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Do prefrontal midline electrodes provide unique neurophysiologic information in Major Depressive Disorder?

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\textbf{A B S T R A C T}

Brain oscillatory activity from the midline prefrontal region has been shown to reflect brain dysfunction in subjects with Major Depressive Disorder (MDD). It is not known, however, whether electrodes from this area provide unique information about brain function in MDD. We examined a set of midline sites and two other prefrontal locations for detecting cerebral activity differences between subjects with MDD and healthy controls. Resting awake quantitative EEG (qEEG) data were recorded from 168 subjects: 47 never-depressed adults and 121 with a current major depressive episode. Individual midline electrodes (Fpz, Fz, Cz, Pz, and Oz) and prefrontal electrodes outside the hairline (Fp1, Fp2) were examined with absolute and relative power and cordance in the theta band. We found that MDD subjects exhibited higher values of cordance \((p = 0.0066)\) at Fpz than controls; no significant differences were found at other locations, and power measures showed trend-level differences. Depressed adults showed higher midline cordance than did never-depressed subjects at the most-anterior midline channel. Salient abnormalities in MDD may be detectable by focusing on the prefrontal midline region, and EEG metrics from focused electrode arrays may offer clinical practicality for clinical monitoring.

1. Introduction

Functional neuroimaging studies of Major Depressive Disorder (MDD) frequently report findings of abnormal activity in frontal mood regulating networks. These networks include the dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex (DMPFC), orbitofrontal cortex (OFC), and the anterior cingulate cortex (ACC), among other regions. Using positron emission tomography (PET), Buchsbaum et al. (1997), Mayberg et al. (1999), and other groups have differences in metabolism in between these areas. Sheline et al. (2010) have proposed that the frontopolar region constitutes a “dorsal nexus” where the function of many of these areas is linked and may differentiate between MDD and control subjects.

Quantitative electroencephalographic (qEEG) studies in MDD have employed arrays of scalp electrodes with varying densities to provide information on brain oscillatory activity that is characteristic of this disorder. Leuchter et al. (2012) have shown that widespread oscillatory synchrony between the frontopolar region and other brain areas distinguishes those with MDD from healthy controls. No study, however, has specifically focused solely on the oscillatory activity recorded from frontopolar electrodes to determine whether this may be uniquely useful for characterizing brain function in subjects with MDD. Differences have been reported in ACC (Holmes and Pizzagalli, 2008; Korb et al., 2008; Mayberg et al., 1997; Mulert et al., 2002, 2007a; Narushima et al., 2010; Pizzagalli et al., 2001, 2003; Poulsen et al., 2009; Saletu et al., 2010; Schrijvers et al., 2008, 2009) as well as in broad frontal (Allen and Kline, 2004; Bruder et al., 1997; Davidson, 2004; Davidson and Irwin, 1999) and prefrontal regions (Bares et al., 2007, 2008; Cook et al., 1998a, 2002, 2005), using surface measures. qEEG studies of MDD have generally employed full-head electrode montages, sampling activity from up to 256 (e.g., Plante et al., 2012) electrode locations.

While high-density electrode arrays contribute to our knowledge of brain function in MDD, some previous investigations of the
relationships between prefrontal EEG signals and activity in deeper structures have reported that qEEG data recorded from midline anterior electrodes provide special information about frontal network function, particularly with regard to theta band activity (Asada et al., 1999; Ishii et al., 1999; Poulsen et al., 2009). Our group has reported (Korb et al., 2009, 2011) that consideration of midline prefrontal electrodes may be critical for characterizing ACC activity with the EEG technique “low resolution brain electromagnetic tomography” (LORETA) (Pascual-Marqui et al., 1994), suggesting that the midline prefrontal region may be a key location for observations related to the neurophysiology of depression.

The objective of our present study was to investigate whether various midline prefrontal electrodes provided unique information about differences in regional brain activity between depressed and non-depressed adults, regardless of the specific anatomic structure(s) responsible for a difference. We examined individual midline electrode locations, overlying the anterior, central, and posterior divisions of the cingulate gyrus, and those over adjacent prefrontal areas, and hypothesized that data from electrodes overlying some portions of the frontal lobe would be sensitive to brain dysfunction in MDD, while electrodes over other regions would not detect these differences.

