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CONVERSION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER'S DISEASE IS PREDICTED BY SOURCES AND COHERENCE OF BRAIN ELECTROENCEPHALOGRAPHY RHYTHMS

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Abstract—Objective. Can quantitative electroencephalography (EEG) predict the conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD)?

Methods. Sixty-nine subjects fulfilling criteria for MCI were enrolled; cortical connectivity (spectral coherence) and (low resolution brain electromagnetic tomography) sources of EEG rhythms (δ=2–4 Hz; θ=4–8 Hz; α 1=8–10.5 Hz; α 2=10.5–13 Hz: β 1=13–20 Hz; β 2=20–30 Hz; and γ=30–40) were evaluated at baseline (time of MCI diagnosis) and follow up (about 14 months later). At follow-up, 45 subjects were still MCI (*MCI Stable*) and 24 subjects were converted to AD (*MCI Converted*).

Results. At baseline, fronto-parietal midline coherence as well as δ (temporal), θ (parietal, occipital and temporal), and α 1 (central, parietal, occipital, temporal, limbic) sources were stronger in *MCI Converted* than *stable* subjects ($P<0.05$). Cox regression modeling showed low midline coherence and weak temporal source associated with 10% annual rate AD conversion, while this rate increased up to 40% and 60% when strong temporal δ source and high midline γ coherence were observed respectively.

Interpretation. Low-cost and diffuse computerized EEG techniques are able to statistically predict MCI to AD conversion.

Key words: mild cognitive impairment, dementia, Alzheimer's disease, EEG, neurodegeneration, cognitive decline.

Mild cognitive impairment (MCI) is a state of the elderly brain intermediate between normal cognition and dementia, being mainly characterized by objective evidence of memory impairment not yet encompassing the definition of dementia (Petersen et al., 1995, 2001).

There is a growing consensus on the idea that MCI is a precursor of Alzheimer's disease (AD) (Scheltens et al., 2002) based on the high rate of progression from this state to AD (Petersen et al., 2001). Indeed, in normal aging population annual conversion rate to AD ranges from 0.17% to 3.86% (Petersen et al., 2001; Frisoni et al., 2004), while in MCI it is remarkably higher ranging between 6 and 40% in the different series (Petersen et al., 2001; Jack et al., 2005), while a significant percentage is not progressing into dementia at all (Petersen et al., 1995, 2001).

In order to plan optimal therapeutic, organizational and rehabilitative interventions for MCI, a reliable prognostic indicator on the likelihood of progression to dementia would be required. Along this line electroencephalogram (EEG) would be an ideal candidate to this issue, since it is a widely diffused, non-invasive and low-cost procedure.

A great deal of attention has been directed to electrophysiological substrate of AD and MCI, to evaluate the "transition" hypothesis of a linear progression from MCI to mild AD. In mild AD, EEG rhythms differ from normal elderly (Nold) and vascular dementia subjects, AD patients being characterized by excessive delta (0–4 Hz) and theta (4–7 Hz) rhythms, and a significant decrement of posterior alpha (8–12 Hz) and beta (13–30 Hz) rhythms (Dierks et al., 1993, 2000; Huang et al., 2000; Ponomareva et al., 2003; Jeong, 2004; Babiloni et al., 2004a, 2006e,f,g; Prichep et al., 1994). These EEG abnormalities were associated with altered regional cerebral blood flow (rCBF)/metabolism and with global cognitive function as evaluated by Mini Mental State Examination (MMSE) (Sloan et al., 1995; Rodriguez et al., 1998; Jeong, 2004). Furthermore, parieto-temporal EEG rhythms and rCBF have been correlated with severity of AD as expressed by MMSE score (Rodriguez et al., 1998). Furthermore, a prominent decrease of EEG spectral coherence at the alpha band in AD has been reported (Jelic et al., 2000; Knott et al., 2000; Adler et al., 2003).

When compared with Nold subjects, MCI subjects have shown increase of theta (4–7 Hz) power (Zappoli et al., 1995; Jelic et al., 1996) as well as decrease of alpha power (Zappoli et al., 1995; Jelic et al., 1996; Huang et al., 2000). In line with the "transition" hypothesis, these EEG parameters have presented an intermediate magnitude in

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Abbreviations: AD, Alzheimer's disease; CI, confidence interval; EEG, electroencephalogram; HR, hazard ratio; IAF, individual alpha frequency; LORETA, low resolution brain electromagnetic tomography; MCI, mild cognitive impairment; MCI Converted, mild cognitive impairment subjects showing progression to clinically evident Alzheimer's disease; MCI Stable, mild cognitive impairment subjects remaining stable; MMSE, Mini Mental State Examination; Nold, normal elderly; rCBF, regional cerebral blood flow; ROI, region of interest; S.E., standard error.

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MCI subjects with respect to those observed in Nold and dementia patients (Elmstahl and Rosen, 1997; Huang et al., 2000; Jelic et al., 2000). Of note, it should be remarked that these results just regard the use of linear approaches, and that further advancements have been obtained with the use of non-linear approaches (for more details see relevant reviews Jeong, 2004; Pereda et al., 2005).

It has been recently evidenced that EEG theta power (3.5–7.5 Hz) is higher in MCI subjects who will convert to AD compared with MCI subjects who will not. Logistic regression provided an overall predictive accuracy of 90% between baseline EEG features and probability of future decline (Prichep et al., 2006). Furthermore, spectral EEG coherence has shown to contribute to the classification of AD from Nold (Adler et al., 2003) and the conversion of MCI subjects to AD (Jelic et al., 2000). However, relatively small patients samples and quite long follow-up epochs have been taken into account; moreover, localization of spectral EEG rhythms and cortico-cortical connectivity have never been previously jointly evaluated.

