White-matter vascular lesions correlate with alpha EEG sources in mild cognitive impairment

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Abstract

It is an open issue if vascular and Alzheimer's disease (AD) lesions represent additive factors in the development of mild cognitive impairment (MCI), as a preclinical stage of Alzheimer's disease (AD) at group level. In the present study, we tested the hypothesis that electroencephalographic (EEG) alpha rhythms, which are affected (i.e. decreased in amplitude) by AD processes, are relatively preserved in MCI subjects in whom the cognitive decline is mainly explained by white-matter vascular load. Resting EEG was recorded in 40 healthy elderly (Nold), 80 MCI, and 40 AD subjects. In the MCI subjects, white-matter vascular load was quantified based on MRI (0–30 Wahlund visual rating scale). 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). Low resolution electromagnetic source tomography (LORETA) was used for EEG source analysis. As expected, we observed that alpha 1 sources in parietal, occipital, and temporal areas were lower in amplitude in the AD and MCI subjects than in the Nold subjects, whereas the amplitude of wide delta sources was higher in the AD than in the Nold and MCI subjects. As novel results, the amplitude of parietal, occipital, and temporal alpha 1 sources was higher in the MCI V+ (high vascular load; $N = 42$; MMSE = 26) than MCI V− group (low vascular load; $N = 37$; MMSE = 26.7). Furthermore, a weak but significant ($p < 0.05$) positive statistical correlation was found between the parietal alpha 1 sources and the score of Wahlund scale across all MCI subjects (i.e. the more severe white-matter lesions, the higher parietal alpha source power). The present results are in line with the additive model of cognitive impairment postulating that this arises as the sum of neurodegenerative and cerebrovascular lesions.
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1. Introduction

It has been shown that modifications of resting electroencephalogram (EEG) across physiological aging in humans

pointed to gradual changes in EEG spectral power as mainly represented by a pronounced amplitude decrease of dominant EEG oscillations, namely rhythms in the alpha range from 8 to 13 Hz (Dujardin, Bourriez, & Guieu, 1994; Dujardin, Bourriez, & Guieu, 1995; Ehlers & Kupfer, 1989; Hartikainen, Soininen, Partanen, Helkala, & Riekkinen, 1992; Klass & Brenner, 1995; Klimesch, 1999; Markand, 1990; Pollock, Schneider, & Lyness, 1990; Van Sweden, Wauquier, & Niedermeyer, 1993). A recent study in a large sample of healthy subjects ($N = 185$; 18–85 years) has confirmed an age-dependent power decrement of

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low-frequency alpha rhythms (8–10.5 Hz) in parietal, occipital, and temporal regions (Babiloni, Binetti, Cassarino, et al., 2006).

Modifications of resting EEG can be observed not only during physiological but also pathological aging. When compared to healthy elderly (Nold) subjects, Alzheimer's disease (AD) patients have been characterized by high power of delta (0–4 Hz) and theta (4–7 Hz) rhythms, and low power posterior alpha (8–12 Hz) and/or beta (13–30 Hz) rhythms (Babiloni, Binetti, et al., 2004; Dierks, Ihl, Frolich, & Maurer, 1993; Ponomareva, Selesneva, & Jarikov, 2003; Prichep et al., 2005). These EEG abnormalities were associated with altered regional cerebral blood flow/metabolism and with impaired global cognitive function as evaluated by mini mental state examination (MMSE; Rodriguez, Copello, et al., 1999; Rodriguez, Nobili, et al., 1999; Sloan, Fenton, Kennedy, & MacLennan, 1995). In this framework, the decrement of posterior alpha power showed peculiar features in AD subjects when compared to cerebrovascular dementia subjects with similar cognitive impairment as revealed by MMSE (Babiloni, Babiloni, et al., 2004; Babiloni et al., 2004a, 2004b, 2004c; Babiloni, Binetti, et al., 2004; Babiloni, Miniussi, et al., 2004). Furthermore, posterior alpha power showed a decrement in subjects with mild cognitive impairment (MCI), a clinical state between elderly normal cognition and dementia in which subjects present objective deficits of memory in some cases together with other cognitive impairment (Babiloni, Binetti, Cassetta, et al., 2006; Elmstahl & Rosen, 1997; Huang et al., 2000; Jelic et al., 2000; Koenig et al., 2005; Zappoli et al., 1995).

