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NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 22 (2004) 57–67

Mapping distributed sources of cortical rhythms in mild Alzheimer's disease. A multicentric EEG study

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Received 17 April 2003; revised 10 September 2003; accepted 10 September 2003

The study aimed at mapping (i) the distributed electroencephalographic (EEG) sources specific for mild Alzheimer's disease (AD) compared to vascular dementia (VaD) or normal elderly people (Nold) and (ii) the distributed EEG sources sensitive to the mild AD at different stages of severity. Resting EEG (10–20 electrode montage) was recorded from 48 mild AD, 20 VaD, and 38 Nold subjects. Both AD and VaD patients had 24–17 of mini mental state examination (MMSE). EEG rhythms were delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–10.5 Hz), alpha 2 (10.5–13 Hz), beta 1 (13–20 Hz), and beta 2 (20–30 Hz). Cortical EEG sources were modeled by low resolution brain electromagnetic tomography (LORETA). Regarding issue i, there was a decline of central, parietal, temporal, and limbic alpha 1 (low alpha) sources specific for mild AD group with respect to Nold and VaD groups. Furthermore, occipital alpha 1 sources showed a strong decline in mild AD compared to VaD group. Finally, distributed theta sources were largely abnormal in VaD but not in mild AD group. Regarding issue ii, there was a lower power of occipital alpha 1 sources in mild AD subgroup having more severe disease. Compared to previous field studies, this was the first investigation that illustrated the power spectrum profiles at the level of cortical (macroregions) EEG sources in mild AD patients having different severity of the disease with respect to VaD and normal subjects. Future studies should evaluate the clinical usefulness of this approach in early differential diagnosis, disease staging, and therapy monitoring.

Keywords: Mild Alzheimer's disease (mild AD); Vascular dementia (VaD); Electroencephalography (EEG); Alpha rhythm; Low resolution brain electromagnetic tomography (LORETA)

Introduction

Quantitative analysis of electroencephalographic (EEG) rhythms in resting subjects is a low-cost and useful neurophysiological approach to the study of normal aging and dementia (Brenner et al., 1986; Coben et al., 1983, 1990; Giaquinto and Nolfe, 1986; Gueguen et al., 1991; Leuchter et al., 1993; Maurer and Dierks, 1992; Schreiter-Gasser et al., 1993; Stigsby et al., 1981; Szelies et al., 1992; Visser et al., 1985). Indeed, scalp EEG rhythms are affected by Alzheimer's disease (AD; Besthorn et al., 1997; Chiaramonti et al., 1997; Schreiter-Gasser et al., 1994). Compared to normal subjects, Alzheimer's disease (AD) patients present an increase of delta (about 0.5–4 Hz) and theta (about 4–8 Hz) mean power along with a decrease of alpha (about 8–13 Hz) and beta (about 13–30 Hz) mean power.

EEG rhythms are also sensitive to the severity of dementia. Delta and/or theta rhythms do increase even in the earlier stages of AD (Schreiter-Gasser et al., 1994) and seem to predict disease

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Available online on ScienceDirect (www.sciencedirect.com.)

1053-8119/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2003.09.028

progression (Ihl et al., 1996; Nobili et al., 1999). In normal subjects, magnitude of alpha rhythm is maximal in scalp occipital areas. While alpha rhythm still peaks in posterior scalp areas in mild AD patients, it is either equally distributed over the scalp or localizes more anteriorly with disease progression (Claus et al., 1998; Ihl et al., 1993, 1996). Similarly, maximum beta rhythm is located more anteriorly in AD patients, as a function of disease severity.

The abnormality of EEG rhythms in dementia is associated with altered regional cerebral blood flow (rCBF)/metabolism and cognitive function, as revealed by positron emission tomography (PET), single photon emission computerized tomography (SPECT), and neuropsychological testing (Celsis et al., 1990; Joannesson et al., 1977; Julin et al., 1995; Ihl et al., 1989; Passero et al., 1995; Rodriguez et al., 1998, 1999; Sheridan et al., 1988; Sloan et al., 1995; Szelies et al., 1992). Indeed, an inverse correlation between delta/theta rhythms and rCBF is observed in parieto-temporal regions of AD patients (Buchan et al., 1997; Kwa et al., 1993; Passero et al., 1995; Stigsby et al., 1981). With few exceptions (Mueller et al., 1997), rCBF directly correlates with alpha rhythms in these regions (Buchan et al, 1997; Rodriguez et al., 1998). Furthermore, EEG rhythms and rCBF seem to correlate with severity of AD as expressed by mini mental state evaluation (MMSE; Rodriguez et al., 1998). In vascular dementia (VaD), decrease of occipital alpha power positively correlates with the occipital and temporo-parietal glucose metabolism at rest (Szelies et al., 1999). In contrast, delta/theta power in VaD inversely correlates with the glucose metabolism, possibly reflecting subcortical lesions and cortical deafferentation (Szelies et al., 1999).

Cortical sources of scalp EEG rhythms have been successfully evaluated in AD patients by single dipole sources deeply located into a spherical brain model (Dierks et al., 1993). Single dipole sources of alpha or beta rhythms are located more anteriorly as a function of AD severity. Such "anteriorization" of the dipole source is observed in AD patients not only with respect to normal subjects but also with respect to subjects with mild cognitive impairment (Dierks et al., 1993; Huang et al. 2000). Notably, the location of the dipole sources correlates with the reduction of rCBF in antero-posterior and latero-lateral brain axes (Dierks et al., 2000).

From a physiological point of view, EEG rhythms reflect the opening–closure ("gating function") of bidirectional connections among several cortical and subcortical (i.e. brainstem, thalamus) structures (Hari et al., 1997; Nunez, 1995; Pfurtscheller and Neuper, 1994; Pfurtscheller and Lopes da Silva, 1999). Therefore, a single dipole source indicates the "center of gravity" of the distributed cortical sources generating the EEG rhythms. An alternative approach for the modeling of these sources is called low resolution brain electromagnetic tomography (LORETA-KEY; Pascual-Marqui and Michel, 1994; Pascual-Marqui et al., 1999), which uses thousands of dipole sources within a 3-D brain model coregistered into Talairach space (Talairach and Tournoux, 1988). LORETA is a functional imaging technique belonging to a family of procedures (Valdés et al., 1998) in which the cortex can be modeled as a collection of volume elements (voxels) in the digitized Talairach atlas. LORETA accommodates neuroanatomical constraints and finds the linear inverse solutions that maximize only the synchronization of strength between neighboring neuronal populations (Pascual-Marqui et al., 2002). This roughly corresponds to the 3-D distribution of electric neuronal activity that has the maximum similarity (i.e. the maximum synchronization) in terms of orientation and strength among neighboring neuronal populations. In a previous review paper, it has been shown that LORETA was quite efficient when compared to other linear inverse algorithms like minimum norm solution, weighted minimum norm solution or weighted resolution optimization (Pascual-Marqui, 1999). Independent validation of LORETA solutions has been provided by recent studies (Phillips et al., 2002; Yao and He, 2001).

LORETA solutions in resting AD patients have shown a significant coupling between rCBF pattern and distributed EEG sources of alpha and beta rhythms (Dierks et al., 2000). Moreover, LORETA provides a better spatial resolution with the advantage of 3-D representation of the cerebral activity compared to the classical scalp quantitative EEG and, with respect to the dipole modeling of cortical sources, no a priori decision of the dipole position is required in LORETA estimation.

The present multicentric study was aimed at defining (i) the distributed EEG sources specific for mild AD compared to VaD or normal aging (Nold) and (ii) the distributed EEG sources sensitive to the mild AD progression. For these aims, resting EEG was recorded from a large group of mild AD, VaD, and normal elderly (Nold) subjects. As normal elderly people, we mean people that could be age-matched with the demented patients and did not present any cognitive impairment or any potential condition altering the EEG profile. Frequency bands of EEG rhythms ranged from delta to beta bands. Cortical sources of these rhythms were modeled by LORETA solutions in macro-cortical regions. On the whole, the present study extended the previous field evidence in terms of fine topographical localization of the EEG sources (LORETA solutions into Talairach space) at specific frequency bands able to characterize the mild AD group.

Methods

Subjects

For the present Italian multicentric study, we recruited 48 mild AD patients, 20 VaD patients, and 38 Nold subjects. Local institutional ethics committees approved the study. All experiments were undertaken with the understanding and overt consent of each participant or caregiver, in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the Author's Institutional Review Board.