2. Methods and materials

2.1. Participants

2.1.1. Subjects with depression

Depressed subjects were 121 adult outpatients diagnosed with unipolar MDD who had been recruited as subjects for antidepressant treatment trials in our laboratory. In accordance with principles of the Helsinki Declaration (as amended, 1975–2008), all protocols had been reviewed and approved by the UCLA Institutional Review Board (IRB), and written informed consent to participate in this research was obtained from all subjects. For the purposes of the present project, we examined each subject’s medication-free baseline EEG. Subjects were free of psychotropic medication for at least 2 weeks prior to enrollment (4 weeks for purposes of the present project, we examined each subject). Our group has reported (Korb et al., 2009, 2011) that consideration of midline prefrontal electrodes may be critical for characterizing ACC activity with the EEG technique “low resolution brain electromagnetic tomography” (LORETA) (Pascual-Marqui et al., 1994), suggesting that the midline prefrontal region may be a key location for observations related to the neurophysiology of depression.

The control subjects did not differ significantly from the depressed group on age (CON: 37.9 (12.9) vs MDD: 40.6 (12.9); t166 = −1.24, p = 0.22) or in gender balance (23M:24F vs 46M:75F; Chi-square 1.47, df = 1, p = 0.23).

2.2. EEG methods

2.2.1. Data acquisition

Using procedures employed in our previous reports and summarized here, recordings were made with the QND System (Neurodata, Inc.; Pasadena, CA) or the NuAmps System (NeuroScan, Inc.; El Paso, Tx), calibrated to ensure equivalence across systems. Resting EEG was recorded in subjects while they lay with eyes closed in a quiet room. Subjects were instructed to remain still and inhibit blinks or eye movements during each recording period. Technicians monitored EEG throughout the recording and alerted subjects every 30–45 s as necessary to prevent drowsiness. Scalp electrodes were placed using an electrode cap (ElectroCap, Inc.; Eaton, OH, USA) using a 35-channel enhanced version of the International 10–20 System of Electrode Placement, with additional electrodes located over prefrontal and parietooccipital regions. Electrode impedances were balanced and under 5 kΩ for all channels. To control for ocular artifact, vertical and horizontal electro-oculograms (EOG) were recorded using bipolar electrodes placed at the supraorbital and infraorbital ridge of the right eye and the outer canthi of the left and right eye, respectively.

A minimum of 10 min of EEG data were recorded using a Pz referenced montage. Signals were digitized using a sampling rate of 256 Hz, a low-frequency filter of 0.3 Hz, a high-frequency filter of 70 Hz, as well as a notch filter at 60 Hz. Digital data were then imported into Brain Vision Analyzer (BVA) software (Brain Products GmbH; Gilching, Germany) in order to remove offsets, optimize scaling, re-reference the data, and segment the data into 2-s non-overlapping epochs. Using the BVA artifact rejection module, segments were removed according to standard thresholds likely to represent artifact based upon voltage step gradient (i.e., 100 μV), absolute values of difference within the epoch, or persistent low activity for greater than 100 ms. A semi-automated interactive process was then used to remove all epochs containing eye movement, muscle, or movement-related artifacts, or amplifier drift. Two technicians then independently inspected the data using multiple bipolar and referential montages, and isolated and removed any remaining data segments suspected of containing artifacts.

2.2.2. Calculation of spectral power and cordance measures

Absolute and relative power values were calculated with a linked-ears reference using BVA and theta band values (4.0–8.0 Hz) were exported for data analysis. Cordance values were calculated using an algorithm that has been detailed elsewhere (Leuchter et al., 1999) and may be summarized as follows. Cordance is computed by a normalization and integration of absolute and relative power values from all electrode sites for a given EEG recording; cordance values are calculated in three steps. First, EEG power values are computed using a re-attributional electrode montage (Fig. 1) in which power values from pairs of electrodes that share a common electrode are averaged together to yield the re-attributed power (Cook et al., 1998b). This approach is similar to the single source method of Hjorth (1975) in which voltage signals are recombined, but the re-attributional montage approach has been shown to provide a
higher association with regional cortical perfusion than the Hjorth method (Cook et al., 1998a, b). These absolute power values are used to derive relative power (percentage of power in each frequency band) for each electrode.

