Abstract

Objective: To evaluate the incidence and clinical correlations of abnormal QEEG features in alcoholic patients.

Methods: Quantitative EEG (frequency analysis, absolute and relative powers of the four classical bands) was assessed in 191 male alcoholic patients admitted in our facility for detoxification process. All underwent psychiatric, medical and neurological examination prior to the EEG recording, in search for specific clinical or paraclinical findings. The presence or absence of relevant clinical features was codified as nominal dichotomic variables to be related to specific QEEG features.

Results: Only 7 patients had normal QEEG. The most frequent alteration (81 cases) was decreased power in slow (delta and theta) bands with a concurrent increase in beta band, followed by decreased power only in slow bands (33), increase only in beta band (29), decrease in both slow and alpha bands without beta alterations (28), decrease only in alpha band (6) and others. Alterations in slow and beta bands were uncorrelated. However, a significant correlation was found between decreased power in slow bands and cortical atrophy as revealed by MRI (especially in patients with early onset of alcoholism), time elapsed from the beginning of alcoholic habits (but only in younger or early onset subjects) and in a lesser degree arterial hypertension, but neither with age nor any other clinical or psychiatric feature. On the other hand, increased power in beta band correlated mainly with the use of benzodiazepines, sensoperceptual alterations (hallucinations, illusions), clinical seizures and family history of alcoholism. The effects of those variables were strongly interrelated.

Conclusions: Decreased power in slow bands in alcoholic patients may be an indicator of brain atrophy or chronic brain damage, while increase in beta band is related to medication use, family history of alcoholism, hallucinations and seizures, suggesting a state of cortical hyperexcitability.

Significance: This study show the relation of specific QEEG alterations to certain clinical features found in alcoholics, in a further attempt to elucidate the semiological value of those alterations in individual patients.

Keywords: Quantitative EEG; Alcoholism; Delta band; Beta band; Clinical correlations

1. Introduction

Abnormal Quantitative EEG features have been extensively described in many psychiatric disorders including alcohol and substance abuse disorders (Alper et al., 1998,1996, 2002; Bauer, 2001; Coutin-Churchman et al., 2003; Porjesz et al., 2005; Fricke et al., 1995; Salletu-Zyhlarz et al., 2004; Struve et al., 1998). However, it has been reasonably argued that statistical deviations from the norm in brain electrical activity are not necessarily signs of brain damage or dysfunction (Kellaway, 1990).

Looking for specificity, some of these statistical alterations in QEEG have been correlated to certain clinical or physiological features. Decreased frontal alpha has been related to anxiety (Enoch et al., 1999; Finn and Justus, 1999), frontal alpha asymmetry to depression (Knott et al., 2001). Cordance (in other words, concordance/discordance between regional absolute and relative power) has been associated to local alterations of cerebral blood flow (Leuchter et al., 1994). “Desynchronization” over frontal areas to the possibility of alcohol relapse (Winterer et al., 1998). Increased theta power to
chronicity of marijuana exposure (Struve et al., 1998); increased delta power in MEG at temporal regions to hallucinations or positive symptoms in schizophrenics (Wienbruch et al., 2003); and decreased delta power to cortical atrophy (Coutin-Churchman et al., 2003), relapse in alcohol consumption (Saletu-Zyhlarz et al., 2004), and clinical depression (Brenner et al., 1986; Wienbruch et al., 2003), although the latter has been instead associated to increased delta activity by others (Knott and Lapierre, 1987).

Electrophysiological alterations have been described extensively in alcoholic patients (for a comprehensive review see Porjesz and Begleiter, 2003), but any attempt of drawing a common picture from QEEG data is difficult due to overwhelming differences in methodology, like the arbitrarily chosen limits for the definition of frequency bands, different filtering methodology, number of channels, the use or not of discriminant functions, Z-scores or neural networks, reference choice or group vs. individual evaluation. However, most reports in alcoholic patients agree in describing alterations mainly within the beta (Bauer, 1994; Costa and Bauer, 1997; Winterer et al., 1998; Rangaswamy et al., 2002, 2004) or alpha bands (Finn and Justus, 1999).

Strong evidence comes from the Collaborative Study on the Genetics of Alcoholism (COGA), relating increased beta activity in alcoholics and their first-degree relatives to molecular alterations at the level of GABA receptors in alcoholics, which can be transmitted to their offspring (Ehlers and Schuckit, 1990; Rangaswamy et al., 2004). The same authors (Rangaswamy et al., 2003) found also increased theta activity in a group of alcoholics compared to matched controls.