Diagnostic criteria

All patients underwent general medical, neurological, and psychiatric assessments. Patients were also rated with a variety of standardized diagnostic and severity instruments that included the MMSE (Folstein et al., 1975), Clinical Dementia Rating Scale (CDRS; Hughes et al., 1982), Geriatric Depression Scale (GDS; Yesavage et al., 1982), Hachinski Ischemic Scale (Rosen et al., 1980), and Instrumental Activities of Daily Living (IADL; Lawton and Brodie, 1969). In addition, patients underwent neuroimaging diagnostic procedures (CT or MRI) and complete laboratory analysis. Notably, patients were not included in the study if there was evidence of concomitant extra-pyramidal symptoms or reversible dementias, including dementia of depression (all patients had GDS score lower than 14). In particular,

Table 1
Personal and neuropsychological data of interest of the present normal aging (Nold), mild Alzheimer's disease (AD), and vascular dementia (VaD) subjects

	Nold	Mild AD	VaD
N	38	48	20
Age (years)	67.5 (± 1.3 SE)	73.7 (± 1.3 SE)	76.4 (± 1.2 SE)
Gender (F/M)	19/19	39/9	10/10
MMSE	29.2 (± 0.2 SE)	20.2 (± 0.3 SE)	20.4 (± 1.1 SE)
Education (years)	8 (± 0.7 SE)	5.5 (± 0.5 SE)	9.7 (± 1 SE)

patients with strong fluctuations in cognitive performance, suggesting a possible Lewy body dementia or patients showing mixed features of dementia, for example, Alzheimer and vascular, were carefully excluded from the study.

Probable AD was diagnosed according to NINCDS-ADRDA (McKhann et al., 1984) and DSM IV criteria. On the other hand, probable 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 MRI scan to select only cases showing widespread subcortical vascular involvement. VaD patients with major vascular cortical impairment (stroke) were excluded due to the high spatial variability of related brain lesions. In line with the aims of the present study, participating AD and VaD patients had a MMSE ranging from 24 to 17. Furthermore, the mild AD patients were further subdivided in mild AD "−" (MMSE 21–24) and mild AD "+" (MMSE 17–20) to address the issue of the increase of the severity of mild AD. Mild AD "−" group was comprised 23 subjects (mean age 74.1 ± 9.8 years; mean education years 5.8 ± 4.1), whereas mild AD "+" was comprised 25 subjects (mean age 73.3 ± 8.4 years; mean education years 5.6 ± 3.5). Of note, here, we used the terms mild AD and VAD instead of "probable" mild AD and VAD just for sake of simplicity.

Antidepressant and/or anxiolitic medications were suspended for 24–48 h before EEG recordings (2 AD−, 8 AD+, and 1 VaD subjects). Four AD subjects (2 AD− and 2 AD+) were regularly treated with AChE inhibitors at the time of the study. Since the removal of this small subgroup of treated patients did not change the EEG source results, they were included in the final statistics.

Nold subjects were recruited mainly among patients' spouses. All normal subjects underwent physical and neurological examinations as well as cognitive screening (including MMSE and GDS). Subjects affected by chronic systemic illnesses, such as diabetes mellitus or organ failure, were excluded, as were subjects receiving psychoactive drugs. Subjects with a history of present or previous neurological or psychiatric disease were excluded as well. All had a GDS score lower than 14.

Table 1 reports mean values of relevant personal and clinical parameters of participating mild AD, VaD, and Nold subjects. As expected, females were overrepresented in the AD group. As there is no previous evidence demonstrating gender-specific effects on EEG rhythms, it was felt that this did not interfere with our results. On the other hand, there was no statistical difference in MMSE between mild AD and VaD patients as revealed by ANOVA ($P > 0.05$). Finally, age and education were used as covariates in the statistical evaluation of cortical sources of EEG rhythms to remove possible confounding effects.

EEG recordings

EEG was recorded by specialized clinical units in resting subjects (eyes closed) whose vigilance was continuously controlled to avoid drowsiness. EEG data were recorded (0.3–70 Hz bandpass) from 19 electrodes positioned according to international 10–20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2). No specific reference was used, since LORETA analysis is reference-free. To monitor eye movements, electrooculogram, both horizontal and vertical, (0.3–70 Hz bandpass) was also collected. 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 2 s. On average, 147 epochs for each subject were examined. For standardization purposes, the preliminary analysis of all data was performed at EEG labs of 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 electroencephalographists then manually confirmed this automatic selection. The EEG epochs contaminated by ocular artifacts were corrected by an autoregressive method (Moretti et al., 2003). Afterwards, the EEG epochs that were found again affected by artifacts were removed from the analysis.

Spectral analysis of EEG data

A digital FFT-based power spectrum analysis (Welch technique, Hanning windowing function, no phase shift) computed the power density of EEG rhythms with 0.5-Hz frequency resolution. The following standard band frequencies were considered: delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–10.5 Hz), alpha 2 (10.5–13 Hz), beta 1 (13–20 Hz), and beta 2 (20–30 Hz). These band frequencies were chosen averaging those used in previous relevant EEG studies on dementia (Besthorn et al., 1997; Chiaramonti et al., 1997; Jelic et al., 1996; Leuchter et al., 1993; Rodriguez et al., 1999a,b).

As a methodological consideration, the utilization of fixed frequency bands allowed a better comparison with previous literature, a more direct comprehension of results, and an enhancement of even slight differences between the examined groups. In particular, we used fixed but narrow bands for delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–10.5 Hz), and alpha 2 (10.5–13 Hz). On the other hand, we could not use narrow frequency bands for beta 1 (13–20 Hz) and beta 2 (20–30 Hz) because power spectra were quite broad at the beta range. Therefore, LORETA results at

Table 2
Brodmann areas included in the cortical regions of interest (ROIs) of the present study

LORETA Brodmann areas into the regions of interest (ROIs)	
Frontal	8, 9, 10, 11, 44, 45, 46, 47
Central	1, 2, 3, 4, 6
Parietal	5, 7, 30, 39, 40, 43
Temporal	20, 21, 22, 37, 38, 41, 42
Occipital	17, 18, 19
Limbic	31, 32, 33, 34, 35, 36

LORETA solutions were collapsed in frontal, central, parietal, temporal, occipital, and limbic ROIs.

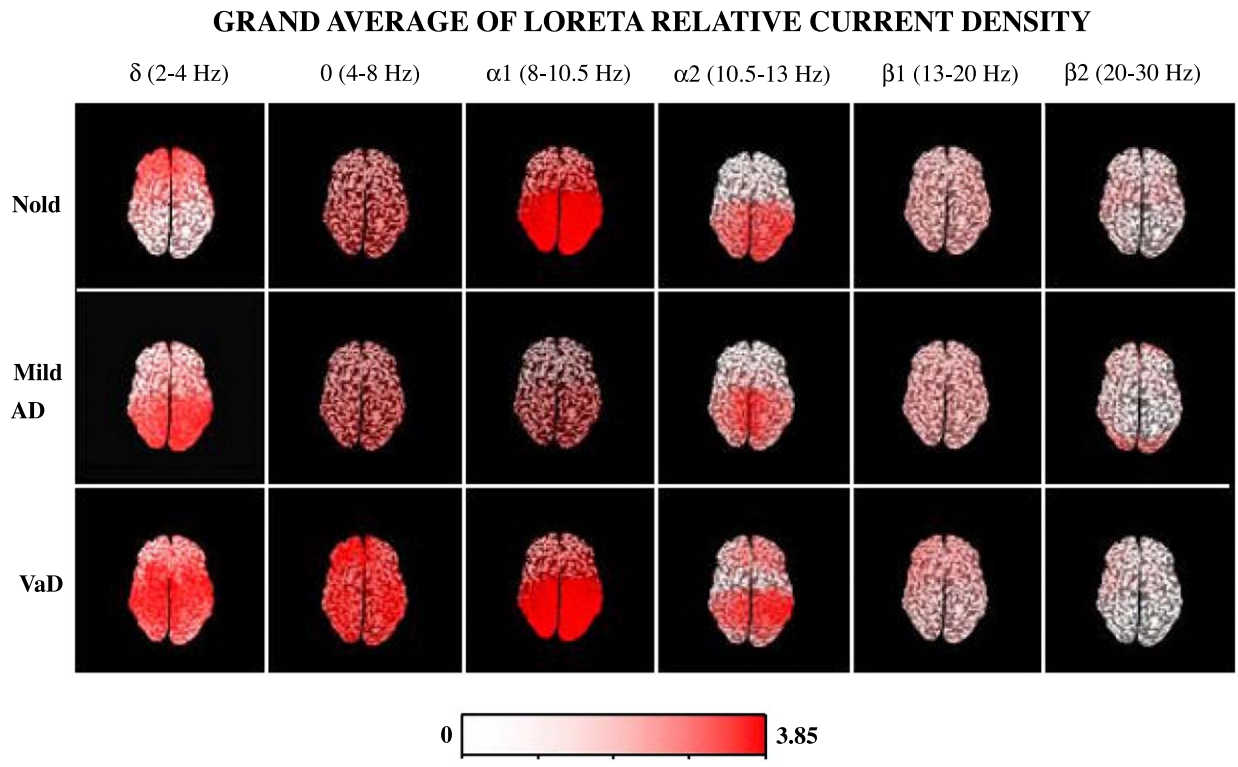

Fig. 1. Grand average of LORETA solutions (i.e. relative current density at cortical voxels) modeling distributed EEG sources for delta, theta, alpha 1, alpha 2, beta 1, and beta 2 bands in Nold, mild AD, and VaD groups. The left side of the maps (top view) corresponds to the left hemisphere. LORETA, low resolution brain electromagnetic tomography. All power estimates were scaled based on the averaged maximum value (i.e. alpha 1 power value of occipital region in Nold) indicated in the scale bar.

beta bands could suffer from the limitations in sensitivity of the EEG spectral analysis for relatively large bands (Szava et al., 1994). As an alternative approach, the frequency band computation might be alternatively based on the estimation of individual markers (Klimesch, 1999), such as individual alpha frequency (IAF) and transition frequency (TF). Future studies should address the utility of a frequency source analysis of resting EEG based on individual-based frequency computation.