Second, these re-attributed absolute and relative power values for each individual EEG recording are normalized across electrode sites, using a z-transformation statistic for each electrode site $s$ in each frequency band $f$ (yielding $A_{\text{norm}}(s,f)$ and $R_{\text{norm}}(s,f)$, respectively). This normalization process places absolute and relative power values into a common unit (standard deviation or z-score units) which allows them to be combined. It is worthwhile to note that these z-scores are based on the average power values in each band for all electrodes within a given qEEG recording (i.e., these are not z-scores referenced to some normative population).

Third, the cordance values are formed by summing the z-scores for normalized absolute and relative power ($Z(s,f) = A_{\text{norm}}(s,f) + R_{\text{norm}}(s,f)$) for each electrode site and in each frequency band. Cordance values have been shown to have higher correlations with regional cerebral blood flow than absolute or relative power alone (Leuchter et al., 1999), and thus this combination measure can be placed in context with prior work in depression that have employed functional measures of brain activity such as PET scan data. As with absolute and relative power measures, we focused on theta band cordance, as activity in that frequency band has been associated with the presence of MDD and with treatment response (Bares et al., 2007, 2008; Broadway et al., 2012; Cook et al., 2002, 2005, 2009; Cook and Leuchter, 2001; Hunter et al., 2012; Knott et al., 1996; Leuchter et al., 1997; Leuchter et al., 2009a,b; Mulert et al., 2007b; Pizzagalli et al., 2001; Ulrich et al., 1988a,b, 1994).

In this study, we first directed our attention to the five individual midline electrodes placed in accordance with the extended International 10–20 montage locations, in prefrontal (Fpz), frontal (Fz), central (Cz), parietal (Pz), and occipital (Oz) regions (Sharbrough et al., 1991). These electrodes overlie the cingulate cortex, moving from anterior regions (e.g., Brodmann Areas BA 32, 24) to more posterior locations (e.g., BA 23, 31 for Oz). To examine two other locations of interest for practical clinical monitoring, we evaluated the prefrontal electrodes Fp1 and Fp2 that flank Fpz laterally, as these are comparison channels located outside the hairline, that overlie prefrontal but not midline structures.

### 2.3. Data analysis

Analyses were performed using the SPSS version 21 software package (IBM Inc.; Armonk, NY). Data were analyzed with 2-tailed t-tests, the chi-square statistic, and ANOVA/ANCOVA models. Within each EEG measure, we adjusted the significance threshold using the Bonferroni approach to correct for tests of seven electrode sites (i.e., $0.05/7 = 0.007$). Effect sizes were computed with GPower (Erdfelder et al., 1996).

### 3. Results

#### 3.1. Overall physiologic differences

As an omnibus test for the presence of differences between groups in physiologic measures, we performed a multiple analysis of variance (MANOVA), examining all EEG measures (absolute power at 7 locations, relative power at 7 locations, and cordance at 7 locations) as dependent variables, and diagnostic group as a fixed factor. The overall test was significant (Wilk’s Lambda 0.791, $F$ 1.84, $p = 0.02$, $\eta^2 = 0.21$).

#### 3.2. Absolute and relative power group differences

In comparing depressed and control subject groups, no significant differences were found in absolute or relative power for any of the five midline electrodes or the two lateral prefrontal locations, after correcting for multiple comparisons (Table 1). Some trend-level associations were observed for absolute power but not for relative power.

#### 3.3. Cordance group differences

Cordance values at the Fpz electrode were significantly higher in the depressed subjects (mean = −0.78 (1.45 sd)) than in the control group (mean = −1.46 (1.44 sd), t$166 = −2.748$, 2-tail $p = 0.0067$, effect size $d = 0.47$). No significant differences were found at the other midline or prefrontal locations after correction for multiple tests (Table 1, Fig. 2). While not statistically significant, there were numerical trends for imbalances in age and gender between MDD and CON groups, so we also performed ANCOVA to examine differences between MDD and CON groups while controlling for these two factors. In this analysis, we found that the main effect on Fpz cordance of diagnostic group was significant in this model ($F = 7.21$, $p = 0.008$), while neither age nor gender were significant covariates.

