

Low-resolution electromagnetic tomography (LORETA) of cerebral activity in chronic depressive disorder[☆]

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Abstract

In this study we compared the current density power and power asymmetry in 15 right-handed, medication-free chronically depressed females (of the unipolar type) and age-matched non-clinical female controls. We used frequency domain LORETA (Low-Resolution Electromagnetic Tomography). In the interhemispheric asymmetry analysis, compared with the control group, the depression group exhibited a left-to-right Alpha2 (10–12 Hz) current density dominance in the left postcentral gyrus. The pattern of left-to-right dominance included frontal (especially medial and middle frontal gyri) and temporal locations. The between groups comparison of spectral power revealed decreased activity in the right middle temporal gyrus in the depressed group. The decrease emerged in the whole frequency spectrum analyzed (2–32 Hz), although it reached significance in the Delta (2–3.5 Hz) band only. These findings are discussed in terms of the existing literature on affect using EEG, PET and SPECT.

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1. Introduction

During the past 25 years considerable evidence has been published showing that unipolar depression and dysthymia have a lateralized localization primarily in the anterior cortex. Early data were reviewed by Davidson (1984, 1987), Silberman and Weingartner (1986) and Tucker (1981). Older literature based on damage from stroke and lesions of the left hemisphere indicate that following such

injury there is increased depression, dysthymia and negative emotions expressed through tears and dysphoric mood changes. In contrast, lesions of the right hemisphere have been associated with inability to understand and interpret emotional states of others, excessive laughter and joking and inappropriate behavior in social settings including pathological laughter (Sackeim et al., 1982). A landmark study by Henriques and Davidson (1991) showed that depressed subjects had left anterior decreased activation characterized by increased alpha activity compared with individuals not experiencing depression. This pattern of left frontal hypoactivation has been interpreted as a deficit in approach mechanisms, whereas right

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frontal hypoactivation is associated with deficits in the withdrawal system (Davidson and Henriques, 2000). These researchers have also described the same asymmetry, increased alpha more prevalent in the left anterior cortex in recovered depressives (Henriques and Davidson, 1990). However, the relationship was not as strong as it was found in people experiencing depression. This same pattern of frontal hypoactivation in alpha has also been identified in infants of mothers experiencing depression as early as one month of age (Jones et al., 1997). Field et al. (1995) reported the same difference in infants ages 3 to 6 months. The left frontal alpha asymmetry marker for depression appears to be powerful enough that it may represent both state and trait levels of the disorder. Subjects with pre-existing left frontal hypoactivation reported a greater degree of global negative affect when shown fear eliciting film clips than subjects experiencing less left frontal hypoactivation (Tomarken et al., 1990). Other investigations have found a significant relationship between reports of happiness associated with left frontal activation (less alpha) whereas elicited disgust was related significantly to activation of the right frontal region. Overall these studies support the hypothesis of the hemispheric separation between approach and withdrawal systems.

In addition to EEG based studies, the relationship of frontal alpha asymmetry and negative emotions has been reported in glucose metabolism measured by 18 fluorodeoxyglucose (FDG) using PET by Sutton et al. (1997). Specifically they found greater metabolic activity in the right dorsolateral prefrontal cortex with stimuli, which elicited aversive emotion than in the homologous left frontal cortex. This is interesting since increased right frontal higher frequency EEG activity is associated with negative affect. Recently, Leuchter et al. (1999) reported that increased cerebral metabolism measured by PET is correlated with increased power in both Beta (13 Hz and higher) and Delta–Theta (less than 7 Hz), but is inversely correlated with Alpha (8–12 Hz) activity. Together these findings show that EEG and metabolic measures may compliment each other in terms of their relationship to emotional state and cortical asymmetry.

