EEG sources in a group of patients with major depressive disorders

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ABSTRACT

EEG sources were assessed in a group of patients with major moderate–severe depressive disorder (MDD) as classified by trained clinicians according to DSM-IV criteria. Frequency Domain Variable Resolution Electromagnetic Tomography (FD-VARETA) was used to calculate EEG sources. The Z-values indicated that EEG sources were abnormal (increase in current density) in all patients, with most demonstrating abnormal EEG sources in both hemispheres but with maximal inverse solution located primarily in the right. Twenty-nine patients had a predominant topography of the abnormal EEG maximal inverse solution in the frontal lobes. The remaining seven patients had a bilateral abnormal increase in current density in the superior parietal lobe. The EEG maximal abnormal inverse solution frequency was observed in both hemispheres such that the increases in current density were prevalent in alpha and theta bands. The results suggest that any of the two hemispheres could be affected by MDD, but abnormal EEG sources can be found more frequently in the right one, with the maximal abnormal inverse solution at the alpha and theta bands in frontal and parietal cortices.

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1. Introduction

In the general population, one of the most frequent diagnoses of mental disorder is depression. It has a lifetime prevalence between 15% and 20%; and about 6% of this population meets the criteria for major depressive disorder (unipolar depression, MDD) or dysthymia at any time when depressive (Keller et al., 1992; Kessler et al., 2003). Epidemiologic studies about depression identify it as a major public health problem (Greenberg et al., 1993) and the economic burden to family members and society is considerable (Broadhead et al., 1990). Although many brain regions have been implicated in regulating emotions, the neural circuitry underlying normal mood and the abnormalities that are the hallmark of depression are unclear. Human brain imaging studies have demonstrated that several brain regions mediate diverse symptoms of depression, with changes in blood flow or related measures in prefrontal and cingulate cortex, hippocampus, striatum, amygdala, and thalamus implicated (Drevets, 2001; Drevets et al., 2004; Liotti and Mayberg, 2001).

Quantitative electroencephalographic (QEEG) has demonstrated a high percentage of depressed patients with increases in alpha or theta power (Monakhov and Perris, 1980; Nystrom et al., 1986; Knott and Lapierre, 1987; John et al., 1988; Pollock and Schneider, 1990; Nieber and Schlegel, 1992; Roemer et al., 1992; Alper, 1995). Furthermore, interhemispheric asymmetry especially in anterior regions in depressed patients has been found, such that alpha power is greater over the left than the right frontal regions, while the opposite pattern (alpha power higher over the right than over the left) for the parietal regions (Henriques and Davidson, 1990, 1991). In addition, there is some evidence to suggest that excessive alpha may be associated with unipolar subtype; while an alpha deficit and a beta excess are characteristic of the bipolar subtype (John et al., 1988; Alper, 1995).

Interest in EEG measures for assessing depression has increased, and Low Resolution Electromagnetic Tomography (LORETA, Pascual-Marqui, 1994, 1995; Pascual-Marqui et al., 1994) and VARETA (Variable Resolution Electrical Tomography, Casanova et al., 1995; Valdés et al., 1995; Bosch et al., 2001) are two techniques for estimating the sources generators of EEG data. LORETA has been used to evaluate different aspects in depressed patients, such as interhemispheric asymmetry, treatment response, patterns of brain activation in various groups of patients and during cognitive challenges (Pizzagalli et al., 2001, 2002; Mientus et al., 2002; Lubar et al., 2003; Flor-Henry et al., 2004). Results have shown increased or decreased current density in several structures, including both left and right hemispheres and all frequency bands.

VARETA has been applied satisfactorily to the study of brain lesions (Fernández-Bouzas et al., 1999, 2000, 2001, 2002, 2004; Prichay et al., 2001), for source localization in psychiatric patients (Chabot et al., 2001;...
Bolwig et al., 2007), and during different mental tasks (Fernández et al., 2000; Harmony et al., 2001). The purpose of the present paper was to study EEG sources in a group of patients with major depressive disorder using the VARETA method.