The aim of the present study was to investigate whether combined analysis of EEG power and coherence provides early and reliable discrimination of MCI subjects who will convert to AD after a relatively brief follow-up; results are extremely encouraging.

EXPERIMENTAL PROCEDURES

Subjects

Sixty-nine MCI subjects were enrolled. A group of fifty age/sex-matched Nold subjects was also recruited, in order to preliminarily confirm that MCI subjects presented the typical changes of the EEG rhythms. During a clinical follow-up of about 14 months 24 MCI subjects—from now designed *MCI Converted*—showed progression to a clinically evident AD (according with the NINCDS-ADRDA criteria; McKhann et al., 1984). Instead, 45 MCI subjects remained stable within that period (MCI Stable). Table 1 summarizes the demographic and clinical data of Nold, MCI Converted and MCI Stable subjects. Of note, benzodiazepines, antidepressant and/or antihypertensive drugs were withdrawn for about 24 h before the EEG recordings. None of the subjects received any cholinergic therapy.

Diagnostic criteria

Inclusion criteria for MCI aimed at selecting elderly persons with objective cognitive deficits, especially in the memory domain, who did not meet yet criteria for a diagnosis of dementia or AD (Petersen et al., 1995, 2001): i) objective memory impairment on neuropsychological evaluation, as defined by performances $\geq$1.5 standard deviation below the mean value of age- and education-matched controls for a test battery including Buschke-Fuld and Memory Rey tests; ii) normal activities of daily living; and iii) clinical dementia rating score of 0.5. Exclusion criteria were: i) mild AD; ii) evidence of other concomitant dementia; iii) evidence of concomitant extrapyramidal symptoms; iv) clinical and indirect evidence of depression as revealed by Geriatric Depression Scale scores $\geq$13; v) other psychiatric diseases, epilepsy, drug addiction, and vi) current or previous uncontrolled systemic diseases or recent traumatic brain injuries.

EEG recordings

EEG were recorded in resting, awake subjects (eyes-closed; 5 min; 0.3–70 Hz bandpass; 256 Hz sampling rate) from 19 AgCl cup electrodes positioned on standardized scalp sites (International 10–20 System) in the research laboratories of three Italian AFaR Hospitals of Brescia (1) and Rome (2) (EEG machines: EBneuro (Firenze, Italy) and Micromed (Treviso, Italy) systems). To monitor eye movements, the electrooculogram (0.3–70 Hz bandpass) was simultaneously acquired. The EEG data were analyzed and fragmented off-line in 2 s consecutive epochs, those with ocular, muscular and other types of artifact being preliminarily identified and discarded by a computerized automatic procedure. Two independent experimenters visually confirmed the EEG segments accepted for further analysis. Even if the type of EEG recording was identical to the one routinely employed within the frame of a diagnostic procedure, since this was gathered in an experimental protocol, 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.

A digital FFT-based power spectrum analysis (Welch technique, Hanning windowing function, no phase shift) computed 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), beta 2 (20–30 Hz), and gamma (30–40 Hz). These band frequencies were chosen according with previous relevant EEG studies on dementia (Leuchter et al., 1993; Jelic et al., 1996; Besthorn et al., 1997; Chiaramonti et al., 1997; Rodriguez et al., 1999a,b; Babiloni et al., 2004a, 2006d,e,f,g). That choice made the results of the present study directly comparable with those of previous field studies. Furthermore, sharing of a frequency bin by two contiguous bands is a widely accepted procedure (Leuchter et al., 1993; Cook and Leutcher, 1996; Jelic et al., 1996; Besthorn et al., 1997; Nobili et al., 1998; Pucci et al., 1997; Kolev et al., 2002; Holschneider et al., 1999). As an additional advantage, this fits the theoretical consideration that near EEG rhythms may overlap at their frequency borders (Klimesch, 1996, 1999; Klimesch et al., 1997, 1998; Babiloni et al., 2004b, c,d,e,f).

Choice of fixed EEG bands did not account for individual alpha frequency (IAF) peak, defined as the frequency associated with the strongest EEG power at the extended alpha range (Klimesch, 1999). However, this should not affect the results, since most of the subjects had IAF peaks within the alpha 1 band

Table 1. Demographic and neuropsychological database of Nold and MCI subjects

Characteristic	Nold	MCI Stable	MCI Converted
N	50	45	24
Age (y)	68.4 ($\pm$0.2 SE)	70 ($\pm$1.1 SE)	72.7 ($\pm$1.1 SE)
Education (y)	9.2 ($\pm$0.5 SE)	7.3 ($\pm$0.6 SE)	9.7 ($\pm$1.1 SE)
Gender (M/F)	22/28	16/29	12/12
I MMSE	28.4 ($\pm$0.2 SE)	26.3 ($\pm$0.3 SE)	25.7 ($\pm$0.4 SE)
II MMSE	—	26.1 ($\pm$0.3 SE)	21.7 ($\pm$0.7 SE)
T2−T1 (mo)	—	14.3 ($\pm$1 SE)	14.8 ($\pm$0.9 SE)
Disease duration (mo)	—	21 ($\pm$0.2 SE)	19.5 ($\pm$2.7 SE)
Apoc ε4	—	36%	35%

MCI subjects were subdivided in two sub-groups: MCI Stable and MCI Converted during the follow-up period. Legend: T2–T1=for MCI Stable, the interval between the last clinical control confirming the permanence in MCI condition (T2) and the date of EEG recording (T1); T2–T1=for MCI Converted, interval (months) between the date of clinical control showing conversion to AD (T2) and the date of EEG recording (T1); I MMSE=MMSE at T1; II MMSE=MMSE at T2.