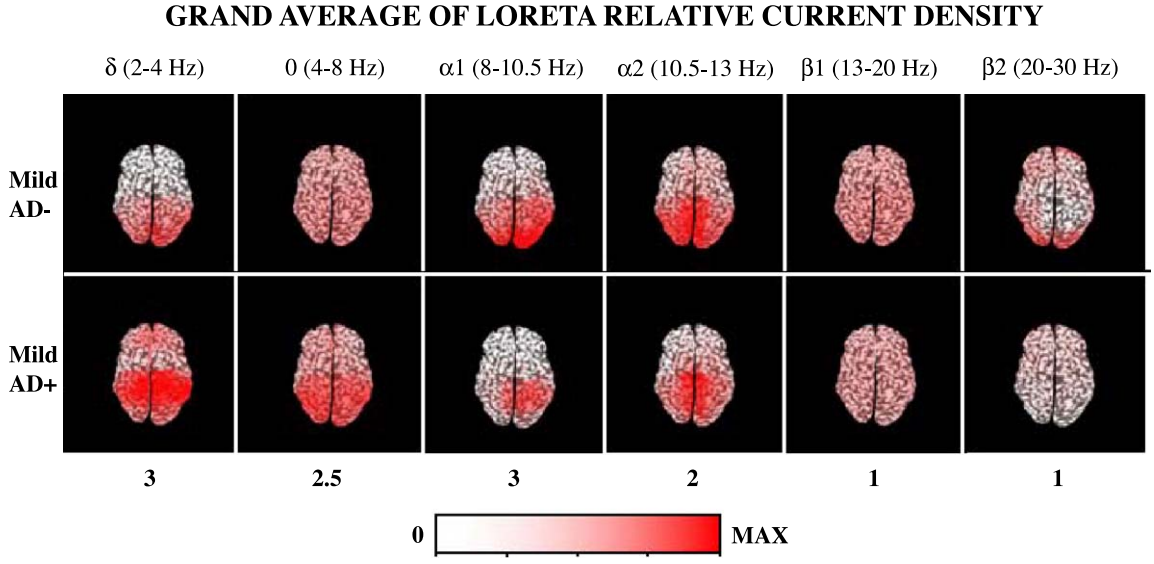

Fig. 2. Grand average of LORETA solutions modeling distributed EEG sources for delta, theta, alpha 1, alpha 2, beta 1, and beta 2 bands in mild AD − (mini mental state evaluation, MMSE 24–21) and mild AD+ (MMSE 17–20) patients. The left side of the maps (top view) corresponds to the left hemisphere. All power estimates were scaled based on the averaged maximum value (i.e. alpha 1 power value of occipital region in Nold). For illustrative purposes, the maximum indicated in the scale bar refers to the averaged maximum value (i.e. alpha 1 power value of occipital region in AD −) of the population subjects in the figure (i.e. AD − and AD+).

Cortical source analysis of EEG rhythms by LORETA

We employed LORETA for the EEG source analysis, which has been extensively tested with simulation paradigms (Pascual-Marqui and Michel, 1994; Pascual-Marqui et al., 1999) and is presently used by several independent labs worldwide. LORETA computed 3-D linear solutions (LORETA solutions) for the EEG inverse problem within a three-shell spherical head model including scalp, skull, and brain compartments. The brain compartment was restricted to the cortical gray matter/hippocampus and was coregistered to the Talairach probability brain atlas, digitized at the Brain Imaging Center of the Montreal Neurologic Institute (Talairach and Tournoux, 1988). This compartment included 2394 voxels (7-mm resolution), each voxel containing an equivalent current dipole.

LORETA solutions consisted of voxel current density values able to predict EEG spectral power density at scalp electrodes. To enhance the "topographical" results, a "spatial" normalization was obtained by normalizing the LORETA current density at each voxel for the LORETA power density averaged across all frequencies (0.5–30 Hz)/voxels of the brain volume. These normalized relative current values were then log transformed (Gasser et al., 1982). The general procedure made Gaussian the data and reduced intersubject variability (Leuchter et al., 1993; Nuwer, 1988). Of note, other methods of normalization using the principal component analysis are effective for estimating the subjective global factor scale of EEG data (Hernández et al., 1994). However, they are not yet available in the LORETA package, so its utilization is prevented to all worldwide users.

Solutions of EEG inverse problem are underdetermined and ill-conditioned when the number of spatial samples (electrodes) is lower than that of the unknowns (current density at each voxel). To account for that, cortical LORETA solutions predicting scalp EEG spectral power density was regularized to estimate distributed rather than punctual EEG sources (Pascual-Marqui and Michel, 1994; Pascual-Marqui et al., 1999). As a result, the spatial resolution of regularized LORETA solutions was much lower than that of SPECT or PET. On the other hand, the smoothing of cortical source solutions (resolution of cm) could reliably take into account the slight change in the cortical volume (resolution of mm) at the mild stage of AD or VaD. On the whole, a good spatial correspondence has been demonstrated when cortical regions of interest (ROIs) rather than single voxels were considered for the comparison of LORETA and PET solutions (Dierks et al., 2000). For this reason, we collapsed LORETA solutions at frontal, central, temporal, parietal, occipital, and limbic regions of the brain model coded into Talairach space. Brodmann areas listed in Table 2 formed each of these ROIs. Noteworthy, the spatial information of that model served to disentangle the activity of these ROIs. For example, the activity of the occipital cortical region was disentangled with respect to that of the contiguous parietal and temporal cortical regions, etc. This was made it possible by the fact that LORETA solves linear inverse problem taking into account the well-known effects of head as a volume conductor. This approach represents a clear methodological improvement compared to the EEG spectral analysis at surface electrodes. Indeed, EEG potentials collected at each scalp electrode are strongly affected by head volume conductor effects. For example, the occipital electrodes collect the scalp potentials generated not only from occipital cortex but also from parietal and temporal cortices due to head volume conductor effects. For these reasons, we preferred to focus on the LORETA solutions rather than on the EEG analysis at scalp electrodes.

Statistical analysis of LORETA solutions

Regional normalized LORETA solutions from mild AD, VaD, and Nold subjects were compared by ANOVA analysis, using relative current density values as dependent variable and subjects' age and education as covariates. Mauchley's test evaluated the sphericity assumption. Correction of the degrees of freedom was made by Greenhouse–Geisser procedure. Duncan test was used for post hoc comparisons ($P < 0.05$).

In particular, two ANOVA designs were used to address the two main scientific issues of the present study. The first ANOVA design focused on distributed EEG sources specific of mild AD. Its factors (levels) were Group (mild AD, VaD, Nold), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (central, frontal, parietal, occipital, temporal, limbic). Results of interest were the regional LORETA solutions (distributed EEG sources) in the mild AD group showing statistically significant differences ($P < 0.05$) with respect to those of VaD and Nold groups.

The second ANOVA design focused on distributed EEG sources sensitive to the severity of mild AD. Its factors (levels) were Group (Nold, mild AD−, mild AD+), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (central, frontal, parietal, occipital, temporal, limbic). Results of interest were the regional LORETA solutions (distributed EEG sources) showing a double statistical pattern ($P < 0.05$), namely, a statistical difference between mild AD− and Nold groups together with a statistical difference between mild AD− and mild AD+ groups.

Results

Topography of EEG cortical sources estimated by LORETA

Fig. 1 maps the grand average of LORETA solutions (i.e. relative current density at cortical voxels) modeling distributed EEG sources for delta, theta, alpha 1, alpha 2, beta 1, and beta 2 bands in Nold, mild AD (MMSE 17–24), and VaD groups. The left side of the maps (top view) corresponds to the left hemisphere. The Nold group presented widespread delta and theta sources having moderate values of relative current density. Instead, alpha sources had strong magnitude and were distributed mainly in parieto-occipital regions. Relative current density prevailed in alpha 1 compared to alpha 2 sources. Finally, beta sources were characterized by low relative current density. Beta 2 sources were circumscribed to central regions compared to widespread beta 1 sources.

