White Matter Vascular Lesions Are Related to Parietal-to-Frontal Coupling of EEG Rhythms in Mild Cognitive Impairment

Claudio Babiloni,^{1,2,3,4} Giovanni B. Frisoni,^{2,3*} Michela Pievani,²
Fabrizio Vecchio,^{1,3,4} Francesco Infarinato,¹ Cristina Geroldi,²
Serenella Salinari,⁵ Raffaele Ferri,⁶ Claudia Fracassi,²
Fabrizio Eusebi,^{1,7,8} and Paolo M. Rossini^{2,3,9}

¹Dip. Fisiologia Umana e Farmacologia, University "La Sapienza", Rome, Italy

²IRCCS "S. Giovanni di Dio-F.B.F.", Brescia, Italy

³A.Fa.R., Dip. Neurosci. Osp. FBF; Isola Tiberina, Rome, Italy

⁴San Raffaele Cassino, Tosinvest Sanità, Cassino (FR), Italy

⁵Department of Informatics and Systems, University "La Sapienza", Rome, Italy

⁶Department of Neurology, Oasi Institute for Research on Mental Retardation and Brain Aging (IRCCS), Troina, Italy

⁷Istituto di Medicina e Scienza Dello Sport-CONI, Rome, Italy

⁸Neuromed IRCCS, Isernia, Italy

⁹Clinical Neurology, University "Campus Biomedico" Rome, Italy

Abstract: Do cerebrovascular and Alzheimer's disease (AD) lesions represent additive factors in the development of mild cognitive impairment (MCI) as a putative preclinical stage of AD? Here we tested the hypothesis that directionality of fronto-parietal functional coupling of electroencephalographic (EEG) rhythms is relatively preserved in amnesic MCI subjects in whom the cognitive decline is mainly explained by white-matter vascular load. Resting EEG was recorded in 40 healthy elderly (Nold) and 78 amnesic MCI. In the MCI subjects, white-matter vascular load was quantified based on magnetic resonance images (0–30 visual rating scale). EEG rhythms of interest were δ (2–4 Hz), θ (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). Directionality of fronto-parietal functional coupling of EEG rhythms was estimated by directed transfer function software. As main results, (i) fronto-parietal functional coupling of EEG rhythms was higher in magnitude in the Nold than in the MCI subjects; (ii) more interestingly, that coupling was higher at θ , $\alpha 1$, $\alpha 2$, and $\beta 1$ in MCI V+ (high vascular load; $N = 42$; MMSE = 26) than in MCI V– group (low vascular load; $N = 36$; MMSE = 26.7). These results are interpreted as supporting the additive model according to which MCI state would result from the combination of cerebrovascular and neurodegenerative lesions. *Hum Brain Mapp* 29:1355–1367, 2008. © 2007 Wiley-Liss, Inc.

Key words: mild cognitive impairment; Alzheimer's disease; electroencephalography; magnetic resonance imaging; white-matter vascular lesion; Walhund scale

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*Correspondence to: Giovanni B. Frisoni, IRCCS "S. Giovanni di Dio-F.B.F.", Brescia, Via Pilastroni 1, 25125 Brescia, Italy.
E-mail: gfrisoni@fatebenefratelli.it

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INTRODUCTION

It has been shown that modifications of resting electroencephalogram (EEG) rhythms can be observed during pathological aging. When compared to healthy elderly (Nold) subjects, Alzheimer's disease (AD) patients have been characterized by high power of δ (0–4 Hz) and θ (4–7 Hz) rhythms, and low power of posterior α (8–12 Hz) and/or β (13–30 Hz) rhythms [Babiloni et al., 2004a; Dierks et al., 1993, 2000; Huang et al., 2000; Jeong, 2004; Ponomareva et al., 2003; Prichep et al., 2005]. These EEG abnormalities have been associated with altered regional cerebral blood flow/metabolism and with impaired global cognitive function, as evaluated by mini mental state examination [MMSE; Jeong, 2004; Rodriguez et al., 1998, 1999a,b; Sloan et al., 1995]. Furthermore, posterior α rhythms have shown a power decrement even in subjects with amnesic mild cognitive impairment (MCI), a clinical state between elderly normal cognition and dementia, which is characterized by the objective evidence of memory deficit either isolated or combined with other cognitive impairment [Babiloni et al., 2006b; Elmstahl and Rosen, 1997; Huang et al., 2000; Jelic et al., 2000; Koenig et al., 2005; Zappoli et al., 1995]. More recently, it has been tested the hypothesis that the amplitude of EEG rhythms, which are affected by AD processes, are relatively preserved in amnesic MCI subjects in whom the cognitive decline is mainly explained by white-matter vascular load [Babiloni et al., submitted for publication]. In the MCI subjects, white-matter vascular load was quantified based on magnetic resonance images (0–30 visual rating scale). As main results, power of parietal α rhythms were higher in MCI V+ (high vascular load) than in MCI V– group (low vascular load), i.e. the more severe the white matter lesions, the higher the parietal α source power. Those results were in line with the additive model of cognitive impairment, postulating that the cognitive impairment arises as the sum of neurodegenerative and cerebrovascular lesions [Nagy et al., 1997; Snowden et al., 1997; Zekry et al., 2002].