(8–10.5 Hz). In particular, mean IAF peak was 9.2 Hz (±0.2 standard error, S.E.) in Nold subjects and 9.1 Hz (±0.1 S.E.) in MCI subjects. In the two MCI subgroups, the mean IAF peak was 8.7 Hz (±0.2 S.E.) in MCI Converted and 9.3 Hz (±0.2 S.E.) in MCI Stable. To control for the effect of IAF on the EEG comparisons between these two sub-groups, the IAF peak was used as a covariate (together with age and education) for further statistics.

Cortical source analysis of EEG rhythms by low resolution brain electromagnetic tomography (LORETA)

LORETA technique was used for the EEG source analysis as provided by a free-accessible, web-based method (http://www.unizh.ch/keyinst/NewLORETA/LORETA01.htm; Pascual-Marqui and Mitchel, 1994; Pascual-Marqui et al., 1999, 2002). LORETA is an EEG functional imaging technique belonging to a large family of linear inverse solution and tomographic procedures (Valdes et al., 1998; Fuchs et al., 2001; Pascual-Marqui et al., 2002; Sekihara et al., 2005), modeling 3-D distributions of EEG sources with comparable performances. LORETA technique computing 3-D linear solutions (LORETA solutions) for the EEG inverse problem within a three-shell spherical head model (scalp, skull, and brain compartments) was used for EEG rhythms source analysis (Pascual-Marqui et al., 2002). This compartment includes 2394 voxels (7 mm resolution), each one containing an equivalent current dipole. In our studies, we preferred to use LORETA for two reasons. Firstly, LORETA has been repeatedly used from data collected by low spatial sampling of 10–20 system (19 electrodes, Isotani et al., 2001; Anderer et al., 2003; Veiga et al., 2003Kawasaki et al., 2004; Laufer and Pratt, 2003a,b; Babiloni et al., 2004a, 2006a). Secondly, several investigation of EEG rhythms in physiological and pathological aging used LORETA, so the results of the present study could be put in a large framework of previous evidence (Anderer et al., 2003; Dierks et al., 2000; Huang et al., 2002; Saletu et al., 2002; Babiloni et al., 2004a, 2006a). This source analysis is reference-free, in that one obtains the same source distribution for EEG data referenced to any electrode including common average. Solutions consist of voxel z-current density values able to predict EEG spectral power density at scalp electrodes. To enhance the topographical results, LORETA current density was normalized at each voxel for the power density averaged across all frequencies (0.5–45 Hz) and voxels of the brain volume. In line with the low spatial resolution of the technique, we collapsed LORETA solutions at frontal, central, temporal, parietal, occipital, and limbic regions of the brain model coded into Talairach space.

EEG coherence

EEG coherence represents the covariance of the EEG spectral activity at two electrode locations and can be considered as a measure of temporal synchronization of the EEG signals recorded at pairs of electrodes. These signals mainly reflect the oscillatory dendrite activity of the cortical pyramidal neurons, so ideally the coherence estimates represent the temporal synchronization or functional coupling of the two cortical populations generating the scalp EEG data collected by the paired electrodes (Nunez, 1997). In reality, the coherence estimates are affected by currents that are volume conducted by remote EEG sources. Furthermore, these estimates are typically not zero in the case of absent coupling; actually the value depends upon the number of epochs used in the computation (Nunez et al., 1997). Finally, coherence analysis just captures the linear component of the functional coupling of the paired EEG oscillations when compared with modern nonlinear approaches (Stam et al., 2004, 2006; Babiloni et al., 2004c, 2006c; Jeong 2004; Nolte et al., 2004; Nunez et al., 1997; Pereda et al., 2005). However, despite the mentioned limitations, the coherence analysis of EEG data is a basic tool available in practically all digital EEG machines used for clinical applications. This is why the analysis of EEG coherence is the most common methodological approach for the study of functional coupling of EEG oscillations in aging. Several studies have shown in clinically evident AD abnormal linear coupling of EEG rhythms between cortical regions, as revealed by spectral coherence (O'Connor et al., 1979; Jelic et al., 1997; Locatelli et al., 1998; Wada et al., 1998a,b; Knott et al., 2000; Adler et al., 2003). The rationale for its use is that functional cortical coupling 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 et al., 2004). Thus, a decrease of cortical EEG coherence may be—among others—an early and reliable marker of AD.

Here, coherence was calculated by the following equation (Leocani and Comi, 1999; Pfurtscheller and Andrew, 1999),:

$$Coh_{xy}(\lambda) = |R_{xy}(\lambda)|^2 = \frac{|f_{xy}(\lambda)|^2}{f_{xx}(\lambda) f_{yy}(\lambda)}$$

where f denotes the spectral estimate of two EEG signals x and y for a given frequency bin (λ). The numerator contains the cross-spectrum for x and y (fxy), while the denominator contains the respective autospectra for x (fxx) and y (fyy). This procedure returns a real number between 0 (no coherence) and 1 (max coherence) at the fronto-parietal electrode pairs of interest (F3–P3, Fz–Pz, F4–P4 according with the international nomenclature; Babiloni et al., 2004b, 2006b).

It should be remarked that we did not measure the coherence on the LORETA sources (taking into account at least in part head volume conduction effects), since the software for this analysis cannot be downloaded by Internet up to date and, hence, is not available for worldwide clinical centers. The use of homemade software to do so would have raised the problem of dissemination of the present results toward future extensive clinical applications.

Statistical analysis

Regional normalized LORETA solutions and coherence values from MCI and Nold subjects were separately used as an input for the ANOVA analyses. Subjects' age, education and IAF peak were used as covariates. Mauchly's test evaluated the sphericity assumption. Correction of the degrees of freedom was made with the Greenhouse-Geisser procedure. Duncan test was used for post hoc comparisons ($P<0.05$).