However, our group (Coutin-Churchman et al., 2003) found instead decreased slow (theta–delta) activity in many alcoholic patients, as in other psychiatric disorders, and this decrease was correlated with cortical atrophy as seen in MRI. Decreased delta power has been reported recently in alcoholics also by Saletu-Zyhlarz et al. (2004), but we are not aware of any systematic approach correlating this and other specific QEEG power alterations in the different frequency bands to particular medical and psychiatric complaints in patients with potentially diffuse cerebral and systemic damage as chronic alcoholics.

Our aim was to study the incidence of the statistical alterations observed in the EEG power spectra of individual alcoholic patients, and their relation to known clinical, structural or humoral evidences of CNS or systemic damage due to chronic alcohol consumption, in order to obtain further evidence on the pathophysiological meaning (if any) of those statistical alterations.

2. Methods

2.1. Patients

The analysis was performed in 191 male alcoholic patients (F10.2 according to ICD-10), with ages between 21 and 67 years, who were admitted to our inpatient facility for detoxification. All were chronic compulsive alcohol consumers, in a range of 1–46 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 a local homemade rum (“miche”) with 45°–50° of alcohol, while other used whisky or rum (40°), for an average 10 g of alcohol per standard drink.

Patients with significant clinical history of neurological (head trauma, epilepsy, cerebrovascular, tumoral or neurodegenerative diseases), psychotic disorders, systemic diseases (diabetes, AIDS or seropositives, collagen diseases etc.), or concurrent drug abuse were not included in the study.

Most clinical features were tabulated as dichotomous nominal (Yes/No) variables according to its presence or not. Data were collected about the presence or not of familial history of alcohol abuse, drug abuse, and of other psychiatric disorders. Clinical scales for depression, anxiety and memory: Brief Psychiatric Rating Scale (BPRS), Hamilton Depression Scale (HDS), Hamilton Anxiety Scale (HAS), Beck Depression Inventory (BDI), Mini

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Descriptive statistics of the continuous variables measured in the patient sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Age</td>
<td>191</td>
</tr>
<tr>
<td>Age of onset</td>
<td>167</td>
</tr>
<tr>
<td>Alcohol intake estimate (g per day)</td>
<td>174</td>
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<tr>
<td>Abstinence range (days)</td>
<td>191</td>
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<tr>
<td>Years consuming</td>
<td>167</td>
</tr>
<tr>
<td>Dose of diazepam (mg per day)</td>
<td>152</td>
</tr>
</tbody>
</table>

* Not reported by 24 patients.
Mental State Evaluation (MMSE) were applied, and each patient was diagnosed as having or not concurrent symptoms of anxiety, depression, disorientation, memory disorders or psychotic symptoms. Clinical records were reviewed for the presence or not of seizures, sensoperceptual alterations (hallucinations, illusions) or other neurological signs at the time of admission. The patients received the type of medication they required, psychoactive (benzodiazepines: Valium®, or neuroleptics, see Table 1), support medication or combinations of the former, and this information was also recorded as a variable (benzodiazepines vs. no benzodiazepines, or neuroleptics vs. no neuroleptics medication). No patient was receiving barbiturates or carbamazepine before or at the date of recording. Chronicity of consumption, estimated as the time elapsed from the beginning of alcohol drinking as reported by the patients, was classified in lower or higher than 10 years from the beginning of systematic alcohol drinking (in general). Age of drinking onset was also recorded, and codified as being lower or higher than 20 years.

All patients had a comprehensive medical examination for the evaluation of cardiovascular, respiratory, renal, endocrine and neurological functions, and blood screenings for renal, hepatic, immunological or endocrine dysfunction, and for levels of concurrent abuse drugs (for fulfilling exclusion criteria). The presence or not of arterial hypertension, malnutrition, liver or kidney disease was determined and tabulated (Table 2).

When available, brain MRI (T1-T2-FLAIR) was performed in another institution, on a 1.5 T device (Picker International). Relevant structural features were tabulated for later correlation with QEEG features as nominal variables (Table 2). The electroencephalographer was blinded to the results of all clinical and laboratory tests.

2.2. Electroencephalographic recording and evaluation

EEG recording was done at least 1 week after admittance, to guarantee at least one alcohol-free week prior to the data collection, but in the vast majority of the cases (156) the EEG recording was made on the third week after, so most patients had about 19 days of abstinence. No recording was made beyond the fourth week after admittance.

