Sources of Cortical Rhythms in Adults During Physiological Aging: A Multicentric EEG Study

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Abstract: This electroencephalographic (EEG) study tested whether cortical EEG rhythms (especially delta and alpha) show a progressive increasing or decreasing trend across physiological aging. To this aim, we analyzed the type of correlation (linear and nonlinear) between cortical EEG rhythms and age. Resting eyes-closed EEG data were recorded in 108 young (Nyoung; age range: 18–50 years, mean age 27.3 ± 7.3 SD) and 107 elderly (Nold; age range: 51–85 years, mean age 67.3 ± 9.2 SD) subjects. The EEG rhythms of interest 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). EEG cortical sources were estimated by low-resolution brain electromagnetic tomography (LORETA). Statistical results showed that delta sources in the occipital area had significantly less magnitude in Nold compared to Nyoung subjects. Similarly, alpha 1 and alpha 2 sources in the parietal, occipital, temporal, and limbic areas had significantly less magnitude in Nold compared to Nyoung subjects. These nine EEG sources were given as input for evaluating the type (linear, exponential, logarithmic, and power) of correlation with age. When subjects were considered as a single group there was a significant linear correlation of age with the magnitude of delta sources in the occipital area and of

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alpha 1 sources in occipital and limbic areas. The same was true for alpha 2 sources in the parietal, occipital, temporal, and limbic areas. In general, the EEG sources showing significant linear correlation with age also supported a nonlinear correlation with age. These results suggest that the occipital delta and posterior cortical alpha rhythms decrease in magnitude during physiological aging with both linear and nonlinear trends. In conclusion, this new methodological approach holds promise for the prediction of dementia in mild cognitive impairment by regional source rather than surface EEG data and by both linear and nonlinear predictors. *Hum Brain Mapp 27:162–172, 2006.*

Key words: physiological aging; electroencephalography (EEG); alpha rhythm; low resolution brain electromagnetic tomography (LORETA)

INTRODUCTION

Quantitative analysis of electroencephalography (EEG) is a low-cost and useful neurophysiological approach to the study of physiological and pathological aging. Previous studies have shown that physiological aging in adults is associated not only with variations of scalp-evoked potentials [Yordanova et al., 1996, 1998, 2004], but also with gradual changes in the power of electroencephalographic (EEG) rhythms at rest [Christian, 1984; Marthis et al., 1980; Niedermeyer, 1993a–c; Obrist, 1954; Van Sweden, 1993; Wieneke et al., 1980].

Most studies have shown global "slowing" of EEG rhythms, pronounced power increase in the slow frequency ranges including delta (2–4 Hz) and theta (4–8 Hz) bands, and power decrease in the higher frequency range including alpha (8–12 Hz) and beta (>14 Hz) bands [Celesia, 1986; Christian, 1984; Ehlers and Kupfer, 1989; Klass and Brenner, 1995; Marsh and Thompson, 1977; Markand, 1990; Obrist, 1954, 1963]. However, changes in the low-frequency EEG power might depend on the cognitive status of the subjects selected as normals. A previous study reported an inverse correlation between delta/theta power and age in normal adults selected to exclude persons with slight cognitive deficits [Hartikainen et al., 1992].

Despite extensive previous evidence, the precise relationship between age and slowing of EEG rhythms is still a matter of debate, due to inconsistent study findings [Duffy et al., 1984; Giaquinto and Nolfe, 1986; Katz and Horowitz, 1982; Pollock et al., 1990]. In this framework, a previous study has shown that such a relationship might be strongly nonlinear at least for the alpha band [Senant et al., 1986]. In that study, a decrease of the alpha power from 20 to about 50 years of age and, surprisingly, an increase after 60 years was observed [Senant et al., 1986]. Discrepancies in the results of previous studies might be due to different methodological approaches including use of absolute vs. relative EEG power analysis, electrode references, and frequency band selection [Klimesch, 1999].

From a physiological point of view, EEG rhythms reflect opening-closure ("gating function") of functional 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]. These rhythms can be considered global functional indices of brain activity. Analysis of EEG rhythms across physiological and pathological aging might unveil fine relationships between age and modulation of the information flow among cortical and subcortical pathways.