The ANOVAs evaluated the working hypothesis, namely the existence of differences in the EEG source power and/or spectral coherence between MCI Converted and MCI Stable subjects. The Nold group was used as a control group. For the evaluation of the EEG power, the ANOVA used Group (Nold, MCI Stable, MCI Converted), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma), and regions of interest—ROI—(central, frontal, parietal, occipital, temporal, limbic) as factors. For the evaluation of the EEG spectral coherence, the ANOVA included the factors Group (Nold, MCI Stable, MCI Converted), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma), and electrodes Pair (F3–P3, Fz–Pz, F4–P4).

In order to better understand the role of EEG parameters indicated by ANOVA in predicting MCI patients at high risk of converting to AD during follow-up, Cox proportional hazard model was applied. All power data (with the exception of temporal delta) benefited of log transformation, while all coherences were log transformed after changing the scale from the original 0-1-0-100. The effects were measured in terms of hazard ratio (HR) with the corresponding 95% confidence intervals (95% CI). Whenever the 95% CI did not include the value 1, a significant effect could be documented with a bilateral alpha error at 0.05. After performing Cox regression with each independent variable entered as alone ("simple Cox regression"), multiple Cox regression was applied with the following criteria: a) age, education and baseline MMSE

were entered as "forced terms" b) only neurophysiological variables resulted significant with simple regression analysis were entered in the multiple regression and forward likelihood ratio procedure was chosen as selection method.

RESULTS

Topography of EEG cortical sources

Fig. 1 contains LORETA solutions' average maps, modeling the distributed EEG sources for the examined rhythms in Nold, MCI Stable, and MCI Converted groups. The Nold group presented alpha 1 sources with maximal values of relative current density distributed in the parieto-occipital regions. Delta, theta and alpha 2 sources had moderate relative current density values when compared with alpha 1. Finally, beta 1, beta 2 and gamma sources were characterized by lowest current density values. Compared with the Nold group, MCI Stable group showed a significant reduction of parieto-occipital alpha 1, along with a slight reduction of occipital theta source strengths. With respect to the Nold and MCI Stable, MCI Converted group showed intermediate magnitude of alpha 1 source and significantly stronger delta source strengths. Finally, compared with MCI Stable, MCI Converted showed an increase of occipital theta source.

Statistical analysis

ANOVA analysis of EEG cortical sources showed a statistical interaction ($F(60,3480)=1.92$; $P<0.0001$) among the factors Group, Band, and ROI (Fig. 2 top). According to the working hypothesis, the planned Duncan post hoc testing showed that parietal, occipital, and temporal alpha 1 sources had stronger amplitudes in the Nold compared with MCI Converted group ($P<0.01$) and in the MCI Converted compared with MCI Stable ($P<0.00001$). Furthermore, temporal delta sources and parietal, occipital and temporal theta sources as well as central and limbic alpha 1 sources were stronger in the MCI Converted vs. MCI Stable ($P<0.03$).

ANOVA analysis of EEG coherence showed a statistical interaction ($F(24,1392)=5.17$; $P<0.00001$) among the factors Group, Band, and Pair (Fig. 2 bottom). According to the working hypothesis, differences between MCI Stable and MCI Converted, especially in the medial fronto-parietal coupling have been found. Specifically, the fronto-parietal coherence was higher in MCI Converted than in MCI Stable patients.

Table 2 shows results of simple Cox regression applied to the EEG power and coherence indexes. Among LORETA band-power solutions, only temporal delta predicted speed and rate of AD conversion, with a HR of 1.635 that was significantly >1 ($P=0.040$). Fronto-parietal coherence along midline electrodes (with the exception of alpha 1) showed a clear effect on AD conversion, with high coherence associated with unfavorable outcome. No evidence of demographic (age and education) and baseline cognitive status (baseline MMSE) effect was found. However, these variables were taken into account in the final model. The multiple Cox regression indicated that spectral EEG coherence for both the fastest (gamma) and the

