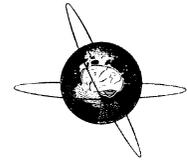




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Clinical Neurophysiology 115 (2004) 299–308



www.elsevier.com/locate/clinph

Individual analysis of EEG frequency and band power in mild Alzheimer's disease

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Accepted 25 September 2003

Abstract

Objective: This EEG study investigates the role of the cholinergic system, cortico-cortical connections, and sub-cortical white matter on the relationship between individual EEG frequencies and their relative power bands.

Methods: EEGs were recorded at rest in 30 normal elderly subjects (Nold), 60 mild Alzheimer disease (AD) and 20 vascular dementia (VaD) patients, comparable for Mini Mental State Evaluation scores (MMSE 17–24). Individual EEG frequencies were indexed by the theta/alpha transition frequency (TF) and by the individual alpha frequency (IAF) with power peak in the extended alpha range (5–14 Hz). Relative power was separately computed for delta, theta, alpha1, alpha2, and alpha3 bands, on the basis of the TF and IAF.

Results: Using normal subjects as a reference, VaD patients showed 'slowing' of alpha frequency (TF-IAF) and lower alpha2 power; Mild AD patients showed lower alpha2 and alpha3 power; delta power was higher in both AD and VaD patients; Theta power was higher only in VaD patients.

Conclusions: Individual analysis of the alpha frequency and power can discriminate mild AD from VaD and normal elderly subjects.

Significance: This analysis may probe pathophysiological mechanisms causing AD and VaD.

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Keywords: Mild Alzheimer's disease; Vascular dementia; Electroencephalography; Alpha rhythm; Delta rhythm

1. Introduction

Quantitative analysis of electroencephalographic (EEG) rhythms in resting subjects is a low-cost and potentially useful neurophysiological approach to the study of normal aging and dementia (Gueguen et al., 1991; Maurer and Dierks, 1992; Szeliés et al., 1992; Leuchter et al., 1993; Schreiter-Gasser et al., 1993; Bennys et al., 2001). This type of analysis includes the estimation of the power density of

selected EEG frequency bands (AD; Besthorn et al., 1997; Chiaramonti et al., 1997; Schreiter-Gasser et al., 1994). Compared to normal subjects, Alzheimer's disease (AD) patients are known to have 'slowing of the EEG,' namely through increase of the delta (0.5–4 Hz) and theta (4–8 Hz) power, along with decrease of the alpha power (8–13 Hz). 'Slowing' of the EEG rhythms may be sensitive and correlate to dementia severity and disease progression from the earliest stages (Schreiter-Gasser et al., 1994; Nobili et al., 1999; Ihl et al., 1996). These findings are considered indirect evidence of the fundamental role of cholinergic system in modulating alpha rhythms, given the well-known selective deficit of acetylcholine occurring from the earliest

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stages of AD. However, the typical ‘slowing’ of EEG rhythms seen in AD (Coben et al., 1983, 1990; Sloan et al., 1995) has also been reported in vascular dementia (VaD; Szelies et al., 1992).

The anchor point for a quantitative analysis of the EEG is the alpha rhythm, which dominates the EEG power spectrum in resting normal subjects (Klimesch, 1999). The neural mechanisms of the alpha rhythm have been studied in animal (Steriade and Llinas, 1988) and computational models (Destexhe and Sejnowski, 1996; Suffczynski et al., 2001). Scalp alpha rhythms result from sequences of inhibitory and excitatory post-synaptic potentials at the dendrites of cortical pyramidal neurons. These potentials depend mainly on the influence of near and distant cortical modules (Nunez et al., 2001), as well as on the interactions of excitatory cortico-thalamo-cortical relay fibers and inhibitory thalamic reticular fibers (Lopes da Silva et al., 1980; Suffczynski et al., 2001). An emerging feature of these integrated cortico-cortical and cortico-thalamo-cortical systems is that, in a resting condition, the higher the number of synchronously active neurons, the higher the amplitude of the alpha rhythm, and the slower the frequency of the alpha power peak (Elul, 1972; Lopes da Silva et al., 1976; Singer, 1993; Pfurtscheller and Lopes da Silva, 1999).

Traditionally, alpha power is evaluated within one or two fixed frequency bands ranging from 8 to 13 Hz. However, reports on age- or disease-related changes in EEG oscillatory activity must be interpreted with caution when broadband analyses are calculated within traditional fixed frequency windows. Studies with individual estimation of EEG frequency (Klimesch, 1999) have indeed shown that a physiological or pathological increase (or decrease) of alpha frequency would result in a shift of alpha peak towards higher (or lower) frequencies. The analysis of fixed frequency band could therefore blur the real alpha peak, masking the age-related modifications or those due to neurological diseases, such as dementia.