In the present EEG study we tested whether cortical EEG rhythms (especially delta and alpha) show a progressive increasing or decreasing trend with physiological aging. To this aim, we analyzed the type of correlation (linear and/or nonlinear) between cortical EEG rhythms and age. Resting EEG data were recorded in a large population of 215 normal subjects ranging in age from 18–85 years. EEG rhythms were evaluated in selected bands from delta to beta. Cortical sources of the EEG rhythms were estimated by low-resolution brain electromagnetic tomography (LORETA) [Pascual-Marqui et al., 1994, 1999, 2002]. LORETA is a functional imaging technique estimating maximally smoothed linear inverse solutions accounting for distributed EEG sources within Talairach space [Pascual-Marqui et al., 2002]. This feature is of special importance for the comparison of EEG results with those of most structural and functional neuroimaging studies on elderly subjects. LORETA has been successfully used in recent EEG studies on pathological aging [Babiloni et al., 2004; Dierks et al., 2000].

SUBJECTS AND METHODS

Part of the procedures (EEG recordings and LORETA analysis) pertinent to the current study, as well as a description of the potential meaning of cortical rhythms in aging, have been extensively described recently [Babiloni et al., 2004]. However, it should be stressed that the aims of the previous and current studies are totally different. The previous study aimed at analyzing (1) the distributed EEG sources specific to mild Alzheimer's disease (AD) as compared to vascular dementia (VaD) or normal aging; and (2) the sensitivity of these sources to disease severity. In contrast, the current study focused on the distributed EEG sources across physiological aging, namely, in healthy young vs. healthy elderly subjects.

Subjects

For the present Italian multicenter EEG study, 108 young (Nyoung; age range: 18–50 years, mean age 27.3 ± 7.3 SD)

TABLE I. Anagraphic and neuropsychological data of interest of the present normal young (Nyoung) and normal elderly (Nold) subjects

	Nyoung	Nold
N	108	107
Age (yr), mean ± SD	27.3 ± 7.3	67.3 ± 9.2
Gender (F/M)	56/52	67/40
MMSE	30	28.5 ± 1.2
Education (yr), mean ± SD	15.9 ± 2.6	9.6 ± 4.2

and 107 elderly (Nold; age range: 51–85 years, mean age 67.3 ± 9.2 SD) subjects were enrolled. Local institutional ethics committees approved the study. All experiments were performed with the informed 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 authors' Institutional Review Board.

Inclusion/Exclusion Criteria

All Nold subjects underwent general medical, neurological, and psychiatric assessments. Standardized diagnostic assessment included the Mini-Mental State Evaluation [MMSE; Folstein et al., 1975], the Clinical Dementia Rating Scale [CDR; Hughes et al., 1982], the Geriatric Depression Scale [GDS; Yesavage. 1983], the Hachinski Ischemic Scale [HIS; Rosen et al., 1980], and the Instrumental Activities of Daily Living Scale [IADL; Lawton and Brodie, 1969]. All Nold subjects had MMSE scores greater than 27 and GDS scores lower than 14. Neuroimaging diagnostic procedures (CT or MRI) and complete laboratory testing were carried out to exclude subjects with AD, frontotemporal dementia, vascular dementia, and pseudo-depressive dementia. Absence of AD was defined according to NINCDS-ADRDA [McKhann et al., 1984] and DSM IV criteria.

Special attention was also devoted to exclude subjects with mild cognitive impairment (MCI) based on previous seminal studies [Albert et al., 1991; Devanand et al., 1997; Flicker et al., 1991; Petersen et al., 1995, 1997, 1999, 2001; Rubin et al., 1989; Zaudig, 1992]. The selected subjects presented no objective sign of cognitive deficits, especially in the memory domain, as ascertained by neuropsychological testing. Finally, subjects affected by chronic systemic illnesses (i.e., diabetes mellitus or organ failure) were excluded, as were subjects with alcohol and drug dependence.

Table I reports the mean values of relevant parameters of Nyoung and Nold subjects. Education was used as a covariate in the statistical evaluation of cortical sources of EEG rhythms to remove possible confounding effects.

EEG Recordings

EEGs were recorded in resting subjects (eyes-closed) by specialized clinical units familiar with the issue of vigilance in resting elderly subjects. In all subjects the state of vigilance was controlled by visual inspection of EEG traces during the recording session and subjects' drowsiness was avoided by verbal warnings. The EEG data were recorded (0.3–70 Hz bandpass) from 19 electrodes positioned according to the international 10–20 system (i.e., Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2). A specific kind of reference electrode was not used in all recording units, since the present preliminary data analysis and LORETA source analysis (reference free) were based on common average reference. To monitor eye movements, electrooculogram (0.3–70 Hz bandpass) was recorded. All data were digitized in continuous recording mode (5 min of EEG; 128–256 Hz sampling rate; the sampling rate was constant in each research unit of the present multicentric study).