Despite the above experimental EEG evidence, physiological mechanisms at the basis of abnormal EEG rhythms in AD and MCI subjects are poorly known. To understand these mechanisms, physiology of brain rhythms in healthy adults is briefly considered in the following. In the condition of slow-wave sleep, corticofugal slow oscillations (<1 Hz) are effective in grouping thalamic-generated delta rhythms (1–4 Hz) and spindling activity (7–14 Hz) rhythms (Steriade, 2003). In the condition of brain arousal, spindles, high and low components of the delta rhythms are blocked by the inhibition of oscillators within, respectively, reticulothalamic (7–14 Hz), thalamo-cortical (1–4 Hz), and intracortical (<1 Hz), neuronal circuits. These rhythms are replaced by fast (beta and gamma) cortical oscillations, which are mainly induced by forebrain (nucleus basalis) cholinergic inputs to hippocampus and cortex as well as by thalamocortical projections (Steriade, Amzica, & Contreras, 1996). In the condition of awake rest, low-band (8–10.5 Hz) alpha would be mainly related to subject's global attentional readiness (Klimesch, Doppelmayr, Pachinger, & Russegger, 1997; Klimesch, Doppelmayr, Russegger, Pachinger, & Schwaiger, 1998; Rossini, Desiato, Lavaroni, & Caramia, 1991; Steriade & Llinas, 1988) and would mainly reflect time-varying inputs of forebrain cholinergic pathways (Ricceri et al., 2004).

Keeping this theoretical framework in mind, it can be speculated that changes of resting alpha rhythms in MCI and mild AD subjects are mainly due to the impairment of cholinergic basal forebrain neurons rather than sparse white-matter vascular lesion. This impairment would uninhibit cortical slow oscillators triggering delta and spindles' pacemakers at thalamic level (Steriade, 2003). Furthermore, it would reduce cortico-cortical functional coupling of EEG rhythms, that is the main generation mechanism of awake resting alpha rhythms at parieto-occipital cortex (Manshanden, De Munck, Simon, & Lopes da Silva, 2002; Nunez, Wingeier, & Silberstein, 2001). In precedence, it has been reported that cholinergic basal forebrain was more structurally impaired in AD (Teipel et al., 2005), especially in non-responders to cholinergic therapy (Tanaka, Hanyu, Sakurai, Takasaki, & Abe, 2003) and that posterior alpha rhythms were found to be modulated by long-term cholinergic therapy in AD subjects (Babiloni, Cassetta, et al., 2006). It also has been reported that in AD patients, early neurodegenerative processes include loss of cholinergic basal forebrain neurons projecting to hippocampus and fronto-parietal areas, and that alpha and slower EEG rhythms can be modulated by these neurons as a function of vigilance (Holschneider, Waite, Leuchter, Walton, & Scremin, 1999; Mesulam, Shaw, Mash, & Weintraub, 2004). Whereas, brainstem cholinergic innervation of the thalamus would be relatively spared (Geula & Mesulam, 1989, 1996, 1999; Mash, Flynn, & Potter, 1985; Mesulam et al., 2004). The treatment of AD with cholinesterase inhibitors would deeply affect not only the mechanisms of EEG generation but also regional cerebral blood flow in areas related to attentional and memory functions (Claassen & Jansen, 2006). This makes it quite complex the relationships among EEG generation, neurodegeneration at cholinergic basal forebrain, and abnormalities of regional cerebral blood flow. On one hand, most of the field studies have explored the relationships among AD symptoms, neurodegeneration lesions (i.e. neurite plaques and intracellular neurofibrillary tangles), and cerebrovascular lesions. Total prevalence of cerebrovascular lesion was found to be significantly higher in AD patients than in normal subjects (Jellinger & Mitter-Ferstl, 2003). In AD patients, cognitive and clinical status was affected by the severity of both neurodegenerative and cerebrovascular lesions in hippocampal, anterior cingulate, and parieto-temporal areas (Etiene et al., 1998). Furthermore, cerebrovascular lesions were associated with greater overall severity of clinical dementia and poorer cognitive performance (Heyman et al., 1998), especially in the earliest stages of AD or in subjects older than 80 years (Esiri, Nagy, Smith, Barnetson, & Smith, 1999; Lee, Olichney, Hansen, Hofstetter, & Thal, 2000; Mungas, Reed, Ellis, & Jagust, 2001). For similar severity of dementia symptoms, there were fewer neurodegenerative lesions in AD patients with vascular lesions than in those without vascular lesions, as whether neurodegenerative and cerebrovascular lesions are additive/synergistic causes of AD (Nagy et al., 1997; Snowdon et al., 1997; Zekry et al., 2002). On the other hand, several field studies have explored the relationships between AD and vascular function. Clinical and cognitive status of AD patients was in part explained by amyloid angiopathy of small vessels (Zekry et al., 2003). Furthermore, AD patients carrying ApoE4 allele as a genetic risk of AD presented an increment of vessel intima-media thickness values with respect to non-carriers and cerebrovascular dementia patients (Altamura et al., 2007). In contrast, no rela-