Absolute (AP) and relative (RP) powers for delta (0.5–3 Hz), theta (3.5–7.5 Hz), alpha (8–13 Hz) and beta (14–25 Hz) bands were computed from 21 channels of at least 1 min artifact-free digital EEG recorded from conventional Ag/AgCl electrodes attached with conductive jelly to the standard 10/20 scalp locations referred to linked ears (plus two channels for ocular movements and one for ECG). Activity was sampled at 256 Hz, and filtered offline between 0.5 and 30 Hz. Impedance was kept below 5 kΩ. Non-consecutive epochs of variable duration, but not shorter than (1s) were manually selected from activity recorded with the 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 ECG contamination, drowsiness or any other visually identifiable artifact, which were discarded for analysis using a “maximalist” instead of a “minimalist” approach (Lawson et al., 2003). Segments containing paroxysmal or other nonstationarities or transient electrical events were also avoided.

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 custom-made software. Additional details of digital EEG recording and analysis techniques employed can be found elsewhere (Coutin-Churchman et al., 2003).

All spectral measures were obtained for referential (linked ears) data (no bipolar, laplacian or average reference measurements were used), and compared to a gender and age-matched normative database using Z-scores. Normative data were collected at our laboratory under the same conditions and according inclusion and exclusion criteria.

### Table 2
Nominal clinical variables in the patient sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>No</th>
<th>Yes</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of alcoholism</td>
<td>75</td>
<td>116</td>
<td>191</td>
</tr>
<tr>
<td>Percent</td>
<td>39.3</td>
<td>60.7</td>
<td>100.0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>134</td>
<td>57</td>
<td>191</td>
</tr>
<tr>
<td>Percent</td>
<td>70.2</td>
<td>29.8</td>
<td>100.0</td>
</tr>
<tr>
<td>Depression</td>
<td>109</td>
<td>82</td>
<td>191</td>
</tr>
<tr>
<td>Percent</td>
<td>57.1</td>
<td>42.9</td>
<td>100.0</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>134</td>
<td>57</td>
<td>191</td>
</tr>
<tr>
<td>Percent</td>
<td>70.2</td>
<td>29.8</td>
<td>100.0</td>
</tr>
<tr>
<td>Seizures</td>
<td>179</td>
<td>12</td>
<td>191</td>
</tr>
<tr>
<td>Percent</td>
<td>93.7</td>
<td>6.3</td>
<td>100.0</td>
</tr>
<tr>
<td>Use of benzodiazepines</td>
<td>39</td>
<td>152</td>
<td>191</td>
</tr>
<tr>
<td>Percent</td>
<td>20.4</td>
<td>79.6</td>
<td>100.0</td>
</tr>
<tr>
<td>Use of neuroleptics</td>
<td>141</td>
<td>50</td>
<td>191</td>
</tr>
<tr>
<td>Percent</td>
<td>73.8</td>
<td>26.2</td>
<td>100.0</td>
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<tr>
<td>Sensoperceptual alterations</td>
<td>99</td>
<td>92</td>
<td>191</td>
</tr>
<tr>
<td>Percent</td>
<td>51.8</td>
<td>48.2</td>
<td>100.0</td>
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<tr>
<td>Disorientation</td>
<td>151</td>
<td>40</td>
<td>191</td>
</tr>
<tr>
<td>Percent</td>
<td>79.1</td>
<td>20.9</td>
<td>100.0</td>
</tr>
<tr>
<td>Memory alterations</td>
<td>159</td>
<td>32</td>
<td>191</td>
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<tr>
<td>Percent</td>
<td>83.2</td>
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<td>100.0</td>
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<tr>
<td>Headache</td>
<td>181</td>
<td>10</td>
<td>191</td>
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<tr>
<td>Percent</td>
<td>94.8</td>
<td>5.2</td>
<td>100.0</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>112</td>
<td>79</td>
<td>191</td>
</tr>
<tr>
<td>Percent</td>
<td>58.6</td>
<td>41.3</td>
<td>100.0</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>167</td>
<td>24</td>
<td>191</td>
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<tr>
<td>Percent</td>
<td>87.4</td>
<td>12.6</td>
<td>100.0</td>
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<tr>
<td>Kidney dysfunction</td>
<td>172</td>
<td>19</td>
<td>191</td>
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<tr>
<td>Percent</td>
<td>90.0</td>
<td>10.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Chronicity &gt; 10 y</td>
<td>30</td>
<td>137</td>
<td>167</td>
</tr>
<tr>
<td>Valid percent</td>
<td>18.0</td>
<td>82.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Onset age &lt;20 y</td>
<td>103</td>
<td>64</td>
<td>167</td>
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<tr>
<td>Valid percent</td>
<td>53.9</td>
<td>46.1</td>
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</tr>
<tr>
<td>Atrophy on MRI</td>
<td>18</td>
<td>25</td>
<td>43</td>
</tr>
<tr>
<td>Valid percent</td>
<td>41.9</td>
<td>58.1</td>
<td>100.0</td>
</tr>
</tbody>
</table>
described in detail elsewhere (Coutin-Churchman et al., 2003).

