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# Intracranial current density (LORETA) differences in QEEG frequency bands between depressed and non-depressed alcoholic patients

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**Abstract**

*Objective:* To assess possible differences in intracranial source distribution of surface QEEG power between depressed and non-depressed alcoholic patients in order to find any symptom-related topographic features of physiopathologic relevance.
*Methods:* Low-Resolution Electromagnetic Tomography (LORETA) for the delta, theta, alpha and beta bands of EEG spectra was estimated from 38 alcoholic patients, 20 with and 18 without clinical depression, in which QEEG showed decreased slow and increased beta activity diffusely. Statistical non-parametric mapping was used to compare depressed and non-depressed groups. Measures of intracranial current density in individual patients at areas of significant differences were correlated with BDI scores.
*Results:* Patients with clinical depression showed areas of significantly lower current density than non-depressed patients in delta band at left anterior temporal, left midtemporal (including amygdala and hippocampus), and both frontopolar cortices mostly on the right; and in theta band at bilateral parietal lobe, anterior cingulate and medial frontal cortex. No differences were found at alpha and beta band. Intracranial current density in delta band at left parahippocampal, left midfrontal cortex and right frontopolar cortex was negatively correlated with BDI score. Theta band also showed negative correlations with BDI at sites of significant differences.
*Conclusions:* Diffusely decreased delta and theta activity in the surface QEEG of alcoholic patients has a different intracranial distribution linked to the presence or not of clinical depression that seems to reveal a dysfunctional neuronal state at several specific limbic and other cortical locations that have been related to a specific clinical disorder such as depression.
*Significance:* These results provided further evidence on the effects of depression in the context of alcohol dependence, in this case decreased slow activity as a possible marker of neuronal damage secondary to alcohol toxicity, clinically expressed as depressive symptoms when present in structures that are known to be related to clinical depression.


*Keywords:* Quantitative EEG; Alcoholism; Depression; Intracranial generators; Slow activity; Limbic cortex

## 1. Introduction

Quantitative electroencephalographic alterations revealing a decreased level of functional activity in the brain have been associated with clinical depression (Henriques and Davidson, 1991; Kwon et al., 1996), in close correlation with anatomic evidence of neuronal and glial degeneration (Rajkowska et al., 1999; Stockmeier et al., 2004).

Most reports deal with alterations in alpha band activity, where some authors reported mainly frontal asymmetries (Knott and Lapierre, 1987; Alper, 1995; Henriques and Davidson, 1991), although other reports reject those findings (Pollock and Schneider, 1990; Debener et al., 2000).

On the other hand, increased delta activity, an obvious feature in visual EEG inspection, has been correlated to

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many types of brain damage through all EEG history, and its pathophysiology is regarded as sign of cortical deafferentation (Amzica and Steriade, 1997) in many neurological diseases and also in psychiatric conditions like schizophrenia (Begic et al., 2000; Sponheim et al., 2000).

However, EEG Fourier spectra reveal a significant amount of physiologic activity of unknown significance in the delta and theta bands in normal waking adult subjects. This physiological activity may be below normal limits in certain pathological conditions (Prichep et al., 1996; Coutin-Churchman et al., 2003, 2006; Lubar et al., 2003; Wienbruch et al., 2003; Saletu-Zyhlarz et al., 2004), but the *physiological* significance of this *statistical* deviation from the norm remains unclear (Nuwer, 2003).

Recent evidence, mainly from neuromagnetic activity, suggests that increased or decreased intracranial focal delta activity at different regions of the brain is related to symptomathology, like increased delta to positive symptoms in schizophrenia (Begic et al., 2000; Sperling et al., 2002) or decreased delta in MEG to depression (Wienbruch et al., 2003). On the other hand, decreased EEG slow band activity has been described in depression (Saletu et al. (2002), and also in other psychiatric conditions like alcohol and drug abuse, (Alper et al., 1998; Coutin-Churchman et al., 2003; Saletu-Zyhlarz et al., 2004), and has been correlated to cortical atrophy as seen in MRI (Coutin-Churchman et al., 2003, 2006).

While former studies have associated depression to increased power in all bands at posterior right hemisphere (Kwon et al., 1996), more recent studies agreed in describing that depressed patients had more alpha and beta activity, and less delta activity than non-depressed controls (Pollock and Schneider, 1990; Debener et al., 2000; Hughes and John, 1999; Knott et al., 2001; Saletu et al., 2002). On the other hand, relatively greater right frontal resting activity (or relatively lower left frontal resting activity) has also been reported in depressed patients (Henriques and Davidson, 1991).

In alcoholic patients, the most widely described QEEG feature is increase in beta activity (Rangaswamy et al., 2004). In a previous work we found an association of increased beta power with benzodiazepine intake (which had no association with any other QEEG feature), family history of alcoholism and hallucinations (Coutin-Churchman et al., 2006). However, in the same work we found also a high incidence of decreased slow activity, diffusely across the scalp. This feature was associated with concomitant arterial hypertension, chronicity of alcohol drinking, and, again, to cortical atrophy as seen in MRI (Coutin-Churchman et al., 2006), but contrary as expected, it was unrelated to psychiatric features frequently found in those patients, like, anxiety or memory disorders, with only a marginal degree of association between decreased slow activity and depression, which failed to reach statistical significance when adjusted by Bonferroni criteria (Coutin-Churchman et al., 2006).

Since a diffusely distributed scalp EEG feature could be caused by different distributions of intracranial generators (the familiar *inverse problem*), several mathematical procedures for localization of sources of scalp fields have been devised in the last decades. Low-Resolution Electromagnetic Tomography (LORETA, Pascual-Marqui et al., 1994) has been widely used for the localization of spontaneous or evoked electrical phenomena in time (Pascual-Marqui, 1999) but also in the frequency domains (Frei et al., 2001), and for statistical comparisons of intracranial current density distributions between patients and controls in different conditions, including psychiatric disorders (Pizzagalli et al., 2001, 2002; Mientus et al., 2002; Flor-Henry et al., 2004). In more recent research using this and other source localization procedures depression was found to be related to focally decreased slow wave activity at left frontal and other areas in both EEG (Lubar et al., 2003; Flor-Henry et al., 2004) and MEG (Wienbruch et al., 2003), or to decrease in all bands at prefrontal or anterior cingulate (Mientus et al., 2002). Others have found no significant differences between depressed and controls, but between depressed patients who were responders or not responders to treatment, and only in theta band at anterior cingulate cortices (Pizzagalli et al., 2002).