Despite the converging evidence of abnormal cortical EEG rhythms in MCI and AD, EEG power alone does not reliably predict conversion from MCI to dementia. A reasonable hypothesis is that the amplitude of EEG rhythms per se does not capture one of the main features of AD, namely the impairment of functional neural connectivity. In this vein, it has been reported that AD patients present an abnormal linear coupling of EEG rhythms between cortical regions, as revealed by spectral EEG coherence [Adler et al., 2003; Jelic et al., 1997; Knott et al., 2000; Locatelli et al., 1998; O'Connor et al., 1979; Wada et al., 1998a,b]. Such a coherence denotes linear temporal synchronicity of coupled EEG rhythms, as a reflection of neural sources whose firing is oscillating with a nearly identical timing and phase. It has been proposed that functional coupling of cortical rhythms is related to brain processes involving the coupled sources and is modulated by cholinergic systems [Xiang et al., 1998]; AD is characterized by a disruption

of basal forebrain cholinergic inputs to cortex and hippocampus [Mesulam, 2004]. This is why a decrease of cortical EEG coherence might be a sensible and reliable marker of AD.

Most of the EEG studies in AD reported prominent decrease of EEG or magnetoencephalographic (MEG) α -band coherence [Adler et al., 2003; Berendse et al., 2000; Besthorn et al., 1994; Jelic et al., 1997, 2000; Knott et al., 2000; Leuchter et al., 1987, 1992; Locatelli et al., 1998; O'Connor et al., 1979; Wada et al., 1998a,b]. α coherence reduction in AD has also been found to be associated with an allelic pattern of ApoE genetics risk, which is supposed to be mediated by cholinergic deficit [Jelic et al., 1997]. δ and θ coherence provided less straightforward findings. Some studies have shown a decrement of slow-band EEG coherence in AD patients [Adler et al., 2003; Dunkin et al., 1994; Gonzalez et al., 2004; Leuchter et al., 1992], whereas others have reported its increase [Brunovsky et al., 2003; Locatelli et al., 1998; Rossini et al., in press]. To improve the evaluation of EEG functional coupling, EEG or MEG data have been analyzed with several procedures inspired by the theory of nonlinear dynamical systems [Arnhold et al., 1999; Le Van Quyen et al., 1998; Schiff et al., 1996; Schreiber, 1999]. Among them, the so-called "synchronization likelihood" combines sensitivity to linear and nonlinear functional coupling of EEG/MEG rhythms [Stam and van Dijk, 2002] being significantly decreased at 10–12 Hz, 14–18 Hz, and 18–22 Hz bands in AD patients when compared to MCI and/or Nold subjects [Babiloni et al., 2004a, 2006a; Pijnenburg et al., 2004; Stam and van Dijk, 2002; Stam et al., 2003a]. Global synchronization likelihood has been found to be lower in mild AD than in Nold subjects at the upper α (10–14 Hz), upper β (18–22 Hz), and γ (22–40 Hz) MEG bands [Stam et al., 2002].

Both spectral coherence and synchronization likelihood have an important limitation: they do not reflect the direction of the information flux within the functional coupling of EEG/MEG rhythms at paired brain sites. One can overcome this limitation by the computation of the directed transfer function [DTF; Kaminski and Blinowska, 1991]. DTF has been proven to be reliable for the modeling of directional information flux within linear EEG functional coupling, as an intrinsic feature of cerebral functional connectivity [Kaminski et al., 1997; Korzeniewska et al., 1997; Mima et al., 2000]. For instance, pre-sleep period is characterized by parietooccipital-to-frontal direction of the cortical information flow, while the opposite holds at sleep onset [De Gennaro et al., 2004]. After selective slow-wave sleep deprivation, the frontal-to-parietooccipital direction shows up in the pre-sleep period [De Gennaro et al., 2005]; and it has been demonstrated that interhemispheric directional flow varies as a function of the state of consciousness (from pre-sleep to early sleep stages) and in relation to different cerebral areas [Bertini et al., 2007]. Concerning the functional role of intrinsic directional connectivity in cognition, a dominant parietal to frontal directional flux within EEG coupling has been reported in healthy awake

subjects during visuo-spatial information processing [Babiloni et al., 2004c, 2006b]. Across pathological aging, it has been shown a reduction of parietal-to-frontal directional information flux within EEG functional coupling in both MCI and mild AD subjects compared to Nold subjects, in line with the idea of a common pathophysiological background linking these conditions [Babiloni et al., pending moderate revision].

In the present study, we tested the hypothesis that directionality of fronto-parietal functional coupling of EEG rhythms, which are affected by AD processes, are relatively preserved in amnesic MCI subjects in whom the cognitive decline is mainly explained by white-matter vascular load (as revealed by MRI). Resting EEG was recorded in Nold and amnesic MCI subjects, while the directionality of fronto-parietal functional coupling of EEG rhythms was estimated by DTF.

METHODS

Subjects and Diagnostic Criteria

In this study, 80 amnesic MCI subjects were enrolled. Furthermore, 40 cognitively normal elderly (Nold) subjects were recruited to form control group. These individual data sets were used for the mentioned parallel EEG studies [Babiloni et al., Submitted for Publication] in which we evaluated the relationships between the power (but not the functional coupling) of EEG rhythms and white-matter vascular load.