Physical reference of the EEG recordings was re-referenced off-line to common average. The EEG data were analyzed and fragmented in consecutive epochs of 2 s. On average, 137 epochs for each subject were examined. For standardization purposes, the preliminary analysis of all data was performed at the EEG laboratories of the Department of Human Physiology and Pharmacology, University of Rome La Sapienza. EEG epochs with ocular, muscular, and other types of artifact were preliminarily identified by a computerized automatic procedure and the EEG epochs with ocular artifacts (<15% of the epochs) were corrected by an autoregressive method [Moretti et al., 2003]. Two independent experimenters visually confirmed the EEG segments accepted for further analysis.

Spectral Analysis of the 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 studied: 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]. This allowed better comparison of our results with the previous literature on dementia but it did not account for individual EEG markers such as the individual alpha and transition frequencies [Klimesch, 1999]. However, it should be noted that the present definition of alpha bands allowed the inclusion of the alpha frequency peaks of the large majority of both Nyoung and Nold subjects within the alpha 1 band (8–10.5 Hz). The mean alpha frequency peak was in fact 10.3 Hz (±1 SD) in the Nyoung and 9.5 Hz (±1.2 SD) in the Nold subjects. Moreover, in the evaluation of the EEG source power density across aging, the individual alpha frequency peak was used as a covariate [Klimesch, 1999].

Of note, we could not use narrower frequency bands for beta 1 (13–20 Hz) and beta 2 (20–30 Hz) because of the variability of beta peaks in the power spectra. The LORETA results for the beta bands could therefore suffer from the

sensitivity limitations of EEG spectral analyses for large bands [Szava et al., 1994].

Cortical Source Analysis of the EEG Rhythms by LORETA

As mentioned, the popular LORETA technique has been previously used for EEG source analysis [Pascual-Marqui et al., 1994, 1999, 2002]. LORETA computed 3D 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 2,394 voxels (7 mm resolution), each voxel containing an equivalent current dipole.

LORETA source analysis is reference-free in that one obtains the same LORETA source distribution for EEG data referenced to any reference electrode including common average. Furthermore, LORETA can be used from data collected by low spatial sampling of the 10–20 system (19 electrodes) when cortical sources are estimated from resting EEG rhythms. Several previous studies have shown that these rhythms are generated by largely distributed cortical sources that can be accurately investigated by the standard 10–20 system and LORETA [Anderer et al., 2000, 2003, 2004; Babiloni et al., 2004; Cincotti et al., 2003b, 2004; Isotani et al., 2001; Kawasaki et al., 2003; Laufer and Pratt, 2003a; Mulert et al., 2001; Sinai and Pratt, 2003; Tanaka et al., 2003a; Veiga et al., 2003; Winterer et al., 2001].

LORETA solutions consisted of voxel current density values able to predict EEG spectral power density at the scalp electrodes. To enhance the topographical results, "spatial" normalization was obtained by normalizing the LORETA current density at each voxel for the LORETA power density averaged across EEG frequencies and voxels of the brain volume. The general procedure fitted the LORETA solutions in a Gaussian distribution 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 the EEG data [Hernandez et al., 1994]. These methods are not available yet in the LORETA package, so they were not used here.

Solutions of the EEG inverse problem are underdetermined and ill-conditioned when the number of spatial samples (electrodes) is lower than that of the unknown samples (current density at each voxel). To account for that, the cortical LORETA solutions predicting scalp EEG spectral power density were regularized to estimate the distributed rather than the punctual EEG sources [Pascual-Marqui et al., 1994, 1999, 2002]. Such spatial smoothing of the LORETA solutions (resolution in centimeters) could reliably take into account the slight change in cortical volume (resolution in millimeters) present in elderly subjects.

TABLE II. LORETA Brodmann areas in 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.

In line with the low spatial resolution of the LORETA technique, we collapsed the LORETA solutions at frontal, central, temporal, parietal, and occipital regions of the brain model coded into Talairach space. The Brodmann areas listed in Table II formed each of these regions of interests (ROIs). Of note, the main advantage of the regional analysis of LORETA solutions was that our modeling could disentangle rhythms of contiguous cortical areas. For example, the rhythms of the occipital source were disentangled with respect to those of the contiguous parietal and temporal sources, etc. This was made possible by the fact that LORETA solves the linear inverse problem by taking into account the well-known effects of the head as a volume conductor. With respect to other procedures of data reduction, this type of lobar approach may represent an important reference for multimodal comparisons with structural and functional neuroimaging methods (SPECT, PET, surface EEG/MEG topography). Finally, it can be stated that the present approach represents a clear methodological improvement compared to surface electrodes EEG spectral analyses. Indeed, the EEG potentials collected at each scalp electrode are strongly affected by head volume conductor effects. For example, occipital electrodes collect scalp potentials generated not only from the occipital cortex but also from parietal and temporal cortices due to head volume conductor effects.