The improved normative database was collected from 240 healthy volunteers recruited from hospital and university staff, students, and people coming from routine medical and psychiatric evaluation required for teachers, medical residents and applicants for flight school, armed forces academies or jobs in security staffs after successfully screened, with ages between 15 and 70 years, grouped by gender and age decade in four subsets of 60 individuals (female 15–39, male 15–39, female 40–70 and male 40–70 years) for purposes of matching. Thus, each subject was compared to his corresponding normative subset of 60 subjects (e.g. male, 40–70 years) by computing the corresponding \( Z \)-score for each measurement at each site.

Since no asymmetry or coherence measurements were used, and no multiparametric measurements were made (such as combinations of scalp sites or bands), the measurements were 21 sites \( \times \) 4 bands \( \times \) 2 measurements each (AP and RP) for a total of 168 \( Z \)-scores for each subject.

Abnormality was considered if increased \((Z>3)\) or decreased \((Z<−3)\) power in one or more bands was present in at least two adjacent electrode sites, following IFCN guidelines (Nuwer et al., 1999). If a given band had discordant results (e.g. increased at several sites and decreased at more than two others), it was coded as ‘discordant abnormality’.

Abnormalities were regarded as focal, if circumscribed to up to four adjacent sites (e.g. left frontal: Fp1, F3, F7, Fz; midcentral: Fz, Cz, C3, C4; right temporal: F8, T4, T6; or right occipitoparietal: O2, P4, T6); anterior or posterior unilateral regional if comprising 5 to 7 sites covering those areas; anterior or posterior bilateral regional if comprising both anterior or posterior areas, hemispheric and diffuse if comprising all or nearly all sites in one or both hemispheres. \( Z \)-scores beyond \( ±3 \) at isolated electrodes were not regarded as abnormalities.

The electroencephalographer was blinded to the clinical information about the patient being analyzed.

2.3. Analysis

Different QEEG profiles of statistical abnormality were established following our previously published methodology (Coutin-Churchman et al., 2003), according to which band or bands were affected, and the nature of alterations (increase or decrease beyond \( Z = ±3 \) in absolute and/or relative power).

However, we gave precedence to absolute power for assigning a record to a given profile, e.g. if a record showed...
decreased delta AP, normal beta AP but increased beta RP, we assumed it as having only decreased delta, and not increased beta, since the increased beta RP would be secondary to the decrease of delta AP.

Conversely, RP alterations without AP alterations in a given band or bands were regarded as primary abnormalities at the affected band(s) only if both AP and RP in the other bands were within normal limits (e.g. increased beta RP without any AP/RP alterations in other bands was regarded as increased beta). Nonetheless, isolated RP alterations were rarely observed in our patients.

Association between individual QEEG profiles and clinical or neuroimaging features were tested using 2×2 contingency tables and the familiar chi-square tests, using the SPSS® v. 11.5 statistical package, configuring groups according to the presence (yes) or absence (no) of a given clinical feature and QEEG alterations. In some instances, two-level contingency tables were used to test possible interactions between the effects of some clinical variables and QEEG features.

3. Results

3.1. QEEG abnormalities

Only 7 out of the 191 patients did not show any abnormality according to the criteria defined above. The remaining 184 patients (96.34%) matched one or more criteria for abnormality. Of the 184 abnormal studies, 81 II (42.4%) showed decreased delta–theta power and increased beta power (all AP/RP), 33 (17.3%) showed only decreased delta–theta power (all AP/RP), 29 (15.2%) had only increased beta power (27 AP/RP, 2 only RP), 28 (14.7%) decreased delta–theta–alpha power (all AP/RP), 6 decreased power only in alpha band (all AP/RP), 3 had decreased power in theta and alpha bands (all AP/RP) and 4 patients had other combinations (Fig. 1). No patient showed discordant abnormality (increase in some sites and decrease in others for the same band).

Since all patients with decreased delta had also decreased theta, and only three had decreased theta without decreased delta, both delta and theta bands were regarded together as slow bands. No patient showed decrease in beta band, and only two had increase in slow bands (AP/RP).