Compared to the Nold group, the mild AD group (MMSE 17–24) showed an increase of widespread delta sources together with a dramatic reduction of parieto-occipital alpha 1 sources. Minor differences were observed in beta sources, keeping in mind their low relative current density.

Compared to the AD group, the VaD group was characterized by an increase of widespread delta and theta sources along with a less dramatic decrease of parieto-occipital alpha 1 sources with respect to the Nold group.

Fig. 2 maps the grand average of LORETA solutions, modeling distributed EEG sources for delta, theta, alpha 1, alpha 2, beta 1,

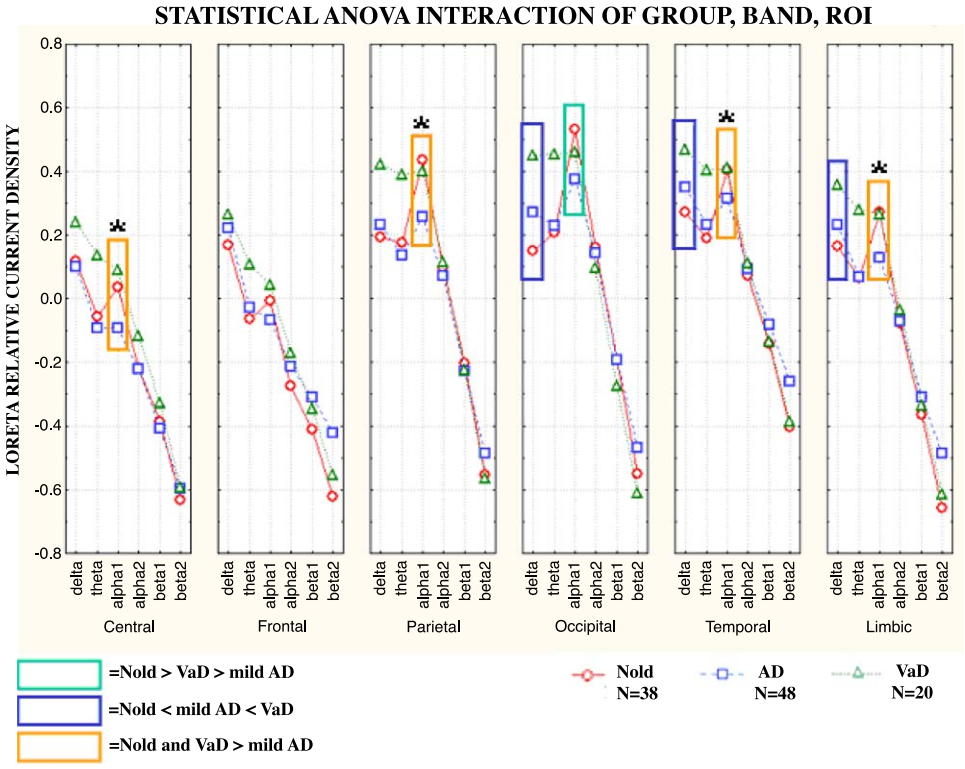

Fig. 3.

and beta 2 bands in mild AD- (MMSE 24–21) and mild AD+ (MMSE 20–17) groups. Again, the left side of the maps (top view) corresponds to the left hemisphere. Compared to the Nold group (see Fig. 1), occipital delta sources were stronger in magnitude with the maximal severity of the disease (mild AD – to mild AD+), along with an evident lesser magnitude of occipital alpha 1 (but not alpha 2) sources. If any, differences in beta sources were less clear.

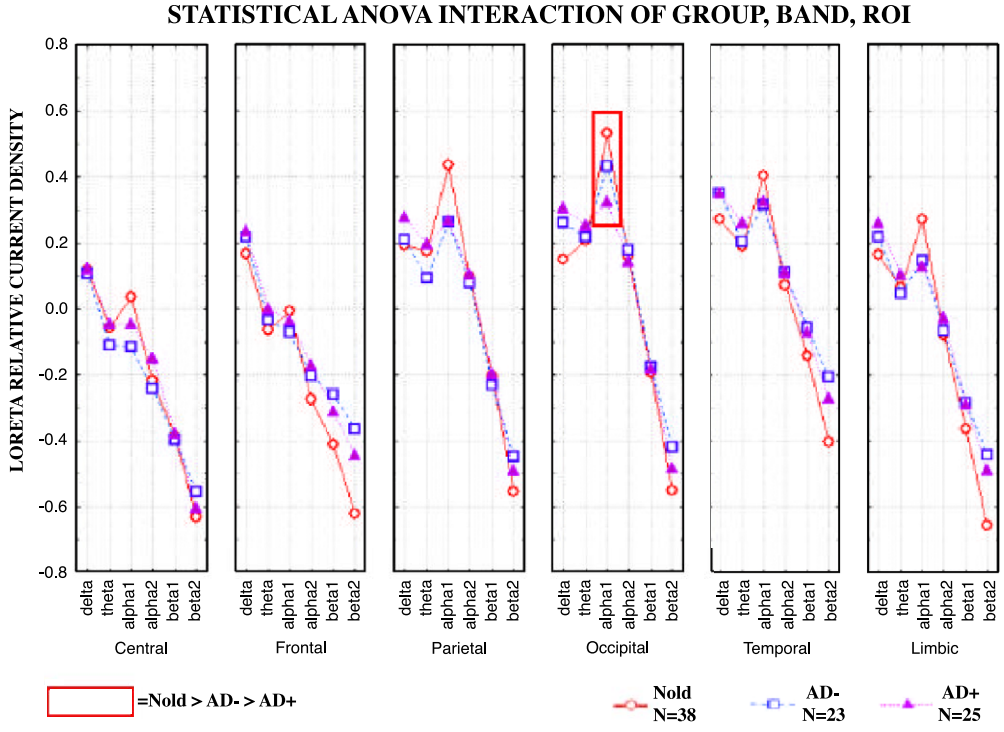

Fig. 4.

Regional LORETA solutions characterizing mild AD group

Fig. 3 shows regional LORETA solutions (distributed EEG sources) relative to a statistical ANOVA interaction [$F(50,2575) = 1.96$; MSe = 0.0120; $P < 0.0001$] among factors Group (mild AD, VaD, Nold), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (central, frontal, parietal, occipital, temporal, limbic). LORETA solutions modeled EEG relative power spectra as revealed by a sort of "virtual" intracranial cortical recordings. Notably, profile and magnitude of these spectra in Nold, mild AD, and VaD differed in the diverse cortical regions, thus supporting the idea that scalp EEG rhythms are generated by a distributed pattern of cortical sources.

Results of interest for Duncan post hoc testing were the regional LORETA solutions in the mild AD group showing statistically significant differences ($P < 0.05$) compared to those computed in VaD and Nold groups. There was a decline of central, parietal, temporal, and limbic alpha 1 (low alpha) sources specific for mild AD respect to Nold and VaD ($P < 0.001$), the two control groups showing similar source current density values. As another important discriminant parameter, distributed theta sources were largely abnormal in VaD ($P < 0.000005$) but not in mild AD compared to Nold. On the other hand, occipital alpha 1 sources showed a strong decline in mild AD compared to VaD ($P < 0.009$). However, this finding was "unspecific", since a certain decline of these sources was also recognized in VaD compared to Nold ($P < 0.000001$). The same "unspecific" trend was true for the increase of occipital, temporal, and limbic delta sources in mild AD and VaD with respect to Nold ($P < 0.01$).

Regional LORETA solutions characterizing severity of mild AD

Fig. 4 plots regional LORETA solutions (distributed EEG sources) relative to a statistical ANOVA interaction [$F(50,2075) = 1.96$; MSe = 0.0120; $P < 0.0001$] among factors Group (Nold, mild AD to, mild AD+), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (central, frontal, parietal, occipital, temporal, limbic). Results of interest for Duncan post hoc testing were the regional LORETA solutions showing a double statistical pattern ($P < 0.05$): a statistical difference between mild AD − and Nold groups together with a statistical difference between mild AD − and mild AD+ groups. This statistical requirement was fitted by occipital alpha 1 sources, which had lower magnitude in mild AD − than Nold groups ($P < 0.001$) and lower magnitude in mild AD+ than mild AD − groups ($P < 0.0007$).

Discussion

Sources of slow EEG rhythms and dementia

In the present LORETA study, an important focus was on the computation of power spectral profiles of cortical (i.e. six macro-regions) EEG sources in probable mild AD patients having different severity of the disease (MMSE 17–24) compared to normal subjects and patients having probable VaD with diffuse subcortical lesions. Indeed, previous studies have shown the power spectra profiles on demented from raw scalp EEG data (Rodriguez et al., 2002) or have just computed statistical voxel-by-voxel differences in EEG source current density among subgroups of patients with dementia (Saletu et al., 2002) or brain tumors (Fernandez-Bouzas et al., 1999).