Statistical Analysis of the LORETA Solutions

Regional normalized LORETA solutions from the Nyoung and Nold subjects were used as dependent variables for analysis of variance (ANOVA) using subjects' education and individual alpha frequency peak [IAF; Klimesch, 1999] as covariates. To test the working hypothesis, the ANOVA factors (levels) were Group (Nyoung, Nold; between factor), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (central, frontal, parietal, occipital, temporal, limbic). Mauchly's test evaluated the sphericity assumption. Correction of the degrees of freedom was made with the Greenhouse-Geisser procedure. Tukey's test was used for post-hoc comparisons ($P < 0.05$). Post-hoc testing was planned in order to focus on between-group but not on within-group differences in magnitude of the LORETA solutions (i.e., Nyoung vs. Nold subjects). In this sense we accepted ANOVA statistical differences that included the factor group.

The LORETA solutions showing significant differences between Nyoung and No1d subjects were evaluated as type (linear and/or nonlinear) of correlation with age in all subjects as a whole group. The linear correlation was computed with the Pearson test (Bonferroni-corrected, $P < 0.05$). The nonlinear correlations were computed evaluating the coefficient of determination r^2 for exponential, logarithmic, and power functions. The r^2 value was computed with the following mathematical formula:

$$r^2 = 1 - (SSE/SST)$$

where:

$$SSE = \Sigma(y_i - ¥_i) \quad \text{and} \quad SST = (\Sigma y_i^2) - ((\Sigma y_i)^2/n)$$

where n is the number of samples (i.e., subjects), y_i is the real value and $¥_i$ is the approximated value calculated with the following formula:

$¥_i = c \ln x_i + b$ for logarithmic functions (c, b constant)

$¥_i = c\, e_i^{bx}$ for exponential functions (c, b constant)

$¥_i = c\, x_i^b$ for power functions (c, b constant)

Finally, r^2 of the nonlinear simple functions was compared with r^2 of the linear function, to evaluate the prevalence of linear or nonlinear EEG correlations between regional LORETA solutions and physiological aging.

RESULTS

Topography of the EEG Cortical Sources Estimated by LORETA

Figure 1 maps the grand average of the LORETA solutions (i.e., relative current density at cortical voxels) modeling the distributed EEG sources for delta, theta, alpha 1, alpha 2, beta 1, and beta 2 bands in the Nyoung and Nold groups. The Nyoung group presented alpha 1 and alpha 2 sources with maximal values of the relative current density distributed in the parieto-occipital regions. Delta and theta sources had moderate relative current density values compared to the alpha sources. Finally, beta 1 and beta 2 sources were characterized by the lowest relative current density values. Compared to the Nyoung group, the Nold group showed a clear reduction of the relative current density of the delta sources in occipital area and of the alpha 1 and alpha 2 sources in limbic, temporal, occipital, and parietal areas.

Statistical Analysis of the EEG Cortical Sources Estimated by LORETA

Figure 2 shows the mean regional LORETA solutions (distributed EEG sources) relative to a statistical ANOVA interaction ($F(25,5325) = 16.7$; $MSe = 0.814$; $P < 0.00001$) among the factors Group (Nyoung, Nold), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (central, frontal, parietal, occipital, temporal, limbic). In the figure, the LORETA solutions had the shape of EEG relative power spectra. Notably, profile and magnitude of these spectra in the Nyoung and Nold groups differed in the diverse cortical regions, thus supporting the idea that scalp EEG rhythms are generated by a distributed pattern of cortical sources. Tukey's post-hoc test assessing the differences in the regional LORETA solutions between Nyoung and Nold subjects showed that delta sources in the occipital area showed stronger amplitude in the Nyoung compared to the Nold group ($P < 0.04$). Furthermore, alpha 1 and alpha 2 sources in parietal, occipital, temporal, and limbic areas showed stronger amplitude in the Nyoung compared to the Nold group ($P < 0.00003$).