The aim of this study is to test if a sample of male alcoholic patients, all with the same surface QEEG profile, have different intracranial distribution of QEEG activity depending on the presence or not of depressive symptoms.

## 2. Methods

### 2.1. Sample

Thirty eight male chronic (>10y) alcoholic patients (F10.2–F10.3, according to ICD-10), who were admitted to our inpatient facility for detoxification. They had ages between 26 and 55 years (Table 1). All were chronic compulsive alcohol consumers, in a range of 10–20 years of continuing alcoholic habits, with a consumption pattern at the time of admission corresponding to a daily or near-daily basis of more than 100 g/ethanol/day (intense or heavy drinkers according to Glund criteria, Schüller, 1991). Most patients had ten or more standard daily drinks of local homemade rum (“miche”) with 45°–50° of alcohol, while others used whisky or brand rum (40°), for an average 10 g of alcohol per standard drink (see Coutin-Churchman et al., 2006).

All the patients were part of the broader sample reported in our previous study (Coutin-Churchman et al.,

Table 1
Demographic data of patients

| | Age | Time consuming alcohol | Dose of DIAZEPAM (mg/day) | BDI | *N* |
|---|---|---|---|---|---|
| Depressed | 41.6 ± 7.55 | 16.72 ± 7.23 | 64.03 ± 23.47 | 26.3 ± 8.1 | 20 |
| Non-depressed | 40.8 ± 8.24 | 16.9 ± 8.12 | 63.81 ± 22.71 | 7.5 ± 3.8 | 18 |

2006), but only those whose QEEG showed similar QEEG profile, abnormally decreased (<3 SD) power in delta and theta bands and increased (>3 SD) beta power, diffusely distributed over the scalp were selected beforehand for this study. The abnormality criteria for absolute and/or relative power were: decreased if below 3 SD. and increased if above 3 SD. from the mean of an age/sex matched norm in at least 3 contiguous electrodes. In this case abnormalities were present at nearly or all the electrodes.

Patients with significant clinical history of neurological (head trauma, epilepsy, cerebrovascular, tumoral or neurodegenerative diseases), psychotic, concurrent drug abuse, or other psychiatric disorders, systemic diseases (diabetes, arterial hypertension, AIDS or seropositives, collagen diseases etc.), or with other clinical features known to be related with QEEG (Coutin-Churchman et al., 2006), like results of MRI scan other than diffuse cortical atrophy, hallucinations or family history of alcoholic habits were also excluded in order to minimize the effect of intervening variables in the design. All patients were taking benzodiazepine medication at the time of recording. Only 38 patients fulfilling all criteria could be found at the end of the process.

All patients were previously screened by a psychiatrist at the alcoholism inpatient facility of our hospital, looking for depressive symptoms using ICD-10 and DSM-IV criteria. The Beck Depression Inventory (BDI, Beck et al., 1961, revised version BDI-II, Beck et al., 1996), applied to the patients the day before the EEG recording by a psychiatrist, was used as a tool for selection purposes. Since one of the shortcomings of the method is that in a concomitant illness the scores could be artificially inflated due to symptoms of the illness rather than depression itself (Moore et al., 1998), we chose a cutoff point slightly higher than the lowest reported for mild depression (14 points) for selecting our groups. Hence, the patient was assigned to the depressed group if his BDI score was greater or equal to 16 points and to the not depressed group if his score was 15 or lower. Twenty patients were assigned to the depressed and 18 to the not depressed group according to the above mentioned criterion. Depressed patients who required medication began their prescribed antidepressant therapy after EEG recording was performed. The electroencephalographer was blind to the condition of the patient at the time of the study.

### 2.2. EEG recording

EEG recording techniques have been described in detail elsewhere (Coutin-Churchman et al., 2003, 2006). EEG recording was done at least one week after admittance, to guarantee at least one alcohol-free week prior to the data collection, but in the vast majority of the cases the EEG recording was made on the second week after, so most patients had about 14 days of abstinence. No recording made beyond the third week after admittance was included in the study.

Digital EEG (21 channels) was recorded from conventional Ag/AgCl electrodes attached with conductive jelly to the standard 10/20 scalp locations (determined by conventional tape measurements of skull landmarks, Jasper, 1958) referred to linked ears (plus two channels for ocular movements and one for EKG). Activity was sampled at 256 Hz, and filtered offline between 0.5 and 30 Hz. Impedance was kept below 5 kΩ. Recordings were made according to usual clinical standards, including 10 min of resting eyes-closed state, 3 min of alternate 10 s of open eyes/closed eyes, 3 min of hyperventilation, 1 min of recovery, and photic stimulation. Analysis was circumscribed to resting closed eyes state (awake).

A Bio-Logic CEEGRAPH-IV® device was used for EEG recording, while revision of EEG, selection of samples and FFT-power spectra calculation were done on a separate reading station using Persyst Insight® EEG reading software. Further analysis was performed using the LORETA-KEY? software package (v03, 2002). Briefly, the 21-channel digital EEG (plus two ocular movements and one EKG channel) was visually edited in the computer for the manual selection of 30–60 non-overlapping, 1-s artifact-free segments, selected over the same epochs used before for conventional QEEG analysis (condition: patient fully awake and with closed eyes). Data were carefully reviewed by the electroencephalographer in order to avoid the selection of epochs with ocular movements, EMG or EKG contamination, drowsiness (defined by suppression of alpha rhythm substituted by slow irregular activity) or any other visually identifiable artifact, which were discarded for analysis using a "maximalist" instead of a "minimalist" approach (Lawson et al., 2003), i.e., any segment showing any suspected source of contamination, even small but detectable baseline shifts, was discarded. Segments containing paroxysmal or other non-stationarities or transient electrical events were also avoided.