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 Author's Institutional Review Board.

The present inclusion and exclusion criteria for amnesic MCI were based on previous seminal studies [Albert et al., 1991; Devanand et al., 1997; Flicker et al., 1991; Petersen et al., 1995, 1997, 2001; Portet et al., 2006; Rubin et al., 1989; Zaudig, 1992], which defined MCI as the condition in which elderly persons do not meet criteria for a diagnosis of dementia but present an objective memory deficit. The inclusion criteria for MCI were the following: (i) objective memory impairment on neuropsychological evaluation, as defined by performances ≥ 1.5 standard deviation below the mean value of age and education-matched controls for a test battery including Busckhe-Fuld and Memory Rey tests; (ii) normal activities of daily living as documented by the history and evidence of independent living; and (iii) clinical dementia rating score of 0.5. The exclusion criteria for MCI included: (i) mild AD; (ii) evidence of concomitant dementia such as frontotemporal, vascular dementia, reversible dementias (including pseudo-depressive dementia), fluctuations in cognitive performance, and/or features of mixed dementias; (iii) evidence of concomitant extra-pyramidal symptoms; (iv) clinical and indirect evi-

dence of depression as revealed by geriatric depression scale scores higher than 13; (v) other psychiatric diseases, epilepsy, drug addiction, alcohol dependence, and use of psychoactive drugs including acetylcholinesterase inhibitors or other drugs enhancing brain cognitive functions; and (vi) current or previous uncontrolled or complicated systemic diseases (including diabetes mellitus) or traumatic brain injuries.

The Nold subjects were recruited mostly among non-sanguineous patients' relatives. All Nold subjects underwent physical and neurological examinations as well as cognitive screening. Subjects affected by chronic systemic illnesses, subjects receiving psychoactive drugs, and subjects with a history of present or previous neurological or psychiatric disease were excluded. All Nold subjects had a geriatric depression scale score lower than 14 (no depression).

Magnetic Resonance Imaging

High-resolution sagittal T1-weighted volumetric magnetic resonance images (MRIs) were acquired in MCI subjects using a 1.0 T Magnetom scanner (Siemens, Erlangen, Germany), with a gradient echo 3D technique: TR = 10 ms, TE = 4 ms, TI = 300 ms, flip angle = 10°, field of view = 250 mm, acquisition matrix 160 × 256, and a slice thickness of 1.3 mm.

To rate the subcortical vascular lesions (SVLs), a single operator visually assessed digital MRI images of MCI subjects [Geroldi et al., 2006]. Inter-rater reliability calculated with weighted k value was 0.67, indicative of moderate agreement (ref Wahlund). We assessed test-retest reliability on a random sample of 20 subjects. The intraclass correlation coefficient was 0.98, values above 0.80 being considered indicative of good agreement. The inter-rater reliability of that expert operator was equal or higher than $r = 0.95$. The SVLs were scored separately for the right and left hemispheres. In each hemisphere, five regions of interest were taken into account, namely the frontal, temporal, parieto-occipital, basal ganglia, cerebellum, and subtentorial areas. Each region of interest received one of the following scores: 0 (no lesion), 1 (focal lesions), 2 (beginning confluence of lesions), or 3 (diffuse involvement of the entire region). This means that each hemisphere could reach a maximum score of 15 and the total maximum score for both hemispheres was 30. Subcortical vascular disease (SVD) was considered as present when the Wahlund [Geroldi et al., 2006] scale total score was 6 or more, or when beginning confluence of lesions (score 2) was observed in at least one region. The MRI data of a MCI subject could not be used for technical problems. Another MCI subject was not further considered due to an abnormal EEG spectrum (exceeding three standard deviations from the mean scalp EEG power of the MCI group). In total, 78 MCI subjects were further considered for the DTF analysis.

TABLE I. Demographic and neuropsychological data of healthy elderly (Nold) and mild cognitive impairment (MCI) subjects

	MCI V–	MCI V+	Nold
Subject	36	42	40
MMSE	26.7 ± 0.3	26.0 ± 0.3	28.4 ± 0.2
Age	68.5 ± 1.3	72.6 ± 1.0	69.1 ± 1.1
Education	7.7 ± 0.7	7.1 ± 0.5	7.6 ± 0.5
IAF	9.4 ± 0.2	9.3 ± 0.2	9.4 ± 0.1
Female/Male	23/13	23/19	22/18

Of note, MCI group was divided in two subgroups: MCI subjects with low degree of lesion of the white matter (MCI V–, score of Wahlund scale <3) and MCI subjects with high degree of lesion of the white matter (MCI V+, score of Wahlund scale ≥3).

Composition of the Experimental Groups of MCI Subjects

Based on the Wahlund scale score, the MCI subjects were subdivided in two subgroups: 36 with low degree of white-matter lesion (MCI V–, score of Wahlund scale <3) and 42 with higher degree of white-matter lesion (MCI V+, score of Wahlund scale ≥3). The two subgroups of MCI subjects were comparable for demographic and clinical features. Table I summarizes the relevant demographic and clinical data of MCI V–, MCI V+, and Nold participants. Of note, age, education, gender, and IAF were used as covariates in the statistical evaluation of the cortical sources of EEG rhythms, to remove possible confounding effects.