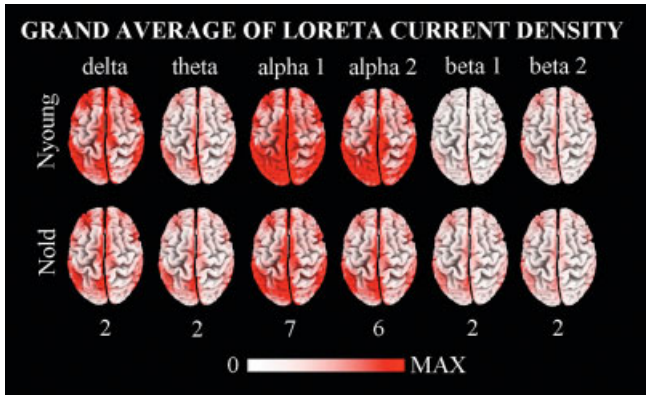

Figure 1.
Grand average of LORETA solutions (i.e., normalized relative current density at the cortical voxels) modeling the distributed EEG sources for delta, theta, alpha 1, alpha 2, beta 1, and beta 2 bands in Nyoung and Nold groups. Left side of the maps (top view) corresponds to the left hemisphere. LORETA, low-resolution brain electromagnetic tomography. Color scale: all power estimates were scaled based on the averaged maximum value (i.e., alpha 1 power value of occipital region in Nyoung). The maximal value of power is reported under each column. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

The nine cortical sources (current density values) discriminating the two groups were used in linear correlation analyses with age in the whole group of subjects (Pearson test; Bonferroni correction for nine test repetitions gave a threshold of $P < 0.00556$ to obtain the Bonferroni-corrected $P < 0.05$). Figure 3 shows the scatterplots of the statistically significant correlations between individual LORETA solutions and age of the statistically significant correlations (uncorrected $P < 0.00556$). Age correlated negatively with occipital delta sources ($r = -0.25$, uncorrected $P = 0.0001$) and with occipital ($r = -0.29$, uncorrected $P = 0.00001$), and limbic ($r = -0.24$, uncorrected $P = 0.0003$) alpha 1 sources. Similarly, age correlated negatively with parietal ($r = -0.31$, uncorrected $P = 0.00001$), occipital ($r = -0.43$, uncorrected P

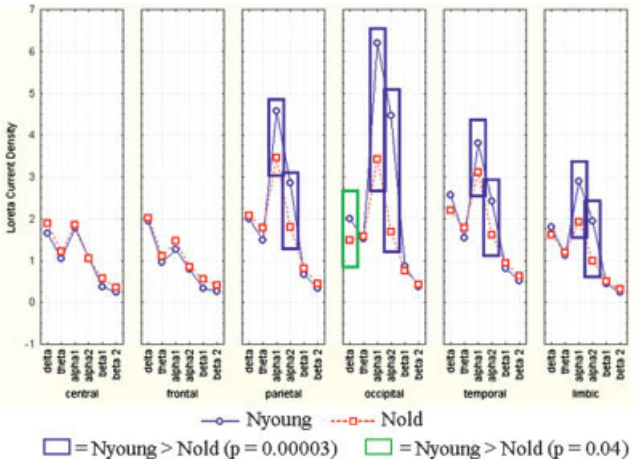

Figure 2.

Regional LORETA solutions (mean across subjects) relative to a statistical ANOVA interaction among factors Group (Nyoung, Nold), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (central, frontal, parietal, occipital, temporal, limbic). This ANOVA design used the normalized relative current density values of the LORETA solutions at the ROI level as a dependent variable. Regional LORETA solutions modeled EEG relative power spectra as revealed by "virtual" intracranial macroelectrodes "placed" on the macrocortical regions of interest. Rectangles indicate the cortical regions and frequency bands in which LORETA solutions presented statistically significant differences between Nyoung and Nold groups ($P < 0.05$, planned Tukey post-hoc testing). See Subjects and Methods for further details. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

= 0.000001), temporal (r = −0.28, uncorrected $P = 0.00002$), and limbic (r = −0.38, uncorrected $P = 0.000001$) alpha 2 sources.

Table III reports the coefficient of the r^2 determination between individual regional LORETA solutions and age in all Nyoung and Nold subjects considered as a single group. Only the nine EEG sources showing statistically significant differences between Nyoung and Nold groups were considered. The r^2 value is reported for linear, exponential, logarithmic, and power functions. In general, r^2 values for linear, exponential, logarithmic, and power functions were quite similar. No clear predominance of nonlinear or linear values was observed.

DISCUSSION

The aim of the present EEG study was to verify whether, in normal subjects, EEG cortical rhythms (especially delta and alpha) show a progressive increasing or decreasing trend with age. To this aim we analyzed linear and nonlinear correlations between EEG cortical sources and age. Nonlinear functions included only simple functions such as logarithmic, exponential, and power ones, since the scatterplot distribution of the data discouraged complex nonlinear functions such as polynomial ones.