tion was found between ApoE4 allele and the presence/grade of carotid plaques both in AD and cerebrovascular dementia patients (Altamura et al., 2007). Finally, evolution of cognitive function in AD patients was unfavorable as a function of impaired cerebral vasomotor reactivity (Silvestrini et al., 2006).

Summarizing, posterior alpha rhythms show a marked power decrement in AD and, to a lesser extent, in MCI subjects; whereas, they are only slightly affected by cerobrovascular dementia (Babiloni, Babiloni, et al., 2004; Babiloni et al., 2004a, 2004b, 2004c; Babiloni, Binetti, et al., 2004; Babiloni, Miniussi, et al., 2004; Babiloni, Binetti, Cassetta, et al., 2006; Elmstahl & Rosen, 1997; Huang et al., 2000; Jelic et al., 2000; Koenig et al., 2005; Zappoli et al., 1995). Thus, posterior alpha rhythms might be sensitive to early neurodegenerative processes in MCI condition as a possible pre-clinical stage of AD. Furthermore, neurodegenerative and cerebrovascular lesions might represent additive/synergistic causes of cognitive decline in pathological aging (Nagy et al., 1997; Snowdon et al., 1997; Zekry et al., 2002). Keeping in mind these data and considerations, it can be hypothesized that for a similar severity of cognitive decline, posterior alpha rhythms in MCI subjects are affected by global neurodegenerative AD processes rather than by global cerebrovascular lesion spanning both cholinergic and non-cholinerigic systems. To better understand the "additive" hypothesis, let us consider the example of two MCI subjects with the same level of cognitive impairment but very different levels of global cerebrovascular lesion: one MCI subject with a high level of cerebrovascular lesion and the other MCI subject with a low level of cerebrovascular lesion. In line with the "additive" hypothesis, the MCI subject having a high level of global cerebrovascular lesion is expected to present a low level of neurodegenerative AD lesion (including cholinergic systems) when compared to the MCI subject having a low level of global cerebrovascular lesion. Since EEG rhythms are supposed to be markedly affected by neurodegenerative AD lesion (including cholinergic lesion), we predict that the MCI subject with high level of global cerebrovascular lesion (and expected low level of neurodegenerative AD-cholinergic lesion) presents better EEG rhythms than the MCI subject with low level of cerebrovascular lesion (and expected high level of neurodegenerative AD-cholinergic lesion) does.

To test the "additive" hypothesis, here awakening eyes-closed EEG data were recorded in Nold, MCI, and AD subjects. In the MCI subjects, white-matter global cerebrovascular lesion was quantified based on magnetic resonance imaging (MRI), and was related to cortical sources of EEG rhythms. The MCI subjects were subdivided in two sub-groups: MCI with low degree of white-matter lesion (MCI V+) and MCI with high degree of white-matter lesion (MCI V−). It was predicted that: (a) the posterior cortical sources of alpha rhythms were stronger in the MCI V+ compared to the MCI V− group and (b) the posterior cortical sources of alpha rhythms were positively correlated with white-matter vascular lesion across all MCI subjects. Differences between the MCI V+ and MCI V− groups in the other EEG frequency bands were also tested for control purposes.