#### 3.4. Depression severity

The relationships between symptom severity (HAM-D$_{17}$ score) and physiologic measures were evaluated within the 121 subjects with MDD with regression analyses. Depression severity was not related to the value of cordance, absolute power, or relative power at any of the electrode sites (e.g., the strongest correlation was in cordance at the Pz location, with $r = 0.14$, $p = 0.74$).

### 4. Discussion

The central finding in this study is that depressed individuals differed from healthy control subjects in qEEG values measured at
the prefrontal midline location (Fpz) overlying the far-anterior midline structures, and did not differ at remaining midline sites or at more lateral prefrontal sites. Importantly, this suggests that clinically salient features may be detectable using observations focusing on a very limited number of electrode sites. These findings indicate that brain oscillatory activity, measured at the frontal pole in the midline, may uniquely reflect features that are highly characteristic of individuals experiencing an episode of MDD.

These findings are consistent with recent work on brain connectivity, which suggests that the far prefrONTAL region constitutes a “nexus” (Sheline et al., 2010) or a “hub node” of functional connectivity (Leuchter et al., 2012) that differentiates individuals with depression from healthy controls. The mood regulating network in the frontopolar region consists of a number of structures that contribute to the rhythmic oscillations recorded from the Fpz electrode. Other studies have also reported differences between depressed subjects and healthy controls, in frontal activity in all these structures (Bench et al., 1992; Drevets et al., 1992; Ito et al., 1996; Brody et al., 2001; Kennedy et al., 2001; Kimbrell et al., 2001; Fitzgerald et al., 2002; Fitzgerald et al., 2008).

It is noteworthy that in our resting state EEGs, the control subjects had significantly lower cordance values than the depressed subjects. This would be consistent with low levels of activity in this region when healthy individuals are observed in the resting state. The ACC has been tied to attentional and emotional processing, and low activity levels have been observed in the resting state in the healthy, well-regulated brain (Posner et al., 2007), so the cognitive dysfunction in depression could reflect impairment of that regulation in MDD (Porter et al., 2007; Zakzanis et al., 1998). Resting state activity has been reported as lower in controls than in MDD subjects in portions of the PFC broadly (Drevets et al., 1992; Brody et al., 2001), consistent with our finding, though some others have reported the reverse pattern (cf. Rigucci et al., 2010).

These differences in prefrontal midline function also may be particularly relevant to interpreting and designing studies of depression using EEG, and to reconciling past discrepancies in the literature. While our data suggest that recording from the Fpz location appears to be particularly important for detecting differences between MDD and control subjects, the classic 19- or 21-channel versions of the International 10-20 System montage do not incorporate this location (Bocker et al., 1994; Jasper, 1958; Nuwer, 1987; Sharbrough et al., 1991). In contrast, later extensions of the 10-20 System do routinely include a midline recording location at the frontal pole (Chatrian et al., 1998; Jurcak et al., 2007). Discrepancies in reports using EEG to study depression could reflect inconsistent inclusion or omission of this recording site, as recent work has examined the impact of the presence or absence of Fpz data (Korb et al., 2009).

While MDD and control groups exhibited a clear difference in activity at Fpz, within the MDD group there was no relationship between Fpz activity and depression severity (HAM-D17 score), suggesting that these deviations from healthy patterns of brain activity reflect something other than simple symptom burden. It is possible that Fpz activity reflects the presence of MDD or of trait vulnerability to the development of MDD, rather than marking a point along a continuum between states of illness and health. This distinction might be clarified by a cross-sectional examination of