There is a body of evidence showing that the analysis of individual EEG frequency bands could reveal additional information about the neurophysiology of brain electrical activity (Kopruner et al., 1984; Niedermayer, 1993; Klimesch, 1999). One of the most important outcomes of this approach is the identification of different sub-bands in the range of the alpha frequency subserving different cognitive functions. These studies, however, have been conducted mainly to define normative values in normal young and elderly populations. Our study aims at extending these results to mild Alzheimer subjects, as compared to normal elderly and vascular demented subjects.

In this study, EEG data were recorded in resting normal subjects (Nold), as well as in mild AD and VaD patients. The main focus was to test the impact of the cholinergic system and cortico-cortical connections (known to be impaired in mild AD) and the sub-cortical white matter (damaged in VaD) on the relationship between individual EEG frequencies and their relative power bands. To take

into account the individual features of the alpha band (Klimesch, 1999), we calculated two individual anchor frequencies obtained, at the EEG spectral profile, by averaging power spectra at all recording electrodes (collapsed spectrum). These frequencies were named theta/alpha transition frequency (TF) and individual alpha frequency (IAF). The IAF was defined as the frequency showing its power peak within the extended alpha range (5–14 Hz) and the TF was defined as the EEG frequency, slower than the IAF, showing the minimum power. Of note, the estimation of local TF and IAF indices at various electrode sites would disclose regional phenomena of alpha frequency synchronicity. This important issue needs to be addressed in future studies focused on spatial features of EEG rhythms in dementia. In this study, we focused on a relatively quick procedure suitable for clinical application, with the great advantage of requiring minimal data and no differential analysis of the EEG rhythmicity at different scalp sites.

The range of individual EEG frequencies was indexed by the TF and IAF. Relative power band values were computed at individual delta, theta, alpha1, alpha2, and alpha3 bands.

2. Methods

2.1. Subjects

For the present Italian multi-center study (<http://hreeg.ifu.uniroma1.it/Alzheimer.htm>), 60 mild AD patients, 20 VaD patients, and 30 Nold subjects were recruited. Local institutional ethics committees approved the study. Informed consent was obtained from all participants or their caregivers, according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) and standards established by the Authors’ Institutional Review Boards.

2.2. Diagnostic criteria

All patients underwent general medical, neurological, and psychiatric assessments. Patients were rated with a series of standardized diagnostic and severity instruments, including the MMSE (Folstein et al., 1975), the Clinical Dementia Rating Scale (CDRS; Hughes et al., 1982), the Geriatric Depression Scale (GDS, Yesavage et al., 1982), the Hachinski Ischemic Scale (Rosen et al., 1980), and the Instrumental Activities of Daily Living (IADL, Lawton and Brodie, 1969). In addition, patients underwent diagnostic neuroimaging procedures (head computed tomography or magnetic resonance imaging (MRI)) and laboratory testing to rule out other causes of dementia. Patients were excluded from the study if there was clinical evidence of reversible dementias, including pseudo-dementia of depression (all patients had GDS score lower than 14), and presence of concomitant extra-pyramidal signs on exam. In particular,

patients with strong fluctuations in standard cognitive performance (McKeith et al., 1996; Briel et al., 1999; Barber et al., 2000), which suggest a possible Lewy body dementia or patients showing features of mixed dementia such as Alzheimer and vascular diseases, were excluded from the study.

Diagnosis of AD was made according to NINCDS-ADRDA (McKhann et al., 1984) and DSM-IV criteria, while VaD was diagnosed according to NINDS-AIREN criteria (Roman et al., 1993). VaD patients had Hachinski Ischemic scores ≥ 4 (Rosen et al., 1980). All VaD patients underwent brain MRI scanning, in order to select only cases with widespread subcortical vascular involvement. VaD patients with large vessel disease and cortical strokes were excluded, because of the high anatomical variability of the lesions. Additionally, in order to select mild cases, both AD and VaD patients had a MMSE ranging between 24 and 17. Antidepressant and/or anxiolytic medications were held 24–48 h prior to EEG recordings (10 AD and one VaD subjects). Four AD subjects were routinely taking stable doses of AChE inhibitors at the time of the study. Since the removal of this small sub-group of treated patients did not change the results, they were included in the final statistics.