The present results showed that physiological aging in adults mainly induces a decrease in magnitude of delta (2–4 Hz) sources in occipital area and of low- (8–10.5 Hz) and high-band (10.5–13 Hz) alpha sources in parietal, occipital, temporal, and limbic areas. For the occipital delta source this decrease linearly correlated with age. Similarly, for the low-band alpha sources this decrease linearly correlated with the age in occipital and limbic areas. For the high-band alpha sources, a similar linear correlation with age was also computed in parietal, occipital, temporal, and limbic areas. However, the present EEG sources showing significant linear correlation with age also unveiled a nonlinear (exponential, logarithmic, and power) correlation with age.

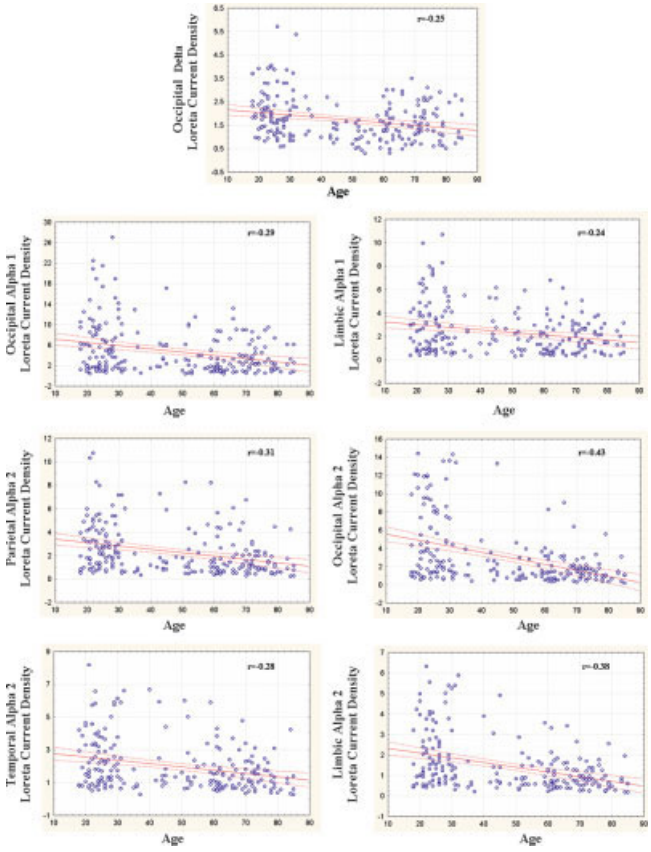

Figure 3.

Scatterplots between individual regional LORETA solutions and age in all Nyoung and Nold subjects considered as a single group. These solutions refer to the EEG sources showing a statistically significant difference in magnitude between Nold and Nyoung groups, namely, occipital delta source as well as occipital, and limbic alpha 1 source as well as parietal, occipital, temporal, and limbic alpha 2 sources. Results of the linear correlation (Pearson test, Bonferroni-corrected at $P < 0.05$) between individual regional LORETA solutions and age are reported in the diagrams. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE III. Correlation between LORETA current density and age (coefficient of determination r^2)

	Linear	Logarithmic	Exponential	Power
Occipital delta LORETA current density	0.07	0.08	0.06	0.08
Parietal alpha 1 LORETA current density	0.03	0.03	0.02	0.02
Occipital alpha 1 LORETA current density	0.09	0.09	0.07	0.07
Temporal alpha 1 LORETA current density	0.01	0.01	0.01	0.01
Limbic alpha 1 LORETA current density	0.06	0.06	0.04	0.04
Parietal alpha 2 LORETA current density	0.1	0.1	0.12	0.12
Occipital alpha 2 LORETA current density	0.18	0.19	0.2	0.2
Temporal alpha 2 LORETA current density	0.08	0.08	0.09	0.08
Occipital alpha 1 LORETA current density	0.14	0.14	0.16	0.16

Correlation between individual regional LORETA solutions and age in all Nyoung and Nold subjects considered as a single group
The r^2 value is reported for linear, exponential, logarithmic, and power function. Of note, only the regional LORETA solutions showing statistically significant differences between Nyoung and Nold groups were considered.

