) and endorsed no comorbid Axis I disorders with the exception of current dysthymia. Current depression was examined categorically (e.g., current MDD status) and dimensionally (e.g., by level of depressive questionnaire symptoms) to determine whether EEG asymmetry findings were simply due to elevated current symptomatology (indicating a state rather than a trait effect). To enhance the ability to identify trait-related variance associated with EEG asymmetry, resting EEG was recorded eight times, twice per day on four separate days within a 2-week period to obtain a reliable measure of trait asymmetry for each participant. Moreover, asymmetry scores were calculated for four reference derivations (average, CSD, Cz, and linked mastoid) to examine whether depression-asymmetry relationships would be found for derivations that are more sensitive to localized potentials versus those that include potentials that are widely distributed or that arise from distant electrical sources.

Method

Participants

Prospective participants were identified using the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) scores obtained either from pretesting in an introductory psychology course at the University of Arizona or from an online survey. The sampling strategy was to recruit not only those with extreme high and low BDI scores but also participants with a broad range of symptoms that would include individuals ranging from no symptoms, to few symptoms, to several symptoms, to full clinical severity. All individuals with BDI pretesting scores over 20 were invited for screening, with other participants drawn from among those individuals with scores in the ranges of 0–5, 6–10, 11–15, and 16–20, with the goal to obtain a sample with scores across the entire range of severity. Prospective participants were initially telephoned by a postbaccalaureate project manager, who determined whether they met exclusionary criteria such as left-handedness, history of head injury with loss of consciousness > 10 min, concussion, epilepsy, electroshock therapy, use of current psychotropic medications, and active suicidal potential necessitating immediate treatment. Individuals receiving current psychotherapy were not excluded. Participants not meeting exclusionary criteria by this screen were invited for an intake interview. All participants accepted into the study were required to be strongly

right-handed (a score of greater than 35 on the 39-point scale of Chapman & Chapman, 1987). Figure 1 provides a detailed flow chart summarizing study recruitment across a 4-year period.

During the intake interview administered by a graduate-level trained clinical rater on a separate day before any EEG evaluations, participants were again screened for the same exclusionary criteria covered in the phone screen, and then further screened for Axis I psychopathology using the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1997). Participants were excluded if they met criteria for any current comorbid DSM-IV Axis I disorder other than lifetime MDD or current dysthymia. Interrater reliability analyses (performed by clinical interviewers and by the first and last authors) for a randomly selected 10% of SCIDs demonstrated high interrater agreement for current and past MDD diagnoses ($\kappa = .81$ and $.91$, respectively). The final sample consisted of 306 participants (95 male), with an age range of 17–34 years ($M = 19.1$, $SE = 0.1$). A total of 143 participants met criteria for the lifetime MDD+ group (Table 1 lists DSM-IV diagnoses for this sample), whereas the remaining 163 participants did not meet criteria for any Axis I disorder and were considered the lifetime MDD– group.

Depression severity was assessed during the intake interview with the BDI-II (Beck, Steer, & Brown, 1996) and the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The intraclass correlation of interrater agreement was $.95$ for a randomly selected sample of 10% of HRSD interviews in the present sample. Because epidemiological studies have indicated an inverse relation between social class and rates of unipolar depression (e.g., Leventhal & Brooks-Gunn, 2000), and because socioeconomic status (SES) has been linked to frontal EEG asymmetry (Tomarken, Dichter, Garber, & Simien, 2004), SES was assessed using the Four Factor Index of Social Status (Hollingshead, 1975).

Table 2 displays participant demographic information as a function of lifetime MDD status and biological sex. Demographic variables (lifetime MDD status by biological sex) were examined using univariate analyses of variance (ANOVAs). A main effect of lifetime MDD status emerged for BDI-II, $F(1, 302) = 112.0$, $p < .001$, $d = 1.30$, and HRSD, $F(1, 302) = 93.4$, $p < .001$, $d = 1.07$, indicating that the MDD+ group had higher scores on current depression measures than the MDD– group (see Table 2). No effects of sex or lifetime MDD status by sex emerged for BDI-II or HRSD (all $ps > .12$). In addition, no effects emerged for SES (all $ps > .22$).

EEG Data Collection and Reduction

Two resting EEG sessions were completed each day, on four separate days with no fewer than 24 hr between visits, and with all four visits completed within a 14-day period (such that the fourth day was not more than 14 days after the first day).¹ Nine participants attended fewer than all four EEG assessment days ($n = 5$ three days, $n = 2$ two days, $n = 2$ one day), but all participants were included in mixed linear model analyses that successfully accommodated missing data (see Bagiella, Sloan, & Heitjan, 2000).