Nold subjects were recruited mainly among patients' spouses. They were people over 60 years of age who presented no cognitive impairment as revealed by standard neuropsychological testing for mild cognitive impairment. All normal controls underwent physical and neurological examinations, as well as cognitive screening (including MMSE and GDS). Subjects with present or previous history of neurological or psychiatric disease, chronic systemic illnesses, (e.g. diabetes mellitus or cardiac, hepatic or renal insufficiency), and all subjects receiving psychoactive drugs were excluded from the study. GDS score had to be lower than 14, in order to exclude potentially depressed individuals.

Table 1 reports the mean values of demographic and clinical characteristics of patients and controls. Sixty mild AD cases, 20 VaD cases, and 30 Nold subjects were studied after the identification of IAF and TF with a spectral profile-based procedure. Women were overrepresented in the AD

group, as expected. Since there are no known gender-specific differences in EEG rhythms, it was felt that this would not interfere with our results. There were no statistical differences in MMSE scores between mild AD and VaD patients, as revealed by ANOVA ($P > 0.05$). Age and education were entered as covariates in all statistical analysis to avoid possible confounding effects.

2.3. EEG recordings

Specialized clinical units recorded all EEGs. Recordings were obtained with subjects resting comfortably, with their eyes closed. Vigilance was continuously monitored in order to avoid drowsiness. EEG data were recorded (0.3–70 Hz bandpass) from 19 electrodes positioned according to the International 10–20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2), with linked-earlobes reference (subsequently recomputed to common average). A simultaneous electrooculogram (0.3–70 Hz bandpass) was also recorded. All data were digitized in continuous recording mode (5 min of EEG; 128–256 Hz sampling rate).

EEG data were analyzed and fragmented off-line in consecutive epochs of 1 s. For standardization purposes, preliminary analysis of all data was centralized at the EEG laboratories of the Department of Human Physiology and Pharmacology (Rome). The EEG epochs with ocular, muscular and other types of artifact were preliminary identified by a computerized automatic procedure (Moretti et al., 2003). Two expert electroencephalographers manually double-checked and confirmed the automatic selections. The EEG epochs contaminated by ocular artifacts were corrected by a standard autoregressive method (Moretti et al., 2003). The EEG epochs in which the ocular artifacts could not be removed with that procedure were rejected from the analysis.

2.4. Analysis of individual frequency bands

A digital FFT-based power spectrum analysis (Welch technique, Hanning windowing function, no phase shift) computed the power density of EEG rhythms with a 1 Hz frequency resolution, ranging from 2 to 40 Hz.

Fig. 1 shows the model of a typical individual EEG spectral profile, averaged across all recording electrodes. Two anchor frequencies were selected according to literature guidelines (Klimesch, 1999), which are the transition theta/alpha frequency (TF) and the individual alpha frequency (IAF) peak. As previously mentioned, the TF marks the transition frequency between theta and alpha bands and it represents an estimate of theta frequency the frequency at which theta and alpha spectra intersect. We computed the TF as the minimum power in the theta frequency range since our EEG recordings were performed at rest. Indeed, there is another method to compute the TF if a task is performed during the EEG recording. In this case,

Table 1

Mean values of demographic and neuropsychological characteristics in normal elderly (Nold), mild Alzheimer's disease (AD), and vascular dementia (VaD) subjects

	Nold	AD	VaD
Number	30	60	20
Age (years)	70.70 (± 1.2 SE)	73.25 (± 1.03 SE)	75.00 (± 1.07 SE)
Gender (F/M)	16/14	46/14	9/11
MMSE	29.09 (± 0.23 SE)	20.58 (± 0.28 SE)	19.58 (± 1.15 SE)
Education (years)	8.60 (± 0.77 SE)	5.70 (± 0.54 SE)	9.50 (± 0.99 SE)

SE, standard error.

TYPICAL EEG/MEG POWER DENSITY SPECTRUM

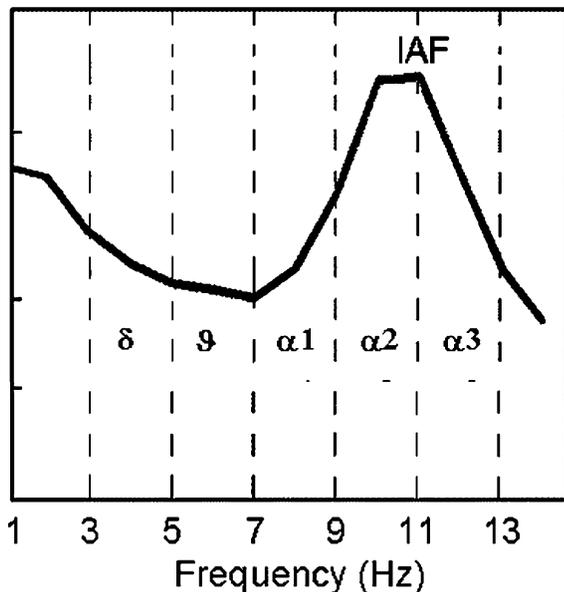


Fig. 1. Scheme illustrating the typical EEG spectral profile of a normal subject. Note the individual alpha frequency (IAF) peak, the transition theta/alpha frequency (TF), and the frequency bands individually determined.