EEG Recordings

EEG data was recorded by specialized clinical units in Nold, MCI V–, and MCI V+ subjects at fully awake, resting state (eyes-closed). EEG recordings were performed (0.3–70 Hz bandpass; cephalic reference between AFz and Fz) 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). To monitor eye movements, the horizontal and vertical electrooculogram (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). Recordings were performed in the late morning. To keep constant the level of vigilance, an experimenter controlled on-line the subject and the EEG traces. He verbally alerted the subject any time when there were signs of behavioral and/or EEG drowsiness.

The duration of the EEG recording (5 min) allowed the comparison of the present results with several previous AD and MCI studies using either EEG recording periods shorter than 5 min [Babiloni et al., 2004a, 2006a,b,c,d; Buchan et al., 1997; Pucci et al., 1999; Rodriguez et al., 2002; Szeliés et al., 1999] or about 1 min [Dierks et al., 1993, 2000]; longer epochs would have reduced data vari-

ability but increased risks for dropping vigilance and arousal. The recorded EEG data were analyzed and fragmented off-line in consecutive epochs of 2 s. The EEG epochs with ocular, muscular, and other types of artifact were preliminary identified by a computerized automatic procedure. EEG epochs with sporadic blinking artifacts (less than 10% of the total) were corrected by an autoregressive method [Moretti et al., 2003]. Two independent experimenters blind to the diagnosis manually confirmed the EEG segments accepted for further analysis. The 2-s artifact-free EEG epochs were 146 for the MCI, 135 for the AD, and 144 for the Nold subjects. There was no statistical difference among the groups as amount of 2-s artifact-free EEG epochs.

Spectral Analysis of the EEG Data

A digital FFT-based power spectrum analysis (Welch technique, Hanning windowing function, no phase shift) computed power density of the EEG rhythms with 1 Hz frequency resolution. The following standard band frequencies were studied: δ (2–4 Hz), θ (4–8 Hz), α 1 (8–10 Hz), α 2 (10–12 Hz), β 1 (13–20 Hz), β 2 (20–30 Hz), and γ (30–40 Hz). These band frequencies were chosen averaging those used in previous relevant EEG studies on dementia [Babiloni et al., 2004a, 2006a–e; Besthorn et al., 1997; Chiaromonte et al., 1997; Jelic et al., 1996; Leuchter et al., 1993; Rodriguez et al., 1999a,b]. Sharing of a frequency bin by two contiguous bands is a widely accepted procedure [Besthorn et al., 1997; Cook and Leuchter, 1996; Holschneider et al., 1999; Jelic et al., 1996; Kolev et al., 2002; Leuchter et al., 1993; Nobili et al., 1998; Pucci et al., 1997]. Furthermore, this fits the theoretical consideration that near EEG rhythms may overlap at their frequency borders [Babiloni et al., 2004b,c,d,e,f; Klimesch, 1996, 1999; Klimesch et al., 1997, 1998].

Choice of the fixed EEG bands did not account for individual α frequency (IAF) peak, defined as the frequency associated with the strongest EEG power at the extended α range [Klimesch, 1999]. However, this should not affect the results, since most of the subjects had IAF peaks within the α 1 band (8–10 Hz). In particular, mean IAF peak was 9.4 Hz (± 0.1 standard error, SE) in Nold subjects, 9.4 Hz (± 0.2 SE) in MCI V– subjects, and 9.3 Hz (± 0.2 SE) in MCI V+ subjects. To control for the effect of IAF on the EEG comparisons between these three groups, the IAF peak was used as a covariate (together with age, education, and gender) for further statistics.

We could not use narrow frequency bands for β 1 (13–20 Hz), β 2 (20–30 Hz), and γ (30–40 Hz), because of the variability of β and γ peaks in the power spectra.

The analysis of the δ band was restricted to 2–4 Hz for homogeneity with previous literature [Babiloni et al., 2004a, 2006a–f] and to avoid the residual effects of uncontrolled head movements—provoking artifacts in the lower δ band—especially in MCI subjects.

Statistical Analysis of EEG Power Density Spectrum

The statistical analysis of the EEG power density spectra across each group allowed the evaluation of the quality of the EEG data as an input for the DTF analysis, with reference to the expected “slowing” of EEG rhythms in pathological aging. EEG power density spectrum values were used as dependent variables for the ANOVA analysis, whereas the ANOVA factors (levels) were Group (MCI V–, MCI V+, Nold; independent variable), Band (δ , θ , α 1, α 2, β 1, β 2, γ), and Electrode (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4). The Mauchly’s test evaluated the sphericity assumption. Correction of the degrees of freedom was made with the Greenhouse–Geisser procedure. Age, gender, education, and IAF were used as covariates. The Duncan test was used for post-hoc comparisons ($P < 0.05$). Of note, the factor Band was included in the statistical design to test the prediction that the most affected EEG rhythms ranged from δ to α in dementia.