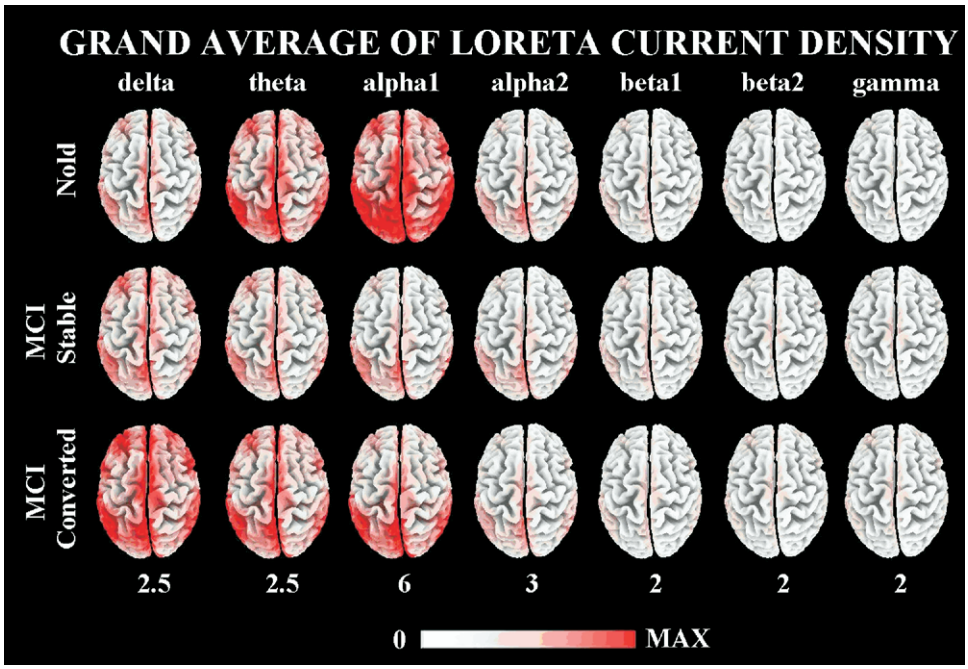

Fig. 1. Grand average of LORETA solutions (i.e. normalized relative current density at the cortical voxels) modeling the distributed EEG sources for delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma bands in Nold, MCI Stable and MCI Converted groups. The left side of the maps (top view) corresponds to the left hemisphere. Color scale: all power estimates were scaled based on the averaged maximum value (i.e. alpha 1 power value of occipital region in Nold). The maximal value of power is reported under each column. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

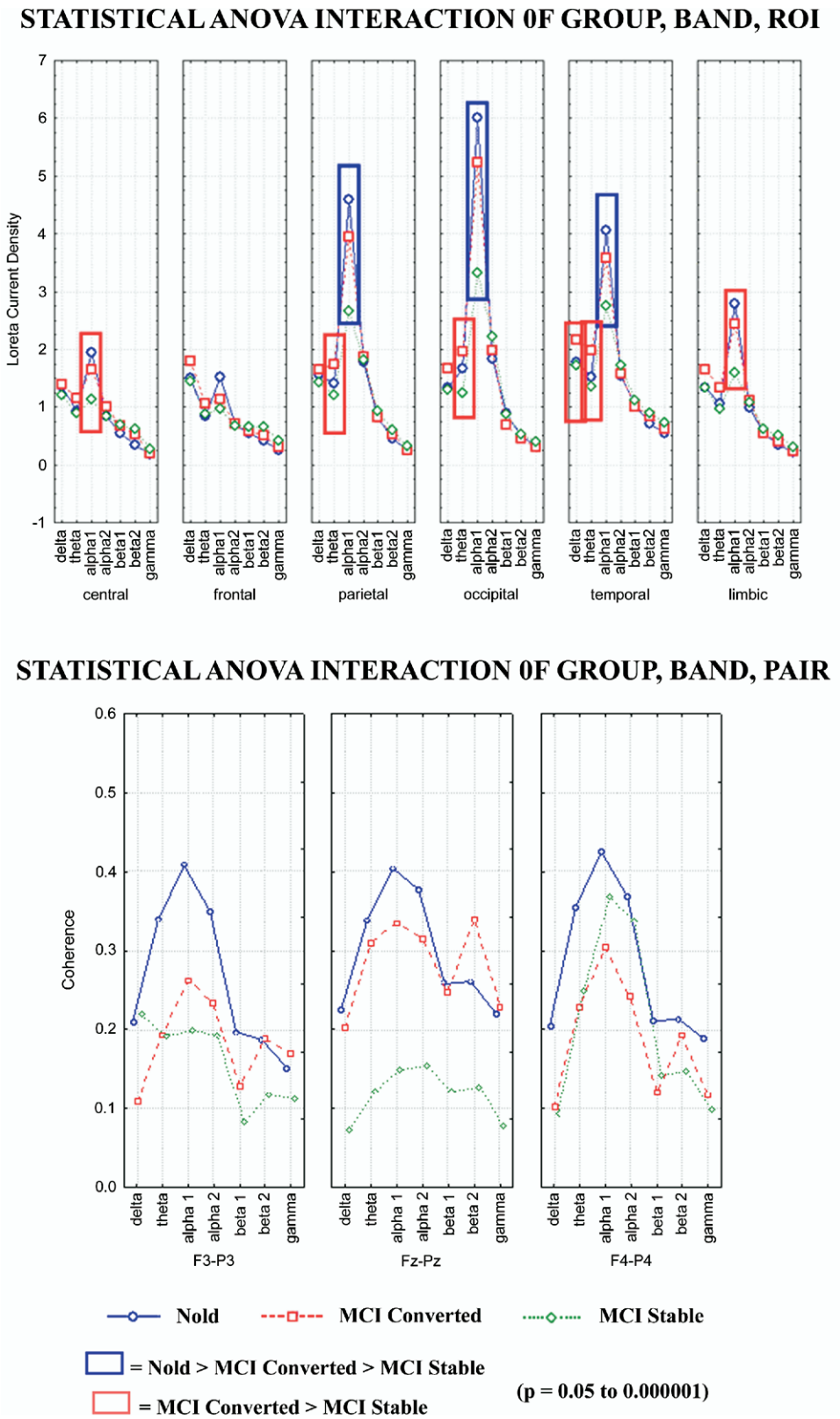

Fig. 2. (Top) Grand average of the LORETA sources relative to the factors Group (Nold, MCI Stable, MCI Converted), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma), and ROI (central, frontal, parietal, occipital, temporal, limbic). The ANOVA analysis among these factors showed statistically significant results ($F(60,3480)=1.92$; $P<0.0001$). (Bottom) Grand average of the coherence values relative to the factors Group (Nold, MCI Stable and MCI Converted), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma), and electrodes PAIR (F3–P3, Fz–Pz, F4–P4 according to international nomenclature). The ANOVA analysis among these factors showed statistically significant results ($F(24,1392)=5.17$; $P<0.00001$).