Frontal asymmetry relating emotion and depression have not always been found (e.g. Reid et al., 1998). There are some methodological concerns, which may partially address the heterogeneity of findings in different laboratories (Davidson, 1998). In order to see the relationship between left frontal hypoactivation and negative affect or right frontal hypoactivation and positive affect it is better to reference recordings to an average reference, an average-ears reference, or to the vertex location CZ. In scalp EEG studies of depression and emotions, frontal asymmetry is better observed recordings from the two frontal locations F3 and F4 (international 10–20 system). In order to calculate asymmetry measures it has been suggested to use the raw difference in log Alpha amplitude or power at homologous contralateral sites (e.g. F4–F3) (Davidson et al., 2000). Other authors suggest normalizing this difference dividing by the total power at the two sites $(F4 - F3)/(F4 + F3)$ (John et al., 1987). This latter formula has been employed clinically by a number of researchers such as Baehr et al. (1999). They showed that it is possible to use EEG biofeedback (neurofeedback) to train individuals with depressive disorders to shift the asymmetry ratio from the left side to the right side or to reduce it. In their research they trained patients with major depressive and dysthymic disorders to reduce or reverse their asymmetry ratios with corresponding improvements in measures on the Beck Depression Inventory. A number of their patients have now been followed for five years or longer and continue to show stable improvements in their depressive symptoms sometimes associated with decreased reliance on antidepressant medications.

In a recent completed doctoral dissertation, Askew (2001) found that 22 chronically depressed females all had negative asymmetries scores indicating greater alpha activity in the left prefrontal cortex measured at location F3 compared with the right prefrontal cortex measured at F4 (CZ reference). He also found a strong correlation between the alpha asymmetry scores and measures on the Beck Depression Inventory ($r = -0.945$, $P < 0.0001$) and on the scale 2 (depression) of the MMPI-II ($r = -0.891$, $P < 0.0001$), indicating that the greater the amplitude of Alpha at F3 as

compared with F4, the more severe the depression symptoms. Similar results were reported by Baehr et al. (1999). These results suggest that the asymmetry ratio may be a powerful neurological marker of depression.

The purpose of the present study was to extend the existing findings using the low-resolution electromagnetic tomography (LORETA) (Pascual-Marqui, 1995, 1999; Pascual-Marqui et al., 1994). LORETA is an inverse solution technique. It has been extensively used in electrophysiological research (e.g. Isotani et al., 2001; Pizzigalli et al., 2001) and has been evaluated independently in several laboratories (e.g. Fuchs et al., 1999). LORETA estimates the distribution of electrical neuronal activity in 3-dimensional space. The reconstruction is independent of the reference used in obtaining the EEG recordings (Pascual-Marqui, 1999). This is a distinctive advantage of LORETA over scalp EEG, which depends on the reference enabling a superior consistency in results obtained across laboratories. In fact the reference issue has been of concern in the literature on depression and EEG. In this study we were particularly interested in examining the distribution of brain current density responsible for the frontal asymmetry found on the scalp by Askew (2001). We also evaluated the current density power for a number of EEG band-passes. The purpose, then, is to extend existing EEG findings from the surface to cortical brain structures in as much as the LORETA inverse solution allows this type of visualization.

2. Methods

2.1. Subjects

Depressive subjects in this study were the group of 22 right-handed females from the original Askew's study. The selection criteria included a diagnosis of unipolar depression without any diagnosis of a comorbid DSM-IV Axis I and Axis II disorder that was provided by a clinical psychologist, psychiatrist or physician. The subjects had not used anti-depressant medications within one month prior to the recording of their EEG. They had not consumed any psychoaddictive substances

or alcohol within 48 h of the EEG recording session. Furthermore, for all included subjects at least 60 s of artifact-free EEG data were available. Depressed subjects were required to complete the Beck Depression Inventory II (Beck et al., 1996) and the MMPI-2 Depression scale (Butcher et al., 1989). In addition, Beck Anxiety Inventory (Beck and Steer, 1989) was used to screen for comorbid anxiety disorders that could introduce confounds. The Beck Hopelessness scale (Beck and Steer, 1986) was used to assess presence of negative attitudes about the future and feelings of hopelessness that had been observed as aspects of depression and suicidality. Finally, for the depressed group a 'semi structured' clinical interview (Zimmerman, 1994) was used to screen for depression mental status and other comorbid Axis I and Axis II disorders. Seven subjects among the original 22 were excluded because of insufficient artifact-free EEG data. Therefore, we were left with 15 clinical individuals. LORETA current density reconstruction is a weighted sum of all scalp potentials. For this reason it is crucial to submit data free of artifact for all channels.