The present results also revealed that, even if statistically significant (up to $P = 0.00003$), the absolute values of the linear correlation were not very high (ranging from $r = 0.24$ to $r = 0.43$). Similar correlative values were obtained with nonlinear procedures. These results indicate that focusing on dual relationships between a single EEG cortical source and physiological aging may be insufficient to model effects of aging on cortical rhythms. This is true even if both linear and nonlinear trends are taken into account. It can be speculated that variance of the correlative data might be explained by considering complex relationships among EEG cortical sources and physiological aging. Future studies using artificial neural networks might reveal that outlier subjects having paradoxical low posterior alpha source activity together with a young age may be characterized by peculiar combinations of several cortical sources and physiological aging, namely, low posterior alpha but high posterior delta together with young age. This may be crucial to enhance the predictive value of such a quantitative EEG analysis for clinical application in the field of physiological and pathological aging.

These results extend in spatial-frequency detail previous EEG evidence on physiological aging that pointed to a distributed decrease of the alpha power at extended (8–13 Hz) alpha band [Christian, 1984; Obrist, 1954, 1963; Marsh and Thompson, 1977; Celesia. 1986; Ehlers and Kupfer, 1989; Markand, 1990; Klass and Brenner, 1995].

From a physiological point of view, the effects of physiological aging on posterior alpha rhythms are not surprising. The posterior alpha rhythms reflect the activity of dominant oscillatory neural networks in resting adults and represent a very global functional feature of the working brain [Klimesch, 1999]. These rhythms are mainly modulated by thalamo-cortical and cortico-cortical interactions facilitating/inhibiting 1) the transmission of sensorimotor information between subcortical and cortical pathways, and 2) the retrieval of semantic information from cortical storage [Brunia, 1999; Pfurtscheller and Lopes da Silva, 1999; Steriade and Llinas, 1988]. High-voltage alpha rhythms in the resting condition are usually considered a sign of healthy brain activity during relaxed wakefulness. The low-band alpha rhythms would be mainly related to a subject's global attentional readiness, whereas the high-band alpha rhythms would reflect the oscillation of specific neural systems for the elaboration of sensorimotor or semantic information [Klimesch, 1996; Klimesch et al., 1997, 1998]. At rest, the voltage of the alpha rhythms would be inversely correlated with the cortical excitability and level of attention processes depending on the novelty and importance of stimulus. For this reason, it has been suggested that the amplitude of alpha rhythms and corresponding cortical excitability reflect at least in part the time-varying inputs of forebrain cholinergic pathways [Ricceri et al., 2004]. These concepts constitute an important element of the current theory on the functional meaning of alpha rhythms.

Keeping in mind the mentioned concepts on the functional meaning of alpha rhythms, the present results can be explained as follows: Across physiological aging the decreased magnitude of the posterior alpha sources might be associated with very early changes in the functioning of the cholinergic basal forebrain system, which is supposed to induce a sustained increase of the excitatory activity in the cholinergic brainstem pathway [Kobayashi and Tadashi, 2002; Sarter and Bruno, 1997, 1998]. As a consequence, the thalamocortical excitability would slightly desynchronize the resting alpha rhythms at the cortical level [Muzur et al., 2002], producing a mild enhancement of cortical excitability. In line with this explanation, previous studies have shown that resting EEG rhythms around alpha are lowered in magnitude by experimentally induced impairment of the cholinergic pathways stemming from the basal forebrain [Holschneider et al., 1998; Mesulam, 2004]. Furthermore, previous EEG evidence has indicated a decrease of the alpha power in MCI and mild AD subjects, who are supposed to suffer from an impairment of cholinergic basal forebrain [Babiloni et al., 2004; Dierks et al., 1993, 2000; Frodl et al., 2002; Grunwald et al., 2001; Huang et al., 2000; Jelic et al., 1996, 2000; Moretti et al., 2004; Rodriguez et al., 1999a,b]. Finally, it has been demonstrated that cholinergic basal forebrain but not cholinergic brainstem innervations are impaired in AD [Geula and Mesulam, 1989, 1996, 1999; Mash et al., 1985; Mesulam, 2004; Tanaka et al., 2003b].

From a functional point of view, the reduced magnitude of the posterior alpha sources across normal aging suggests

progressive linear changes of the thalamo-cortical and cortico-cortical systems impinging upon visual-spatial attention. This explanation is in line with the well-known clinical findings of an increase of visual-spatial deficits from MCI to mild AD [Arnaiz and Almkvist, 2003; Wang and Zhou, 2002]. In parallel, the limbic sources of alpha activity point to progressive changes across physiological aging of the thalamo-cortical and cortico-cortical systems regulating the attentional tone for memorization [Wolf et al., 2003].