### 2.3. EEG analysis

Selected EEG segments (each with 256 time points per channel) were saved to disk in "text" format from the Insight® software to be read by the cross-spectral matrix calculator integrated in the LORETA-KEY® software. One cross-spectral matrix was computed for each patient from all data segments, with a resolution of 1 Hz, from 0 to 25 Hz. Current density vectors (CD) were calculated for each frequency, but we averaged together the CD values for each "classic" EEG band in order to perform the statistical analysis: delta (1–3 Hz, excluding zero Hz activity), theta (4–7 Hz), alpha (8–13 Hz) and beta (14–25 Hz). LORETA-KEY® provided a solution space restricted to cortical gray matter and hippocampus in the Talairach Human Brain Atlas, which was covered by 2394 voxels at 7-mm spatial resolution.

In order to determine significant regional statistical differences in intracranial current density (CD) between the depressed and non-depressed alcoholics, voxel-wise Statis-

tical Non-parametric Mapping (SnPM) with independent samples, provided in the LORETA-KEY? package, was used. "*The method* (...) *performed t-tests for the comparison of two independent groups, 1-way, 2-conditions* (depressed–nondepressed) *on a voxel by voxel basis. The exact* (*corrected for multiple comparisons*) *critical t-values for* $p < 0.05$ *and* $p < 0.01$ *were obtained. These values are calculated via randomization* (Nichols and Holmes, 2002). *The method does not need any distributional assumptions*" (Pascual-Marqui, 1999). This method yielded an adjusted threshold statistic $t_{crit}$ that is effective for controlling Type I error (Flor-Henry et al., 2004).

Although the LORETA software specifications claim their corrected $t_{crit}$ for $p < 0.05$ level as significant enough for testing 2394 voxels in one comparison (as used by other authors like Arai et al., 2003 and Flor-Henry et al., 2004), since we made comparisons for each frequency band, applying the Bonferroni adjustment criteria (Sankoh et al., 1997) for four comparisons, 36 (N1 + N2-2) degrees of freedom, and assuming no correlation between frequency bands, we obtained an adjusted alpha threshold of 0.0125. Hence, we regarded as areas of significant differences only those voxels showing *t*-values below (or above) the highest among the critical values ($t_{crit}$) for $p = 0.01$ estimated by LORETA for the four bands (see Table 2), in order to further decrease the chance of false positives due to repeated testing for the four bands, excluding also isolated voxels.

In the case of finding significant regional differences, the local average CD for that band at the regions of highest differences was measured by cursoring at the LORETA image (average CD between band limits as defined above) from each patient at the corresponding sites. Those values were correlated with the magnitude of depressive symptoms as measured by BDI scores.

A curve fitting procedure (GraphPad® v4.0) was applied to the data in order to calculate if a linear or non-linear (power) model gives the best description of the relationship. Regression coefficients, $r$, $r^2$, standard error of the estimate, and analysis-of-variance tables were calculated. To statistically validate which model achieved the best fit to the data, the extra sum-of-squares $F$ test (Motulski and Christopoulos, 2003) was used for comparisons between models, testing the null hypothesis that the data are best fitted by the simpler (linear) model against the alternative hypothesis (best fit by non-linear model).

Table 2
Exact (corrected for multiple comparisons) critical *t*-values for $p < 0.05$ and $p < 0.01$ calculated via randomization (Nichols and Holmes, 2002)

| | $p''$ | $t$ (min) | $t$ ($p < .01$) | $t$ ($p < .05$) |
|---|---|---|---|---|
| Delta | **0.0013** | −3.83 | 3.4199 | 2.7252 |
| Theta | **0.0028** | −3.81 | 3.3759 | 2.7352 |
| Alpha | 0.0184 | −2.96 | 3.1424 | 2.5609 |
| Beta | 0.0396 | −2.74 | 3.2842 | 2.6332 |

″: Best (smallest, most significant) *p* value of maximum and minimum *t*-statistic (Significant values in bold type).
*t* (min): value of *t* at the site of highest difference.
t($p < .01$): *t*-threshold for $p < .01$.
t($p < .05$): *t*-threshold for $p < .05$.
*Source.* Non-paired (independent samples) LORETA data, no normalization, no transformation.
Number of bootstraps = 5000.
Adjusted significance threshold for $\alpha = 0.05$ after Bonferroni correction: 0.0125.

## 3. Results

### 3.1. Intracranial differences in EEG CD between depressed vs. non-depressed alcoholics

Although lower current density values were observed in depressed alcoholics in comparison with non-depressed alcoholics for all frequency bands, significant differences were found only for delta and theta bands, but in different locations. Alpha and beta bands showed no significant differences between groups.

#### 3.1.1. Delta band

Comparison of non-depressed with depressed alcoholics showed the highest significant differences ($t = -3.83$, $t_{(p < 0.01)} = -3.41$) in the delta band on a broad region within the anterior half of the left temporal lobe, mainly at the pole (Brodmann areas 20, 21, 38, corresponding to the anterior part of inferior, middle and superior temporal gyri, fusiform gyrus), area 28 (uncus), areas 36–37 (parahippocampal gyrus), and area 13 (insula), inferior left frontal lobe including areas 47, 45, 44 (inferior frontal gyrus), 46 (middle frontal gyrus); and bilateral frontal medial cortices at areas 9 (medial frontal gyrus), but extended to the right area 10 (superior frontal gyrus) near and at the frontal pole (Fig. 1, blue-shaded areas).