TF is the intersection point of two different power spectra, obtained one for a resting period and the other during task performance.

The IAF represents instead the frequency with the power peak within the extended alpha range (5–14 Hz). The TF and IAF could be clearly identified in 60 mild AD patients, 20 VaD patients, and 30 Nold subjects, whose EEG data were then statistically analyzed.

Based on the TF and IAF we estimated for each subject the frequency band range as follows: delta from TF-4 to TF-2, theta from TF-2 to TF, low alpha (alpha1 and alpha2) from TF to IAF and high alpha band (or alpha3) from IAF to IAF + 2. We introduced a slight variation in the estimation of alpha1 and alpha2 band range respect to the Klimesch method. According to Klimesch, alpha1 ranges from IAF-4 (or TF frequency) to IAF-2 and alpha2 band from IAF-2 to IAF. This computation had the risk of an overlapping between theta and alpha if the distance from IAF and TF is less than 4 Hz. On the other hand, if the distance is more than 4 Hz there is the risk to leave some portions of the spectrum uncovered. It is of note that in demented subjects we found a great variability in the IAF-TF distance if compared with our normal elderly and with the mean normative values from Klimesch's work. Thus, we computed for each subject alpha1 and alpha2 band as follows: alpha1 from TF to the middle point of the TF-IAF range and alpha2 from this middle point to IAF peak. No variation was introduced in the computation of the other frequency bands. Finally, in the frequency bands so determined we computed

the relative power spectra for each subject. The relative power density for each frequency band was computed as the ratio between the absolute power and the mean power spectra from 2 to 40 Hz. The relative band power at each band was defined as the mean of the relative band power for each frequency bins within that band.

2.5. Statistical analysis

For the statistical comparison of the frequency and the relative power of EEG rhythms, analysis of variance was carried out using education and age as covariates (ANCOVA). Duncan's test was used for post hoc comparisons ($P < 0.05$). The ANCOVA addressed the 'slowing' of the TF and IAF using the frequency values as a dependent variable and the Group factor (AD, VaD, Nold) as the independent variables. For the analysis of the EEG relative power, the ANCOVA used the factors Groups (AD, VaD, Nold) and Frequency band (delta, theta, alpha1, alpha2, alpha3). Moreover, the correlations between MMSE scores and all the EEG indexes were computed in the whole group of 80 demented subjects (VaD plus AD) as well as in each of the two groups separately. The MMSE score was correlated with frequencies (TF and IAF) and relative band power (delta, theta, alpha1, alpha2, alpha3) using Pearson's coefficient.

3. Results

Fig. 2 shows the superimposition of individual collapsed power spectra of the AD, VaD, and Nold subjects who were included in the statistical analysis. The TF and IAF are clearly recognized in all groups.

Fig. 3 plots the mean and standard error of the TF and IAF for Nold, AD, and VaD. These values were as follows: TF = 5.4 Hz (± 0.8 SE) and IAF = 9.1 Hz (± 1.1) for Nold, TF = 5.3 Hz (± 1.07) and IAF = 8.7 Hz (± 1.3) for AD, TF = 4.75 Hz (± 0.1) and IAF = 8.3 Hz (± 1.4) for VaD subjects. It should be noted that the low alpha bandwidth of the AD group was slightly narrower than the Nold (0.3 Hz) and VaD (0.25) groups, whereas Nold and VaD groups had practically the same low alpha bandwidth.

ANCOVA was performed pooling both TF and IAF since they are indexes of alpha frequency. ANCOVA showed a trend toward a statistically significant difference in the mean effect of the Group factor ($F(2, 105) = 2.64$; $P = 0.07$). The greater 'slowing' of alpha frequency was observed in VaD as compared to both Nold ($P = 0.004$) and AD ($P = 0.04$) subjects.