2. Methods

2.1. Subjects and diagnostic criteria

In this study, 80 MCI subjects (63% amnesic) were enrolled. Furthermore, 40 Alzheimer's disease patients (AD) and 40 cognitively normal elderly (Nold) subjects were recruited to form control groups. Part of the individual data sets was used for previous EEG studies (Babiloni, Binetti, et al., 2004; Babiloni, Benussi, Binetti, Bosco, et al., 2006; Babiloni, Benussi, Binetti, Cassetta, et al., 2006; Babiloni, Binetti, Cassarino, et al., 2006; Babiloni, Binetti, Cassetta, et al., 2006; Babiloni, Cassetta, et al., 2006; Babiloni, Frisoni, et al., 2006) never dealing with the evaluation of the relationships between sources of EEG 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 the MCI condition were based on previous seminal studies (Devanand, Folz, Gorlyn, Moeller, & Stem, 1997; Flicker, Ferris, & Reisberg, 1991; Rubin, Morris, Grant, & Vendegna, 1989; Zaudig, 1992) defining elderly persons with objective cognitive deficits, especially in the memory domain, who did not meet criteria for a diagnosis of dementia. These criteria were as follows: (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 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, as diagnosed by the procedures described below; (ii) evidence of concomitant dementia such as frontotemporal, vascular dementia, reversible dementias including pseudo-depressive dementia (i.e. all patients have been followed regularly every 6 months with a telephone interview and annually with a full clinical assessment. Length of follow-up averages about 3 years), fluctuations in cognitive performance, and/or features of mixed dementias; (iii) evidence of concomitant extra-pyramidal symptoms; (iv) clinical and indirect evidence of depression as revealed by Geriatric Depression Scale scores >13 (Babiloni, Benussi, Binetti, Bosco, et al., 2006; Babiloni, Benussi, Binetti, Cassetta, et al., 2006; Babiloni, Binetti, Cassarino, et al., 2006; Babiloni, Binetti, Cassetta, et al., 2006; Babiloni, Cassetta, et al., 2006; Babiloni, Frisoni, et al., 2006; Burke, Houston, Boust, & Roccaforte, 1989; Burke, Nitcher, Roccaforte, & Wengel, 1992; Gilley & Wilson, 1997; Nitcher, Burke, Roccaforte, & Wengel, 1993); (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.

A battery of neuropsychological tests was performed to assess cognitive performance in the domains of memory, language, executive function/attention, and visuo-construction abilities. The tests to assess memory were the immediate and delayed recall measure of the Rey Auditory Verbal Learning Test (Carlesimo et al., 1996; Rey, 1958), the delayed recall of Rey figures (Rey, 1968), the delayed recall of a three-word list (Chandler et al., 2004), and the delayed recall of a story (Spinnler & Tognoni, 1987). The tests to assess language were the 1-min verbal fluency for letters (Novelli, 1986), the 1-min verbal fluency for fruits, animals or car trades (Novelli, 1986), and the Token test (De Renzi & Vignolo, 1962; Spinnler & Tognoni, 1987). The tests to assess executive function and attention were the Trail Making Test part A and B (Reitan, 1958), the Digit forward, the Digit backward (Orsini et al., 1987), and the attentional matrices (Spinnler & Tognoni, 1987). Finally, the tests to assess visuo-construction were the copy of Rey figures (Rey, 1968), the Raven of Progressive matrices (Raven, 1965), and the Clock Drawing test (Shulman, Gold, Cohen, & Zucchero, 1993).

Probable AD was diagnosed according to NINCDS-ADRDA (McKhann et al., 1984). Patients underwent general medical, neurological and psychiatric assessments and were also rated with a number of standardized diagnostic and severity instruments that included MMSE (Folstein, Folstein, & McHugh, 1975), Clinical Dementia Rating Scale (Hughes, Berg, Danziger, Coben, & Martin, 1982), Geriatric Depression Scale (Yesavage et al., 1983), Hachinski Ischemic