#### 3.1.2. Theta band

Depressed alcoholics showed significantly ($t = -3.81$, $t_{(p < 0.01)} = -3.41$) lower CD than non-depressed extensively over bilateral parietal lobes, but more extended to the right, including Brodmann areas 7 (superior parietal lobes, precuneus) 5 (paracentral lobule), extended to right areas 40 and 39 (superior parietal lobule, postcentral gyrus, inferior parietal lobule), as well as in anterior cingulate (areas 24 and posterior part of 32) and bilateral midfrontal cortex (area 9, medial frontal gyrus) (Fig. 2, blue-shaded areas). An isolated voxel at left area 37 was not regarded as significant.

### 3.2. Relationship between CD at specific loci and magnitude of depression

#### 3.2.1. Delta band

Fig. 3 shows plots of local CD measured at left temporal pole cortex, right superior frontal cortex and left parahippocampal cortex. In all cases, an inverse relation can be observed, but the plots show an initial abrupt decay that resembles an exponential or power decay curve rather than

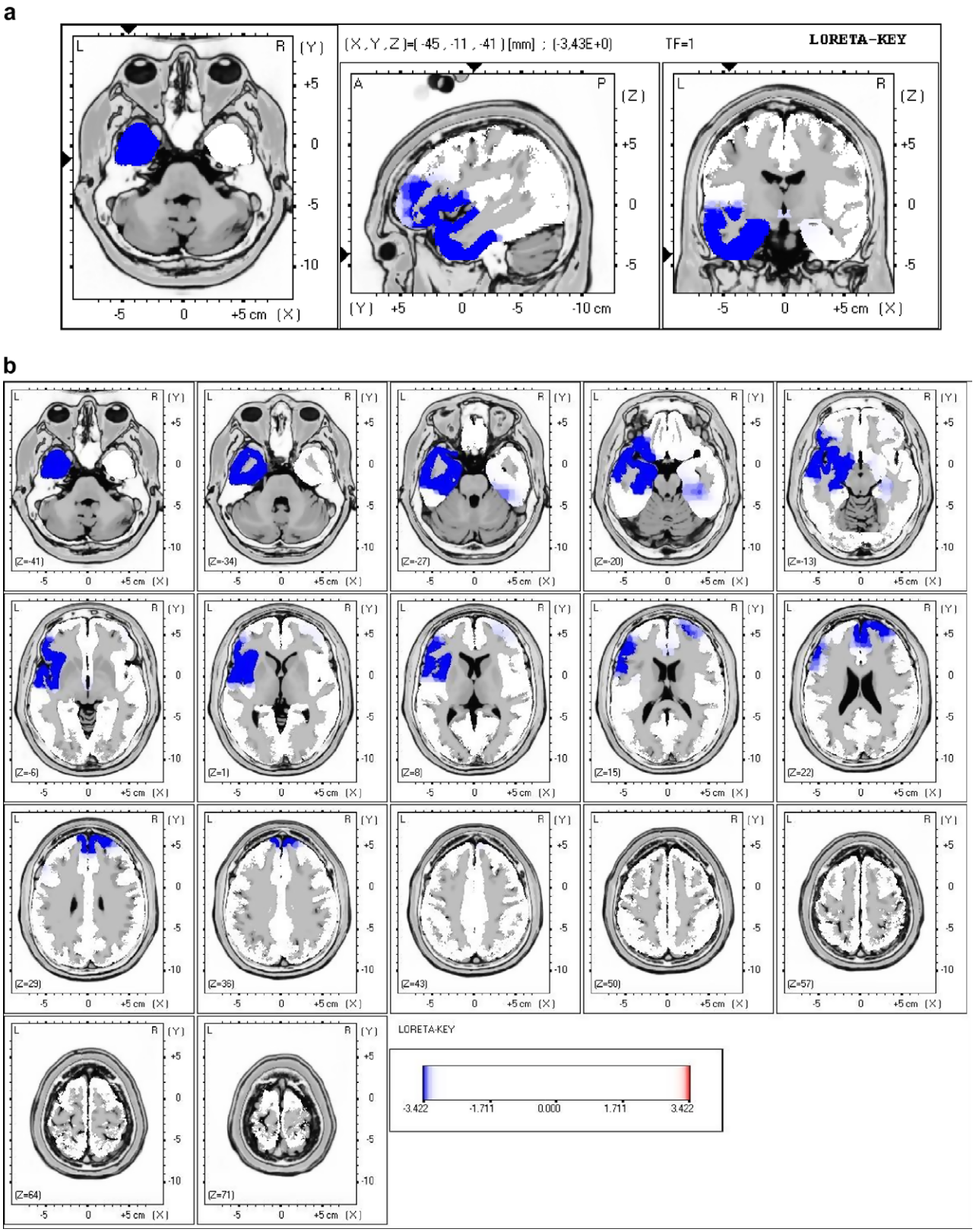


Fig. 1. Intracranial maps of LORETA statistical differences of delta (1–3 Hz) activity comparing depressed and non-depressed patients. (a) Orthogonal images projected at *X*, *Y* and *Z* axes intersected at the site of highest significance (left inferior temporal gyrus, BA 20). (b) Multislice maps. Blue-shaded areas represent voxels with significantly lower ($p < 0.01$) delta activity in depressed patients compared to non-depressed, located within the left temporal lobe, mainly at the pole, corresponding to the anterior part of inferior, middle and superior temporal gyri, fusiform gyrus, uncus, parahippocampal gyrus, amygdala, and insula, inferior and middle frontal gyrus and bilateral medial frontal gyrus, but extended to the right superior frontal gyrus near and at the frontal pole. The linearity of the color scale was modified for showing only areas with values below or at $t_{crit}$ for $p = 0.01$ ($-3.41$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.)