Individual frequency bands were selected on the basis of the TF and IAF, and the corresponding relative power density was computed in collapsed spectra. The ANCOVA analysis (Fig. 4) of these values showed a significant interaction between Group factor and Band ($F(8, 428) = 4.87$; $P < 0.00001$). Duncan post hoc testing

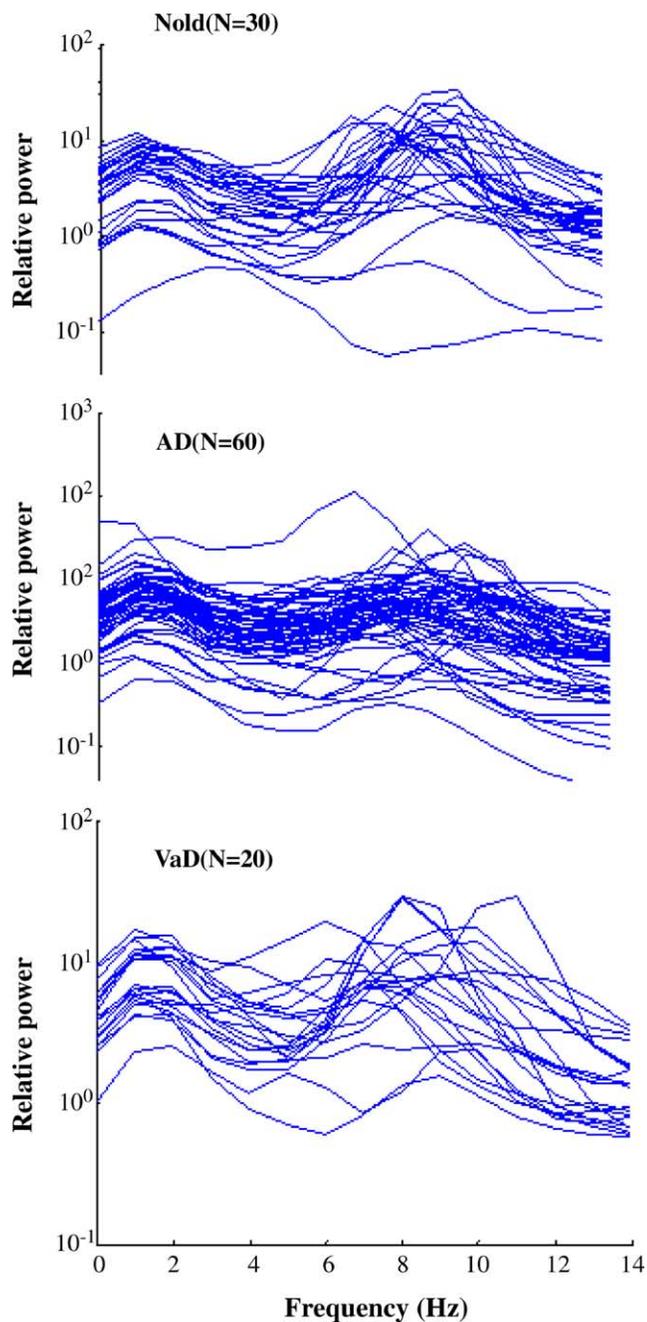


Fig. 2. Diagrams of superimposed individual EEG power spectral profile for the study subjects (Nold, mild AD and VaD groups). The EEG power spectral profile of each subject is derived from the average of the EEG power spectral profiles at all recording electrodes. The TF and IAF are clearly visible in individual EEG power spectral profiles.

showed a strong decrease in the relative power of low alpha (alpha2) in AD cases as compared to both Nold ($P < 0.00002$) and VaD patients ($P < 0.03$), and of high alpha (alpha3) as compared to VaD patients ($P < 0.05$). Furthermore, the delta relative power was greater in both AD and VaD patients compared to Nold subjects ($P = 0.05$), while theta power increased only in VaD as compared to Nold ($P = 0.05$).

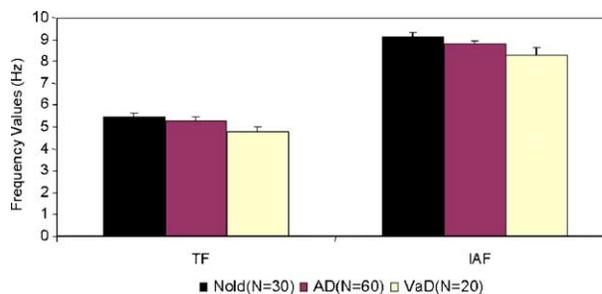


Fig. 3. Diagrams of the mean and standard error of the TF and IAF for Nold, AD, and VaD groups.

The correlations between the MMSE score and all EEG indexes were computed for all demented patients considered as a group, as well as for each of the two groups. None of these correlations was significant at the $P < 0.05$ level.