The vast majority of alterations were widely distributed across all scalp locations: while only in 6 out of 111 patients the decreased slow activity was restricted to anterior leads (anterior bilateral regional), all patients with beta increase or alpha decrease showed it in all channels (see Fig. 2), while no focal (2–4 contiguous electrodes) or unilateral hemispheric alterations were found at any band in any patient.

Nominal dichotomic variables encoding the presence or not of decreased power in slow bands, decreased power in alpha band and increased power in beta band were then defined (Table 3). Overall, 147 patients (77%) had decreased power in slow bands, and 114 (59.7%) increased beta power, while only 39 (20.4%) had decreased alpha power.

However, although decreased slow activity and increased beta were frequently present in the same patient, this association had no statistical significance when tested by contingency tables.

These variables were later correlated with clinical or paraclinical features using 2×2 contingency tables with the Chi-square statistic, using Sidak’s adjustment of critical P

![Fig. 2. Quantitative EEG analysis in an alcoholic patient: the upper two rows show "raw" absolute and relative powers in the four main bands. Most power is concentrated in alpha band at occipital regions, and in a lesser degree in beta at anterior regions, with almost no contribution from theta and delta bands. The lower two rows show maps for Z-score absolute power (upper) and Z-score relative power (lower). Blue areas represent Z-scores below −3 SD. Red areas represent Z-scores above +3 SD. Absolute power is abnormally decreased in delta and theta band all over the scalp, totally normal in alpha band, while is abnormally increased in beta band at all scalp. Relative power is abnormally decreased in delta, theta and alpha bands, and increased in beta across the entire scalp. Patient was classified has having decreased slow and increased beta power. Power spectra (right column) show the typical occipital peak in alpha band, and a broad increase in beta band.](image-url)
The second strongest association was with high (>10 y) chronicity of alcohol consumption ($\chi^2=4.712, df=1, P=0.03$), although it was above the adjusted significance level of $P=0.018$. However, although (logically) chronicity of alcohol consumption was strongly correlated with age ($\chi^2=11.769, df=1, P=0.001$), decreased slow activity had no statistically significant relation with patient age, either when using comparison by decades ($\chi^2=0.095, P=0.448$), or by two age groups (younger and older than 40 years, $\chi^2=2.27, P=0.384$). Using the latter as a control variable, separate contingency tables and tests were calculated for decreased slow activity vs. chronicity (Fig. 4, top left). Surprisingly, the association of chronicity and decreased slow activity was increased to significant levels, but restricted to the younger (<40) group ($\chi^2=6.246, df=1, P=0.017$), while in the older group, the association was not significant ($\chi^2=0.352, df=1, P=0.385$). The Cochran’s and Mantel-Haenszel statistics revealed the interdependence between the two variables ($P=0.028$).

Decreased slow activity showed no significant association with onset age of alcohol consumption ($\chi^2=0.401, df=1, P=0.329$). Chronicity and onset age had also no significant association ($\chi^2=2.755, df=1, P=0.097$). On the other hand, when using onset age as a control variable to test the relationship of decreased slow activity to chronicity, an interesting effect was observed: in patients with onset age below 20 years the association of chronicity to decreased slow activity (Fig. 4) was not significant at all ($\chi^2=0.027$). However, in the group of patients with onset age higher than 20 years it was not significant at all ($\chi^2=0.122, df=1, P=0.486$). Again, the Cochran and Mantel-Haenszel’s statistics revealed the interdependence between the two variables ($P=0.021$). In summary, younger or early onset subjects, with long history of alcohol intake had the higher rate of decreased slow activity (Fig. 4).

The third strongest association was with the presence of diastolic arterial hypertension ($\chi^2=3.713, df=1, P=0.038, N=191$). However, when using Sidak’s adjustment, this association failed to reach the significance limit of $P=0.018$.

No association could be demonstrated between chronicity and arterial hypertension, chronicity and atrophy on MRI, or arterial hypertension and atrophy on MRI.