In addition to the individuals experiencing unipolar depression a group of 15 aged matched, right-handed, non-clinical, female controls were included in the study. All subjects were voluntary participants. Normative data were collected at the University of Tennessee as part of a larger study aimed to develop a normative database for EEG. All subjects were recruited from undergraduate and graduate courses. They were meticulously screened and considered for inclusion in the normative database if they or their first degree relatives had no history of depression, anxiety, epilepsy, eating disorder or any other psychiatric disorders that would confound their status as non-clinical controls. All normative subjects were required to be alcohol and medication free for 48 h prior to recording. Furthermore, they were required to sign an informed consent. For these subjects as well at least 60 s of artifact-free EEG data was available. All subjects, both clinical and controls had some or had completed college education. All aspects of this study were approved by the University of Tennessee Human Subjects Review Board. Age of subjects was rounded to

the closest integer. There was no difference in the mean age of the two groups. The Standard deviation of the ages was 7.22 for the depressive group and 8.15 for the controls.

2.2. Procedure

In preparation for recording a measure of the distance between nasion and inion was used to determine the appropriate electrode cap size for recording purposes (Electrocap Inc.). The forehead was prepared as well as the ears with Nuprep, a mild abrasive gel to remove any oil from the skin. The cap was then fitted and each electrode site carefully injected with electrogel and prepared so that impedances between each electrode site and each ear measured individually was between 3 and 5 K Ω as well as the impedance between ears themselves. The EEG was then recorded at the standard 10–20 system 19 locations (FP1, FP2, F3, F4, Fz, F7, F8, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1 and O2) using the Neurosearch-24 (Lexicor Medical Technologies, Inc.). The EEG was sampled by 12 bit AD converter at 128 samples per seconds and the low and high pass filters were set at 0.5 Hz and 32 Hz, respectively. All EEG recordings in this study were acquired during standard eyes closed resting conditions. For each individual in the study approximately 3–4 min of data were collected continuously in a dimly illuminated and sound attenuated room at the Neuropsychology and Brain Research laboratory of the University of Tennessee. Data were acquired using the Lexicor V-41E acquisition program. Data were then transported into the EEG Workstation 2.0 software (NovaTech EEG, Inc.), where they were plotted and carefully inspected for manual artifact-rejection. All episodic artifacts including eye blinks, eye movements, teeth clenching, body movements, or EKG artifact were removed from the stream of EEG. Particular care was taken to eliminate periods of EEG containing continuous muscle artifact in temporal locations T3, T4, T5 or T6.

2.3. Data analysis

For each subject in the study, average cross-spectral matrices were computed for the classical