Resting EEG at each session was recorded for eight 1-min baselines of eyes open (O) and eyes closed (C), in one of two counterbalanced orders (OCCOCOOC or COOCOCCO). Sessions within day were separated by approximately 20 min. All EEG data

were collected using a 64-channel NeuroScan Synamps2 amplifier (Compumedics Neuroscan, Charlotte, NC) and acquisition system, using the international 10-20 system for electrode placement. Two electrooculogram (EOG) channels (vertical: superior and inferior orbit of the left eye; lateral: outer canthi) were collected for ocular artifact rejection. All impedances were kept under 10K ohms. Data for each resting session were digitized continuously at 1000 Hz, amplified 2,816 times, and filtered with 200 Hz low-pass filter prior to digitization. EEG data were acquired with an online reference site immediately posterior to Cz and subsequently rereferenced offline to four different references: (a) average of all EEG leads = AVG, (b) CSD (using algorithms from Kayser & Tenke, 2006, and based on the spherical spline approach summarized by Perrin, Pernier, Bertrand, & Echallier, 1989, 1990), (c) Cz, and (d) averaged (“linked”) mastoids = LM.

After acquisition, visual inspection removed epochs with movement and muscle artifacts. Data reduction was implemented using custom scripts in MATLAB (The Mathworks, Inc., Natick, MA). A blink rejection algorithm rejected data segments where ocular activity exceeded ± 75 microvolts in the vertical ocular channel, and an artifact rejection algorithm rejected segments with large fast deviations in amplitude in any channel (e.g., direct current shifts and spikes) that may have eluded human inspection. Data were segmented into 1-min EEG blocks and further epoched into 117 epochs of 2.048 s per block, overlapping by 1.5 s. This overlapping compensates for the minimal weight applied to the end of the epoch by the use of the Hamming window function. Following windowing, a Fast Fourier Transform was applied to all artifact-free epochs. The power spectra from all artifact-free epochs across all 8 min were averaged to provide a summary spectrum for each resting session.² Total alpha power (8–13 Hz) was then extracted from the spectrum for each resting session and site. An asymmetry score for each resting session for each reference montage was calculated by subtracting the natural log-transformed scores (i.e., $\ln[\text{Right}] - \ln[\text{Left}]$) for each homologous left and right pair (e.g., F1 & F2, F3 & F4, F5 & F6, F7 & F8). Higher values on this index putatively reflect relatively greater left activity (i.e., greater right than left alpha; cf. Allen, Coan, & Nazarian, 2004). Asymmetry scores for the two resting sessions within each day were then averaged together to create a measurement of regional brain activity per day. Thus, separate asymmetry scores for 4 days for each of four reference montages were used in analyses, resulting in 16 asymmetry scores per participant at each homologous pair. Although asymmetry scores were computed for all homologous site pairs, analyses for the present study focused on a specific subset of those pairs (F2–F1, F4–F3, F6–F5, F8–F7) that correspond to regions commonly studied throughout the asym-

¹ Of the 21 participants who did not complete their sessions within a 14-day period, 15 completed all sessions within 16 days, whereas the remaining six completed all sessions within 18–20 days.

² Although several studies have demonstrated that eyes-open and eyes-closed alpha power do not differ from each other (e.g., Henriques & Davidson, 1990, 1991; Reid et al., 1998), total alpha power was also calculated separately for usable eyes-open and eyes-closed epochs, and EEG asymmetry analyses performed for both types of data indicated that results generally replicated those of alpha power averaged across all 8 min of each resting session.

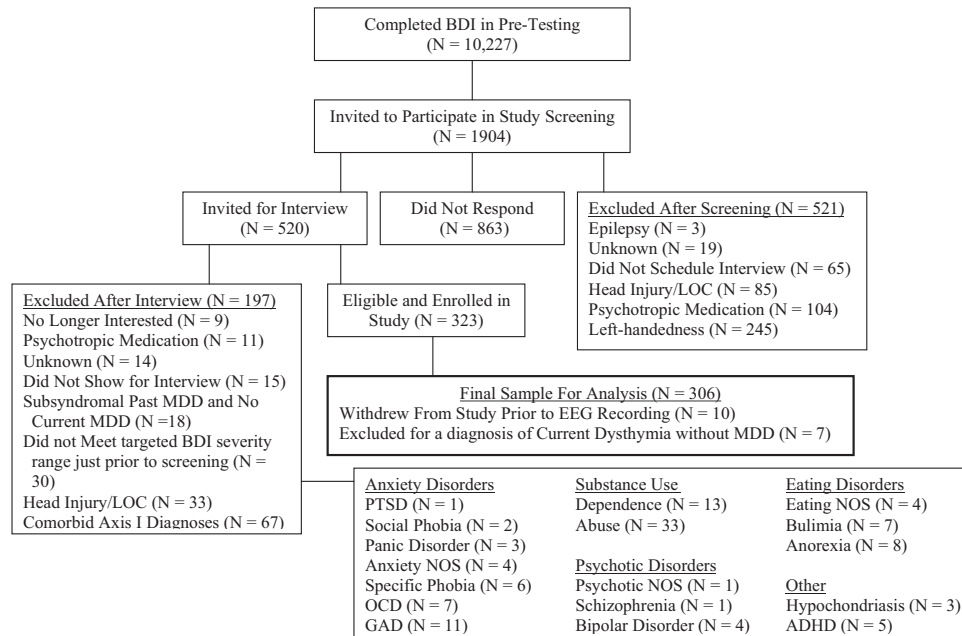


Figure 1. Flowchart of participant screening and enrollment. BDI = Beck Depression Inventory; LOC = loss of consciousness; MDD = major depressive disorder; EEG = electroencephalographic; PTSD = posttraumatic stress disorder; NOS = not otherwise specified; OCD = obsessive compulsive disorder; GAD = generalized anxiety disorder; ADHD = attention deficit hyperactivity disorder.