![Fig. 2. Midline cordance values.](image-url)
other individuals with MDD of lesser severity, or with “minor” or “subsyndromal” depression diagnoses, or longitudinal comparisons of MDD subjects when ill vs in remission, or of healthy subjects transiently experiencing depressed mood (e.g., from immersion in an affective task); this might also aid in interpreting the numerical value of Fpz cordance in this context. Alternatively, the brain dysfunction detected at Fpz could reflect an aspect of being ill with MDD that is not reflected in that rating scale score. Although the HAM-D_{17} scale is a widely-employed measure, its limitations in comprehensively capturing aspects of MDD have been acknowledged (Bagby et al., 2004; Gibbons et al., 1993; Trivedi et al., 2009). Other work from our lab (Hunter et al., 2013) found that measures of rACC activity varied over the course of a depressive episode, and that the level measured closest in time to the start of antidepressant treatment was the better predictor of clinical response, independent of HAM-D_{17} score. Future work might examine relationships between Fpz activity and other metrics that characterize MDD, such as neurocognitive performance or functional abilities (e.g., in the home and workplace, or in relationships).

Because our clinical subjects all met diagnostic criteria for unipolar major depression, our study also cannot evaluate the specifi-
city of this finding to depression in that illness (e.g., in contrast with the depressed phase of bipolar disorder). Structural and functional abnormalities have been reported in the midline structure in bipolar disorder (Fountoulakis et al., 2008). Importantly, however, research evidence also points to ACC involvement in psychotic depression (McCormick et al., 2009), dementia (Assal and Cummings, 2002), schizophrenia (Baiano et al., 2007), social phobia (Ahls et al., 2009; Rauch et al., 1995), pain syndromes (Peyron et al., 2000), borderline personality disorder (Minzenberg et al., 2008), autism (Delmonte et al., 2013; Hall et al., 2013) and other disorders, possibly reflecting the role of the this region in mental functions that are disrupted across a variety of illnesses (van Veen and Carter, 2002, 2006). As such, we believe it would not be appropriate to consider qEEG measurements at Fpz as a substitute for conventional clinical diagnosis. Future projects may determine whether Fpz-detected differences are disorder-specific or reflect a common substrate for multiple neuropsychiatric illnesses, perhaps by including subjects with a CNS disorder where the midline frontal structures are not believed to be as central to the manifestations of the illness (e.g., Parkinson’s disease). Another concern is that we were able to include data from more MDD subjects than from healthy control individuals. Future work should strive to include a larger sample of healthy adults. A technical consideration is the possibility of misattributing cerebral activity to residual artifact, either from subtle eye movements or from muscle activity in the face. We have employed a well-established set of procedures to eliminate these and other types of artifact (Cook et al., 1998a, b; Cook and Leuchter, 2001, 2002, 2005, 2009; Hunter et al., 2010, 2013, 2006; Korb et al., 2008, 2009, 2011; Leuchter et al., 1999, 2002, 2008, 2012). Indeed, facial muscle and/or eye movement artifact would be expected to be found at Fpz and also at the adjacent electrodes, so the localization of the significant differences to the Fpz location alone argues against contamination and in favor of this finding reflecting a true neurophysiologic aspect of depression.

Some limitations of our findings relate to our subject pool’s characteristics. Because our subjects were all adults, it is unknown whether these differences would be found in depressed children and adolescents. Individuals with co-morbid substance use disorders were excluded from this project, yet represent a large subset of those seeking care for depression, and the applicability of these findings in that population are unknown. An additional limitation of the present report is that only midline and prefrontal sites were considered in our hypothesis, but the standard cordance calculation algorithm incorporates a spatial normalization step requiring data from electrodes across the head. While the midline, far prefrontal Fpz location may offer a key answer to the question of “where to look” for salient physiologic differences, it appears that some different metric, computed using signals from a limited set of locations, will be needed to offer a more practical way to address the matter of “how to look”. Future extensions of this work could examine new approaches to spatial normalization from a more limited set of locations, particularly those outside the hairline and easily accessible for electrode placement, or altogether different measures derived from these channels.

Similarly, this examination focused on theta band activity, because prior work had led us to hypothesize that theta activity may reveal physiologic differences between groups. Other bands could also exhibit differences, or slowing of the posterior dominant rhythm from the alpha range to the theta range could also have occurred. These questions can be addressed in future research. Nonetheless, our findings suggest a useful approach in studying clinically-relevant issues in depression using qEEG, and future extensions may seek to examine a wider frequency range.