The interaction in the association between decreased slow activity, arterial hypertension and chronicity was tested using the latter as control variable. Again, a differential effect was found, but in this case the effect of hypertension was restricted to the group of high (>10 y) chronicity ($\chi^2=4.401, df=1, N=137, P=0.027$), closer to the adjusted significance limit, while in the group of low (<10 y) chronicity the effect was not significant at all ($\chi^2=0.625, df=1, N=30, P=0.350$). The Cochran and Mantel-Haenszel’s interaction statistics were also significant in this case ($P=0.027$ and 0.044). In summary, patients with longer history of alcoholic habits and arterial hypertension tended to have the higher rates of decreased slow activity (Fig. 4).
Unfortunately, interactions of chronicity or arterial hypertension on the relation between decreased slow activity and cortical atrophy on MRI could not be tested by contingency tables since no scans were available for the

patients in subgroups (chronicity < 10 y and decreased slow activity = No) and (arterial hypertension = Yes and decreased slow activity = No). However, in the subgroup of patients without arterial hypertension, the relation

(***): Significant at p< 0.01
between cortical atrophy and decreased slow activity was still significant ($\chi^2 = 8.955, df = 1, N = 29, P = 0.004$).

On the other hand, using onset age as a control variable for the association of decreased slow activity to cortical atrophy on MRI revealed another differential effect: In patients with onset age below 20 years, the correlation of decreased slow activity to cortical atrophy was even more significant ($\chi^2 = 13.247, df = 1, N = 17, P = 0.001$), while in patients with age onset above 20 years it did not reach statistical significance ($\chi^2 = 4.667, df = 1, N = 21, P = 0.066$). In fact, no patient with onset age below 20 years and without atrophy on MRI showed decreased slow activity (Fig. 4, bottom right).

No significant association was found between decreased slow activity and any other of the evaluated clinical variables.

### 3.3. Correlates of increased beta activity

Significant associations (see Table 5) of increased power in the beta band were found with the presence of family history of alcoholism ($\chi^2 = 9.216, df = 1, N = 191, P = 0.002$), clinical seizures at the time of admission ($\chi^2 = 8.649, df = 1, N = 191, P = 0.002$), sensoperceptual (hallucinations, illusions) alterations ($\chi^2 = 7.2, df = 1, N = 191, P = 0.005$) and the use of benzodiazepines ($\chi^2 = 7.092, df = 1, N = 191, P = 0.007$) (Fig. 5), but not with the use of neuroleptics. The statistical significance of associations was roughly the same for all the former variables, well above the adjusted significance limit of 0.018.

However, when testing for interactions between the effects of the different significant variables, some interesting observations could be made (Fig. 6).

The presence of clinical seizures at admission was strongly correlated with the presence of family history of alcoholism: In fact, from 12 patients having suffered seizures (all of them with increased beta too), 11 had family history of alcoholism, so the effects were impossible to separate.

The presence of sensoperceptual alterations was not related to family history of alcoholism. However, when using family history as a control variable, the association of increased beta with the presence of sensoperceptual alterations was significant only for patients without family history of alcoholism ($\chi^2 = 5.692, df = 1, N = 72, P = 0.01$). In patients with family history of alcoholism, it was well above the significance limit ($\chi^2 = 3.238, df = 1, N = 119, P = 0.054$). The Cochran and Mantel-Haenszel’s statistics revealed that this interaction between the effects of both variables was significant ($P = 0.004$ and 0.006).

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Fig. 5. Significant associations between clinical features and beta band increase: Top left: the vast majority of patients with family history of alcoholism showed increased beta power. Top right: although the majority of patients without seizures showed increased beta power, no patient with seizures had normal beta power. Bottom left: the vast majority of patients with sensoperceptual alterations had increased beta power. Bottom right: Increased beta power predominates in patients with benzodiazepine medication. Bar height represents number of cases.
There was no correlation between the clinical variables use of benzodiazepines and family history of alcoholism. However, when using family history as a control variable, the effect of medication was barely significant in the group without family history of alcoholism ($\chi^2 = 5.499$, $df = 1$, $N = 119$, $P = 0.019$) but was not significant in the group with family history ($\chi^2 = 3.999$, $df = 1$, $N = 72$, $P = 0.05$). Again, the Cochran and Mantel-Haenszel’s statistics revealed a significant interaction between the effects of both variables ($P = 0.002$ and 0.004). Conversely, when using medication as a control variable, the relation of family history to increased beta activity did not reach significance for the group with benzodiazepine medication ($\chi^2 = 3.305$, $df = 1$, $N = 39$, $P = 0.07$), while in the group without medication the relation was statistically significant ($\chi^2 = 8.293$, $df = 1$, $N = 152$, $P = 0.003$). In summary, the effect of benzodiazepine medication and family history of alcoholism on EEG beta power seems to reinforce each other, being the beta increase much less frequent in patients without benzodiazepine medication and without family history of alcoholism.