metry literature (pairs F4–F3 and F8–F7; see review by Coan & Allen, 2004) as well as pairs of channels that neighbor these pairs to provide better resolution of the lateral and medial extent of depression-related frontal asymmetry.³ Intraclass correlations indicated that these frontal EEG asymmetry scores were relatively stable across sessions for each reference montage (AVG range = .71–.77; CSD range = .67–.72; Cz range = .67–.72; LM range = .62–.66).

Table 1
DSM–IV Diagnoses Endorsed in Lifetime MDD+ Group
(N = 143)

Diagnosis	Biological sex	Frequency
Current MDD only	Men	5
	Women	9
Past MDD only	Men	20
	Women	55
Current MDD and past MDD	Men	10
	Women	29
Current MDD and current dysthymia	Men	0
	Women	2
Past MDD and current dysthymia	Men	1
	Women	5
Current MDD, past MDD, and current dysthymia	Men	3
	Women	4

Note. DSM–IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; MDD = major depressive disorder.

Results

Frontal EEG Asymmetry as a Function of Lifetime DSM–IV-Defined Depression

Lifetime MDD status. To examine the relationship between lifetime MDD status and frontal EEG asymmetry, a full-factorial mixed linear model (SAS 9.2) tested the relationship between lifetime MDD status and frontal EEG asymmetry. Lifetime MDD status (past and/or current MDD = lifetime MDD+, never depressed = lifetime MDD–) and biological sex (male, female) were centered between-subjects variables, whereas visit day (4), reference (4: AVG, CSD, Cz, and LM), and channel (4: F2–F1, F4–F3, F6–F5, F8–F7) were within-subjects variables. EEG asymmetry score based on total 8–13 Hz alpha power was the dependent variable.⁴ Cohen’s *d* is reported for significant differences between lifetime MDD groups.

³ Because parietal EEG asymmetry has also been suggested as a risk marker for depression and therefore deserves its own in-depth examination, results for parietal channels are presented in an additional article (Stewart, Towers, Coan, & Allen, 2010). To summarize the relationship between frontal and parietal channels, effects of frontal EEG asymmetry tended to reverse direction in the parietal region, particularly for AVG and LM.

⁴ Asymmetry scores were also computed for lower alpha power (8.5–10.0 Hz) because differential effects associated with psychopathology have been observed in this band (e.g., Davidson et al., 2000; Tomarken et al., 2004), and findings for lower alpha power largely replicated total alpha power results. In order to follow up on asymmetry metric results involving lifetime MDD and current depression severity, analyses examining hemispheric differences in total alpha power (as opposed to differences in asymmetry scores) are included in online supplementary analyses.

Table 2
Group Demographics

MDD status	Biological sex	Caucasian %	BDI-II	HRSD	SES
			<i>M</i> (<i>SE</i>)	<i>M</i> (<i>SE</i>)	<i>M</i> (<i>SE</i>)
Lifetime MDD+	Men (<i>n</i> = 39) ^b	71.8	15.2 (1.3)	9.6 (0.9)	44.3 (2.2)
	Women (<i>n</i> = 104) ^a	77.9	17.6 (0.8)	11.7 (0.5)	41.9 (1.3)
Lifetime MDD-	Men (<i>n</i> = 56) ^a	66.1	5.7 (1.1)	3.9 (0.7)	42.6 (1.8)
	Women (<i>n</i> = 107)	71.0	6.2 (0.8)	4.0 (0.5)	44.3 (1.3)

Note. MDD = major depressive disorder; BDI-II = Beck Depression Inventory II; HRSD = Hamilton Rating Scale for Depression; SES = socioeconomic status as determined by Hollingshead (1975).

^a One participant did not report SES. ^b Two participants did not report SES.

Several effects not involving lifetime MDD status emerged. Results indicated that main effects of reference, $F(3, 906) = 122.3$, $p < .001$, and channel, $F(3, 906) = 39.2$, $p < .001$, were qualified by a Reference \times Channel interaction, $F(9, 2718) = 5.8$, $p < .001$, and supplemental mixed models for each reference separately indicated that main effects of channel emerged for AVG, CSD, and LM (all $ps < .001$) but not for Cz ($p > .09$). For AVG and LM, F2–F1 was associated with the largest relative left frontal activity, followed by F4–F3, F6–F5, then F8–F7 (all channels were significantly different from each other at $p < .05$ with the exception of F2–F1 and F4–F3 for AVG). For CSD, F2–F1 and F4–F3 were associated with higher relative left frontal activity than F6–F5 and F8–F7 (all $ps < .05$), but frontal asymmetry did not differ within medial channels (F2–F1 and F4–F3) or within lateral channels (F6–F5 and F8–F7).