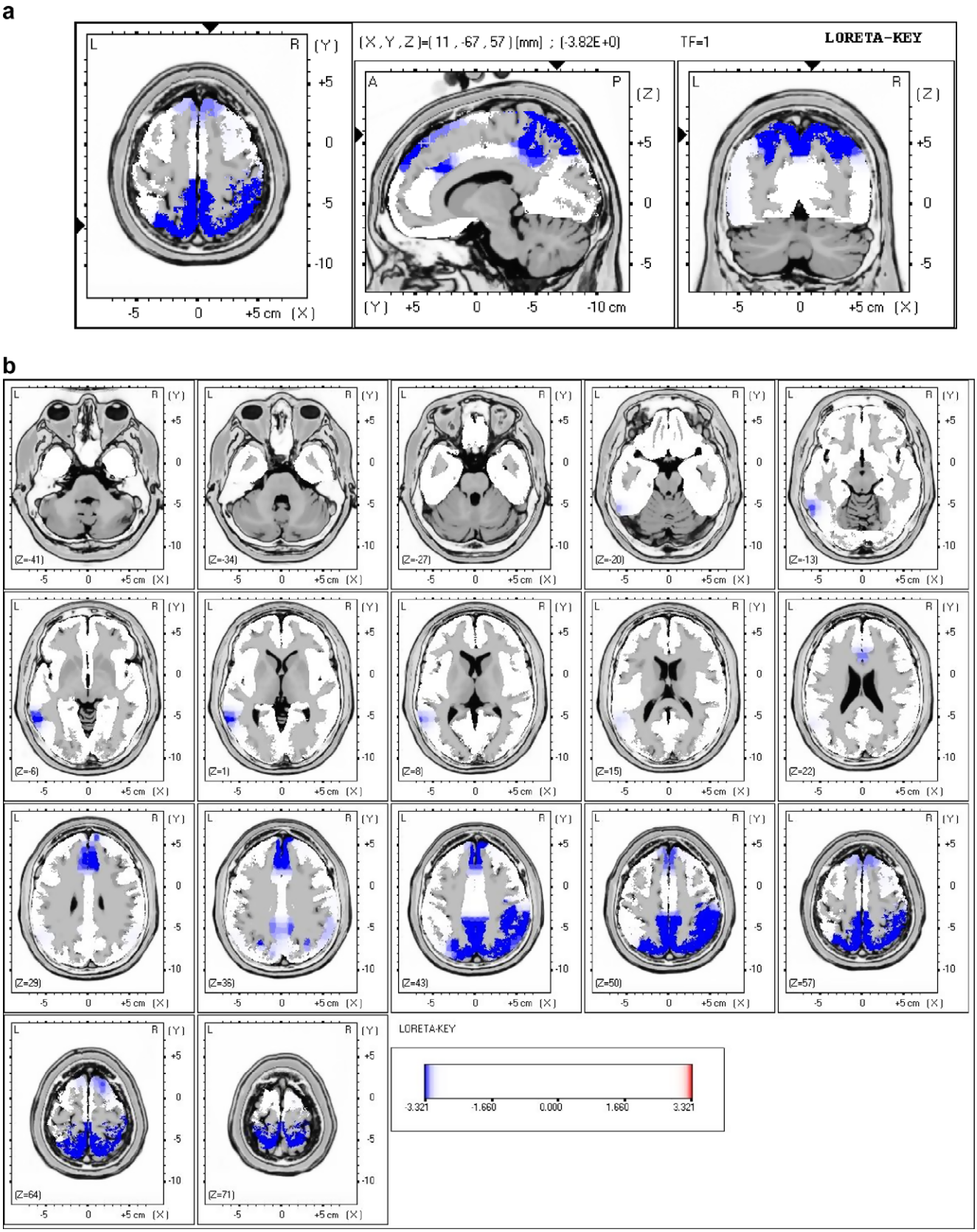


Fig. 2. The same intracranial statistical maps for theta (4–7 Hz) activity. Blue-shaded areas represent zones where depressed patients had significantly less ($p < 0.01$) theta activity than non-depressed, localized extensively over bilateral parietal lobes, but more extended to the right superior parietal lobule, postcentral gyrus, inferior parietal lobule, as well as in anterior cingulate and bilateral midfrontal cortex, all with $t \leqslant -3.32$). An isolated voxel at left temporal cortex was not regarded as significant. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.)