DTF Analysis: “Direction” of the Functional Connectivity Estimated by the Mvar Model

Before computing the DTF, the EEG data (cephalic reference) were preliminarily normalized by subtracting the mean value and dividing by the variance, according to standardized rules by Kaminski and Blinowska [1991]. An important step of the DTF method was the computation of the so-called Mvar model [Blinowska et al., 2004; Kaminski and Blinowska, 1991; Kaminski et al., 1997; Korzeniewska et al., 1997; Kus et al., 2004]. EEG data at nine electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) were simultaneously given as an input to the Mvar model toward the computation of the directional information flux among all the pair combinations of these electrodes. This model was used to estimate the “direction” of the information flow within the EEG rhythms between the frontal and parietal regions (F3–P3, Fz–Pz, F4–P4). In nonmathematical terms, coefficients of the Mvar model fitted to the data can be interpreted as causal influence of signal recorded from Electrode A on signal recorded from Electrode B, or information flow between Electrodes A and B. A direction of information flow from A to B is stated when that case is statistically more probable than a directionality from B to A. This Mvar model has already been used successfully to estimate the “direction” of the cortico-cortical and cortico-muscular information flow [Babiloni et al., 2004g,h; Mima et al., 2001].

The mathematical core of the Mvar algorithm used in this work is based on the ARfit programs running on the platform Matlab 6.5. The model order was 7, as estimated by the Akaike criterion suggested in previous DTF studies; that order has been demonstrated to be valid for the evaluation of EEG rhythms at both low- and high-frequencies along wakefulness and sleep [Kaminski and Blinowska, 1991; Kaminski et al., 1997; Korzeniewska et al., 1997]. The

goodness of fit was evaluated by visual inspection of the values of noise matrix V of the Mvar model.

The Mvar model is defined as

$$\sum_{j=0}^p A_j X_{t-j} = E_t$$

where X_t is the L -dimensional vector representing the L -channel signal at time t ; E_t is white noise; A_j is the $L \times L$ matrix of the model coefficients; and p is the number of time points considered in the model. From the identified coefficients of the model A_j , spectral properties of the signals can be obtained by the following z -transformation of the above equation:

$$X(z) = H(z)E(z)$$

where $H(z)$ is a transfer function of the system

$$H(z) = \left(\sum_{j=0}^p A_j z^{-j} \right)^{-1}$$

and

$$z^{(-j)} = \exp(-2\pi i f j \, dt)$$

where f is frequency and dt is the time step.

Since the transfer function $H(f)$ is not a symmetric matrix, the information transmission from the j th to the i th channel is different from the i th to the j th channel. The DTF from the j th channel to the i th channel is defined as the square of the element of $H(f)$ divided by the squared sum of all elements of the relevant row.

$$DTF_{ij}(f) = \frac{|H_{ij}|^2}{\sum_{m=1}^L |H_{im}(f)|^2}$$

A substantial difference between $DTF(f)_{ij}$ and $DTF(f)_{ji}$ may suggest an asymmetric information flow from Electrode i to Electrode j . When $DTF(f)_{ij}$ is greater in magnitude than $DTF(f)_{ji}$, the “direction” of the information flow is from Electrode j to Electrode i . On the other hand, the “direction” of the information flow is from Electrode i to Electrode j , when $DTF(f)_{ji}$ is greater in magnitude than $DTF(f)_{ij}$. Of note, the normalization of the DTF depends on the denominator of the previous formula.

To simplify the visualization and statistical analysis of the DTF results, the anterior-posterior directional flow of information of EEG functional coupling was indexed as “parietal-to-frontal” minus “frontal-to-parietal” DTF values, namely anterior-to-posterior DTFdiff values. Positive anterior-to-posterior DTFdiff values indicated a prevalence of parietal-to-frontal over frontal-to-parietal direction of the information flux.

The fact that the DTF analysis was done on the difference between the two reciprocal DTF directions should require a careful interpretation of the results. A zero value

10-20 System (19 electrodes)

Anterior-Posterior

Figure 1.

Anterior–posterior (F3–P3, Fz–Pz, F4–P4) pairs of electrodes at which DTFdiff values were computed. Electrodes positioned according to the International 10–20 System. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

of such a difference meant equivalence of the two opposite DTF directions within the period of EEG data acquisition; namely, that the DTF directions were equally strong or equally weak or both equal to zero in the EEG period taken into account. It should be emphasized that this equivalence is true for the whole EEG period, but not necessarily for subperiods. At this preliminary stage of the study, we preferred to evaluate the DTF values for the entire EEG period, since the DTF values for shorter periods are supposedly less reliable from the statistical point of view [Babiloni et al., 2004a,b].

Statistical Analysis of DTFdiff Values

Statistical comparisons were performed by repeated measure ANOVAs. The Mauchly test evaluated the sphericity assumption, and correction of the degrees of freedom was carried out using the Greenhouse–Geisser procedure. Subjects' age, gender, education, and IAF were used as covariates in the statistical design. The Duncan test was used for post-hoc comparisons ($P < 0.05$).

GRAND AVERAGE

Figure 2.