Of key interest were effects involving lifetime MDD status. Figure 2 illustrates that a main effect of lifetime MDD emerged, $F(1, 302) = 4.7$, $p = .03$, that was qualified by a Lifetime MDD \times Reference interaction, $F(3, 906) = 22.2$, $p < .001$, and supplemental full-factorial mixed models performed separately for each

reference montage indicated that a main effect of lifetime MDD emerged for CSD ($p < .001$ and $d = 0.93$), demonstrating that the lifetime MDD+ group displayed relatively less left frontal activity than the MDD- group. In contrast, no effects of lifetime MDD emerged for AVG ($p > .06$), Cz ($p > .26$), or LM ($p > .43$). No Lifetime MDD \times Sex or Lifetime MDD \times Sex \times Reference interactions emerged for the omnibus analysis (both $ps > .29$). In addition, no Lifetime MDD \times Channel or Lifetime MDD \times Channel \times Reference interactions emerged (both $ps > .92$), indicating that the lifetime MDD effect was not differentially manifest across the four frontal sites.

Follow-up analyses: Current MDD status and depression severity. We used two approaches to assess whether the apparent link between lifetime MDD status and frontal EEG asymmetry for the CSD-referenced data was due to current levels of depressive symptoms. The first approach reran the full-factorial linear mixed model with CSD-referenced data, but instead of lifetime MDD status, the model included current MDD status (current MDD+ = all participants with current MDD, regardless of past MDD status; past MDD+ = participants with past MDD but not current MDD

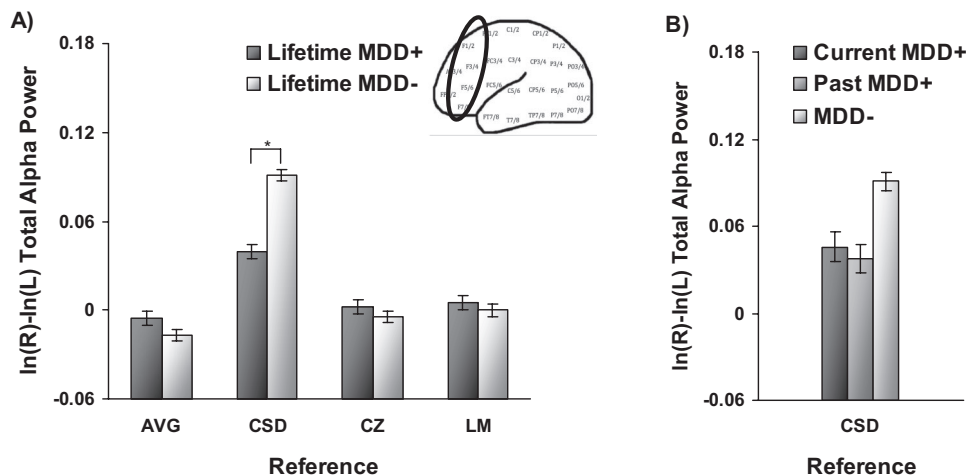


Figure 2. Panel A shows frontal alpha asymmetry scores (8–13 Hz at F2–F1, F4–F3, F6–F5, F8–F7) by lifetime MDD status for each reference montage across all four frontal regions depicted on the head insert. Error bars reflect standard error. Panel B shows results of a follow-up assessment indicating that the relationship of lifetime MDD status to CSD-referenced asymmetry is not solely accounted for by current MDD status. The y-axis is $\ln \mu V^2$ for AVG, Cz, and LM references, and $\ln \mu V^2/cm^2$ for CSD referenced data. MDD = major depressive disorder; AVG = average; CSD = current source density; CZ = Cz; LM = linked mastoid.

or current dysthymia; MDD- = participants without current or past MDD or dysthymia; six participants with past MDD but current dysthymia were not included in these analyses). Current MDD status was the between-subjects variable, day and channel were within-subject variables, and EEG asymmetry score was again the dependent variable. Cohen's d is reported for significant differences between current MDD+, past MDD+, and MDD- groups. On the basis of EEG asymmetry results, the main effect of current MDD status was the effect of importance. Figure 2 illustrates that a main effect of current MDD status emerged, $F(2, 297) = 14.1, p < .001$, indicating that the current MDD+ group and past MDD+ group displayed relatively less left frontal activity than the MDD- group (both $ps < .001$, and $d = 0.57$ and 0.58 , respectively) but did not differ significantly from each other. These findings suggest that the previously reported effects of lifetime MDD were not accounted for solely by those with current MDD, as individuals with past MDD appear indistinguishable from those with current MDD in terms of frontal EEG asymmetry.