Table 2. Simple and multiple Cox regression for LORETA sources and coherence values

Characteristic	Simple Cox regression				Multiple Cox regression			
	HR	95% CI for HR		Sig.	HR	95% CI for HR		Sig.
		Lower	Upper			Lower	Upper	
Age	0.999	0.938	1.065	0.985	0.994	0.922	1.072	0.878
Education	1.027	0.95	1.11	0.511	0.922	0.832	1.021	0.118
MMSE	0.875	0.702	1.09	0.234	1.166	0.886	1.534	0.274
LORETA current density								
Temporal delta	1.635	1.024	2.612	0.04	1.874	1.005	3.494	0.048
Parietal theta	1.169	0.89	1.536	0.261				
Occipital theta	1.138	0.863	1.501	0.359				
Temporal theta	1.24	0.919	1.673	0.16				
Central alpha 1	1.124	0.928	1.36	0.231				
Parietal alpha 1	1.085	0.967	1.217	0.163				
Occipital alpha 1	1.049	0.951	1.158	0.341				
Temporal alpha 1	1.125	0.921	1.373	0.248				
Limbic alpha 1	1.197	0.939	1.526	0.147				
Coherence								
Fz–Pz delta	2.447	1.367	4.381	0.003	1.934	1.033	3.621	0.039
Fz–Pz theta	2.114	1.287	3.473	0.003				
Fz–Pz alpha 1	1.266	0.832	1.927	0.272				
Fz–Pz alpha 2	1.861	1.107	3.13	0.019				
Fz–Pz beta 1	2.429	1.347	4.381	0.003				
Fz–Pz beta 2	2.428	1.435	4.111	0.001				
Fz–Pz gamma	2.225	1.39	3.562	0.001	1.977	1.081	3.616	0.027

slowest (delta) rhythms are heralding the rate of "MCI conversion to AD." Independently, an additional effect could be ascribed to temporal delta power.

The relatively small sample size of the present study, the need to obtain reliable cutoffs of a validation from independent samples and, more generally, the "disadvantages of dichotomizing" (Royston and Sauerbrei, 2005) pushed us to avoid the recoding of continuous predictors into categorical variables by grouping values into two or more categories. However, for a graphical representation of the predictive ability of EEG, we tentatively dichotomized our continuous neurophysiological parameters by means of smoothed ROC curves. This procedure indicated that the "optimal" cutoff was 2.57 for temporal delta LORETA current density, 2.07 for Fz–Pz delta coherence (log) and 2.62 for Fz–Pz gamma coherence (log). The survival curves plotted in Fig. 3 (top) for each dichotomized variable are adjusted for the effect of the others (entered as continuous variables). In Fig. 3 (bottom), annual rates (computed by means of the person-year method) of conversion from MCI to AD are represented for each significant neurophysiological parameter.

Control analyses

As reported above, the IAF peaks at baseline EEG recordings were slightly different in three groups (9.2 Hz in Nold subjects, 8.7 in MCI Converted, and 9.3 in MCI Stable). This raises the working hypothesis that future investigations should test this hypothesis of some further changes of the IAF at the follow-up in MCI subjects. To corroborate the use of IAF in future studies, here we performed a control analysis on the stability of IAF at relatively short-term in normal subjects. Resting EEG data (eyes closed) were recorded in 10 normal subjects at baseline and short-term follow up (after 5 days). The procedures of EEG data recording and analysis were those described in the Experimental Procedures section. The ANOVA analysis used IAF as a dependent variable and the factor Session (baseline, follow-up). The results showed no statistically significant difference ($P>0.05$). Fig. 4 shows the grand average of regional LORETA solutions in these subjects at baseline and follow-up. It is noted that the regional LORETA solutions were practically identical.

To evaluate the possible effect of log-transformation on the ANOVA results, regional normalized LORETA solutions and coherence values were subjected to such a transformation before the ANOVA analysis.

The ANOVA designs were equal to those using non-log-transformed data. On one hand, the ANOVA analysis of the LORETA sources showed a statistical interaction ($F(60,3480)=1.43$; $P<0.017$) among the factors Group, Band, and ROI. On the other hand, ANOVA analysis of EEGcoherenceshowedastatisticalinteraction($F(24,1392)=3.90$; $P<0.00001$) among the factors Group, Band, and Pair (Fig. 2 bottom). The statistical post hoc contrasts of the two ANOVAs fully confirmed those obtained on the non-log-transformed data.

Delta oscillations at the temporal lobe were an important variable in the above final statistical model. For this reason, we performed a control analysis of inter-hemi-