bands Delta (2–3.5 Hz), Theta (4–7.5 Hz), Alpha (8–12.5 Hz), and Beta (13–21 Hz). In addition, we investigated the narrow bands Alpha1 (8–10 Hz) and Alpha2 (10–12) for asymmetry analysis. For each subject, cross-spectral matrices (FFT) were computed and averaged over 4-s epochs resulting in one cross-spectral matrix for each subject and for each of the discrete frequencies within each band. Following previous literature on LORETA analysis, we employed a rectangular window. Sliding overlapping windows (93.75%) allowed reliable and smooth spectral estimates. LORETA current density in the frequency domain is conveniently computed directly from the average cross-spectral matrix (Frei et al., 2001). The LORETA-Key package (Pascual-Marqui, 1999) was used for this purpose. This LORETA implementation incorporates a three-shell spherical head model registered to the Talairach and Tournoux (1988) anatomical brain atlas and makes use of EEG electrode coordinates derived from cross-registration between spherical and realistic head geometry (Towle et al., 1993). The solution space is restricted to cortical gray matter using the digitized probability atlas of the Brain Imaging Center at the Montreal Neurological Institute. The solution space is divided in 2394 voxels of size 7 \times 7 \times 7 mm. For every frequency band and subject the current density modules at each voxel (LORETA power) were smoothed with a 10.5 mm three-dimensional moving average filter, normalized and finally log-transformed. Log-transformation of power estimates is routinely performed in EEG and LORETA and aims to approximate data gaussianity (John et al., 1987). Spatial smoothing and spatial normalization are routinely performed with PET and fMRI (Petersson et al., 1999). With LORETA, little smoothing is advisable to reduce anatomical and localization errors due to inter-individual differences in head geometry and electrodes placement. As a consequence of these factors local maxima can be visualized in slightly different locations. Smoothing reduces the error introduced. Spatial normalization (for each subject the square root of the sum of squared current density values at all voxels is normalized to equal unity) allows the elimination of confounding variables such as the inter-individual variability in

skull thickness and electrode impedance, without constraining the analysis on relative power measures, which is the solution usually adopted in EEG studies. LORETA power estimates computed and pre-processed as described provided the data for power statistical analysis.

Asymmetry scores are usually defined as the difference between measurements across contralateral points. Power asymmetry analysis in neuroimaging requires particular care (Davidson, 1998; Davidson et al., 2000). The digitized Talairach atlas as used in the LORETA-Key software is not exactly symmetrical around the sagittal midline. There are 1204 voxels in the left hemisphere and 1190 voxels in the right hemisphere. There are at least two procedures to obtain voxel-by-voxel asymmetry scores. One is, starting from one hemisphere, examine each voxel and find the closest match on the contralateral side. The closest match is defined as the voxel in the other hemisphere with minimum distance (in Talairach and Tournoux space) from the exact contralateral point. Doing this we found that 86.72% of the closest matches were 1 mm apart from the exact contralateral points, 12.61% of them were between 6 and 8 mm apart and the remaining 0.66% were displaced up to 15.68 mm. Considering asymmetry of larger regions instead of that at the voxel level would provide more valid estimates of brain asymmetry. This leads to idea for the second procedure: let us start from one hemisphere and examine 21 mm radius spherical regions with center at each voxel in that hemisphere. On the contralateral side let us define a corresponding region with center on the exact contralateral point. The asymmetry scores are the contralateral differences of the smoothed (moving average) current densities within those spherical regions. This latter procedure was the one chosen for our analysis. We always computed asymmetry starting from the left hemisphere, so all asymmetry refers to left-right differences, with positive numbers indicating stronger current density on the left as compared with the right and negative numbers indicating stronger current density on the right as compared with the left. Davidson et al. (2000) note that considering the hemispheric differences we take into account the influence of confounding variables such as the

global current density in the entire volume. In fact subjective confounding variables cancel out in the difference. Hence, for asymmetry analysis we processed non-normalized data. As for power analysis, current density reconstructions were log-transformed and spatially smoothed with a 10 mm three-dimensional moving average. Asymmetry scores were computed on these pre-processed current densities and constituted the data for the power asymmetry statistical analysis.

Our aim was to identify current density power and power asymmetry differences between the depression and control group. For statistical analysis we relied on the randomization-permutation multiple comparison approach illustrated for neuroimaging data by Holmes et al. (1996) and by Nichols and Holmes (2001). The distinctive advantage of this approach is that it adaptively accounts for the correlation structure of the variables, an embedded feature of all electrophysiological measurements. Furthermore, the approach does not rely on asymptotic results hence it is appropriate for the sample size of this study. We performed a single test for power analysis including data from all four bands (Delta, Theta, Alpha, and Beta). For the whole data set (2394×4 variables), voxel-by-voxel paired (age-matched) *t*-tests were computed. For power asymmetry we submitted to analysis data from Delta, Theta, Alpha, Alpha 1, Alpha 2 and Beta bands.