In the second approach, continuous measures of depression severity were used. The between-group analysis above necessarily resulted in reduced sample sizes per cell, and additionally those diagnosed with past MDD still had some level of depressive symptoms, so continuous measures of symptomatology (as indexed by BDI-II and HRSD) were used to assess whether current severity was responsible for the lifetime MDD effects observed in the CSD-referenced data. Hierarchical linear mixed models using Type 1 (rather than Type 3) sums of squares were used to examine whether significant lifetime MDD results could be accounted for by depressive symptoms measured dimensionally in a model that included either BDI-II or HRSD scores as a main effect. Session day and channel were entered first, followed by BDI-II or HRSD (z scored), then lifetime MDD was added to the model. EEG asymmetry score based on total 8–13 Hz alpha power was again the dependent variable. If EEG asymmetry results represent trait effects that are not due to current depressive symptomatology, a lifetime MDD effect should still emerge. A main effect emerged for BDI-II, $F(1, 303) = 11.0, p = .001$, indicating that higher BDI-II scores were associated with relatively less left frontal activity (estimated -1 SD on BDI-II: $M = .069$ and $SE = .01$ vs. estimated $+1$ SD on BDI-II: $M = .063, SE = .01, d = 0.05$). A main effect also emerged for HRSD, $F(1, 303) = 20.2, p < .001$, demonstrating that higher HRSD scores were associated with relatively less left frontal activity (estimated -1 SD on HRSD: $M = .077$ and $SE = .01$ vs. estimated $+1$ SD on HRSD: $M = .054, SE = .01, d = 0.21$). More important, however, the main effect of lifetime MDD remained significant when entered after BDI-II, $F(1, 303) = 12.7, p < .001, d = 0.50$, or HRSD, $F(1, 303) = 18.6, p < .001, d = 0.43$, indicating that relationship of lifetime MDD status to CSD-referenced frontal asymmetry could not be accounted for by current levels of depression symptoms.

Supplementary Asymmetry Analyses for Other Reference Montages

In an attempt to reconcile nonsignificant AVG, Cz, and LM results of the present study with prior research that has been based on these reference montages and that has found significant rela-

tionships between frontal EEG asymmetry and BDI-defined depressive groups (e.g., Reid et al., 1998; Schaffer, Davidson, & Saron, 1983), supplementary analyses were performed by creating depression groups on the basis of a measure of current depression symptom severity, the BDI-II. Asymmetry differences were examined as a function of BDI-II-defined depression status for each reference separately. This conceptualization of depression may replicate several studies in which questionnaire indices have been used to define depression groups in conjunction with, or instead of, *DSM-IV* measures of depression (see Thibodeau et al., 2006, for several examples). Three groups were established after examination of the mean and standard deviation of BDI-II intake scores across the entire sample ($M = 11.1, SD = 9.6$): low (BDI-II scores from 0–10; males $n = 58$, females $n = 104$), moderate (BDI-II scores from 11–20; males $n = 23$, females $n = 65$), and high (BDI-II scores 21 or greater; males $n = 14$, females $n = 42$).

Separate full-factorial mixed models for AVG, Cz, and LM each included BDI-II group and biological sex as centered between-subjects variables, and day and channel were within-subjects variables. EEG asymmetry score was again the dependent variable. Although no main effect of BDI group emerged for AVG, Cz, or LM (all $ps > .22$), a BDI Group \times Sex interaction emerged for AVG, $F(2, 300) = 4.5, p = .01$; Cz, $F(2, 300) = 3.8, p = .02$; and LM, $F(2, 300) = 8.4, p < .001$, so follow-up mixed models were performed for each sex separately to examine BDI-II group differences. Cohen's d is reported for significant differences between BDI-II depression groups.

Results for women (see Figure 3, upper panel) indicated that main effects of BDI-II group emerged for AVG, $F(2, 208) = 7.5, p < .001$, wherein women with high BDI-II scores displayed lower relative left frontal activity than women with moderate BDI-II scores ($p = .04$ and $d = 0.42$) and women with low BDI-II scores ($p < .001$ and $d = 0.70$). In addition, a main effect of BDI-II group emerged for LM, $F(2, 208) = 6.8, p < .01$, demonstrating that women with high and moderate BDI-II scores displayed lower relative left frontal activity than women with low levels of depression (both $ps < .01$, and $ds = 0.58$ and 0.45 , respectively).

In contrast, findings for men (see Figure 3, lower panel) demonstrated that main effects of BDI-II group emerged for Cz, $F(2, 92) = 3.5, p = .03$, wherein men with moderate BDI-II scores exhibited lower relative left frontal activity than men with low BDI-II scores ($p = .01$ and $d = 0.63$), but those with high BDI-II scores did not differ from either group (both $ps > .18$). A main effect of BDI-II group also emerged for LM, $F(2, 92) = 3.8, p = .03$, indicating that men with moderate and high BDI-II scores displayed higher relative left frontal activity than men with low scores ($p < .05$ and $d = 0.50$, and $p = .02$ and $d = 0.68$, respectively). No main effect of BDI-II group emerged for AVG-referenced data ($p > .36$).

Finally, BDI-II group analyses were also run for the CSD reference to examine the concordance of results with previously reported CSD findings. Results indicated that a main effect of BDI-II group emerged, $F(2, 300) = 9.3, p < .001$, wherein participants with moderate and high BDI-II scores displayed lower relative left frontal activity than those with low scores (both $ps < .001$ and $ds = 0.50$ and 0.48 , respectively). These findings are consistent with lifetime MDD and current MDD findings, which demonstrated no interactions between depression and sex for the CSD reference.

