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

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ABSTRACT

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 healthy control subjects and those with MDD in many of 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

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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 fluoxetine); the duration of this period reflected a balance between the scientific desirability of an extended washout period and the ethical considerations of imposing a treatment-free period on ill patients. Diagnoses were determined by trained, expert raters using a structured interview for DSM-IV, and inclusion criteria included intake scores $\geq$16 on the 17-item Hamilton Depression Rating Scale (HAM-D_{17}) (Hamilton, 1960). Exclusionary criteria included current dementia; delirium; bipolar disorder; substance-related or eating disorder; cluster A or B Axis II diagnoses; active suicidal plan or intent; the presence of any poorly controlled medical illness that could affect brain function (e.g., untreated hypothyroidism); concurrent use of medications that could interfere with EEG activity (e.g., benzodiazepines); ECT within the prior 6 months; or any history of head trauma, brain surgery, or skull defect. Recruitment mechanisms as well as inclusion and exclusion criteria were comparable for these protocols, and subjects showed no significant differences among trials with regard to age, gender balance, or depression severity. Reports of the treatment trial subjects and the healthy controls have previously appeared in the literature (e.g., Cook et al., 2002, 2009; Hunter et al., 2006, 2010, 2013; Leuchter et al., 2002, 2008, 2012; Korb et al., 2008, 2009, 2011); none have focused on the questions addressed in this report.

2.1.2. Never-depressed control subjects

Healthy control subjects were 47 adults without current or past history of depression who had given informed consent to enroll in a study in our laboratory of the effects of antidepressant medication on healthy subjects (Leuchter et al., 2008) or in cognitive activation studies. Subjects underwent a structured clinical examination to confirm the absence of any history of mood, anxiety, psychotic, or cognitive illness or of substance abuse or dependence disorders. The control subjects did not differ significantly from the depressed group on age (CON: 37.9 (12.9) vs MDD: 40.6 (12.9); $t_{166} = -1.24$, $p = 0.22$) 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 re-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 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