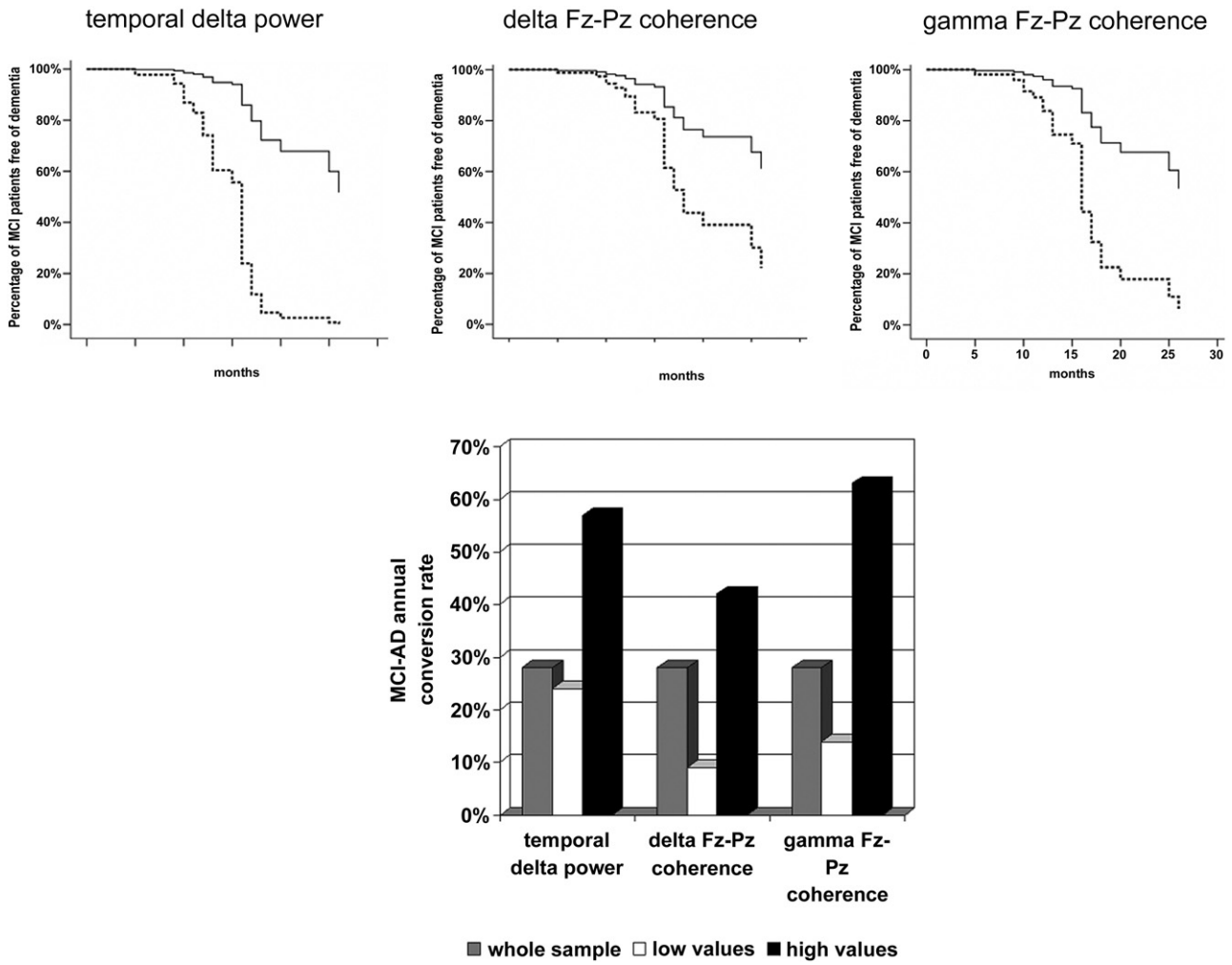

Fig. 3. (Top) Survival curves describing the time to MCI to AD conversion as a function of dichotomized neurophysiological parameters (continuous line=below, dashed line=above the estimated cutoffs: 2.57 for temporal delta LORETA current density, 2.07 for Fz–Pz delta log coherence and 2.62 for Fz–Pz gamma log coherence). Of note, the progression to conversion is faster in patients with high temporal delta and high coherence (delta and gamma). (Bottom) Annual rates computed by means of the person-year method of conversion from MCI to AD for each significant neurophysiological parameter.

spheric EEG coherence at the paired temporal electrodes (i.e. T3–T4). The ANOVA analysis of the temporal EEG coherence included the factors Group (Nold, MCI Stable, MCI Converted) and Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma). Results showed no statistically significant interaction ($F(6, 402)=.16877$, $P=0.98498$) between the factors Group and Band. Fig. 5 illustrates for illustrative purposes the means of the temporal EEG coherence for all frequency bands and groups. There are slight mean differences of these coherence values among groups.

DISCUSSION

The novelty of the present study was the combination of LORETA source and coherence analyses of EEG rhythms to estimate the risk of conversion to AD in MCI patients ($N=69$). The important advantage of these techniques is the wide availability for all clinical units, which is a crucial aspect toward the application to large MCI populations worldwide. However, it should be remarked that coherence analysis presents some limitations in the modeling the functional coupling of EEG rhythms when compared with recent (less popular) linear and non-linear approaches (Stam et al., 2004, 2006; Babiloni et al., 2004c, 2006c; Nunez et al., 1997).

The results of the present study showed that, during a clinical follow-up of about 14.8 months, 24 MCI subjects showed progression to a clinically evident AD. Instead, 45 MCI subjects remained stable within that period. Therefore, the annual conversion rate to AD in our MCI group was of 28.2%, in line with previous evidences showing an annual conversion rate comprised between 6 and 40% (Petersen et al., 2001; Jack et al., 2005). Concerning the EEG results, it is hereby demonstrated for the first time that EEG sources for delta (temporal areas), theta (parietal, occipital, temporal ar-

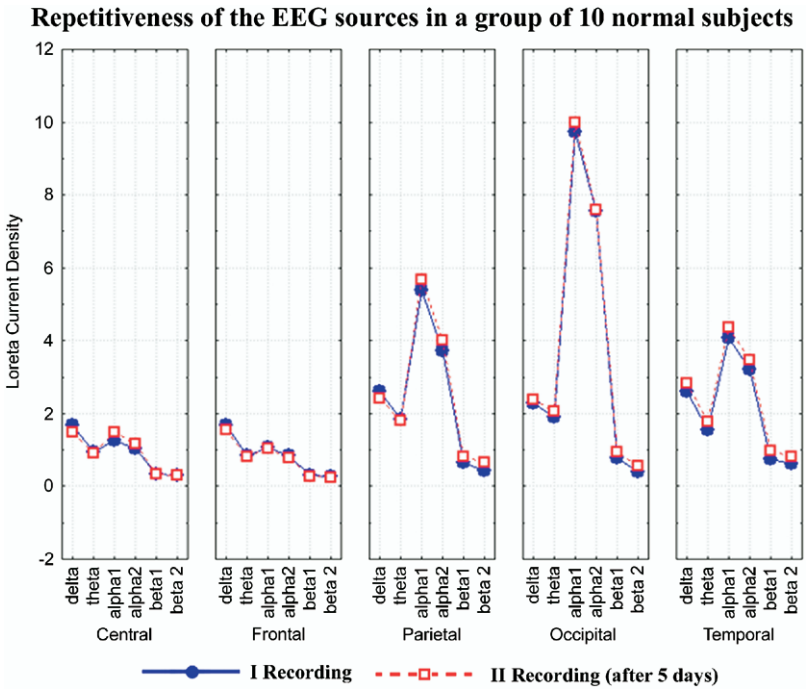

Fig. 4. Regional LORETA solutions (distributed EEG sources) relative to two EEG recording sessions performed one after 5 days the other in a group of 10 normal subjects. Of note, the group LORETA solutions of the two sessions were practically identical.