Grand average of the EEG spectral power density values computed in the Nold, MCI V–, and MCI V+ subjects for the electrodes of interest [F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4; following a spatial order from anterior (left of the figure) to posterior (right of the figure) side] and for all frequency bands considered (δ , θ , $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$, γ). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Figure 3.

Means of anterior-posterior DTFdiff values computed in the Nold, MCI V-, and MCI V+ subjects for all frequency bands of interest (δ , θ , $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$, γ). These means were obtained averaging the anterior-posterior DTFdiff values of the three electrode pairs (F3–P3, Fz–Pz, F4–P4), to represent a two-way ANOVA interaction [$F(12,690) = 3.65$; $P < 0.000001$] between the factors group (MCI V-, MCI V+, Nold) and frequency band (δ , θ , $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$, γ). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Statistical analysis of the anterior-to-posterior DTFdiff values (“direction” of the information flow between frontal and parietal regions) was performed using a three-way ANOVA including the factors Group (MCI V-, MCI V+, and Nold; independent variable), Band (δ , θ , $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$, γ), and Electrode pair (F3–P3, Fz–Pz, and F4–P4). The working hypothesis was a statistical effect indicating a progressive reduction of anterior-to-posterior DTFdiff values across Nold, MCI V-, and MCI V+ subjects. Figure 1 illustrates the spatial localization of the electrodes of interest for these statistical analyses at the scalp level.

RESULTS

EEG Power Density Spectrum

Figure 2 illustrates the grand average of the EEG spectral power density values computed in the Nold, MCI V+, and MCI V- for the electrodes of interest (F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4) and for all frequency bands considered (δ , θ , $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$, γ). Nold subjects showed maximum power density values at $\alpha 1$ band in the posterior regions; minimum values of EEG power density were detected at high frequency bands (β and γ). Compared to the Nold subjects, the amnesic MCI subjects were characterized by lower power density values at $\alpha 1$ and $\alpha 2$.

Statistical ANOVA analysis of EEG spectral power density values showed a significant interaction [$F(965,424) = 2.72$; $P < 0.00001$] among the factors Group (MCI V-, MCI V+, Nold; independent variable), Band (δ , θ , $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$, γ), and Electrode (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4). Duncan post-hoc testing showed that the EEG power density spectra matched the pattern Nold $>$ MCI V+ $>$ MCI V- at $\alpha 2$ band (Pz; $P < 0.000002$ to $P < 0.0000004$), and the pattern Nold $>$ MCI V+ and Nold $>$ MCI V- at $\alpha 1$ band (Pz; $P < 0.00001$ to $P < 0.0000006$).

Fronto-Parietal Functional Coupling as Revealed by DTF

The Nold subjects showed wide positive anterior-to-posterior DTFdiff values (parietal-to-frontal DTF values prevailing over frontal-to-parietal values), which were maximum in magnitude at $\alpha 2$ for all electrode pairs of interest (F3–P3, Fz–Pz, F4–P4). Compared to Nold subjects, MCI V- patients were characterized by a decrease of these DTFdiff values. MCI V+ subjects showed intermediate values of anterior-to-posterior DTFdiff values, when compared to those of Nold and MCI V-.

Statistical ANOVA analysis of the anterior-to-posterior DTFdiff values showed a two-way ANOVA interaction [$F(12,690) = 3.65$; $P < 0.000001$] between the factors Group (MCI V-, MCI V+, Nold) and Frequency band (δ , θ , $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$, γ). Duncan post-hoc testing showed that the anterior-posterior DTFdiff values matched the patterns Nold $>$ MCI V+ $>$ MCI V- (θ : $P < 0.019$ to $P < 0.000002$; $\alpha 1$: $P < 0.0016$ to $P < 0.000001$; $\alpha 2$: $P < 0.0015$ to $P < 0.000001$; $\beta 1$: $P < 0.015$ to $P < 0.000002$).

Figure 3 shows the mean anterior-to-posterior DTFdiff values computed in the Nold, MCI V+, and MCI V- subjects, for all frequency bands of interest (δ , θ , $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$, γ), obtained by averaging the anterior-to-posterior DTFdiff values of the three electrode pairs (F3–P3, Fz–Pz, F4–P4). These values represent the above-mentioned two-way ANOVA interaction.

To better clarify the relationships between DTF direction (i.e. DTFdiff) and subcortical white-matter vascular lesions

TABLE II. Results of correlation between DTFdiff values—obtained by averaging the anterior-to-posterior DTFdiff values of the three electrode pairs (F3–P3, Fz–Pz, F4–P4)—and subcortical vascular lesions scores for θ , $\alpha 1$, $\alpha 2$, and $\beta 1$ bands

	θ	$\alpha 1$	$\alpha 2$	$\beta 1$
r^2	0.064425	0.07357	0.090296	0.048504
p	0.024939	0.016303	0.007515	0.05268

A nonparametric correlation was computed with the r^2 values of the Spearman test ($P < 0.05$). According to Bonferroni correction (i.e. $P < 0.012$), statistical significance was obtained only for $\alpha 2$ band.

scores (i.e. SVLs), nonparametric correlation (Spearman test, $P < 0.05$) were computed averaging the anterior-to-posterior DTFdiff values of the three electrode pairs (F3–P3, Fz–Pz, F4–P4). Table II reports the results of these correlation analyses. According to Bonferroni correction (i.e. $P < 0.012$) statistical significance was obtained only for $\alpha 2$ band.