Mild AD showed occipital, temporal, and limbic (EEG) delta sources having greater magnitude than those observed in normal aging. However, the magnitude of these delta sources was even greater in VaD. This suggests that delta power increase is related aspecifically to the slowing of cortical function, linked either to the impairment of subcortical inputs in vascular dementia or to the impairment of cortical connectivity in AD.

The increase of source delta power in VaD compared to mild AD was less evident in anterior regions in agreement with a previous study (d'Onofrio et al., 1996). The source of delta power was present in anterior regions even in normal people, probably due to a state of active inhibition of frontal cortex at rest condition. This could also explain the minor difference in anterior regions at delta power between normal and demented subjects and between mild AD and VaD patients. On the other hand, the cut off of delta frequency at 2 Hz could have subtracted some power at this frequency band, smoothing the difference among the groups. On the whole, abnormal delta sources in mild AD may depend on unspecific effects of dementia. In contrast, distributed theta sources were largely abnormal in VaD but not in mild AD, thus assuming a remarkable importance as a possible peculiar feature for the differential early diagnosis of mild AD with respect to VaD. Noteworthy, these findings need to be confirmed in a larger sample of VaD and in other kinds of dementia.

The present findings agree with previous studies in which subcortical damage in mild VaD patients was responsible for a large and widespread increase of theta source activity (Coben et al., 1983; Duffy et al., 1984; Gloor et al., 1977; Jordan et al., 1989) and for the correlation of slow EEG rhythms and widespread rCBF/metabolism (Szelies et al., 1999). Furthermore, the present findings agree with previous AD studies in which hypo-perfusion (rCBF) of

Fig. 3. Regional LORETA solutions (distributed EEG sources) relative to a statistical ANOVA interaction among factors Group (mild AD, VaD, Nold), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (central, frontal, parietal, occipital, temporal, limbic). This ANOVA design was focused on the features of EEG sources characterizing mild AD with respect to VaD and Nold. We identified the EEG sources in which the power current density was (i) statistically different in mild AD compared to VaD, in mild AD compared to Nold, and in VaD compared to Nold and (ii) statistically different in mild AD compared to both VaD and Nold and with no difference between VaD and Nold. The EEG sources having this latter distinctive feature were indicated with a star. LORETA solutions modeled EEG relative power spectra as revealed by a sort of "virtual" intracranial macro-electrodes disposed on cortical regions. The rectangles indicate the cortical regions and frequency bands in which LORETA solutions presented statistically different values ($P < 0.05$, Duncan post hoc test) in mild AD patients with respect to both VaD and Nold subjects.

Fig. 4. Regional LORETA solutions (distributed EEG sources) relative to a statistical ANOVA interaction among factors Group (Nold, mild AD − , mild AD+), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (central, frontal, parietal, occipital, temporal, limbic). This ANOVA design was focused on the features of EEG sources characterizing the severity of mild AD. The rectangles indicate Duncan post hoc results of interest ($P < 0.05$).

posterior associative cortex was spatially coupled with increased regional slow EEG rhythms (Brenner et al., 1986; Kwa et al., 1993; Nobili et al., 1998; Passero et al., 1995; Rae-Grant et al., 1987; Stigsby et al., 1981).

The present LORETA solutions showed no significant change at theta band sources (4–8.5 Hz band) between mild AD and normal subjects. There are two possible reasons for that. First, theta band might be not yet impaired at a very early stage of mild AD, but its impairment could be expressed later. Second, some masking effect in mild AD might be because 4–8.5 Hz band may be a frequency range in which a theta band increment could be compensated by an alpha band increment. Future studies should address this issue using individual landmarks of alpha and theta bands for the EEG frequency analysis (Klimesch, 1999).

Sources of alpha rhythms characterized mild AD

Cortical alpha 1 sources characterized mild AD from VaD and normal aging. Compared to VaD and normal aging, mild AD showed a significant decrease of alpha 1 sources in all cortical regions. In particular, the most specific marker for mild AD was the reduction in magnitude of central, parietal, temporal, and limbic alpha 1 sources compared to normal aging and VaD. Thus, it could be considered a marker specific for mild AD. On the other hand, the reduction of the alpha 1 sources in mild AD group with respect to the control groups was clearly less evident in the central cortical region when compared to the parietal, occipital, and temporal cortical regions. Furthermore, it was practically absent in the frontal region. The present results enlighten the so-called "anteriorization" of scalp alpha rhythms in AD, repeatedly reported in previous studies using EEG mapping and single dipole localization (Claus et al., 1998; Dierks et al., 2000; Ihl et al., 1993, 1996). Such an "anteriorization" may result from the fact that, in mild AD, alpha 1 sources decline in magnitude much more in parieto-occipital than frontal cortical regions, thus producing a "virtual displacement" of the "center of gravity" of the alpha rhythm.

From a physiological point of view, alpha rhythms are mainly modulated by thalamo-cortical interactions facilitating or inhibiting (i) the transmission of sensorimotor information among subcortical and cortical pathways and (ii) the retrieval of semantic information from cortical storage (Brunia 1999; Pfurtscheller and Lopes da Silva 1999; Steriade and Llinas 1988). Furthermore, a large amount of scalp alpha rhythms in resting conditions is usually considered as a sign of brain wakeful idling. Within the extended alpha band (8–13 Hz), alpha 1 (low alpha) would be mainly related to attentional components, whereas alpha 2 (high alpha) would reflect processing of task-specific sensorimotor or semantic information (Klimesch, 1996, 1997; Klimesch et al., 1998). Based on this theoretical background, the present results suggest that, in mild AD, thalamocortical systems may be impaired in the attentional modulation (alpha 1) of central and temporal cortical regions, ready to be involved in the sensorimotor and semantic memory functions. Moreover, the decrease of alpha 1 source in limbic (temporo-mesial) region could be related with the well-known impairment of memory function typical of AD. Of course, resting EEG data did not allow for the evaluation of these functions when they operate.

Compared to normal aging, magnitude reduction of widespread alpha 1 sources in mild AD can be explained in terms of an abnormal increase of cortical excitation or disinhibition during the resting state. This explanation is in line with previous evidence showing abnormal central EEG rhythms or evoked potentials in AD subjects who performed voluntary movements or received somatosensory stimuli (Babiloni et al., 2000; Ferri et al., 1996). Furthermore, it has been reported an abnormal hyperactivity of AD primary motor cortex as revealed by EEG rhythms related to self-paced movements and transcranial magnetic stimulation (Alagona et al., 2001; Ferreri et al., 2003; Pennisi et al., 2002). These findings raise the issue of the role of inhibitory neurotransmitters in mild AD.

Occipital alpha 1 sources were sensitive to mild AD at different stages of disease severity

In the present LORETA study, another important focus was on specific features characterizing distributed cortical sources of EEG rhythms during the different stages of severity of mild AD. For this reason, the AD patients were divided in two subgroups, namely, mild AD− having MMSE 21–24 and mild AD+ having MMSE 17–20. Occipital alpha 1 sources had a stronger magnitude in Nold than mild AD− and in mild AD− than mild AD+. These results localized to occipital cortical region confirm previous scalp EEG evidence showing decreased alpha during AD progression (Besthorn et al., 1997; Chiaramonti et al., 1997; Claus et al., 1999; Dierks et al., 2000; Huang et al., 2000; Leuchter et al., 1993; Nobili et al., 1999; Rodriguez et al., 1999a,b; Wada et al. 1997). Furthermore, the present results generally agree with previous evidence indicating that AD severity affected the coupling of alpha rhythms and rCBF/metabolism in posterior cortical regions (Buchan et al., 1997; Haxby et al., 1986; Jagust et al., 1988, 1997; Mueller et al., 1997; Nobili et al., 1998; Rapoport, 1991, 1997; Sachdev et al., 1997).

The present abnormal sources of occipital EEG rhythms between mild AD at different stages of severity may be due to early pathological changes in extrastriate occipital areas (Armstrong and Syed, 1996; Armstrong et al., 1990) and their connections (Cronin-Golomb et al, 1991, 1993; Hof and Bouras, 1991; Morrison et al., 1991). Functional correlates in AD might be represented by impairments in color discrimination, spatio-temporal resolution, stereoscopy, contrast sensitivity, or visuospatial analysis (Hof and Bouras, 1991). In this regard, neurophysiological findings in AD subjects have shown to be coupled with a reduced rCBF/metabolism in extrastriate visual cortex (Fujimori et al., 2000; Mielke et al., 1995) as well as with abnormal visual evoked potentials (Arakawa et al. 1993; Bajalan et al. 1986; Holl et al., 1992; Nobili and Sannita 1997; Sannita, 1995; Sannita et al., 1993).