The procedure for multiple hypothesis testing correction is known as *t*-max test. We used the step-down version of the procedure (Blair and Karniski, 1994; Holmes et al., 1996; Westfall and Young, 1993) with 10 000 random data permutations. The *t*-max test has been shown to exercise strong control over the family-wise error (FWE), that is, for a given type I error, the test ensures that the probability to falsely reject any hypothesis is no more than alpha. The Type I error in this study was fixed to 0.05. Therefore, all results reported are significant at the 0.05 level after correction for multiple testing.

3. Results

3.1. LORETA current density power

For all bands we tested the hypothesis of a shift in the mean current density power of the two

Fig. 1

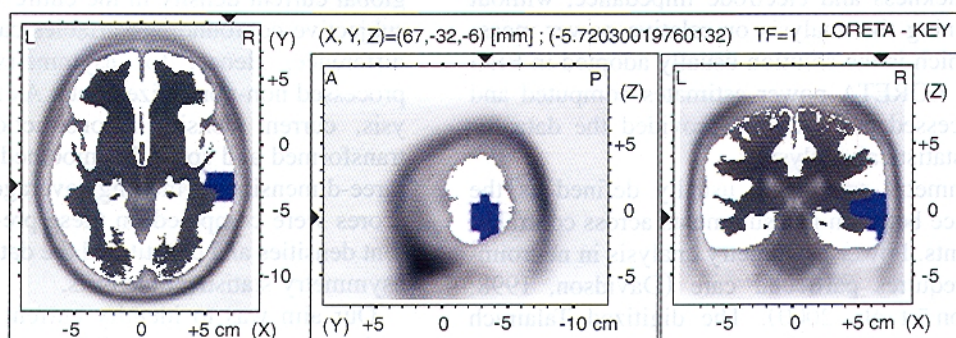


Fig. 2

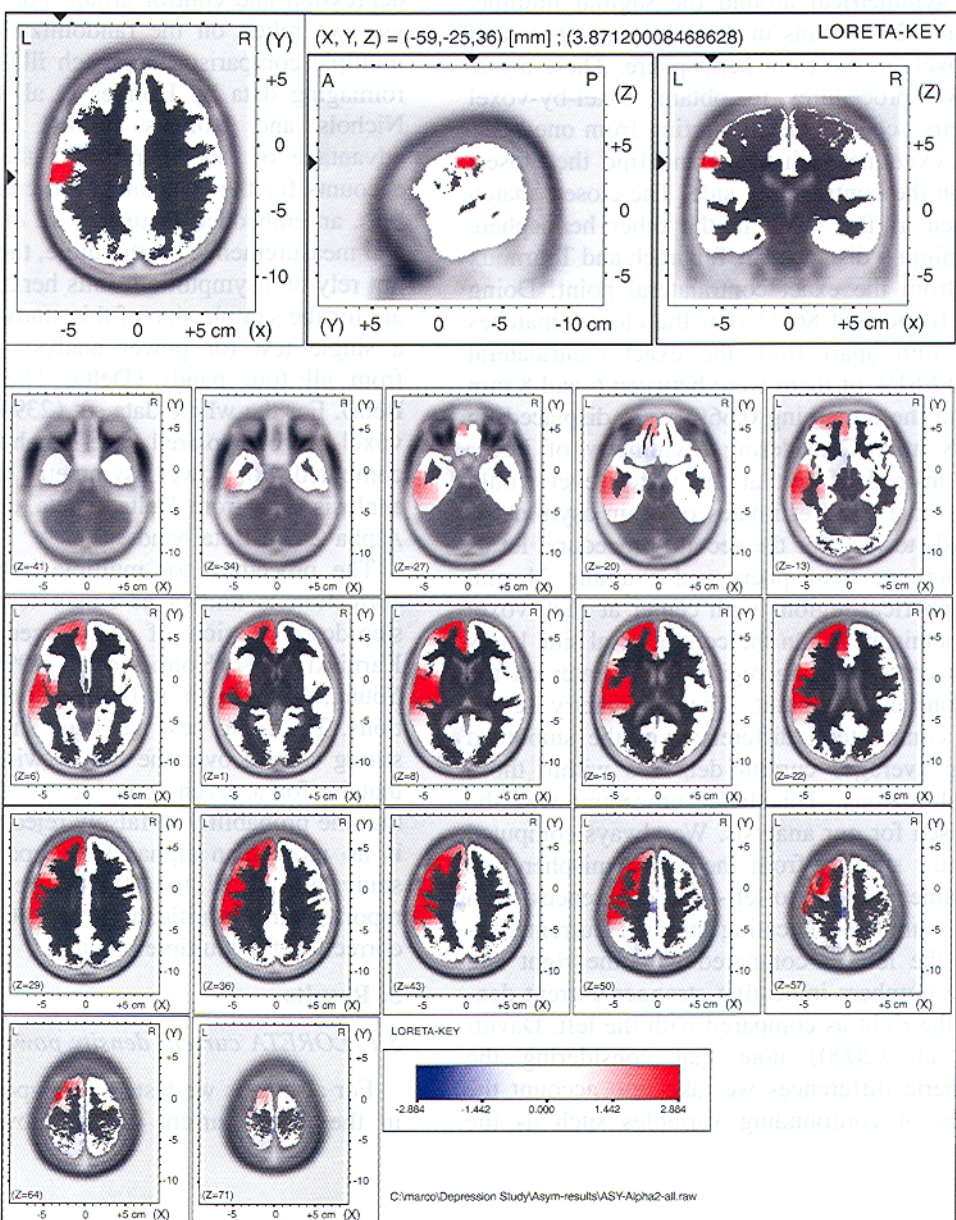


Table 1

Summary of Current Density Power LORETA analysis. The first column reports the frequency bands. The second reports the number of significant voxels found. The third, the volume covered by those voxels. Columns 4 to 6 report the local maximal *t*-statistic, the coordinates in the Talairach and Tournoux (1988) space and the anatomical labeling

Delta (2–4 Hz)	Number significant voxels	Volume (cm ³)	Local max <i>t</i> -statistic	Local max coordinates (x, y, z)	Local max description
Delta (2–4 Hz)	24	8.232	–5.72	67, –32, –6	R Temporal, Middle Temporal Gyrus, BA 21 (also involving BA 20 and BA 22)

groups (Depression minus Control). Comparisons were at the voxel level and data from all four bands considered entered the permutation test at once. This resulted in 2394×4 simultaneous tests. All tests were two-sided. Results presented are those voxels exceeding the threshold of significance of the *t*-max test (corrected for multiple comparisons). Results are summarized in Table 1 and Fig. 1.

Significant results were found in the Delta (2–3.5 Hz) band. Current density in Delta was weaker in depressed patients as compared with controls in a large region (24 voxels) covering from the inferior to the superior right temporal gyrus (Brodmann area 20, 21 and 22). The strongest effect was found in the right middle temporal gyrus (Table 1). A similar trend in this region was present across all frequency spectrum although in Theta, Alpha and Beta bands it did not reach significance. For the voxel exhibiting maximum *t*-value within the region the group-effect monoton-

ically decreased across the spectrum. The maximum *t*-statistic was equal –5.72, –4.33, –3.70, –2.15 for Delta (2–3.5 Hz), theta (4–7.5 Hz), Alpha (8–12.5 Hz) and Beta (13–21 Hz), respectively.