2. Materials and methods

2.1. Participants

A total of 36 patients ranging from 23 to 56 years old (mean age = 39.3, S.D. = 10.5), 27 female and 9 male, with recurrent depression and who were seeking treatment for their illness, were enrolled in the study between January 2004 and December 2006, from the outpatient unit of the National Institute of Psychiatry, in Mexico City.

To be considered in the study, patients had to be experiencing an episode of unipolar depression according to Research Diagnostic Criteria as extracted from the Structured Clinical Interview for DSM-IV. Other inclusion criteria were age, between 20 and 60 years; score of ≥20 on the 21-item Hamilton Depression Rating Scale (HDRS). Exclusion criteria were presence of comorbid axis I disorders (other than anxiety disorders, hypomania, adult-onset dysthymia, and eating disorder not otherwise specified); full-criteria antisocial or borderline personality disorder; history of substance abuse or dependence within the past 2 years; history of a manic episode, or any medical condition (excluding pregnancy) incompatible with the use of a selective serotonin reuptake inhibitor (SSRI); presence of suicide risk or any psychotic symptom at the moment of the first interview. Every patient was screened for thyroid profile, Blood Cell Count and a traditional EEG was taken in order to exclude those that showed epileptiform activity. Every patient signed an Informed Consent Form previously approved by the institutional ethics board.

2.2. EEG acquisition

Subjects were awake with eyes closed in a dimly lit, not acoustically shielded room. The EEG was recorded from Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Pz, Cz, and Pz of the 10-20 system, using linked earlobes as reference. EEG was recorded from a supraorbital electrode and from an electrode on the external canthus of the left eye. Impedance levels were ≤5 kΩ. The amplifier bandwidth was set between 0.5 and 30 Hz, and the EEG was sampled every 5 ms using the Medicale 4 system and edited off-line. The total recording period of the EEG was between 20 and 30 min.

2.3. EEG analysis

Twenty-four artifact-free EEG segments of 2.56 s were selected independently with visual editing by two independent judges. The segments were included only if both agreed on the selection. EEG analysis was carried out off-line. Fast Fourier transform (FFT) and cross-spectral matrices were calculated every 0.39 Hz.

2.4. EEG source spectral analysis

Frequency Domain VARETA (FD-VARETA) was used to calculate distributed sources for each frequency. This method is a discrete, spline-distributed solution that imposed different amounts of spatial smoothness for distinct types of generators and that restricted current sources to gray matter by using a probabilistic mask that prohibited solutions where the mask is zero such as cerebrospinal fluid and white matter (Bosch-Bayard et al., 2001; Fernández-Bouzas et al., 1999). Z-values for the logarithmic value of current at each point of the grid (Z image) were calculated (John et al., 1977; Duffy et al., 1979, 1981). Population parameters used for EEG sources were derived from a regression function of age-dependent mean values and standard deviation obtained from 211 normal subjects (Valdés et al., 1990). Z values greater than 1.96 were considered abnormal.

3. Results

One of the inclusion criteria was a score ≥20 on the 21-item Hamilton Depression Rating Scale, with patient values between 21 and 40 (M = 28.8, SD = 4.6). This result implies that in general the severity of depression was in a moderate–severe level.

Table 1 shows the frequency, Z-value, and topography of EEG sources corresponding to the maximal abnormal inverse solution in the whole sample. Age and sex of each patient are also shown. The Z-values indicate that EEG sources were abnormal (increase in current density) in all patients. Most of them (35 of 36 patients) had abnormal EEG sources in both hemispheres but with maximal inverse solution located, basically in the right one: the amount of patients with this topography duplicated the one from the left hemisphere (24 vs. 12).

About 80% of the patients (29/36) had a predominant topography of the abnormal EEG maximal inverse solution in the frontal lobes and besides, 43.5% of the patients with abnormal EEG sources located in the dorsolateral prefrontal cortex (DLPFC) involved the anterior cingulate cortex (ACC). The remaining seven patients had a bilateral abnormal increase in current density in the superior parietal lobe. Fig. 1 summarizes the percentages and the brain regions where we found abnormal EEG sources in the patients of the sample.