It can be argued that the reduced magnitude of the cortical alpha rhythms across physiological aging was merely due to slowing of the alpha frequency peak, defined as the frequency associated with the strongest EEG power in the extended alpha range. Indeed, a clear slowing of the alpha frequency peak in normal adults during physiological aging has been reported [Kopruner et al., 1988; Klimesch, 1999]. In contrast, another study has shown that such a slowing was nonsignificant across physiological aging but was evident only between 60 and 80 years [Duffy et al., 1984]. Finally, a trend has also been demonstrated towards a reduction of alpha power with age, partly due to the effects of low education in the oldest subjects [Hartikainen et al., 1992]. With reference to this issue, it is improbable that the present results on alpha source power can be explained as an effect of the slowing of the alpha frequency peak and of differences in education across aging. In the vast majority of our young and elderly subjects the alpha frequency peak was observed in the low-band alpha range (8–10.5 Hz). Furthermore, effects of aging were observed on the alpha source power with similar magnitude for both low-band and high-band alpha rhythms but not for the contiguous theta rhythms (4–8 Hz). This is clearly incompatible with the claim that, across aging, these effects are due to a transition of alpha frequency peak towards the theta range. Finally, in our study alpha frequency peak and education were used as covariates in group comparisons of the alpha source power between Nyoung and Nold.

The decrease of occipital delta EEG sources with age contradicts previous EEG evidence showing a power increase at delta (2–4 Hz) and theta (4–8 Hz) bands other than the well-known strong power decrease at alpha bands [Celesia. 1986; Christian, 1984; Ehlers and Kupfer, 1989; Marsh and Thompson, 1977; Obrist, 1954, 1963; Markand, 1990; Klass and Brenner, 1995]. However, although less frequently, age has been reported to inversely relate to the amount of delta/theta, indicating that the amount of slow activity in quantitative EEG does not increase with age in the context of good health status [Hartikainen et al., 1992]. In one study the subjects' cognitive status was evaluated after 2 years [Hartikainen et al., 1992] and deterioration in learning ability at the follow-up correlated with an increase in delta activity in seven of the subjects. Keeping in mind these data, a tentative explanation of the present findings might be that a significant magnitude increase of low-band EEG sources is not a marker of physiological aging. Rather, it may be a marker of subclinical cognitive deterioration in physiological aging. This explanation is based on the fact that the subjects in our study were carefully selected to exclude persons having early cognitive decline compatible with MCI, early mild AD, vascular and/or extrapyramidal comorbidity. Furthermore, the explanation is compatible with the fact that, compared to normal subjects, delta and/or theta rhythms do increase even in the earlier stages of AD [Schreiter-Gasser et al., 1994] and seem to predict disease progression [Ihl et al., 1996; Nobili et al., 1999]. In addition, MCI subjects also have shown an increase of the theta (4–7 Hz) power [Grunwald et al., 2001; Jelic et al., 1996; Zappoli et al., 1995] and decrease of the alpha power [Frodl et al., 2002; Grunwald et al., 2001, 2002; Huang et al., 2000; Jelic et al., 1996; Zappoli et al., 1995]. It is noteworthy that these EEG parameters have presented an intermediate magnitude in MCI subjects with respect to those observed in Nold and dementia patients [Elmstahl and Rosen, 1997; Huang et al., 2000; Jelic et al., 2000].

CONCLUSIONS

This electroencephalographic (EEG) study tested whether cortical EEG rhythms (especially delta and alpha) show a progressive increasing or decreasing trend across physiological aging. To this end, we analyzed the type of correlation (linear and nonlinear) between cortical EEG rhythms and age. Statistical results showed that delta sources in the occipital area had significantly ($P = 0.04$) less magnitude in the Nold compared to the Nyoung subjects. Similarly, the alpha 1 and alpha 2 sources in the parietal, occipital, temporal, and limbic areas had significantly ($P = 0.00003$) less magnitude in the Nold compared to the Nyoung subjects. These nine EEG sources were given as an input for the evaluation of the type (linear, exponential, logarithmic, and power) of correlation with age. In the subjects considered as a single group, there was a significant linear correlation with age of the magnitude of delta sources in the occipital area and of alpha 1 sources in the occipital and limbic areas. The same was true for the alpha 2 sources in parietal, occipital, temporal, and limbic areas. The EEG sources showing significant linear correlation with age also pointed to a strong nonlinear correlation with age. On the whole, the present results suggest that occipital delta and posterior cortical alpha rhythms showed a progressive decrease with age with both linear and nonlinear components. This new methodological approach holds promise for the prediction of dementia in mild cognitive impairment by regional source rather than surface EEG data and by both linear and nonlinear predictors.

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