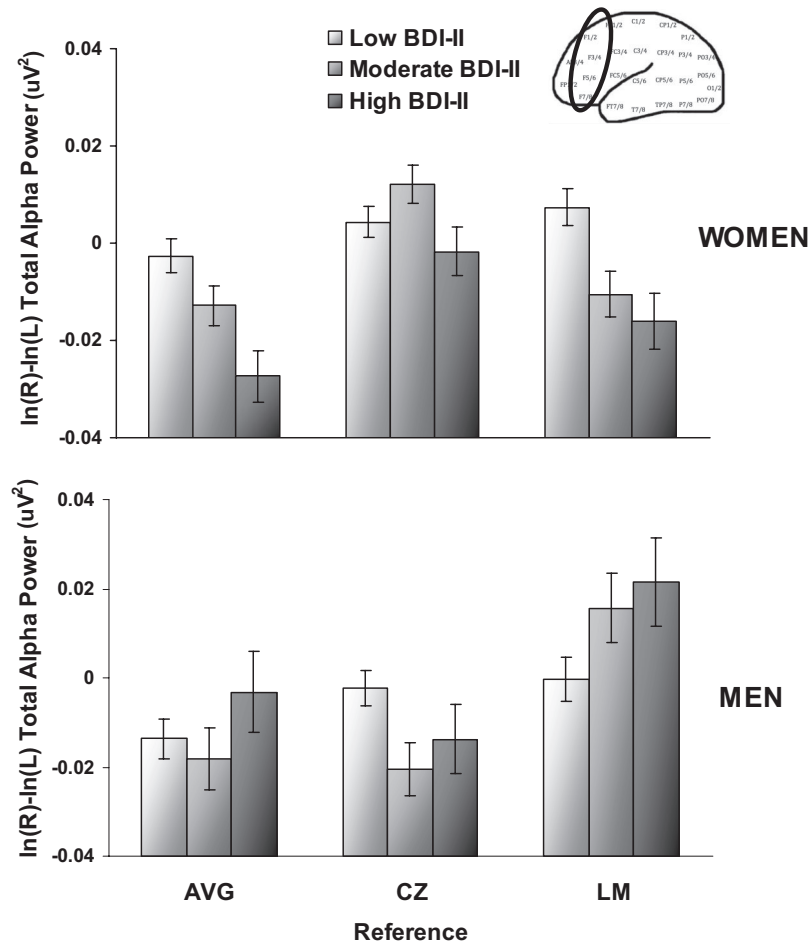


Figure 3. Frontal alpha asymmetry scores (8–13 Hz collapsed across F2-F1, F4-F3, F6-F5, and F8-F7) for women (top panel) and men (lower panel) as a function of BDI-II group and reference. Error bars reflect standard error. BDI-II = Beck Depression Inventory-II; AVG = average; CZ = Cz; LM = linked mastoid.

Discussion

The present study provided an examination of the relationship between asymmetries in frontal brain activity and depression, using both categorical *DSM* diagnoses as well as measures of depressive severity. The key findings are that (a) CSD-referenced frontal EEG asymmetry differentiates those individuals with lifetime MDD from those without, an effect not related to current depression, and consistent with the notion that frontal asymmetry can function as an endophenotype of risk for depression; (b) EEG asymmetry derived from other reference montages—those that have been used with some frequency in the literature to produce a pattern of results that is plagued by some inconsistencies—produced a pattern of findings that suggests some degree of relationship between frontal asymmetry and depressive severity in women, but not consistently so for men.

Lifetime MDD and EEG Asymmetry

Results examining lifetime MDD status are consistent with the proposition that CSD-referenced frontal EEG asymmetry is an endophenotype related to risk for depression in both women and

men, unconfounded by current symptom severity. Participants with lifetime MDD (both current MDD and past MDD) displayed less relative left frontal activity than never-depressed participants, and measures of current depression (BDI-II and HRSD scales) did not account for this effect. These findings indicate that CSD-referenced EEG asymmetry may be a liability marker, identifying a vulnerability to develop depression (e.g., Allen, Urry, et al., 2004; Gotlib et al., 1998; Henriques & Davidson, 1990, 1991) and related dysphoric conditions (Accortt & Allen, 2006; Coan & Allen, 2008), although prospective studies are needed to definitively test this proposition.

Current Depression Severity and Sex Differences in EEG Asymmetry

Unlike the CSD reference, frontal asymmetry was not related to lifetime MDD using the average, Cz, or linked mastoid references, which are the reference montages commonly used in the EEG asymmetry literature. Instead, the nature of the relationship between depression and EEG asymmetry was modified by current depression severity as measured by the BDI-II and sex. Analyses

examining BDI-II depression groups indicated that for average and linked mastoid references, women with high levels of depressive symptoms exhibited relatively less left frontal brain activity at rest than women with low levels of depressive symptoms, with women with moderate levels of depression displaying means in between low and high groups. These findings for women replicate several studies with predominately or exclusively female samples that find current depression is linked to relatively less left- than right frontal activity (see Coan & Allen, 2003, and Thibodeau et al., 2006).