A similar effect was observed when using medication as a control variable for testing its interaction with the relationship of increased beta activity with sensoperceptual alterations: for the group with medication the effect was not significant ($\chi^2 = 0.011$, $df = 1$, $N = 39$, $P = 0.593$) while in the group without medication the relation was significant ($\chi^2 = 8.022$, $df = 1$, $N = 152$, $P = 0.004$). Interestingly, the same situation was observed when using sensoperceptual alterations as a control variable for the effect of medication: in the group with sensoperceptual alterations there was no relationship between benzodiazepine medication and increased beta activity ($\chi^2 = 0.99$, $df = 1$, $N = 99$, $P = 0.39$), while the relation holds significant for the group without sensoperceptual alterations ($\chi^2 = 7.399$, $df = 1$, $N = 92$, $P = 0.01$). In other words, the effects of benzodiazepine medication and sensoperceptual alterations on EEG beta power seem to reinforce each other.

However, although nine of the 12 patients who had seizures were also on benzodiazepine medication, the remaining three had also increased beta activity, and hence no statistical inference on interactions between seizures, medication and increased beta activity could be made here. Since no segments containing paroxysmal activity were included in spectral analysis, the presence of paroxysmal discharges (if any) played no role in increasing the power in beta band in our data.

The bar graphs in Fig. 6 illustrate the joint effect of benzodiazepine medication, family history of alcoholism and the presence of sensoperceptual alterations on increased beta activity. As expected, the highest ratio of increased beta activity (38/49, 78%) was observed in those patients who scored positive for the three variables, while none of the 8 patients who scored negative for benzodiazepine medication, family history of alcoholism and sensoperceptual alterations showed increased beta activity. When isolating the effects of each variable (Fig. 6), the highest proportion corresponded to family history of alcoholism (45%), followed by benzodiazepine medication (33%) and sensoperceptual alterations (22%).

No significant relation was found between increased beta activity and any other of the clinical variables collected in our study.

4. Discussion

It can be hypothesized that some effects of chronic alcohol exposure on cortical neurons are simultaneously reflected by both the clinical features and EEG alterations observed in our patients (Fig. 7). While a bulk of evidence supports a marked effect of alcohol in suppressing inhibition via the effect on GABAA receptors, other authors provided evidence of an increased glutamatergic excitation (Tsai et al., 1995), and reported ethanol effects on glycine, neuronal nicotinic and 5-HT receptors (Davies, 2003). According to Tsai et al. (1995) and Davies (2003), acute effects of ethanol
disrupt glutamatergic neurotransmission by inhibiting the response of the N-methyl-D-aspartate (NMDA) receptor. Prolonged inhibition of the NMDA receptor by ethanol results in development of supersensitivity; acute removal of ethanol causes as a rebound effect marked augmentation of activity of postsynaptic neurons, showing as consequences hallucinations, seizures and increased beta activity. This can be potentiated by GABAa receptor suppression (that may be inherited in the case of family history of alcoholism, as suggested by the findings of Porjesz et al. (2002, 2005) in the offspring of alcoholics within a cluster of GABAa receptor genes in the short arm of chromosome 4). Chronic glutamate-induced excitotoxicity and derived neuronal atrophy (revealed by MRI) potentiated by systemic factors like arterial hypertension may be reflected by decreased delta activity.

The most extensively QEEG feature reported in alcoholic patients is increased power in beta band (Bauer, 2001; Costa and Bauer, 1997; Porjesz et al., 2002; Rangaswamy et al., 2004; Winterer et al., 1998). Putting aside the classic effect of benzodiazepine medication, also found in our study, increased beta activity reflecting abnormally enhanced cortical excitability (Parekh et al., 1995), has been attributed to GABAa receptor dysfunction (Porjesz et al., 2002; Whittington et al., 2000), particularly in alcoholics (Abi-Dargham et al., 1998).

Beta activity has been previously considered as indicative of background excitation involving a frequency potentiation mechanism at the synaptic level of the recurrent loops (Whittington et al., 1997). In a spontaneously active network of interneurons, inhibitory GABA and glycine receptors generate periodic oscillatory burst patterns with remarkable regularity in burst period and duration observed at many brain sites (Porjesz et al., 2002; Whittington et al., 1997). This finding suggests that beta frequencies typically observed in the human EEG reflect a state of central nervous system activation, with GABAa receptor action as pace-makers. On the other hand, classical benzodiazepines such as diazepam bind to GABAa receptors containing the α subunits α1, α2, α3 or α5. Benzodiazepines produce a strong increase in EEG beta power that is more marked in frontal regions. Benzodiazepines disrupt the beta (excitatory pyramidal cell)—gamma (inhibitory interneuron) oscillations at the cellular level and produce a “beta buzz.” (Porjesz et al., 2002).