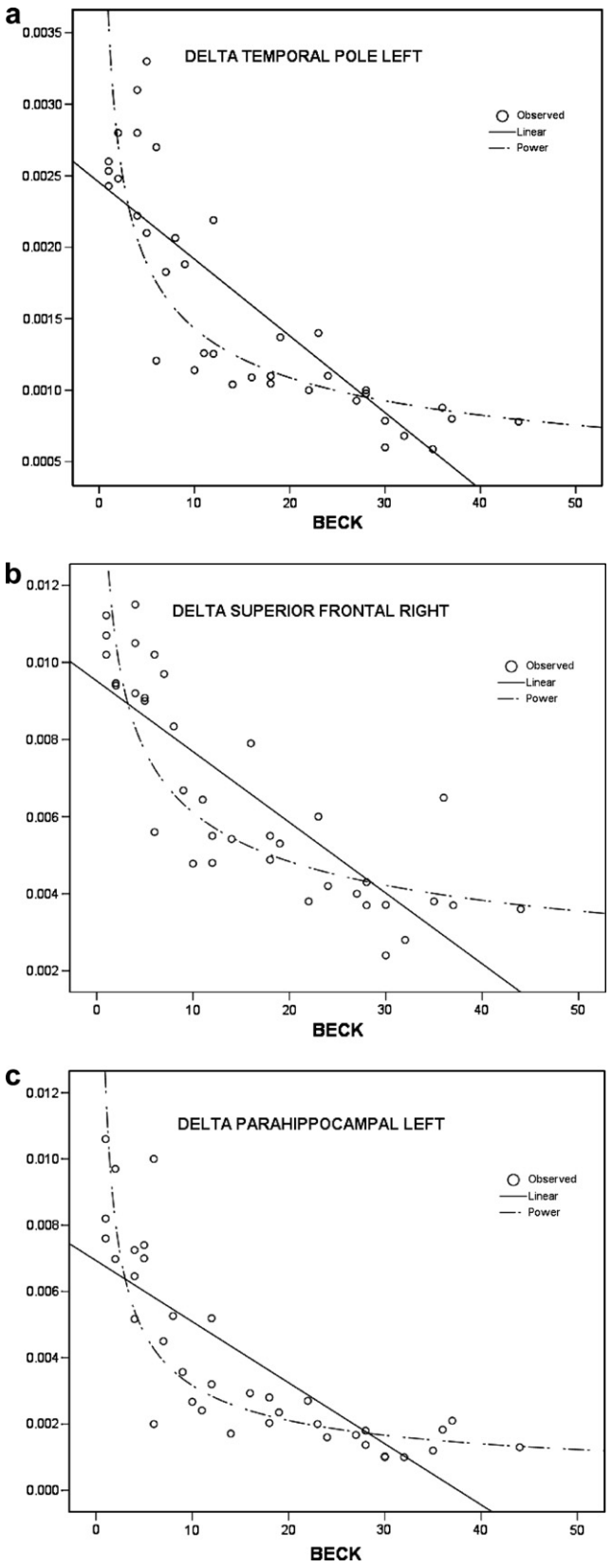


Fig. 3. Association between intracranial current density (CD) in delta band and magnitude of depression as measured by the Beck Depression Inventory (BDI) at (a) left temporal pole; (b) right superior frontal gyrus; (c) left parahippocampal gyrus. The relationships were obviously non-linear, being best-fitted by a negative potential curve, with a highly significant correlation.

a linear one. The results of curve fitting for both models are shown on Table 3, showing the r, $r^2$, standard error of estimation, $F$ scores, regression parameters and statistical significance. In all sites the best fit (given by the highest $r^2$ and F score values) was achieved when using the non-linear model: a negative power function of the form $y = b \cdot x^m$ (Table 3). The extra sum-of-squares $F$ test confirmed these results as statistically significant, rejecting the null hypothesis in all cases (Table 4).

### 3.2.2. Theta band

Here also significant inverse associations with BDI were found at the areas of significant differences (Fig. 4), but in a slightly lesser degree than in delta band, and with a less obvious decay pattern. The highest correlations were found at right parietal cortex, both medial frontal cortices and anterior cingulate (Fig. 4c). The best fit was achieved by the power model only at anterior cingulate, while in the other sites the null hypothesis (better fit by the linear mode) could not be rejected (Table 5).

## 4. Discussion

The long quest for typical patterns of scalp EEG activity corresponding to specific psychiatric or neurological diseases has been disappointing, since, although some general tendencies have been stated (Saletu et al., 2002), in fact, the same QEEG features may be present in different disorders, and patients with the same disorder can exhibit different QEEG patterns (Coutin-Churchman et al., 2003).

However, the possibility of increasing a putative diagnostic-specificity of electrophysiological alterations, leading to a better understanding of physiopathology, received a further impulse with the development of tomographic mathematic estimation for locating the intracranial sources of a given scalp measurements (Hämäläinen and Ilmoniemi, 1994; Pascual-Marqui et al., 1994; John et al., 1997; Bosch-Bayard et al., 2001), but regardless of these advances, the final result will also be hampered by two persistent problems: the differences in methodology and the physiological interpretations of the results.

This is certainly the case for the slow activity of the EEG, where an increasing body of evidence shows that not only increased, but also decreased power may reveal underlying neuronal dysfunction. Our results show that, as a group, alcoholic patients showing diffusely decreased delta-theta power in the surface EEG had less activity for these bands in certain areas according to the presence or not of clinical depression. Unfortunately, the version of LORETA available when we processed our data did not allow the comparison of an individual intracranial map to normative or control data, in order to assess the reliability of these results in individuals. However, the current density of delta and theta activity measured at those statistically significant areas in individual patients is inversely correlated to the magnitude of clinical depression as measured by their individual BDI scores, a fact that has been

Table 3
Goodness of fit of Delta CD and BDI dependency models at specific sites

| Band/site | Model | $r$ | $R2$ | Standard error | $F$ | Parameters | $p$ |
|---|---|---|---|---|---|---|---|
| Delta/parahippocampal left | Power | −.88 | .777 | .348 | 121.9 | $m = -.587$; $b = .012$ | .0000 |
| | Linear | −.79 | .625 | .002 | 58.27 | $m = -.0002$; $b = .007$ | .0000 |
| Delta/temporal pole left | Power | −.85 | .717 | .234 | 88.56 | $m = -.337$; $b = .013$ | .0000 |
| | Linear | −.83 | .682 | .002 | 75.17 | $m = -.002$; $b = .01$ | .0000 |
| Delta/superior frontal right | Power | −.86 | .738 | .262 | 98.6 | $m = -.398$; $b = .004$ | .0000 |
| | Linear | −.83 | .685 | .0005 | 76.27 | $m = -5.4 \times 10^{-5}$; $b = .002$ | .0000 |

*Notes.* $p$ regarded as significant if below 0.01.
Linear model whose equation is $y = m.x + b$.
Power model whose equation is $y = b\ (x^m)$ *or* $ln(Y) = m{\cdot}\ln(x) + \ln(b)$.
Where $x$: BDI score; $y$: CD.

Table 4
Goodness of fit of Theta CD and BDI dependency models at specific sites

| Band/site | Model | $r$ | $R2$ | Standard error | $F$ | Parameters | $p$ |
|---|---|---|---|---|---|---|---|
| Theta/right midfrontal | Power | −.60 | .360 | .182 | 20.12 | $m = -.144$; $b = .004$ | .0001 |
| | Linear | −.56 | .312 | .001 | 16.35 | $m = -4 \times 10^{-5}$; $b = .04$ | .0003 |
| Theta/right parietal | Power | −.74 | .540 | .265 | 42.61 | $m = -.305$; $b = .0060$ | .0000 |
| | Linear | −.70 | .495 | .001 | 35.34 | $m = -7.1 \times 10–5$; $b = .0042$ | .0000 |
| Theta/AC | Power | −.80 | .644 | .294 | 65.02 | $m = -.034$; $b = .0037$ | .0000 |
| | Linear | −.70 | .487 | .001 | 34.13 | $m = -7.8 \times 10–5$; $b = .0036$ | .0000 |

previously reported by others (Pizzagalli et al., 2002; Wienbruch et al., 2003), and will be discussed in detail below.