In contrast to women, who demonstrated a relatively consistent pattern of EEG asymmetry results as a function of current depression severity, men exhibited a weak relationship and also inconsistent patterns of findings across these three reference montages. For example, men with moderate depressive symptoms, but not those with high levels of depressive symptoms, displayed relatively less left frontal activity than men with low levels of depression for the Cz reference; conversely, linked mastoid results demonstrated that men with high levels of depression exhibited relatively greater left frontal brain activity at rest than men with low levels of depression. Results for the average reference were nonsignificant. The linked mastoid findings are consistent with one study in which gender differences were directly compared using an average reference (Miller et al., 2002), yet inconsistent with another study in which a male sample was examined using a linked-ears reference (Jacobs & Snyder, 1996). Although the latter study found that men with relative left frontal EEG asymmetry displayed lower BDI scores, significant results were confined to only one site (whereas results for the present study extend across a wide region of frontal cortex), with EEG asymmetry measured on only one occasion, and the range of BDI scores in that study appeared very limited, with few men endorsing scores in the high depressive range of the present study (BDI-II scores of 21 or higher).

In summary, women and men displayed opposing patterns of frontal EEG asymmetry as a function of current depression severity for the linked mastoid reference (and the pattern of means for the average reference was consistent with the linked mastoid pattern). Whether these findings signify different mechanisms underlying depression in men and women remains an open question. Although it is possible that these asymmetry findings may reveal different causal pathways, they might also reflect different symptom constellations in depression in men and women (e.g., Kornstein et al., 2000; Silverstein, 2002). For example, pure MDD+ men suffer more sudden spells of anger and aggression than pure MDD+ women (Winkler, Pjrek, & Kasper, 2005), suggesting anger could be a moderator of EEG asymmetry that could explain sex differences in depression, because relatively greater left frontal activity characterizes individuals with trait anger at rest (e.g., Harmon-Jones & Allen, 1998). Additional evidence in support of this argument of anger as a moderator of frontal brain asymmetry are findings demonstrating that boys without oppositional defiant disorder display relatively less left frontal EEG activity, consistent with the EEG asymmetry pattern exhibited by MDD- men in the present study, whereas oppositional defiant boys (who had higher rates of depression than healthy boys) demonstrated no asymmetry (Baving, Laucht, & Schmidt, 2000). Therefore, limited research supports the assertion that anger and related aggressive behaviors may influence patterns of frontal brain activity differently in depressed and nondepressed men.

Choice of Reference and EEG Asymmetry

The present study indicates that a pattern of relatively less left frontal EEG activity as measured by the CSD reference reflects a traitlike marker of depression risk for men and women, whereas a similar pattern of EEG asymmetry measured by average and linked mastoid references appears to reflect a severity-related marker of current depression, at least in women. Because the CSD algorithm attenuates broad electrical sources, such as distal parietal and occipital sources in which EEG alpha activity is typically quite large (Hagemann et al., 2001; Kayser & Tenke, 2006), it is more probable that the traitlike index of CSD-referenced EEG asymmetry reflects predominantly frontal sources. By contrast, the severity-related indices of EEG asymmetry derived from AVG, Cz, and LM reference montages will potentially reflect considerable non-frontal activity, because these references reflect both proximal and distal sources, in part due to lower signal-to-noise ratios in the measurement of frontal EEG activity than those derived from the CSD reference (Hagemann et al., 2001). In order for frontal EEG asymmetry to be an endophenotype for depression risk, it must converge with other possible risk indicators for depression (e.g., genetic variations in serotonin genes involved in the transmission and maintenance of depression), and CSD-referenced EEG asymmetry appears most promising in this endeavor (cf. Bismark et al., 2010).

The Cz reference produced atypical results for men and null findings for women, yet this is not inconsistent with the fact that a majority of significant effects for the Cz reference in depression-related studies (e.g., 19 in the Thibodeau et al., 2006, meta-analysis) used infants or children as participants, not young adults. Only four studies with adults from the Thibodeau et al. (2006) meta-analysis demonstrated Cz-related differences in depressed groups (and two of the four consisted of small samples of middle-aged adult participants: Baehr, Rosenfeld, Baehr, & Earnest, 1998; Henriques & Davidson, 1991), whereas the present study replicated larger studies that reported null results with the Cz reference in young adults (e.g., Bruder et al., 1997; Reid et al., 1998). EEG asymmetry researchers have shown that there is little convergence between Cz and other references (e.g., Hagemann et al., 2001; Reid et al., 1998) and have advocated the use of references other than Cz because variations in power at this active EEG site can distort the direction and strength of asymmetry recorded from lateral sites in either hemisphere (e.g., Davidson, 1998; Hagemann et al., 2001).