Scale (Rosen, Terry, Fuld, Katzman, & Peck, 1980), and Instrumental Activities of Daily Living Scale (Lawton & Brodie, 1969). Neuroimaging diagnostic procedures (CT or MRI) and complete laboratory analyses were carried out to exclude other causes of progressive or reversible dementias (see above for criteria), in order to have a homogenous mild AD patient sample. The exclusion criteria included, in particular, any evidence of: (i) frontotemporal dementia diagnosed according to criteria of Lund and Manchester Groups (1994); (ii) vascular dementia as diagnosed according to NINDS-AIREN criteria (Roman et al., 1993); (iii) extra-pyramidal syndromes; (iv) reversible dementias; (v) clinical and indirect evidence of depression as revealed by Geriatric Depression Scale scores >13; and (vi) Lewy body dementia according to the criteria by McKeith et al. (1999). The detection of the vascular component in dementia and MCI was accounted based on previous theoretical guidelines from our research network (Frisoni et al., 1995; Geroldi, Galluzzi, Testa, Zanetti, & Frisoni, 2003; Galluzzi, Sheu, Zanetti, & Frisoni, 2005). Furthermore, the above neuropsychological tests were performed on the AD subjects. Of note, benzodiazepines, antidepressant and/or antihypertensive drugs when present, were withdrawn for about 24 h before the EEG recordings.

The Nold subjects were recruited mostly among non-consanguineous 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 <13 (no depression).

2.2. Magnetic resonance imaging (MRI)

High-resolution sagittal T1-weighted volumetric 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.

In order to rate the subcortical vascular lesions (SVLs), an expert operator (R.R.), blind to the clinical conditions or history of falls of subjects, visually assessed digital MRI images of MCI subjects (Geroldi et al., 2006). SVLs were scored separately for the right and left hemispheres in five regions (frontal, temporal, parieto-occipital, basal ganglia, cerebellum and subtentorial areas) as 0 (no lesions), 1 (focal lesions), 2 (beginning confluence of lesions) and 3 (diffuse involvement of the entire region). A sum score was computed with theoretical score = ranging between 0 and 30 (Inter Rater Reliability 0.95). Subcortical vascular disease (SVD) was considered as present when the Wahlunds 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, so that the final group of MCI subjects was formed by 79 subjects. Of note, a rater reliability higher than 0.95 was obtained with reference to the evaluation of the operator in a second session in which the MRI images were rated again.

2.3. Composition of the experimental groups of MCI subjects

Based on the Wahlund scale score, the MCI subjects were subdivided in two sub-groups: 37 with low degree of white-matter lesion (MCI V−, score of Wahlund scale <3; mean 0.8 ± 1.2 standard error, S.E.) and 42 with high degree of white-matter lesion (MCI V+, score of Wahlund scale ≥3; mean

6.9 ± 0.5S.E.). Of note, a cut-off of three for Wahlund scale score was chosen to subdivide MCI subjects in two sub-groups having a similar number of subjects and MMSE score (26.7 for MCI V−, 26 for MCI V+). The percentage of the amnesic subjects was 57% in the MCI V− group and 69% in the MCI V+ group. An ANOVA using the factor Group (MCI V−, MCI V+) was performed to evaluate the presence or absence of statistically significant differences among the MCI V− and MCI V+ groups as percentage of the amnesic subjects. No statistically significant difference was found ($p > 0.25$). Furthermore, the Chi-square distribution showed a higher statistically significant percentage of amnesic than non-amnesic MCI subjects for both groups (MCI V−: Chi-square = 28.8, $p < 0.00001$; MCI V+: Chi-square = 32.3, $p < 0.00001$). Table 1 summarizes the relevant demographic and clinical data of the Nold, MCI V−, MCI V+, and AD participants. Four ANOVAs using the factor Group (Nold, MCI V−, MCI V+, and AD) were computed to evaluate the presence or absence of statistically significant differences among the Nold, MCI V−, MCI V+, and AD groups for the subjects' age, education, gender, and MMSE. No statistically significant differences for the education ($p > 0.5$) and gender ($p > 0.4$) were found. On the contrary, the ANOVA for the age showed a statistically significant difference ($F(3,155) = 2.67$; $p < 0.05$), indicating that the age was higher in the MCI V+ compared to the MCI V− group ($p < 0.03$). Similarly, as expected, the ANOVA for the MMSE showed a statistically significant difference ($F(3,155) = 106$; $p < 0.0001$), indicating that the MMSE values were higher in the Nold group compared to the MCI V−, MCI V+ and Nold groups ($p < 0.0002$) as well as in the MCI V− and MCI V+ groups compared to the AD group ($p < 0.00001$). Of note, the subjects' age, education, and gender were used as covariates in the statistical evaluation of the cortical sources of EEG rhythms, to remove possible confounding effects.