4. Discussion

4.1. Relative power and frequency of alpha rhythms in mild dementia

In this study we found that, compared to normal elderly subjects, VaD patients showed a trend toward a significant ‘slowing’ of the alpha frequency in both the beginning (TF) and the peak of alpha band (IAF). Moreover, VaD patients showed a substantial change in alpha power only in alpha2 band. The mild AD patients were characterized instead, by a significant reduction of the individual alpha power in both alpha2 and alpha3 bands without a substantial slowing of alpha frequency. Finally, relative delta power increased in both AD and VaD patients while theta power increased only

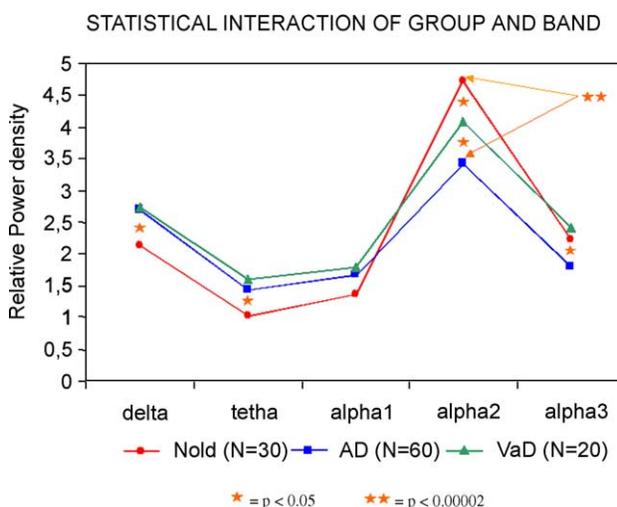


Fig. 4. Statistical ANOVA interaction ($F(8, 364) = 4.19$; $MSe = 4.023$; $P < 0.0001$) among Groups factor (Nold, mild AD, VaD) and relative band power (delta, theta, alpha1, alpha2, alpha3). The star indicates the significant differences among groups based on Duncan post hoc testing.

in VaD patients. We found that the low alpha bandwidth in the AD group was slightly narrower than both Nold (0.3 Hz) and VaD (0.25 Hz) groups. This result merits to be discussed since previous studies (Jonkmann et al., 1992; Salansky et al., 1998) have demonstrated that small differences (0.3 Hz) in the EEG bandwidth could affect the estimation of band power magnitude. However, it should be remarked that in the present study the low alpha band was divided in two sub-bands (alpha1 and alpha2), so that the mean difference of the alpha sub-band widths in the normal and AD subjects were practically negligible, i.e. 0.15 Hz for each alpha sub-band width. Furthermore, the band power was computed as the mean but not the sum of the power frequency bins within that band. Therefore, the bandwidth per se could not affect the estimation of the band power.

It should be noted that the evaluation of absolute power band values could have given different results compared to those obtained considering relative power band values. According to extant literature, we preferred the analysis of the relative power band values, which are not affected by the influences of amplitude of EEG depending on electrical properties of head volume conductor. Furthermore, relative power band values present a lower group variability than absolute power band values do. The use of relative band power values has been recommended in previous influential EEG studies in dementia (Nuwer, 1988; Rodriguez et al., 1999; Leuchter et al., 1993).

The results of our study seem to emphasize a different role for the cholinergic systems and cortico-cortical connections (mainly impaired in mild AD) and the cerebral white matter (mainly damaged in our VaD) in regulating the frequency and power of the alpha rhythm. Moreover, they would put into question the classical notion of an inverse relationship between frequency and power of the alpha rhythm, i.e. the higher the amplitude of the alpha rhythm, the slower the frequency of the alpha power peak. The reduction of the alpha power in mild AD patients, in fact, was not associated with a proportional change of the alpha frequency, whereas slowing of the alpha frequency in VaD patients was not associated with a proportional change of the alpha power. In this respect, the present findings should be considered with extreme caution, since the inverse relationship of power and frequency is usually applied to the entire spectral range of EEG oscillations. Instead, the effects of the dementia process on the alpha rhythmicity did not involve all alpha sub-bands in the same manner.

The present results confirm previous evidence (Leuchter et al., 1993; Besthorn et al., 1997; Rodriguez et al., 1999) that the cholinergic and intracortical deficits of AD mainly impair synchronization mechanisms at the basis of the resting alpha power, which is modulated by cortico-cortical and cortico-thalamo-cortical interactions (Steriade and Llinas, 1988; Pfurtscheller and Lopes da Silva, 1999; Nunez et al., 2001). Based on the determination of individual EEG sub-bands, the power reduction in AD was noted to occur at the low (about 8–10 Hz) and high

alpha bands (about 10–12 Hz). From a functional point of view, the low- alpha band power (8–10 Hz) could relate to attentional systems, in contrast to the high- alpha band power (10–12 Hz) that reflects processing of task-specific sensorimotor or semantic information (Klimesch, 1999). Therefore, the reduction of the alpha band power in mild AD can be explained in terms of an abnormal increase of cortical excitation or disinhibition during the resting state. This possible explanation is in line with previous evidence of abnormal central EEG rhythms or evoked potentials in AD subjects performing voluntary movements or perceiving somatosensory stimuli (Babiloni et al., 2000; Ferri et al., 1996). Furthermore, abnormally hyperexcitable primary motor cortex has been recently reported in AD, as revealed by EEG rhythms related to self-paced movements and transcranial magnetic stimulation (Babiloni et al., 2000; Pennisi et al., 2002; Ferreri et al., 2003;).