DISCUSSION

Power of EEG Rhythms Changes Across Nold, MCI V+, and MCI V– Subjects

A first statistical analysis allowed the comparison of resting EEG power in the recruited Nold and MCI subjects. The MCI subjects were classified as having lower or higher white-matter vascular lesion (MCI V– or MCI V+, respectively). When compared to the Nold, the power of parietal $\alpha 1$ rhythms was maximum in the Nold, intermediate in the MCI V+, and low in the MCI V– subjects. These results are globally in line with previous evidence showing a power decrease of α rhythms in AD and MCI when compared to Nold subjects [Babiloni et al., 2004a, 2006a,b,c,d,e; Dierks et al., 1993, 2000; Moretti et al., 2004; Rodriguez et al., 1999a,b; Rossini et al., 2007]. From a methodological viewpoint, the results of the first statistical comparison validated our procedures for the subjects' selection and the EEG data recordings.

Relationships Between White-Matter Vascular Lesion and Fronto-Parietal Coupling

A second statistical analysis evaluated the relationships between directionality of fronto-parietal functional coupling of resting EEG rhythms and white-matter vascular lesion in the MCI subjects. As novel results, the dominant parietal-to-frontal direction of the functional coupling at θ , α , and β was higher in the MCI V+ than in the MCI V– group. Namely, a high white-matter vascular lesion was associated with a relatively lower effect on the directionality of the fronto-parietal EEG coupling in the MCI subjects. These results confirm the hypothesis that parietal-to-frontal EEG coupling is more preserved in amnesic MCI subjects in whom the global cognitive status is more impaired for the white-matter vascular lesion than for the neurodegenerative disease. In the same line of reasoning, those fluxes would be reduced in power in amnesic MCI subjects in whom the global cognitive status is mainly affected by the neurodegenerative disease with respect to the white-matter vascular lesion. In this sense, it can be speculated that in MCI subjects, directionality of fronto-parietal EEG coupling might be a marker sensitive to neurodegenerative rather than to white-matter vascular lesion.

The results of the present study are in line with previous evidence pointing to a stronger impairment of EEG power

in the MCI V+ than in the MCI V– group [Babiloni et al., Submitted for Publication]. Furthermore, they extend previous evidence showing that dominant parietal-to-frontal EEG coupling was more affected in AD patients and MCI subjects than in Nold subjects. Finally, they complement the findings of a recent study [Koenig et al., 2005] on the zero-phase lag synchronization of EEG signals in aging (diversely, DTF is sensitive to nonzero-phase EEG coupling). As the present one, that recent study has investigated the temporal relationships between EEG signals at paired sites regardless of the signal amplitude, and has shown a decrease of EEG coupling at α and β rhythms in MCI with respect to Nold subjects. Both studies suggest that the underlying mechanisms of zero- and nonzero-phase lag synchronization of EEG signals may be associated in pathological aging. Keeping in mind these data, it can be speculated that dominant directionality of the fronto-parietal EEG coupling at relaxed condition might be implied in the brain mechanisms reflecting back-ground intrinsic neural activity, which is paradoxically related to a high expenditure of energy when compared to event-related neural activity [Raichle and Gusnard, 2005]. Indeed, a back-ground “default” functional connectivity represents one of the largest fraction of the brain's functional activity [Raichle and Mintun, 2006], and would be a critical physiological context underlying task-driven neuronal responses and disorganization of the brain function in pathological aging [Fox et al., 2005].

A crucial question is then “Why do neurodegenerative processes but not (or marginally) white-matter vascular lesion affect dominant parietal-to-frontal EEG coupling in MCI subjects posed at relaxed state?” In the condition of wakening rest, θ , α , and β rhythms would be mainly related to subject's global attentional readiness [Klimesch, 1996; Klimesch et al., 1997, 1998; Rossini et al., 1991; Steriade and Llinas, 1988], and would mainly reflect time-varying inputs of forebrain cholinergic pathways to cortex [Ricceri et al., 2004]. Therefore, it can be speculated that changes of the parietal-to-frontal EEG coupling in MCI and mild AD subjects are mainly due to the impairment of cholinergic basal forebrain neurons rather than to sparse white-matter vascular lesion. This impairment would reduce cortico-cortical functional coupling of EEG oscillations, therefore affecting the main mechanism for resting dominant EEG rhythms [Manshanden et al., 2002; Nunez, et al., 2001]. Several lines of evidence have shown that experimental lesions of cholinergic basal forebrain affected the amplitude of EEG rhythms including α frequencies [Buzsaki et al., 1988; Ray and Jackson, 1991; Stewart et al., 1984]. The same was true in AD subjects supposed to have an impairment of cholinergic basal forebrain [Babiloni et al., 2004a; Dierks et al., 1993, 2000; Huang et al., 2000; Mesulam et al., 2004; Moretti et al., 2004; Rodriguez et al., 1999a,b], but a relatively spared thalamic cholinergic innervations from the brainstem [Geula and Mesulam, 1989, 1996, 1999; Mash et al., 1985; Mesulam et al., 2004]. Furthermore, it has been reported that cholinergic basal forebrain

was more structurally impaired in AD [Teipel et al., 2005], especially in patients nonresponding to cholinergic therapy [Tanaka et al., 2003]. Finally, resting EEG rhythms were found to be modulated by long-term cholinergic therapy in AD subjects [Babiloni et al., 2006f].