eas), and alpha 1 (central, parietal, occipital, temporal, limbic areas) rhythms were significantly stronger in those MCI who rapidly progress to AD condition. Furthermore, the EEG fronto-parietal coherence did also provide different results (higher at several frequency bands in the right hemisphere; lower at the fronto-parietal midline) in the MCI Converted vs. MCI Stable. These findings indicate that both spectral power and coherence of resting cortical EEG rhythms characterized MCI subjects who converted to AD in a relatively short time.

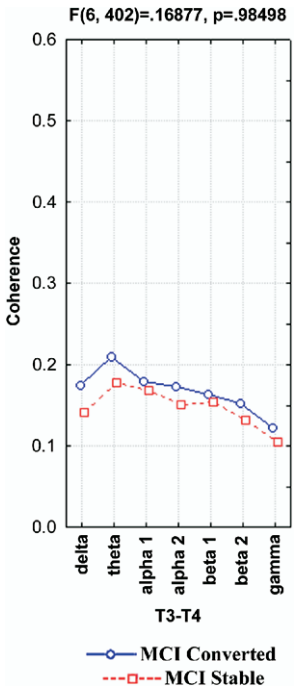

Fig. 5. Grand average of the coherence values relative to the factors Group (Nold, MCI Stable, MCI Converted), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma), and electrodes PAIR (F3–P3, Fz–Pz, F4–P4). The ANOVA analysis among these factors showed no statistically significant results ($P>0.05$).

Why do EEG power and coherence of cortical rhythms differ in MCI Converted vs. Stable subjects? And why are power (i.e. alpha) and coherence of physiological EEG rhythms higher in amplitude in MCI Converted than MCI Stable subjects? The latter clearly sounds like a paradox, since one would expect that neurodegenerative processes reduce alpha rhythms and functional cortical connectivity as revealed by spectral EEG coherence. Indeed, dominant alpha rhythms and low-amplitude delta rhythms characterize a healthy wakeful brain ready to process information; a sort of "reciprocal inhibition" between delta and alpha generators (Rossini et al., 1991; Brunia, 1999; Pfurtscheller and Lopes da Silva, 1999). In the case of brain arousal, high and low components of delta and alpha are blocked and replaced by fast oscillations (beta and gamma bands), which are mainly induced by forebrain (nucleus basalis) cholinergic inputs to hippocampus and cortex as well as by thalamocortical projections (Steriade, 2003). On the basis of this theoretical framework, it can be speculated that MCI Converted subjects are characterized by an impairment of the cholinergic basal forebrain altering the mentioned mechanism of "reciprocal inhibition" between delta and alpha rhythms. This would produce a pattern of EEG synchronization, where the selectivity for frequency of EEG oscillations as probed by spectral power and coherence is

lost or severely affected. As a net result, there would be an unselective increase in power and coherence across several EEG bands in MCI Converted compared with MCI Stable subjects. This hypothesis is in accordance with previous evidence of unselective higher amplitude of delta to alpha rhythms in AD patients who will not respond to long-term (one year) cholinergic therapy when compared with AD patients who will respond to it (Babiloni et al., 2006d).

Spatio-temporal characteristics of EEG rhythms contain relevant information on neurodegenerative processes underlying AD. These processes start long before the presentation of clinical symptoms (Davies et al., 1988) and are probably contrasted for a long time by "plastic" reorganization of the surviving neuronal circuitries, toward a net maintenance of function (Arendt et al., 1997; Babiloni et al., 2000; Ferreri et al., 2003). It is worth reminding that, in the MCI Converted subjects, the integrated analysis of EEG power and coherence provided reliable predictions of MCI to AD progression within a relatively short time-frame. Indeed, Cox regression modeling demonstrated that low temporal delta source and low gamma band coherence along the fronto-parietal midline predicted around 10% of annual rate of conversion to AD (Fig. 3). Although this was just an explorative study, we could practically use information provided by the dichotomization of temporal delta sources, delta fronto-parietal coherence, and gamma fronto-parietal coherence around certain cutoff points. The progression to AD conversion was predicted to be faster across about 1 year in individual MCI patients with delta sources and fronto-parietal coherence higher than the mentioned cutoff points (see Results). These results extend previous evidence gathered in relatively small patient samples and for quite a long follow-up (Prichep et al., 2006) showing that logistic regression of EEG theta power at the time of initial MCI diagnosis provides an overall predictive accuracy of 90% of future decline toward AD at a follow-up epoch of 7–9 years.

CONCLUSION

In conclusion, the results of the present study suggest that low-cost and diffuse computerized EEG techniques (i.e. LORETA and coherence analyses) might estimate the risk for the progression to AD in MCI patients. At the present stage of research, the current results refer to a too small MCI population to be considered as normative values. However, they clearly motivate the extension of the methodological approach to a larger MCI population toward a true clinical application, namely periodic monitoring of the risk of conversion to AD in MCI patients.

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