In this study, VaD patients with diffuse vascular lesions of the white matter, showed slowing of the alpha frequency with a decrement of the band power only in low alpha range. A previous study (d'Onofrio et al., 1996) has shown a slowing in the beginning of alpha frequency in vascular demented subjects that fits our findings, although the mentioned study was carried out using fixed but not individual frequency bands. Furthermore, these results are in line with previous evidence showing that lesions of the white matter in VaD were directly related to a widespread slowing of EEG rhythmicity (Szelies et al., 1992, 1999). The white matter lesions of multiple sclerosis also decreased the frequency of the alpha rhythm (Leocani et al., 2000), while successful immunosuppressive treatment, probably restoring appropriate nerve propagation, resulted in recovery of normal alpha frequency without effects on the relative power (Colon et al., 1981). Finally, tumors of the cerebral white matter, but not of the gray matter, decrease the frequency of the alpha rhythm (Gloor et al., 1968; Goldensohn, 1979).

A reasonable explanation of the present results is that the slowing of the alpha frequency in VaD could be mainly ascribed to impairment of the bidirectional connectivity along cortico-thalamo-cortical fibers. Such impairment could slow the conduction time of the action potentials throughout the cortico-thalamo-cortical pathways (Tomasch, 1954; Steriade and Llinas, 1988; Pfurtscheller and Lopes da Silva, 1999), interfering with the inhibitory control of the reciprocal cortico-thalamo-cortical modulations (Sarter and Bruno, 1997; Destexhe et al., 1998; Doiron et al., 2003). Computational models have previously shown that the EEG frequency relies on axonal delay and synaptic time of the cortico-thalamo-cortical interactions as well as on the activity of inhibitory reticulo-thalamic neurons (Lopes da Silva et al., 1976; Nunez et al., 2001; Doiron et al., 2003). Additionally, the prevalence of the white matter damage could not exclude an impairment of the gray matter, even though less evident than in AD patients. Moreover, definitive conclusions in vascular

demented patients could be drawn in future studies recruiting a larger group size.

Taken together, our data suggest that the regulation of the alpha power during wakeful rest is related to the full integrity of the cholinergic systems and cortico-cortical connections (mainly impaired in mild AD) more than to integrity of the white matter (mainly damaged in VaD patients). The cholinergic systems are essential for the control of selective attention (Sarter and Bruno, 1997, 1999, 2000) and are mainly represented by two projection systems directly affecting the cortex. The first projection system connects basal forebrain structures to the cortex and the thalamus, while the second projection system connects the rostral brainstem (pedunculopontine and lateral dorsal tegmentum) to the cortex via the thalamus (Kobayashi and Tadashi, 2002). At rest, the afferent cholinergic inputs of these projection systems would synchronize long-range cortico-cortical connections that are also affected in AD due to loss of dendritic spines, neurons and to beta-amyloid plaque deposition. Accordingly, these cholinergic inputs would sustain the power of the alpha rhythm (Holschneider et al., 1998; Villa et al., 2000). This explanation agrees with the reduction of functional cortico-cortical coupling, revealed by EEG coherence studies, in AD patients compared to normal controls (Leocani et al., 2000) and VaD patients (Leuchter et al., 1992). The regulation of the alpha frequency would otherwise be relatively independent of the full integrity of the cholinergic systems and cortico-cortical connections (mainly impaired in mild AD). Rather, it would mainly depend on the integrity of the white matter (mainly damaged in VaD). As a speculation, the present findings suggest that mild AD may have no major damage of the white matter and a relatively spared transmission of inhibitory cortico-thalamo-cortical inputs modulating the alpha frequency.