The above “cholinergic” explanation agrees with the mentioned previous evidence. However, the relationships between cholinergic tone and neurodegenerative processes in AD patients may be nonlinear. Indeed, two studies have suggested that cognitive deficits in MCI and early AD subjects were not associated with the loss of cholinergic levels [Davis et al., 1999; DeKosky et al., 2002]. In the first study [Davis et al., 1999], neocortical cholinergic deficits were characteristic of severely demented AD patients, but cholinergic deficits were not apparent in individuals with mild AD. In the second study [DeKosky et al., 2002], the cholinergic system determined compensatory responses during the early stage of dementia [DeKosky et al., 2002]. This up-regulation was seen in frontal cortex and could be an important factor in preventing the transition of MCI subjects to AD [DeKosky et al., 2002]. Furthermore, it should be remarked that abnormal EEG rhythms can be observed not only in people with pathological aging but also in other kinds of neurologic disorders not clearly related to an impairment of cholinergic systems [Priori et al., 2004]. Finally, brain arousal and corresponding EEG oscillations would depend on a complex balance among cholinergic, serotonergic, histaminergic, noradrenergic, glutamatergic, and GABAergic neurotransmitters systems. Therefore, AD process cannot be merely explained in terms of abnormal cholinergic systems. Together with cholinergic systems, monoaminergic [Dringenberg, 2000] and non-NMDA versus NMDA glutamatergic unbalance [Di Lazzaro et al., 2004] might affect cortical excitability and EEG rhythms in AD patients.

The results of the present study complements the recent notion that cholinergic basal forebrain not only arouses cerebral cortex but also contribute to event-related enhancement of cerebral blood flow at the basis of cognitive functions [Claassen and Jansen, 2006]. The above cholinergic-vascular explanation fits the evidence showing that the relationships between cholinergic tone and neurodegenerative processes in AD may be nonlinear [Babiloni et al., 2006a] and might depend on vasomotor reactivity of cerebral circulation [Claassen and Jansen, 2006; Silvestrini et al., 2006]. On the whole, the present results allow a specification of cholinergic-vascular hypothesis in AD. Health of cholinergic systems as revealed by dominant parietal-to-frontal EEG coupling was not negatively correlated with diffuse white-matter vascular lesion in MCI (i.e. low white-matter vascular lesion, high directionality of the coupling). In contrast, the relationship was opposite (i.e. low white-matter vascular lesion, high directionality of the coupling), showing a minor effect of cerebrovascular impairment on cholinergic systems at the level of amnesic MCI.

The present results support the notion that cerebrovascular and AD lesions represent additive or synergistic fac-

tors in the development of cognitive impairment associated with AD [Regan et al., 2005; Snowden et al., 1997; Zekry et al., 2002]. Along this vein, it has been previously demonstrated [Snowden et al., 1997] that patients of the “Nun” study with typical AD pathological markers at autopsy (neurite plaques and neurofibrillary tangles in the neocortex) had poorer cognitive function and higher prevalence of dementia when they had concomitant cerebrovascular lesions (lacunar infarcts in the basal ganglia, thalamus, or deep white matter); moreover, fewer neuropathologic lesions of AD were found in subjects with lacunar infarcts in the basal ganglia, thalamus, or deep white matter than in those without infarcts. In another seminal study, the typical AD pathological markers have been found to be significantly lower in the AD subgroups in which cerebrovascular lesions were thought to make a major contribution to the patients’ cognitive deficit [Nagy et al., 1997]. Finally, it has been shown that AD patients with the same degree of severity of clinical cognitive impairment had fewer typical AD markers in the temporal and frontal isocortex when large vascular lesions were present [Zekry et al., 2002].

CONCLUSIONS

It is an open issue if vascular and AD lesions represent additive factors in the development of amnesic MCI, as a preclinical stage of AD at group level. In the present study, we tested the hypothesis that dominant parietal-to-frontal EEG coupling, which is affected by AD processes, is relatively preserved in amnesic MCI subjects in whom the cognitive decline is mainly explained by white-matter vascular load. As main results, the dominant parietal-to-frontal EEG coupling at θ , α , and β rhythms was maximum in Nold, intermediate in MCI V+, and low in MCI V- subjects. These results are in line with the additive model of cognitive impairment, postulating that the cognitive impairment arises as the sum of neurodegenerative and cerebrovascular lesions. EEG might be especially sensitive to aging neurodegenerative processes and would be relatively spared in elderly subjects in whom the cognitive impairment is mainly explained by cerebrovascular lesions. The results of the present study motivate future investigations aimed at evaluating the functional coupling of frontal and parietal sources of EEG activity as revealed by high-resolution techniques including linear or nonlinear inverse estimation and realistic modeling of the head as a volume conductor.

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