Conclusions

In the present Italian multicentric study, we showed (i) distributed EEG sources specific for mild AD (MMSE 17–24) compared to VaD or normal aging and (ii) the distributed EEG sources sensitive to the increase of the severity of mild AD. Regarding issue i, There was a decline of central, parietal, temporal, and limbic alpha 1 (low alpha) sources specific for mild AD respect to Nold and VaD. On the other hand, occipital alpha 1 sources showed a strong decline in mild AD compared to VaD. However, this finding was "unspecific", since a certain decline of these sources was also recognized in VaD compared to Nold. The same "unspecific" trend was true for the increase of occipital, temporal, and limbic delta sources in mild AD and VaD respect to Nold.

Finally, distributed theta sources were largely abnormal in VaD but not in mild AD. Regarding issue ii, the maximal severity of mild AD was related to the lowest occipital alpha 1 sources. The present findings specified spatial features of cortical sources of resting EEG rhythmicity in mild AD. On the whole, these findings stress the reliability of the LORETA approach to the study of cortical rhythmicity in resting mild AD. For the first time, they illustrated the power spectrum profiles at the level of cortical (i.e. six macroregions) EEG sources in mild AD patients having different severity of the disease with respect to VaD and normal subjects. Future studies using discriminant analysis or artificial neural networks should evaluate 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 this EEG multicentric study (http://www.hreeg.ifu.uniroma1.it/Alzheimer.htm).

Acknowledgments

We thank Dr. Fabio Babiloni, Mrs. Gabriella Busonero, Dr. Paola Chiovenda, Dr. Davide Capanni, Dr. Filippo Carducci, Dr. Febo Cincotti, Dr. Claudio Del Percio, Mrs. Matilde Ercolani, Mrs. Rita Fini, Dr. Giovanni Frisoni, Dr. Massimo Gennarelli, Dr. Nicola Girtler, and Dr. Katiuscia Sosta for their precious help in the development of the present study. We thank also Prof. Fabrizio Eusebi for his continuous support. The research was granted by Foundation Telethon Onlus (project EC0985).

References

Alagona, G., Bella, R., Ferri, R., Carnemolla, A., Pappalardo, A., Costanzo, E., Pennisi, G., 2001. Transcranial magnetic stimulation in Alzheimer disease: motor cortex excitability and cognitive severity. Neurosci. Lett. 314 (1–2), 57–60 (Nov. 13).

Arakawa, K., Peachey, N.S., Celesia, G.G., Rubboli, G., 1993. Component-specific effects of physostigmine on the cat visual evoked potential. Exp. Brain Res. 95, 271–276.

Armstrong, R.A., Syed, A.B., 1996. Alzheimer's disease and the eye. Ophthalmic Physiol. Opt. 16, S2–S8.

Armstrong, R.A., Nochlin, D., Sumi, S.M., Alvord, E.C., 1990. Neuropathological changes in the visual cortex in the Alzheimer's disease. Neurosci. Res. Commun. 6, 163–171.

Babiloni, C., Babiloni, F., Carducci, F., Cincotti, F., Del Percio, C., De Pino, G., Maestrini, S., Priori, A., Tisei, P., Zanetti, O., Rossini, P.M., 2000. Movement-related electroencephalographic reactivity in Alzheimer disease. Neuroimage 12 (2), 139–146.

Bajalan, A.A.A., Wright, C.E., Van der Vliet, V.J., 1986. Changes in the uman visual evoked potentials caused by the anticholinergic agent hyoshine hydrobromide: comparison with results in Alzheimer's disease. J. Neurol., Neurosurg. Psychiatry 49, 175–182.

Besthorn, C., Zerfass, R., Geiger-Kabisch, C., Sattel, H., Daniel, S., Schreiter-Gasser, U., Forstl, H., 1997. Discrimination of Alzheimer's disease and normal aging by EEG data. Electroencephalogr. Clin. Neurophysiol. 103 (2), 241–248.

Brenner, R.P., Ulrich, R.F., Spiker, D.G., Sclabassi, R.J., Reynolds III, C.F., Marin, R.S., Boller, F., 1986. Computerized EEG spectral analysis in elderly normal, demented and depressed subjects. Electroencephalogr. Clin. Neurophysiol. 64, 483–492.

Brunia, C.H., 1999. Neural aspects of anticipatory behavior. Acta Psychol. (Amst.) 101 (2–3), 213–242 (Apr.).

Buchan, R.J., Nagata, K., Yokoyama, E., Langman, P., Yuya, H., Hirata, Y., Hatazawa, J., Kanno, I., 1997. Regional correlations between the EEG and oxygen metabolism in dementia of Alzheimer's type. Electroencephalogr. Clin. Neurophysiol. 103 (3), 409–417.

Celsis, P., Agniel, A., Le Tinnier, A., Viallard, G., Demonet, J.F., Rascol, A., Marc Vergnes, J.P., 1990. Lateral asymmetries in primary degenerative dementia of the Alzheimer type. A correlative study of cognitive, haemodynamic and EEG data, in relation with severity, age of onset and sex. Cortex 26, 585–596.

Chiaramonti, R., Muscas, G.C., Paganini, M., Muller, T.J., Fallgatter, A.J., Versari, A., Strik, W.K., 1997. Correlations of topographical EEG features with clinical severity in mild and moderate dementia of Alzheimer type. Neuropsychobiology 36 (3), 153–158.

Claus, J.J., Kwa, V.I., Teunisse, S., Walstra, G.J., van Gool, W.A., Koelman, J.H., Bour, L.J., Ongerboer de Visser, B.W., 1998. Slowing on quantitative spectral EEG is a marker for rate of subsequent cognitive and functional decline in early Alzheimer disease. Alzheimer Dis. Assoc. Disord. 12 (3), 167–174.

Claus, J.J., Strijers, R.L.M., Jonkman, E.J., Ongerboer, B.W., Jonker, C., Walstra, G.J.M., Scheltens, P.H., van Gool, W.A., 1999. The diagnostic value of electroencephalography in mild senile Alzheimer's disease. Clin. Neurophysiol. 110, 825–832.

Coben, L.A., Danziger, W., Storandt, M., 1983. A longitudinal EEG study of mild dementia of Alzheimer type: changes at 1 year and 2.5 years. Electroencephalogr. Clin. Neurophysiol. 55, 372–380.

Coben, L.A., Chi, D., Snyder, A.Z., Storandt, M., 1990. Replication of a study of frequency analysis of the resting awake EEG in mild probable Alzheimer's type. Electroencephalogr. Clin. Neurophysiol. 75, 148–154.

Cronin-Golomb, A., Corkin, S., Rizzo, J.F., Cohen, J., Growdon, J.H., Banks, K.S., 1991. Visual dysfunction in Alzheimer's disease: relation to normal aging. Ann. Neurol. 29 (1), 41–52.

Cronin-Golomb, A., Sugiura, R., Corkin, S., Growdon, J.H., 1993. Incomplete achromatopsia in Alzheimer's disease. Neurobiol. Aging 14 (5), 471–477.

Dierks, T., Ihl, R., Frolich, L., Maurer, K., 1993. Dementia of the Alzheimer type: effects on the spontaneous EEG described by dipole sources. Psychiatry Res. 50 (3), 51–162.

Dierks, T., Jelic, V., Pascual-Marqui, R.D., Wahlund, L.O., Julin, P., Linden, D.E.J., Maurer, K., Winblad, B., Nordberg, A., 2000. Spatial pattern of cerebral glucose metabolism (PET) correlates with localization of intracerebral EEG-generators in Alzheimer's disease. Clin. Neurophysiol. 111, 817–824.

D'Onofrio, S., Salvia, S., Petretta, V., Bonavita, V., Rodriguez, G., Tedeschi, G., 1996. Quantified-EEG in normal aging and dementias. Acta Neurol. Scand. 93 (5), 336–345.

Duffy, F.H., Albert, M.S., McAnulty, G., Garvey, A.J., 1984. Age-related differences in brain electrical activity of healthy subjects. Ann. Neurol. 4, 430–438.

Ferreri, F., Pauri, F., Pasqualetti, P., Fini, F., Dal Forno, G., Rossini, P.M., 2003. Motor cortex excitability in Alzheimer's disease: a transcranial magnetic stimulation study. Ann. Neurol. 53 (1), 102–108.

Ferri, R., Del Gracco, S., Elia, M., Musumeci, S.A., Spada, R., Stefanini, M.C., 1996. Scalp topographic mapping of middle-latency somatosensory evoked potentials in normal aging and dementia. Neurophysiol. Clin. 26 (5), 311–319.

Fernandez-Bouzas, A., Harmony, T., Bosch, J., Aubert, E., Fernandez, T., Valdes, P., Silva, J., Marosi, E., Martinez-Lopez, M., Casian, G., 1999. Sources of abnormal EEG activity in the presence of brain lesions. Clin. Electroencephalogr. 30 (2), 46–52.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. 'Mini Mental State': a practical method for grading the cognitive state of patients for clinician. J. Psychiat. Res. 12, 189–198.