The findings using average-, linked mastoid-, and Cz-referenced asymmetry scores are only partially consistent with the extant literature. They are consistent in that (a) to the extent that asymmetry relates to depression under these reference montages, it does so in women, and most of the extant depression and EEG asymmetry literature is based on female samples (Coan & Allen, 2004; Thibodeaux et al., 2006) and (b) relatively less left frontal activity was observed among those with higher levels of depressive symptoms. The findings are inconsistent in that they fail to support the idea that frontal EEG asymmetry recorded under these reference montages is related to a lifetime history of MDD. For example, Gotlib et al. (1998) found that individuals with any history of depression, regardless of whether currently symptomatic, showed relatively less left frontal activity as assessed using a Cz reference montage, and Henriques and Davidson (1990) found that previously depressed but euthymic individuals showed relatively less

left frontal activity than never-depressed controls using the linked mastoid reference montage. One key difference between these studies and the present study might be that the present study obtained a sample that spanned a wide range of depressive severity, such that the participants with no history of major depression did not have an absence of depressive symptoms. The lifetime MDD– participants in the present study had a mean BDI-II score of 6.2, whereas the never-depressed controls in the Henriques and Davidson (1990) study had comparatively little symptomatology (mean BDI of 1.4). Because lifetime MDD– participants had at least some level of symptomatology, the present examination may have been at a disadvantage to find differences between lifetime MDD+ and lifetime MDD– if frontal EEG asymmetry under these montages tracks symptom severity to some extent.

Methodological Issues and Limitations

The design of the present study was advantageous for examining the relationship between lifetime MDD and EEG asymmetry in women and men due to (a) the recruitment of a large sample of medically healthy, interview-diagnosed, medication-free individuals with no comorbid anxiety disorders; (b) repeated sessions of EEG recording that provided a reliable estimate of trait asymmetry; and (c) a systematic examination of reference montages, including the first to examine the CSD montage in depression. The consistency of the findings extended across both medial and lateral regions of frontal cortex, but different references indexed different aspects of depression, with the CSD-referenced data serving as a viable endophenotype, whereas average- and linked mastoid-referenced data appear to show a female-specific relationship to depressive severity. The relationship to depressive severity was found across persons, not within persons over time, and there is no support from the literature that, within persons, changes in EEG asymmetry track changes in levels of symptoms over intervals of weeks or months (Allen, Urry, et al., 2004; Debener et al., 2000). Future work can examine whether changes in severity over longer intervals track frontal asymmetry using average and linked mastoid references.

Limitations of the present study include a younger cohort, suggesting that these findings may not be assumed to apply for later-life onset depression. Our early-onset sample, however, might be expected to have a recurrent or chronic course of depression (cf. findings with chronic depression; Klein et al., 1999) and thus may generalize to individuals with severe depression later in life. In addition, these results may not be generalizable to depressed individuals with comorbid *DSM-IV* conditions such as anxiety and substance use disorders, which are common in MDD patients (e.g., Kessler et al., 2003). Furthermore, it is unclear whether these findings may extend to persons with MDD who are being treated with psychotropic medications, but to date no evidence suggests that antidepressants impact frontal EEG asymmetry. Finally, the present study offers a cross-sectional investigation to address a within-subjects question, namely, whether an individual's pattern of regional frontal brain activity predicts subsequent development of MDD, so prospective, longitudinal data are needed to firmly establish that EEG asymmetry is a vulnerability marker for depression.

Synopsis

Findings from CSD-referenced data indicated that a pattern of less relative left frontal activity (inferred from relatively greater left frontal alpha power) was evident for individuals with lifetime MDD compared with never-depressed individuals, regardless of sex or current severity of depressive symptoms. These findings clearly suggest the promise of CSD-referenced frontal EEG asymmetry as an endophenotype of depression risk. EEG asymmetry for average and linked mastoid references, however, showed evidence of sex-specific contributions related to CSD severity, reducing the likelihood that EEG asymmetry under these reference montages can serve profitably as an endophenotypic marker of depression. For these references, a pattern of less relative left frontal activity characterized women with currently high levels of depressive symptoms as compared with women with low levels of current depression. For men, by contrast, in the largest study of EEG asymmetry of depression to date, findings from the linked mastoid reference revealed that men with moderate or high levels of depressive symptoms showed relatively greater left frontal activity, a finding opposite to women, but nonetheless replicating one previous study with a sizable male sample (Miller et al., 2002). The implications of this finding for men must await further investigation, but it is clear that future studies of frontal brain asymmetry and risk for depression must take sex differences into consideration.

Because resting frontal EEG asymmetry has demonstrated inconsistencies in its relationship to depression and emotion in previous studies, because its underlying mechanisms are poorly if at all understood and because it is characterized by many methodological quirks (including its predominant manifestation as a difference score and reference-dependent effects), resting frontal EEG asymmetry has occupied a decidedly (and deservedly) tentative status as a potential endophenotypic marker of depression (Coan & Allen, 2008). Although the present study has not entirely resolved the many methodological and theoretical mysteries long associated with frontal EEG asymmetry as an index of psychopathology, it has brought the measure significantly up to date in a larger and more representative sample of individuals than has previously been reported. If associations between frontal EEG asymmetry and depression were illusory or otherwise absent, the present study was sufficiently powered to advocate just such a conclusion. The strength of the results reported here suggests, by contrast, that associations between frontal EEG asymmetry and affective psychopathology are real, important, and worthy of considerable scientific inquiry as the pursuit of endophenotypic markers of depression vulnerability continues.

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