4.2. Low EEG rhythms in mild dementia

Compared to the normative data, the landmark of the slow EEG frequency (TF) was slowed by VaD but not by mild AD subjects. Mild dementia affected the power of the EEG slow rhythms more than frequency. Namely, the magnitude of the delta power was greater in VaD and AD patients than in Nold subjects, as if it depended on non-specific effects of dementia. These findings agree with previous reports in which white matter lesions in mild VaD induced a large and widespread increase of the slow EEG power (Gloor et al., 1968; Coben et al., 1983), correlated with a reduction in regional cerebral metabolism (Szeliés et al., 1999). The present findings also agree with previous studies in AD demonstrating an increase in slow EEG rhythms together with a reduction of regional cerebral blood flow (Rae-Grant et al., 1987; Stigsby et al., 1981; Brenner et al., 1986; Nobili et al., 1999).

Theta frequency increased only in VaD subjects so it might represent an earlier index of vascular dementia.

The present findings agree with previous studies in which subcortical damage in mild VaD patients were responsible for a large and widespread increase of theta source activity (Gloor et al., 1977; Coben et al., 1983). Of note, the increase of theta could be linked to the general slowing of the dominant frequency in VaD and this could explain why it is less evident in mild AD. On the other hand, it could be possible that in AD theta band is not yet impaired in a very early stage of disease, but its impairment could be expressed later.

Converging evidence from the relevant literature indicates that the power of the slow EEG rhythms may represent a global state of cortical deafferentation due to various anatomic-functional substrates including cholinergic projections (impaired in mild AD) and white matter (impaired in our VaD patients). This slow oscillatory mode of the brain would prevent an efficient processing of internal or external stimuli, as it may occur during deep stages of sleep, which are characterized by high-power low frequency EEG rhythms. According to previous suggestions (Llinas et al., 1999), a pathological increase of slow EEG power might rely on a cortico-thalamo-cortical dysrhythmia involving the non-specific thalamic system. Of note, this system must not be confused with the brain network modulating a narrow EEG slow band (theta) during cognitive efforts, which is induced upon frontomedial/cingulate areas by (para)hippocampal formation (Klimesch, 1999). In the present protocol (resting EEG), this issue could not be addressed.

4.3. Correlation between EEG and MMSE

The correlations between the MMSE score and all EEG indices were not significant in either the demented patients considered as a group or in each group. This was apparently at variance with previous studies (Rodriguez et al., 1999; Matousek et al., 2001) showing significant correlations of MMSE score with EEG frequency and band power. However, it should be remarked that in the mentioned studies the correlations between MMSE and EEG parameters were observed mainly at circumscribed temporo-parietal scalp regions. Therefore, it is possible that the lack of correlations between the MMSE score and the present EEG indices was due to averaging of the spectral parameters across electrodes of the whole scalp. This explanation is consistent with recent evidence showing no correlation between MMSE score and EEG parameters (2–14 Hz) collapsed across all sensors (Stam, 2000; Stam et al., 2002, 2003). It can be concluded that the averaging of EEG indices across all electrodes is useful for data reduction purposes but it can mask some correlations with mental functions localized in specific brain areas.

5. Conclusions

The present EEG study investigated the respective role of the cholinergic system and cortico-cortical connections

(impaired in mild AD), and the sub-cortical white matter (lesioned in VaD) on the relationship between individual EEG frequencies and their relative power bands.

Compared to normal elderly subjects, VaD patients showed a significant ‘slowing’ of the alpha frequency not associated with a proportional change in the alpha band power. On the other hand, the AD patients’ EEGs were characterized by a significant reduction of the alpha power not associated with a substantial change in alpha frequency.

Finally, the relative delta power increased in both AD and VaD patients while theta power increased only in VaD subjects. These results put into question the classical inverse relationship between the frequency and power in normal EEG rhythms and emphasize the differential role of specific abnormalities in these two forms of dementia in the regulation of the frequency and power of alpha rhythms. Furthermore, they suggest that individual analysis of alpha frequency and power could discriminate mild AD from VaD and normal elderly subjects. Future investigations are needed to validate the clinical usefulness of these findings in early differential diagnosis, disease staging, and therapy monitoring.

The results of the present study will be made available at the WEB site of the present multi-centric study (<http://hreg.ifu.uniroma1.it/Alzheimer.htm>).

Acknowledgements

We thank Dr. Fabio Babiloni, Mrs. Gabriella Busonero, Dr. Paola Chioventa, Dr. Filippo Carducci, Dr. Febo Cincotti, Mrs. Matilde Ercolani, Mrs. Rita Fini, Dr. Giovanni Frisoni, Dr. Massimo Gennarelli, Dr. Nicola Girtler, Dr. Katuscia Sosta, Dr. Franca Tecchio, and Dr. Filippo Zappasodi for their precious help in the development of the present study. We thank also Professor Fabrizio Eusebi for his continuous support. The research was granted by Foundation Telethon Onlus (project EC0985).

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