3.2. LORETA current density power asymmetry

We tested the hypothesis of a shift in the mean current density power asymmetry score of the two groups (Depression minus Control) at the (smoothed) voxel level. Asymmetry scores were computed as left minus right hemisphere. For the alpha, alpha 1, and alpha 2 bands, the test was one-tailed because the large body of literature cited in the introduction allowed us to predict a left-to-right dominance for Alpha. That is, when compared with controls, the current density of depressed patients in Alpha was expected to be stronger on the left side as compared with the contralateral right side. There were 1204 simulta-

Fig. 1. Significant results for Current Density Power Analysis in the Delta band. Displayed are the horizontal (left), sagittal (middle), and coronal (right) sections through the voxel with maximal *t*-statistic (local maximum). In the horizontal and coronal sections, left of the figure represents left of the brain. In the sagittal section, the anterior part of the brain is on the left of the figure. Coordinates and *t*-values for this voxel are printed above the picture of the sagittal section. See also Table 1. All *t*-statistics are negative and are displayed in blue (the mean of depression group is smaller than the mean of the control group). See text for details.

Fig. 2. Results for Asymmetry Analysis. The figure at the top displays the horizontal (left), sagittal (middle) and coronal (right) sections through the voxel with maximal *t*-statistic. Coordinates and *t*-values for this voxel are printed above the picture of the sagittal section. See text for details. This figure shows significant results only. The figure at the bottom displays all horizontal slices. Slices are 7 mm spaced. Bottom of the brain: top-left slice. Top of the brain: bottom-right slice. This figure is a map of all *t*-statistics revealing the pattern of asymmetry. The magnitude of *t*-values is color-coded. The positive *t*-statistics are displayed in red (the mean left minus right asymmetry is larger for the depression group as compared with the controls). Negative *t*-statistics are displayed in blue (the mean left minus right asymmetry is smaller for the depression group as compared with the controls).

neous tests performed for each band. Significant results were found in Alpha (8–12 Hz) and Alpha 2 (11–12 Hz) only. The Alpha 2 band is included in the Alpha band. Indeed the two maps of univariate *t*-tests and the significant effects were very similar. For this reason we present results for Alpha 2 only, where the effect was stronger. Significant effects were found for a cluster of four voxels (maximum $t=3.87$) covering the left postcentral gyrus, Brodmann area 2 and 3 (see Fig. 2).

Because of the 20 mm smoothing used for asymmetry scores computation, the effect may involve also the adjacent left precentral gyrus, Brodmann area 4 and the left inferior parietal lobule, Brodmann area 40. The bottom portion of Fig. 2 shows all *t*-statistics for brain asymmetry in Alpha 2. Secondary local maxima with more positive asymmetry scores in the depressed group were in the middle frontal gyrus (coordinates: $-52, 3, 43$; BA 6; $t=3.71$), medial frontal gyrus (coordinates: $-3, 59, 22$; BA 10; $t=3.28$), and in several other frontal and temporal locations. Although these secondary differences were not significant after correction for multiple comparisons, we report these findings because they are significant at the univariate level and in the same direction and locations found in the previously cited literature on frontal asymmetry. No significant result for asymmetry was found in the other bands.

4. Discussion

In summary, in this study employing LORETA imaging for individuals with a long history of significant depression we observed a pattern of more central, temporal, superior fronto-lateral and medial frontal asymmetry (increased Alpha 2 current density on the left hemisphere as compared to the right hemisphere). A strong and significant asymmetry was localized in the postcentral gyrus. Alpha electrical activity is negatively correlated with blood-flow (Leuchter et al., 1999). Using PET, Sutton et al. (1997) found that elicitation of positive affect predominantly increased the metabolism in the left pre and postcentral gyri. Based on previous EEG studies on asymmetry we pre-