2.4. EEG recordings

EEG data was recorded by specialized clinical units in Nold, MCI V−, MCI V+, and mild AD subjects at resting state (eyes-closed). EEG recordings were performed (0.3–70 Hz bandpass; cephalic reference) 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. In order 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 there were signs of behavioral and/or EEG drowsiness.

The recorded EEG data were analyzed and fragmented off-line in consecutive epochs of 2 s. On average, 150 EEG epochs (5 min) for each subject were examined. The EEG epochs with ocular, muscular, and other types of artifact were preliminary identified by a computerized automatic procedure. The EEG epochs with sporadic blinking artifacts (less than 10% of the total) were corrected by an autoregressive method (Moretti et al., 2003). In brief, this method subtracted the projection of EOG artefacts on EEG data based on the estimation of weights performed by an autoregressive technique (Moretti et al., 2003). Two independent experimenters blind to the diagnosis manually confirmed the EEG segments accepted for further analysis. Of note, a special attention was devoted to avoid the inclusion of EEG segments and individual data sets with EEG signs of drowsiness or pre-sleep stages. Furthermore, the experimenters were blind to the diagnosis of the subjects at the moment of the preliminary EEG data analy-

Table 1
Demographic data of healthy elderly (Nold), mild cognitive impairment (MCI), and mild Alzheimer's disease (AD) subjects

	Nold	MCIV−	MCIV+	AD	p-Value (ANOVA)
N	40	37	42	40	
Age	69.1 (±1.4S.E.)	68.5 (±1.4S.E.)	72.6 (±1S.E.)	71.4 (±1.2S.E.)	<0.05
Education	7.6 (±0.7S.E.)	7.7 (±0.8S.E.)	7.1 (±0.5S.E.)	7.4 (±0.6S.E.)	>0.5
Gender (F/M)	22/18	24/13	23/19	23/17	>0.4
MMSE	28.4 (±0.2S.E.)	26.7 (±0.3S.E.)	26 (±0.3S.E.)	20.4 (±0.5S.E.)	<0.001

Of note, MCI group was divided in two sub-groups: MCI subjects with low degree of cerebrovascular lesion of the white matter (MCI V−, score of Wahlund scale <3) and MCI subjects with high degree of cerebrovascular lesion of the white matter (MCI V+, score of Wahlund scale ≥3). p-Values ranged from 0 to 1 with cut-off for significance at 0.05.

sis. At the end of the preliminary EEG data analysis, the mean of the individual artifact-free EEG epochs lasting 2 s was 122 (±4S.E.) in the Nold subjects, 115 (±5S.E.) in the MCI V− subjects, 120 (±3S.E.) in the MCI V+ subjects, and 111 (±4S.E.) in the AD patients. This means that there was a sufficient amount of 2 s-EEG epochs for further EEG data analysis. Of note, an ANOVA using the factor Group (Nold, MCI V−, MCI V+, and AD) served to compare the amount of artifact-free EEG epochs among the Nold, MCI V−, MCI V+, and AD groups. No statistically significant difference was found ($p > 0.2$).

2.5. 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 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 averaging those used in previous relevant EEG studies on dementia (Babiloni, Binetti, et al., 2004; Babiloni, Benussi, Binetti, Bosco, et al., 2006; Babiloni, Benussi, Binetti, Cassetta, et al., 2006; Babiloni, Binetti, Cassarino, et al., 2006; Babiloni, Binetti, Cassetta, et al., 2006; Babiloni, Cassetta, et al., 2006; Babiloni, Frisoni, et al., 2006; Jelic, Shigeta, & Julin, 1996; Rodriguez, Copello, et al., 1999; Rodriguez, Nobili, et al., 1999). Sharing of a frequency bin by two contiguous bands is a widely accepted procedure (Besthorn et al., 1997; Cook & Leuchter, 1996; Kolev, Yordanova, Basar-Eroglu, & Basar, 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, Babiloni, et al., 2004; Babiloni, Miniussi, et al., 2004; Klimesch, 1996, 1999; Klimesch et al., 1997, 1998).