Previous qEEG studies have indicated that early and pre-treatment physiologic biomarkers may predict response and/or remission from antidepressant treatment (Bares et al., 2007, 2008; Cook et al., 2002, 2005; Cook and Leuchter, 2001; Juckel et al., 2007; Mulert et al., 2007b; Pizzagalli et al., 2001). Most of these studies have utilized a “full head” recording montage. To the extent that both MDD and treatment response affect aspects of frontal activity, a greatly reduced montage focusing on the midline prefrontal regions may be able to provide much of the information necessary to monitor salient aspects of brain function related to treatment outcome in MDD. Indeed, the recent BRITE-MD trial (“Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression”, NCT00289523) employed a focused array (Fpz, FT9, FT10, A1, A2 electrodes) and found that EEG features at baseline and emerging in the first week of treatment were significantly predictive of later clinical outcome (Leuchter et al., 2009a, b). The qEEG biomarker used in the BRITE-MD trial also may predict the likelihood and speed of achieving a sustained remission (Cook et al., 2013), so the use of practical neurophysiologic monitoring in MDD may soon be justifiable as an evidence-based aspect of practice. For physiologic monitoring to be integrated into routine clinical practice, however, a streamlined electrode array would be central to a practical recording and monitoring system. Future studies should focus on the unique information on brain function that may be recorded from the Fpz site and other electrode locations that may reflect activity in salient brain regions.

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Contributors

Dr. Cook developed the hypothesis tested in this work and the approach, and wrote the initial draft of the manuscript. Drs. Cook and Leuchter designed and executed the underlying clinical studies, assessed the research subjects clinically, and reviewed EEG recordings for reliability, and contributed to the revisions of the paper. Drs. Cook, Hunter, and Korb performed the statistical analyses.
and contributed to the conceptualization of the findings presented in this report. Drs. Cook, Hunter, Korb, and Leuchter and all contributed substantively to the final manuscript and approved it.

Conflict of interest

Over his career, Dr. Cook has received research support from Aspect Medical Systems/Covidien, Cyberonics, Eli Lilly and Company, High Q Foundation, John E. Fetzer Foundation, John A. Hartford Foundation, MedAvante, Merck, NARSAD, NIH, NeoSync, Neurontics, Novartis, Pfizer, Sepracor/Sunovion, Seaside Therapeutics, and the West Coast College of Biological Psychiatry, as Principal Investigator or Co-Investigator. At times he has served as an advisor or consultant to Allergan, Ascend Media, Bristol-Myers Squibb, Covidien, Cyberonics, Eli Lilly and Company, Forest Laboratories, Janssen, Neurontics, NeuroSigma, Pfizer, Scale Venture Partners, and the U.S. Departments of Defense and Justice. He has spoken on behalf of Bristol-Myers Squibb, CME LLC, Eli Lilly & Company, Medical Education Speakers Network, Pfizer, Neurontics, NeuroSigma, and Wyeth. Dr. Cook’s biomedical device patents are assigned to the University of California. Dr. Cook is not a shareholder in any pharmaceutical company, and he has been granted stock options in NeuroSigma, the licensee of some of his inventions.

Dr. Leuchter has provided scientific consultation or served on advisory boards for Aspect Medical Systems, Eli Lilly and Company, Novartis Pharmaceuticals, MEDACorp, AstraZeneca, Takeda Pharmaceuticals, and Merck & Co. He has served on a speaker’s bureau for Eli Lilly and Company and Wyeth-Ayerst Pharmaceuticals. He has received research/grant support from the National Institute of Mental Health, the National Center for Complementary and Alternative Medicine, Aspect Medical Systems, Eli Lilly and Company, Novartis Pharmaceuticals, Wyeth-Ayerst Pharmaceuticals, Merck & Co., Pfizer, Vivometrics, and MedAvante. He also previously was a minor stockholder in Aspect Medical Systems. His patents are assigned to the University of California.

Dr. Hunter is an inventor of an UCLA-assigned method patent to predict antidepressant effects. Dr. Korb reported no biomedical financial interests or potential conflicts of interest.

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