Although our results are valid only in the context of depression associated with alcoholism in male subjects, several correspondences could be established with previous work on the field of depression.

Our results are in close correspondence with the report of Flor-Henry et al. (2004) on reduced delta source power lateralized to the left hemisphere of depressed patients. However, since we chose the $p = 0.01$ limit for statistical significance, we found more restricted areas of significant differences. Unfortunately, our results are not suitable for more direct comparison with theirs, since those authors did not study the classical rest, eyes-closed condition that they had indeed recorded, but rather used eyes-open and cognitive challenge states for comparison with controls, and made no correlations with the severity of depression. On the other hand, in agreement with our results, Lubar et al. (2003) found decreased "delta" (2–3.5 Hz) activity in depressed patients at temporal sites but in the right side. However, their sample also differed form ours in gender, since they studied only females.

Our data also is in agreement with the results of Mientus et al. (2002), regarding the involvement of theta band at anterior cingulate cortex, and with Wienbruch et al. (2003) in showing decreased delta in prefrontal cortex. However, the latter failed to detect delta decreases at left midtemporal, or any other areas as we did, since their analysis was restricted to relatively large areas, apparently by technical constraints (their *prefrontal* probably including anterior cingulate). In both cases, the authors studied mixed-gender samples, while our study, like in Flor-Henry et al. (2004), included only male patients. Provided known gender-related differences in both anatomical and physiological findings in alcoholism, and also in depression (Hommer et al., 2001; Pfefferbaum et al., 2001), the role of gender as an intervening variable in these analyses is a question still needing to be addressed.

The most striking feature pointing to the functional significance of decreased slow activity and its distribution in our patients is the close correlation with the severity of depression as measured by BDI, only at certain specific locations, and with different distribution for delta and theta bands. Inverse correlation between delta power and BDI was also previously reported for MEG at frontal areas by Wienbruch et al. (2003), while Pizzagalli et al. (2002) found a positive correlation for theta activity recovery with BDI in depressed non-alcoholic patients responding to treatment, although they only found this effect at anterior cingulate cortex, while in our data it was extended widely over parietal and prefrontal cortex as well. However, their study group differs from ours in gender, since they included only females. Unfortunately, the usual Babylonian confusion in QEEG analysis procedures which hampers any comparison and interpretation of results was present here: their "theta" band was rather restricted to its upper half (6.5–8 Hz), and their "delta" (1.5–6 Hz) band was in fact a mixture of upper delta and lower theta, according to the conventional textbook definition of band limits we chose to follow.

On the other hand, Williams et al. (2004) found an inverse linear correlation between glucose utilization at medial prefrontal cortex and BDI, also in depressed alcoholics, like what we found for theta activity in most sites. However, the decrease of delta CD (and theta at anterior cingulate) with the severity of depression as measured by BDI in our patients was not linear, but rather in the form

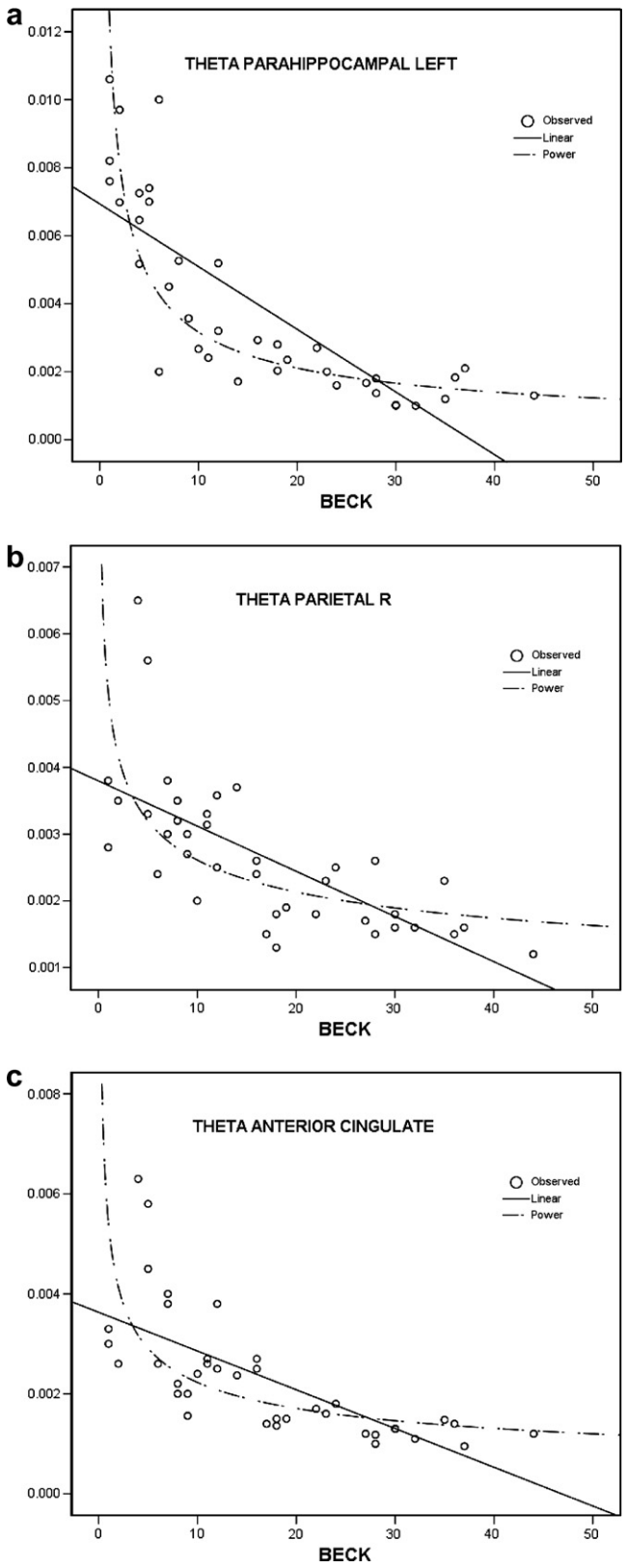


Fig. 4. Association between intracranial current density (CD) in theta band and magnitude of depression as measured by the Beck Depression Inventory (BDI) at (a) right medial frontal cortex; (b) right parietal cortex; (c) left anterior cingulate. Significant inverse linear associations were found in all but anterior cingulate, where the association was best-fitted by a negative potential curve.