Choice of the 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 (8–10.5 Hz). In particular, mean IAF peak was 9.4 Hz (±0.2 standard error, S.E.) in Nold subjects, 9.4 Hz (±0.2S.E.) in MCI V− subjects, 9.3 Hz (±0.2S.E.) in MCI V+ subjects, and 8.5 Hz (±0.2S.E.) in AD patients. An ANOVA served to compare IAF peak values among the Nold, MCI V−, MCI V+, and AD groups. The ANOVA showed a statistically significant difference ($F(3,155) = 5.11$; $p < 0.002$), indicating that the mean IAF peak was lower in the AD group compared to the Nold, MCI V−, and MCI V+ groups ($p < 0.004$). Although no statistically significant difference was observed between the MCI V− and MCI V+ groups ($p > 0.6$), the IAF peak was used as a covariate (together with age, education and gender) for further statistics.

The analysis of the delta band was restricted to 2–4 Hz for homogeneity with previously quoted field literature and to avoid the residual effects of uncontrolled head movements—provoking artifacts in the lower delta band- especially in MCI and AD subjects.

2.6. Cortical source analysis of the EEG rhythms by LORETA

Low resolution electromagnetic source tomography (LORETA) was used for the EEG source analysis as provided at http://www.unizh.ch/keyinst/NewLORETA/LORETA01.htm (Pascual-Marqui, Esslen, Kochi, & Lehmann, 2002; Pascual-Marqui & Michel, 1994). LORETA is a functional imaging technique belonging to a family of linear inverse solution procedures (Valdès et al., 1998) modeling 3D distributions of EEG sources (Pascual-Marqui et al., 2002). With respect to the dipole modeling of cortical sources, no a priori decision of the dipole position is required by the investigators in LORETA estimation. In a previous review paper, it has been shown that it was quite efficient when compared to other linear inverse algorithms like minimum norm solution, weighted minimum norm solution or weighted resolution optimization (Phillips, Rugg, & Friston, 2002; Yao & He, 2001). Finally, LORETA has been successfully used in recent EEG studies on pathological brain aging (Babiloni, Binetti, et al., 2004; Babiloni, Benussi, Binetti, Bosco, et al., 2006; Babiloni, Benussi, Binetti, Cassetta, et al., 2006; Babiloni, Binetti, Cassarino, et al., 2006; Babiloni, Binetti, Cassetta, et al., 2006; Babiloni, Frisoni, et al., 2006; Dierks et al., 2000). LORETA computes 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 is restricted to the cortical gray matter/hippocampus of a head model co-registered to the Talairach probability brain atlas and digitized at the Brain Imaging Center of the Montreal Neurological Institute (Talairach & Tournoux, 1988). This compartment includes 2394 voxels (7 mm resolution), each voxel containing an equivalent current dipole.

LORETA can be used from EEG data collected by low spatial sampling of 10–20 system (19 electrodes) when cortical sources are estimated from resting EEG rhythmst, since these rhythms are generated by largely distributed cortical sources that can be accurately investigated by this way (Anderer, Saletu, & Pascual-Marqui, 2000; Anderer, Saletu, Semlitsch, & Pascual-Marqui, 2003; Babiloni, Binetti, et al., 2004; Babiloni, Benussi, Binetti, Bosco, et al., 2006; Babiloni, Benussi, Binetti, Cassetta, et al., 2006; Babiloni, Binetti, Cassarino, et al., 2006; Babiloni, Binetti, Cassetta, et al., 2006; Babiloni, Frisoni, et al., 2006; Laufer & Pratt, 2003a, 2003b; Mulert et al., 2001; Veiga et al., 2003; Winterer et al., 2001). LORETA solutions consisted of voxel z-current density values able to predict EEG spectral power density at scalp electrodes, being a reference-free method of EEG analysis, in that one obtains the same LORETA source distribution for EEG data referenced to any reference electrode including common average. A normalization of the data was obtained by normalizing the LORETA current density at each voxel with the power density averaged across all frequencies (0.5–45 Hz) and across all 2394 voxels of the brain volume. After the normalization, the solutions lost the original physical dimension and were represented by an arbitrary unit scale. This procedure reduced inter-subjects variability and was used in previous EEG studies (Babiloni, Binetti, et al., 2004; Babiloni, Benussi, Binetti, Bosco, et al., 2006; Babiloni, Benussi, Binetti, Cassetta, et al., 2006; Babiloni, Binetti, Cassarino, et al., 2006; Babiloni, Binetti, Cassetta, et al., 2006; Babiloni, Frisoni, et al., 2006). The general procedure fitted the LORETA solutions in a Gaussian distribution and reduced inter-subject variability (Leuchter et al., 1993; Nuwer, 1988).