dicted mainly frontal alpha asymmetry. Our test failed to reject the null hypothesis explicitly in frontal locations. One possible explanation for this is that the asymmetry effect is not spatially consistent in each depressed patient. Also, the sample size to number of hypotheses ratio was low in this experiment. In EEG studies the asymmetry is tested for a few locations (e.g. F3/F4, P3/P4), whereas in this experiment with LORETA the asymmetry was measured in 1204 locations. As a consequence our statistical test was less powerful. Another consideration is that the multiple hypothesis testing procedure we employed controls the FWE in the strong sense (Holmes et al., 1996). Being based on the randomization distribution of maximal statistics this procedure tends to be unduly conservative when the effect is spread (Troendle, 1995). Because of all these factors the power of our testing procedure may not have been sufficient to specifically localize frontal asymmetry differences between depressed patients and matched controls. Nevertheless, in the entire frontal lobe the asymmetry was found to be in the predicted direction and in several portions it was marginally significant (Fig. 2). Overall these asymmetry findings are in line with those that have been described and summarized by the work of Davidson and colleagues over the past 20 years.

Power Analysis revealed significant results in Delta. It is important to point out that lateralized power results cannot be interpreted as an indication of brain asymmetry. The latter has to be specifically tested (Davidson, 1998; Davidson et al., 2000). Before entering the power analysis stage, data was spatially normalized. This consists of eliminating inter-subject variability in the total current density within the brain volume. As a result, all effects shown for a particular region have to be interpreted as stronger current density as compared with the rest of the volume. Decreased delta current density power was found in a large portion (24 voxels) of the right temporal lobe. This effect in Delta was also seen as a trend in Theta, Alpha and Beta bands. The scalp potentials are believed to increase proportionally to the number of cells acting simultaneously and synchronously (Nunez and Silberstein, 2000). These authors note that while hemodynamic and meta-

bolic measures are believed to increase with neuronal firing rate, EEG/EMG signatures increase as a function of synchrony only. Thus, while a decrease in current density indicates desynchronization of local neuronal activity, it is not known if the metabolism associated with a decrease in current density would be greater or smaller. Using SPECT, Kocmur et al. (1998) found higher perfusion in the right frontal and temporal regions of depressed patients without medication. After pharmacotherapy, perfusion decreased in the right temporal regions. Using the same technique and ^{123}I labeled iofetamine (IMP), Amsterdam and Mozley (1992) found substantially increased IMP activity in the right temporal lobe affecting a group of depressed individuals more than a group of controls. The right temporal lobe of depressed patient appears to be hyperactive and desynchronized. The desynchronization of right temporal neurons we found concerned the whole frequency spectrum, although it was strong enough to appear significant in the Delta range only. Our interpretation of results is that neuronal regions in the right temporal cortex of depressed patients may lack basic modulation properties. It appears that they lack small scale local organization, which results in hypermetabolic desynchronized activity.

As a caveat, seldom is EEG data spatially normalized before performing statistical analysis. Furthermore, EEG data are collected using diverse reference electrodes. Therefore, comparison of our findings with previous EEG data is limited by these technical differences.

In conclusion, the main purpose of the present paper was to examine the often reported left vs. right hypoactivation in depressed patients. We also tested the intercortical distribution of current density power for a number of different band passes. Our basic finding of increased alpha current source distribution in the left anterior quadrant correlates with published EEG, PET and SPECT findings. The maximal activation in our study was located in central regions. The decreased Delta activity in the right temporal region is perhaps a new finding. In this study we undertook considerable care in recording and artifact rejection procedures. Also, we used a conservative statistical approach. As a consequence of using these procedures we believe

that the differences we reported between the depressives and non-clinical controls represent strong and replicable shifts in the means of the two groups.

Future studies on Depression using LORETA might benefit from a larger sample size if the control of the FWE is sought in the strong sense. Also, it might be useful to evaluate, in as much as it is possible, LORETA distributions for depressed and non-depressed patients under different task conditions. This will be challenging because movement and EMG artifacts easily contaminate LORETA images. However, it could provide further insight on the electrophysiological correlates of this disorder.

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