The EEG maximal abnormal inverse solution frequency was observed in either of the hemispheres such that the increases in current density were prevalent in alpha band (55.6%), followed by beta band (30.6%) and the remaining cases (13.8%) corresponded to beta and delta bands. Fig. 2 presents an abnormal EEG source at 10.9 Hz (Z=8.9) in one of the patients of the sample. The existence of a

<table>
<thead>
<tr>
<th>Case</th>
<th>Age &amp; sex</th>
<th>Frequency (Hz)</th>
<th>Z-value</th>
<th>Topography (according to Talairach coordinates)</th>
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correlation between HDRS values and the frequency of the EEG maximal abnormal inverse solution was also explored, but none was found (Pearson’s Correlation Coefficient $= -0.01$, $p<0.97$).

4. Discussion

Several studies have shown increased or decreased current density in several structures, including both left and right hemispheres and all classic frequency bands in depressed patients (Pizzagalli et al., 2001, 2002; Mientus et al., 2002; Lubar et al., 2003; Flor-Henry et al., 2004). The present study found that all patients had an abnormal increase in current density but one of the most striking result was the presence of bilateral localization of the abnormal maximal inverse solution (35 of 36 patients). That is, both hemispheres were affected but with a clear dominance of the right over the left one (24 vs. 12). The majority of these patients (about 80%) had a predominant topography of the abnormal EEG maximal inverse solution in the frontal lobes, and 43.5% of the patients with abnormal EEG sources located in the DLPFC involved the ACC. Neuroimaging studies appear to provide valuable information to understand why the proportion of abnormal frontal EEG sources was significantly larger than abnormal parietal EEG sources in the total sample.

Functional imaging studies comparing MDD subjects to normal controls at baseline, have shown a decreased DLPFC activity. Other findings on abnormal regions in baseline studies include the ACC, temporal lobe, and basal ganglia (Galynker et al., 1998; Brody et al., 2001; Liotti and Mayberg, 2001; Drevets et al., 2004). Fitzgerald et al. (2006) reported a considerable heterogeneity in the results between studies concerning DLPFC in MDD patients, although changes in Brodmann area 9 were relatively consistently identified; but there was little consistency in the hemisphere in which they were found. Nevertheless, decrease in cerebral blood flow (Galynker et al., 1998; Mayberg et al., 1999) and metabolic rates (Biver et al., 1994) in the right parietal cortex of depressed patients were identified.

In structural imaging studies, decreased frontal lobe, hippocampal, and basal ganglia volumes are the most commonly reported findings (Brody et al., 2001). Thomas et al. (2002) demonstrated the presence of deep white matter hyperintensities more frequently located at the level of DLPFC. Diffusion tensor imaging has been used (Taylor et al., 2004; Bae et al., 2006) to examine white matter microstructural abnormalities of the dorsolateral prefrontal cortex and anterior cingulate cortex. Depressed patients evinced lower fractional anisotropy values in white

![Fig. 1](image1.png)

**Fig. 1.** Percentages and brain locations where abnormal EEG sources were found: dorsolateral prefrontal cortex, precentral gyrus, and superior parietal cortex. Abnormal EEG sources were located in both hemispheres, but with predominant maximal abnormal inverse solution in the right one and in the frontal lobe.

![Fig. 2](image2.png)

**Fig. 2.** EEG source at 10.9 Hz ($Z=8.9$) in the patient number 16, a female of 43 years old. As can be noted, the maximal abnormal inverse solution was located at the right hemisphere and involved the ACC.

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matter of the right ACC, bilateral superior frontal gyri, and left middle frontal gyrus (Bae et al., 2006).