Fujimori, M., Imamura, T., Hirono, N., Ishii, K., Sasaki, M., Mori, E., 2000. Disturbances of spatial vision and object vision correlate differently with regional cerebral glucose metabolism in Alzheimer's disease. Neuropsychologia 38, 1356–1361.

Gasser, T., Bacher, P., Mocks, J., 1982. Transformations towards the normal distribution of broadband spectral parameters of the EEG. Electroencephalogr. Clin. Neurophysiol. 53, 119–124.

Giaquinto, S., Nolfe, G., 1986. The EEG in the normal elderly: a contribution to the interpretation of aging and dementia. Electroencephalogr. Clin. Neurophysiol. 63, 540–546.

Gloor, P., Ball, G., Schaul, N., 1977. Brain lesions that produce delta waves in the EEG. Neurology 27 (4), 326–333.

Gueguen, B., Derouesne, C., Bourdel, M.C., Guillou, S., Landre, E., Gaches, J., Hossard, H., Ancri, D., Mann, M., 1991. Apport de l'EEG quantifiee au diagnostic de demence de type Alzheimer. Neurophysiol. Clin. 21, 357–371.

Hari, R., Salmelin, R., Makela, J.P., Salenius, S., Helle, M., 1997. Magnetoencephalographic cortical rhythms. Int. J. Psychophysiol. 26 (1–3), 51–62.

Haxby, J.V., Grady, C.L., Duara, L., Schlageter, M., Berg, G., Rapoport, S.I., 1986. Neocortical metabolic abnormalities precede non memory cognitive defects in early Alzheimer's type dementia. Arch. Neurol. 43, 882–885.

Hernández, J.L., Valdés, P., Biscay, R., Virués, T., Szava, S., Bosch, J., Riquenes, A., Clark, I., 1994. A global scale factor in brain topography. Int. J. Neurosci. 76, 267–278.

Hof, P.R., Bouras, C., 1991. Object recognition deficit in Alzheimer's disease: possible disconnection of the occipito-temporal component of the visual system. Neurosci. Lett. 122, 53–56.

Holl, G., Straschill, M., Thomsen, T., Fischer, J.P., Kewitz, H., 1992. Effect of the cholinesterase inhibiting substance galanthamine on human EEG and visual evoked potentials. Electroencephalogr. Clin. Neurophysiol. 82, 445–452.

Huang, C., Wahlund, L.O., Dierks, T., Julin, P., Winblad, B., Jelic, V., 2000. Discrimination of Alzheimer's disease and mild cognitive impairment by equivalent EEG sources: a cross-sectional and longitudinal study. Clin. Neurophysiol. 11, 1961–1967.

Hughes, C.P., Berg, L., Danziger, W.L., Cohen, L.A., Martin, R.L., 1982. A new clinical rating scale for the staging of dementia. Br. J. Psychiatry 140, 1225–1230.

Ihl, R., Eilles, C., Frlich, L., Maurer, K., Dierks, T., Perisic, I., 1989. Electrical brain activity and cerebral blood flow in dementia of the Alzheimer type. Psychiatry Res. 29 (3), 449–452.

Ihl, R., Dierks, T., Froelich, L., Martin, E.M., Maurer, K., 1993. Segmentation of the spontaneous EEG in dementia of the Alzheimer type. Neuropsychobiology 27 (4), 231–236.

Ihl, R., Dierks, T., Martin, E.M., Frolich, L., Maurer, K., 1996. Topography of the maximum of the amplitude of EEG frequency in dementia of the Alzheimer type. Biol. Psychiatry 39, 319–325.

Jagust, J., Friedland, P., Budinger, F., Koss, E., Ober, B., 1988. Longitudinal studies of regional cerebral metabolism in Alzheimer's disease. Arch. Neurol. 38, 909–912.

Jagust, W.J., Eberling, J.L., Reed, B.R., Mhatis, C.A., Budinger, T.F., 1997. Clinical studies of cerebral blood flow in Alzheimer's disease. Ann. N. Y. Acad. Sci. 826, 254–262.

Jelic, V., Shigeta, M., Julin, P., Almkvist, O., Winblad, B., Whalund, L.O., 1996. Quantitative electroencephalography power and coherence in Alzheimer's disease and mild cognitive impairment. Dementia 7 (6), 314–323 (Nov–Dec).

Joannesson, G., Brun, A., Gustafson, I., Ingvar, D.H., 1977. EEG in presenile dementia related to cerebral blood flow and autopsy findings. Acta Neurol. Scand. 56, 89–103.

Jordan, S.E., Nowacki, R., Nuwer, M., 1989. Computerized electroencephalography in the evaluation of early dementia. Brain Topogr. 4, 271–282.

Julin, P., Wahlund, L.O., Basun, H., Persson, A., Mare, K., Rudberg, U., 1995. Clinical diagnosis of frontal lobe dementia and Alzheimer disease: relation to cerebral perfusion, brain atrophy and electroencephalograhy. Dement. Geriat. Cogn. Disord. 6, 142–147.

Klimesch, W., 1996. Memory processes, brain oscillations and EEG synchronization. Int. J. Psychophysiol. 24, 61–100.

Klimesch, W., 1997. EEG-alpha rhythms and memory processes. Int. J. Psychophysiol. 26 (1–3), 319–340.

Klimesch, W., 1999. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res. Rev. 29, 169–195.

Klimesch, W., Doppelmayr, M., Russegger, H., Pachinger, T., Schwaiger, J., 1998. Induced alpha band power changes in the human EEG and attention. Neurosci. Lett. 244 (2), 73–76.

Kwa, V.I., Weinstein, H.C., Posthumus-Meyjes, E.F., Van Royen, E.A., Bour, L.J., Verhoeff, P.N., Ongerboer de Visser, B.W., 1993. Spectral analysis of the EEG and 99m-Tc-HMPAO-SPECT-scan in Alzheimer's disease. Biol. Psychiatry 33 (2), 100–107.

Lawton, M.P., Brodie, E.M., 1969. Assessment of older people: self maintaining and instrumental activity of daily living. J. Gerontol. 9, 179–186.

Leuchter, A.F., Cook, I.A., Newton, T.F., Dunkin, J., Walter, D.O., Rosenberg Tompson, S., Lachenbruch, P.A., Weiner, H., 1993. Regional differences in brain electrical activity in dementia: use of spectral power and spectral ratio measures. Electroencephalogr. Clin. Neurophysiol. 87, 385–393.

Maurer, K., Dierks, T., 1992. Functional imaging procedures in dementias: mapping of EEG and evoked potentials. Acta Neurol. Scand. 139, 40–46.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E.M., 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 34, 939–944.

Mielke, R., Kessler, J., Fink, G., Herholz, K., Heiss, W.D., 1995. Dysfunction of visual cortex contributes to disturbed processing of visual information in Alzheimer's disease. Int. J. Neurosci. 82 (1–2), 1–9.

Moretti, D.V., Babiloni, F., Carducci, F., Cincotti, F., Remondini, E., Rossini, P.M., Salinari, S., Babiloni, C., 2003. Computerized processing of EEG-EOG-EMG artifacts for multicentric studies in EEG oscillations and event-related potentials. Int. J. Psychophysiol. 47 (3), 199–216.

Morrison, J.H., Hof, P.R., Bouras, C., 1991. An anatomic substrate for visual disconnection in Alzheimer's disease. Ann. N. Y. Acad. Sci. 640, 36–43.

Mueller, Th.J., Strik, W.K., Thome, J., Dierks, T., Scheubeck, M., Frölich, L., Hissnauer, G., Maurer, K., 1997. Relations of EEG-brain mapping and HMPAO-SPECT with the severity of Alzheimer's dementia (DAT). Psychiatry Res. Neuroimag. 68 (2–3), 172.

Nobili, L., Sannita, W.G., 1997. Cholinergic modulation, visual function and Alzheimer's dementia. Vision Res. 37 (24), 3559–3571.

Nobili, F., Taddei, G., Vitali, P., Bazzano, L., Catsafados, E., Mariani, G., Rodriguez, G., 1998. Relationships between 99m Tc-HMPAO ceraspect and quantitative EEG observations in Alzheimer's disease. Arch. Gerontol. Geriatr. 6, 363–368.

Nobili, F., Copello, F., Vitali, P., Prastaro, T., Carozzo, S., Perego, G., Rodriguez, G., 1999. Timing of disease progression by quantitative EEG in Alzheimer's patients. J. Clin. Neurophysiol. 16 (6), 566–573.

Nunez, P., 1995. Neocortical Dynamics and Human EEG Rhythms. Oxford Univ. Press, New York.

Nuwer, M.R., 1988. Quantitative EEG: I. Techniques and problems of frequency analysis and topographic mapping. J. Clin. Neurophysiol. 5, 1–43.

Pascual-Marqui, R.D., 1999. Review of methods for solving the EEG inverse problem. Int. J. Bioelectromagn. 1, 75–86.