Table 5
Statistical significance of differences between Linear vs Power curve models of CD vs BDI dependencies

| Band/site | *F* | DF | *p* | Best model |
|---|---|---|---|---|
| Delta/temporal pole | 9.509 | (1,35) | 0.004 | Power |
| Delta/left parahippocampal | 24.53 | (1,35) | $P < 0.0001$ | Power |
| Delta/Right Superior frontal | 15.30 | (1,35) | 0.0004 | Power |
| Theta/AC | 6.951 | (1,35) | 0.0124 | Power |
| Theta/right midfrontal | 3.682 | (1,35) | 0.0632 | Linear |
| Theta/right Parietal | 1.371 | (1,35) | 0.2496 | Linear |

of an inverse power decay curve of CD as BDI increased, suggesting an earlier involvement of the generator mechanism of slow activity in these structures on the development of clinical depression as measured by BDI. Further evolutive studies would reveal additional interesting data on this issue.

While other functional neuroimaging data have a more obvious relationship with the state of local neuronal *activation*, this is not the case for EEG spectral parameters (except for the classical effects in alpha activity, which correlates negatively with metabolic activity in most cortical areas). While *increased* slow activity have been associated with hypoactivation due to deafferentation (Amzica and Steriade, 1997), this association might hold true only in some specific pathological conditions, while in other the hypoactivation might be reflected instead by a *decrease of physiologic slow wave* activity. This view can be supported by data from PET showing hypometabolism (Baxter et al., 1989; Mayberg et al., 1999, and especially Williams et al., 2004), SPECT showing decreased blood flow at frontal and anterior cingulate cortices (Gonul et al., 2004) and anatomic and morphometric studies showing cellular degeneration (Kanner, 2004; Rajkowska et al., 1999; Stockmeier and Rajkowska, 2004) in the dorsolateral prefrontal cortex, anterior cingulate cortex, orbitofrontal cortex, hippocampus, and amygdala in depressed patients, while chronic alcohol consumption has been associated with reduced hippocampal volume (Agartz et al., 1999; De Bellis et al., 2001; Pfefferbaum et al., 1998), and ultimately to impaired neurogenesis at the hippocampus (Herrera et al., 2003). These are the areas in which we found decreased slow activity in our depressed alcoholics compared to the non-depressed patients. Theta or delta decrease was not found at orbitofrontal cortex, but certainly at anterior frontal, left midtemporal and anterior cingulate, areas involved in a proposed model of limbic-frontal circuitry in depression based on FDG-PET data (Seminowicz et al., 2004), and also in more posterior and medial areas for theta activity, in a similar way of the report of Fingelkurts et al. (2006).

However, although "physiological activation" not always implies "functional efficiency" (Rotenberg, 2004) our data apparently do not fit with the recent conclusion of this author on the predominantly right hemisphere dysfunction in depression, also supported by recent data (Stockmeier et al., 2004; Von Gunten and Ron, 2004) showing decreased volume and neuronal population in

the right hippocampus of depressed patients. Since it is difficult to differentiate the "relative hyperactivation at right hemisphere" from the "relative hypoactivation at left hemisphere" that seems to be reflected by decreased slow activity in our depressed alcoholics compared with the non-depressed subjects. These data agree with former findings of Starkstein and Robinson in left anterior stroke (Starkstein and Robinson, 1988). So, the issue of brain laterality and depression still have many paradoxes, although these paradoxes are less puzzling when approached with a more dynamic point of view, i.e., some left areas predominating in a given (dys)functional role, and some right areas in other within a common framework, in which *"an interconnected distributed neural network with pathologic patterns of neurotransmission and multiple brain oscillations are involved to a greater or lesser extent, depending on the imbalance in monoamines and neuropeptides"* (Fingelkurts et al., 2006), like in our data with predominant left temporal effect for delta and bilateral but predominant right parietal for theta bands when comparing depressed and non-depressed alcoholics. However, the different distribution of delta and theta effects suggests that activity in these two frequency bands reflects a different functional substrate, which should receive further addressing.

The absence of significant differences in alpha or beta band between depressed and non-depressed alcoholics is in line with the findings of Pizzagalli et al. (2002); Lubar et al. (2003) using LORETA comparing depressed patients with controls, while we fail to detect the increased alpha-beta power in depressed reported by Fingelkurts et al. (2006), although they also described less delta-theta power. However, since our depressed patients were alcoholics, no direct comparison can be drawn here; although one plausible hypothesis is that brain damage (regarding decreased slow activity as a sign of it) caused by alcohol abuse in our patients might be selectively enhanced in certain regions on certain cases, and be expressed in this case in the form of depressive symptoms. A design including also non-alcoholic male depressed patients and control subjects may help to solve these apparent contradictions.

In summary, LORETA helped to define decreased slow activity as a sign of a dysfunctional neuronal state probably secondary to chronic alcohol consumption, that when present in several specific limbic and other cortical locations that have been related to a specific clinical disorder like depression, is proportional to its magnitude. Further studies in a greater sample of patients, correlating selected symptoms quantified by adequate scales with the intracranial source distribution of this and other EEG features would shed more light on the physiopathological significance of the different QEEG alterations in its true role as signs of brain dysfunction.

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