The present findings on the frequency of the EEG maximal inverse solution showed that in both hemispheres, the increases in current density were prevalent in alpha band followed by theta, beta, and delta bands. Thus, in agreement with previous QEEG results, the present findings demonstrated a high percentage of depressed patients with increases in alpha or theta power (Monakhov and Perras, 1980; Nystrom et al., 1986; Knott and Lapierre, 1987; John et al., 1988; Pollock and Schneider, 1990; Nieber and Schlegel, 1992; Roemer et al., 1992; Alper, 1995).

Although the present abnormal EEG sources are not identical to those previously reported, there is some agreement concerning frequency and topography of the abnormal EEG sources (Lubar et al., 2003; Flor-Henry et al., 2004). Lubar et al. (2003) compared the current density power asymmetry in 15 unipolar depressed females and age-matched non-clinical female controls using LORETA. The depressed group exhibited a left-to-right Alpha2 (10–12 Hz) current density dominance in the left postcentral gyrus and frontal (especially medial and middle frontal gyr) locations. Flor-Henry et al. (2004) also using LORETA compared the source-current densities from a group of 25 male subjects with depression and a group of 65 matched controls. Regions of significantly increased current density were found in depression compared to controls and were generally in the right hemisphere, while regions of significantly decreased current density were generally frontal and in the left hemisphere.

Klimesch et al. (2007) have pointed out the role of the relationship between alpha and brain metabolism as an indirect evidence of different states of brain activation. Goldman et al. (2002) and Laufs et al. (2003a, b) used simultaneous EEG and fMRI to assess the relation between hemodynamic and electrical indices of brain function in awake subjects at rest with eyes closed. They observed a negative correlation between alpha power and metabolic activity in different regions: lateral frontal, inferior frontal, cingulate, parietal, superior temporal, and occipital cortices. QEEG results have demonstrated that previously depressed subjects had less left-sided anterior and less right-sided posterior activation (i.e., more alpha activity) than did never depressed subjects; in addition, depressed subjects failed to show activation in posterior right hemisphere regions during spatial task performance (Henriques and Davidson, 1990, 1997). However, Videbech et al. (2003) suggest that abnormalities in the prefrontal cortex in depression are qualitative in nature rather than quantitative, which implies that depression involves dys-coordination of neural activity in the frontal lobes rather than a simple reduction in activity.

Bae et al. (2006) have suggested the hypothesis that altered connectivity between brain regions contributes to the risk of depression. Fingalkurs et al. (2007) used EEG structural synchrony approach as a measure of functional connectivity and they showed that an increase in brain functional connectivity occurs in major depression: the number and strength of short cortex functional connections were significantly larger for the left than for the right hemisphere, while the number and strength of long functional connections were significantly larger for the right than for the left hemisphere. They also found that some of the functional connections involving alpha and theta frequency bands were positively linked with severity of depression. Despite the methodological differences between these two studies (Fingalkurs et al. and us), it is noteworthy that the results pointed out to dysfunctions in either hemispheres and to alpha and beta abnormalities. These findings support the hypothesis of the whole brain being affected in MDD as indicated by other neuroimaging findings.

It is unclear why the increase in current density for the beta band in three patients was observed. However, there is some evidence suggesting that beta excess characterize the bipolar subtype (John et al., 1988; Alper, 1995), so it is impossible to rule out the possibility that these patients could be bipolar without a previous manic episode. Finally, even though evidence has been presented indicating that both hemispheres are involved in MMD, Kawasaki et al. (2004) also demonstrated prevalent abnormalities in the right hemisphere using LORETA analysis of event-related potentials in 22 unmedicated depressed patients compared with those from 22 age-and gender-matched normal controls. Differences in P300 current density between patients and controls were remarkably larger over the right than the left hemisphere, thereby supporting the hypothesis of right hemisphere dysfunction in depression.

In this paper we have used Z values for the evaluation of EEG current sources abnormality. This statistical comparison against a data base of a normal population gives important support to our results. In conclusion, they suggest that any of the two hemispheres could be affected by MDD, but abnormal EEG sources can be found more frequently in the right one. Our most common finding was EEG sources with maximal abnormal inverse solution at the alpha and theta bands, and located in frontal and parietal cortices, especially in the former.

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