Our data support the view that the abnormally increased cortical excitability and deficient inhibitory tone, associated to the lowered benzodiazepine-GABAa receptor density (reported in alcoholics by Abi-Dargham et al. (1998)) and potentiated by benzodiazepine binding to those receptors, may act as an underlying mechanism for “abnormal” beta increase (Begleiter and Porjesz, 1999). This could be the base for the association (and complex, potentiating interactions) of benzodiazepine medication, family history of alcoholism, perceptual alterations and seizures with increased beta power in our patients. In fact, at least one of these factors had to be present in every patient showing increased beta power in our sample.

However, even though previous research had stressed the importance of decreased slow activity as a marker of brain dysfunction secondary to drug or alcohol abuse (Alper et al., 1998; Prichep et al., 1996; Roemer et al., 1995; Saletu-Zyhlarz et al., 2004), as in other cases, the possible effects of alcohol in slow bands had received much less interest.

Although both increased beta and decreased slow activity were simultaneously present in many of our patients, the statistical association between them was not significant, suggesting that mechanisms underlying the effect of alcoholism in slow band activity are largely independent of those affecting the fast oscillations in beta band, and hence each one should logically be related to different factors.

Decreased slow activity had also been described in disorders like depression and alcoholism (Brenner et al., 1986; Coutin-Churchman et al., 2003; Saletu-Zyhlarz et al., 2004; Wienbruch et al., 2003). In our study, decreased delta–theta power was the most frequent feature in alcoholic patients, 17% more frequent than increased beta power, while only two patients showed increased slow activity. On this aspect, our results disagree from the findings of Rangaswamy et al. (2003), who reported diffusely increased theta activity in their alcoholic patients. However, the methodology used by these authors for EEG analysis differs from ours in several significant items. For instance: they used close bipolar instead of referential monopolar measurements, used automatic eye movement rejection instead of visual recognition of contaminated segments, and reported group differences in the mean value of theta power.
instead of sampling the frequency of individual cases showing Z-score deviations from a normative database.

Our data confirms our previous results on the association between decreased slow activity and cortical atrophy as seen in MRI (Coutin-Churchman et al., 2003). Moreover, the significant association of decreased slow activity with other factors likely to cause chronic brain damage (such as arterial hypertension and chronicity of alcohol consumption, especially in younger subjects) found in our data should stress the role of this QEEG feature as a specific marker of brain dysfunction, and not only as an statistical deviation from the norm. The association of decreased slow activity in younger or early onset subjects with chronic alcohol habits might be related to a higher vulnerability of the brain to an early exposure to alcohol that should be further investigated. On the other hand, the overlapping effects of arterial hypertension and chronic alcoholic habits in the incidence of decreased slow activity seem to be another indication of chronic brain insult.

On the other side, contrary to the expected, we found no association between decreased slow activity and specific psychiatric symptoms possibly linked to some degree of brain damage, like depression, memory alterations or disorientation. Although, Wienbruch et al. (2003) found decreased slow activity in the MEG proportional to the magnitude of depression; this was focalized at orbitofrontal cortex. While in most cases our patients (depressed or not) showed a widely distributed decreased slow band power across the scalp, this diffuse distribution could be the result of different intracranial configurations could be indeed related to specific clinical features like depression, as previously suggested by John et al. (1997), Prichet et al. (2002) and Wienbruch et al. (2003).

Even in the case decreased slow activity do not directly reflect decreased neuronal population or decreased neuronal activity, but “fluid shunting of electrical signals” (Nuwur, 2003), in this case secondary to cortical atrophy, it would only mean that decreased slow activity is not an artifact, but just an indirect sign of neural damage. Up to date, we have not found decreased slow activity in the QEEG of any normal subject. Additional longitudinal studies would allow further clarification of the nature of this controversial QEEG feature.

In conclusion, the two most frequent QEEG alterations found in our alcoholic patients have significant correlations, each with different clinical and structural features, suggesting they are linked to different physiological mechanisms. Decreased slow activity correlated mainly with brain atrophy as showed by MRI, with chronicity of alcohol consumption, especially in patients of early onset of alcohol consumption, and in a marginal degree with arterial hypertension, suggesting a correlation with chronic brain damage. Increased beta activity correlated with the use of benzodiazepines, sensoperceptual alterations, seizures and family history of alcoholism, suggesting that this feature could be a marker of cortical hyperexcitability.

References