Pascual-Marqui, R.D., Michel, C.M., 1994. LORETA (low resolution brain electromagnetic tomography): new authentic 3D functional images of the brain. ISBET Newsl. ISSN 5, 4–8.

Pascual-Marqui, R.D., Lehmann, D., Koenig, T., Kochi, K., Merlo, M.C., Hell, D., Koukkou, M., 1999. Low resolution brain electromagnetic tomography (LORETA) functional imaging in acute, neuroleptic-naive, first-episode, productive schizophrenia. Psychiatry Res. 90 (3), 169–179.

Pascual-Marqui, R.D., Esslen, M., Kochi, K., Lehmann, D., 2002. Functional imaging with low resolution brain electromagnetic tomography (LORETA): a review. Methods Find. Exp. Clin. Pharmacol. 24, 91–95.

Passero, S., Rocchi, R., Vatti, G., Burgalassi, L., Battistini, N., 1995. Quantitative EEG mapping, regional cerebral blood flow, and neuropsychological function in Alzheimer's disease. Dementia 6, 148–156.

Pennisi, G., Alagona, G., Ferri, R., Greco, S., Santonocito, D., Pappalardo, A., Bella, R., 2002. Motor cortex excitability in Alzheimer disease: one year follow-up study. Neurosci. Lett. 329 (3), 293 (Sep. 6).

Pfurtscheller, G., Lopes da Silva, F.H., 1999. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin. Neurophysiol. 110 (11), 1842–1857 (Review, Nov.).

Pfurtscheller, G., Neuper, C., 1994. Eventrelated synchronization of mu rhythm in the EEG over the cortical hand area in man. Neurosci. Lett. 174 (1), 93–96.

Phillips, C., Rugg, M.D., Friston, K.J., 2002. Systemic regularization of linear inverse solutions of the EEG source localization problem. Neuroimage 17, 287–301.

Rae-Grant, A., Blume, W., Breslau, C., Hachinski, V.C., Fisman, M., Merskey, H., 1987. The electroencephalogram in Alzheimer type dementia. A sequential study correlating the electroencephalogram with psycometric and quantitative pathological data. Arch. Neurol. 44, 50–55.

Rapoport, S.I., 1991. Positron emission tomography in Alzheimer's disease in relation to disease pathogenesis: a clinical review. Cerebrovasc. Brain Metab. Rev. 3, 297–335.

Rapoport, S.I., 1997. Discriminant analysis of brain imaging data identifies subjects with early Alzheimer's disease. Int. Psychogeriatr. 9, 229–235.

Rodriguez, G., Nobili, F., Rocca, G., DeCarli, F., Gianelli, M.V., Rosadini, G., 1998. Quantitative electroencephalography and regional cerebral blood flow: discriminant analysis between Alzheimer's patients and healthy controls. Dement. Geriatr. Cogn. Disord. 9, 238–274.

Rodriguez, G., Copello, F., Nobili, F., Vitali, P., Perego, G., Nobili, F., 1999a. EEG spectral profile to stage Alzheimer's disease. Clin. Neurophysiol. 110, 1831–1837.

Rodriguez, G., Nobili, F., Copello, F., Vitali, P., Gianelli, M.V., Taddei, G., Catsafados, E., Mariani, G., 1999b. 99mTcHMPAO regional Cerebral Blood Flow and quantitative Electroencephalography in Alzheimer's disease: a correlative study. J. Nucl. Med. 40, 522–529.

Rodriguez, G., Vitali, P., De Leo, C., De Carli, F., Girtler, N., Nobili, F., 2002. Quantitative EEG changes in Alzheimer patients during long-term donepezil therapy. Neuropsychobiology 46, 49–56.

Roman, G.C., Tatemichi, T.K., Erkinjuntti, T., Cummings, J.L., Masdeu, J.C., Garcia, J.H., Amaducci, L., Orgogozo, J.M., Brun, A., Hofman, A., et al., 1993. Vascular dementia: diagnostic criteria for research studies. Report of the NINDSAIREN International Workshop. Neurology 43 (2), 250–260.

Rosen, W.G., Terry, R.D., Fuld, P.A., Katzman, R., Peck, A., 1980. Pathological verification of ischemic score in differentiation of dementias. Ann. Neurol. 7 (5), 486–488.

Sachdev, P., Gaur, R., Brodaty, H., Walker, A., Meares, S., Koder, D., Haindl, W., 1997. Longitudinal study of cerebral blood flow in Alzheimer's disease using single photon emission tomography. Psychiatry Res. Neuroimag. 68, 133–141.

Saletu, B., Anderer, P., Saletu-Zyhlara, G.M., Pascual-Marqui, R.D., 2002. EEG topography and tomography in diagnosis and treatment of mental disorders: evidence for a key-lock principle. Methods Find. Exp. Clin. Pharmacol. (Suppl. D), 97–106.

Sannita, W.G., 1995. Cholinergic transmission and electrphysiological investigation of the uman visual system. In: Karmos, G., Molnar, M., Csepe, V., Czigler, I., Desmedt, J.E. (Eds.), Perspectives of Event-Related Potentials Research. EEG Suppl., vol. 44. Elsevier, Amsterdam, pp. 156–160.

Sannita, W.G., Balestra, V., Di Bon, G., Marotta, V., Rosadini, G., 1993. Human flash-VEP and quantitative EEG are independently affected by acute scopolamine. Electroencephalogr. Clin. Neurophysiol. 86, 275–282.

Schreiter-Gasser, U., Gasser, Th., Ziegler, P., 1993. Quantitative EEG-analysis in early onset Alzheimer's disease: a controlled study. Electroencephalogr. Clin. Neurophysiol. 86, 15–22.

Schreiter-Gasser, U., Gasser, T., Ziegler, P., 1994. Quantitative EEG analysis in early onset Alzheimer's disease: correlations with severity, clinical characteristics, visual EEG and CCT. Electroencephalogr. Clin. Neurophysiol. 90 (4), 267–272.

Sheridan, P.H., Sato, S., Foster, N., Bruno, G., Cox, C., Fedio, P., Chase, T.N., 1988. Relation of EEG alpha background to parietal lobe function in Alzheimer's disease as measured by positron emission tomography and psychometry. Neurology 38, 747–750.

Sloan, E.P., Fenton, G.W., Kennedy, N.S.J., MacLennan, J.M., 1995. Electroencephalography and single photon emission computed tomography in dementia: a comparative study. Psychol. Med. 25, 631–638.

Steriade, M., Llinas, R.R., 1988. The functional states of the thalamus and associated neuronal interplay. Physiol. Rev. 68, 649–742.

Stigsby, B., Johannesson, G., Ingvar, D.H., 1981. Regional EEG analysis and regional cerebral blood flow in Alzheimer's and Pick's diseases. Electroencephalogr. Clin. Neurophysiol. 51, 537–547.

Szava, S., Valdés, P., Biscay, R., Galán, L., Bosch, J., Clark, I., Jimenez, J.C., 1994. High resolution quantitative EEG analysis. Brain Topogr. 6, 211–219.

Szelies, B., Grond, M., Herholz, K., Kessler, J., Wullen, T., Heiss, W.D., 1992. Quantitative EEG mapping and PET in Alzheimer's disease. J. Neurol. Sci. 110, 46–56.

Szelies, B., Mielke, R., Kessler, J., Heiss, W.D., 1999. EEG power changes are related to regional cerebral glucose metabolism in vascular dementia. Clin. Neurophysiol. 110, 615–620.

Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Human Brain. Thieme, Stuttgart.

Valdés, P., Picton, T.W., Trujillo, N., Bosch, J., Aubert, E., Riera, J., 1998. Constraining EEG-MEG source imaging with statistical neuroanatomy. Neuroimage 4, 635.

Visser, S.L., Van Tilburg, W., Hoijer, C., Jonker, C., De Rijke, W., 1985. Visual evoked potentials (VEPs) in senile dementia (Alzheimer type) and in nonorganic behavioural disorders in the elderly; comparison with EEG parameters. Electroencephalogr. Clin. Neurophysiol. 60, 115–121.

Yao, D., He, B., 2001. A self-coherence enhancement algorithm and its application to enhancing three-dimensional source estimation from EEGs. Ann. Biomed. Eng. 29, 1019–1027.

Yesavage, J.A., Brink, T.L., Rose, T.L., Lum, O., Huang, V., Adey, M., Leirer, V.O., 1982–1983. Development and validation of a geriatric depression screening scale: a preliminary report. J. Psychiatr. Res. 17 (1), 37–49.

Wada, Y., Nanbu, Y., Yan-Jiang, Z., Koshino, Y., Yamaguchi, N., Hashimoto, T., 1997. Electroencephalographic abnormalities in patients with presenile dementia of the Alzheimer type: quantitative analysis at rest and during photic stimulation. Biol. Psychiatry 41, 217–225.