Solutions of the EEG inverse problem are under-determined 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 distributed rather than punctual EEG source patterns (Pascual-Marqui & Michel, 1994). In line with the low spatial resolution of the adopted technique, a home-made MATLAB software averaged the amplitude of LORETA solutions for all voxels belonging to each macroregion of interest such as frontal, central, parietal, occipital, temporal, and limbic. Each of these macroregions of interest (ROIs) was constituted by all the voxels of the Brodmann areas listed in Table 2. The belonging of a LORETA voxel to a Brodmann area was defined by original LORETA package.

Finally, the main advantage of the regional analysis of LORETA solutions – using an explicit source model coregistered into Talairach space – was that our modeling could disentangle rhythms of contiguous cortical areas (namely those from the occipital source were disentangled with respect to those of the contiguous parietal and temporal sources, etc.).

2.7. Statistical analysis of the LORETA solutions

The main statistical analysis aimed at evaluating two working hypotheses. The first hypothesis was that cortical sources of EEG rhythms as revealed by the regional normalized LORETA solutions had difference in amplitude among the

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

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

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

Nold, MCI V−, MCI V+, and AD subjects. To this aim, the regional normalized LORETA solutions from Nold, MCI V−, MCI V+ and AD subjects were used as an input for a MANOVA. Subjects' age, education, gender and IAF peak served as covariates. Mauchly's test evaluated the sphericity assumption. Correction of the degrees of freedom was made with the Greenhouse–Geisser procedure. The MANOVA used the factors Group (Nold, MCI V−, MCI V+, AD; independent variable), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma), and ROI (central, frontal, parietal, occipital, temporal, limbic). The first hypothesis would be confirmed by the following two statistical results: (i) a statistical MANOVA effect including the factor Group ($p < 0.05$); and (ii) a post hoc test indicating statistically significant differences of the (LORETA) EEG sources with the pattern Nold ≠ MCI V− ≠ MCI V+ ≠ AD (Duncan test, $p < 0.05$).

The second hypothesis regarded the correlation between white-matter vascular lesion and the regional normalized LORETA solutions in the MCI subjects considered as a single group (i.e. MCI V− plus MCI V+ subjects). This hypothesis would be confirmed by statistically significant correlations (partial correlation analysis, Bonferroni corrected, $p < 0.05$) between the Wahlund scale score and the amplitude of the regional normalized LORETA solutions. Of note, only the regional normalized LORETA solutions fitting the pattern Nold ≠ MCI V− ≠ MCI V+ ≠ AD were considered for that correlation analysis. Age and education were used as confound variables.

3. Results

3.1. Topography of the EEG cortical sources as estimated by LORETA

For illustrative purposes, Fig. 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, beta 2 and gamma bands in the Nold, MCI V−, MCI V+, and AD groups. The Nold group presented alpha 1 sources with the maximal values of amplitude distributed in parietal and occipital regions. Delta, theta, and alpha 2 sources had moderate amplitude values when compared to alpha 1 sources. Furthermore, beta 1, beta 2 and gamma sources were characterized by lowest amplitude values. Compared to the Nold group, both MCI V− and MCI V+ groups showed a decrease in amplitude of the parietal, occipital and temporal alpha 1 sources. This decrement was stronger in the MCI V− than MCI V+ group. With respect to the Nold and MCI groups, the AD group showed an amplitude increase of widespread delta sources, along with a strong amplitude reduction of parieto-occipital alpha 1 sources. Finally, there were relatively high values of the theta sources in the AD group.

3.2. Statistical comparisons of LORETA EEG sources

Fig. 2 shows mean regional normalized LORETA solutions (distributed EEG sources) relative to a statistical MANOVA interaction ($F(90, 4650) = 7.7$; M.S.E. = 0.5; $p < 0.0001$) among the factors Group (Nold, MCI V−, MCI V+, AD), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma), 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 Nold, MCI
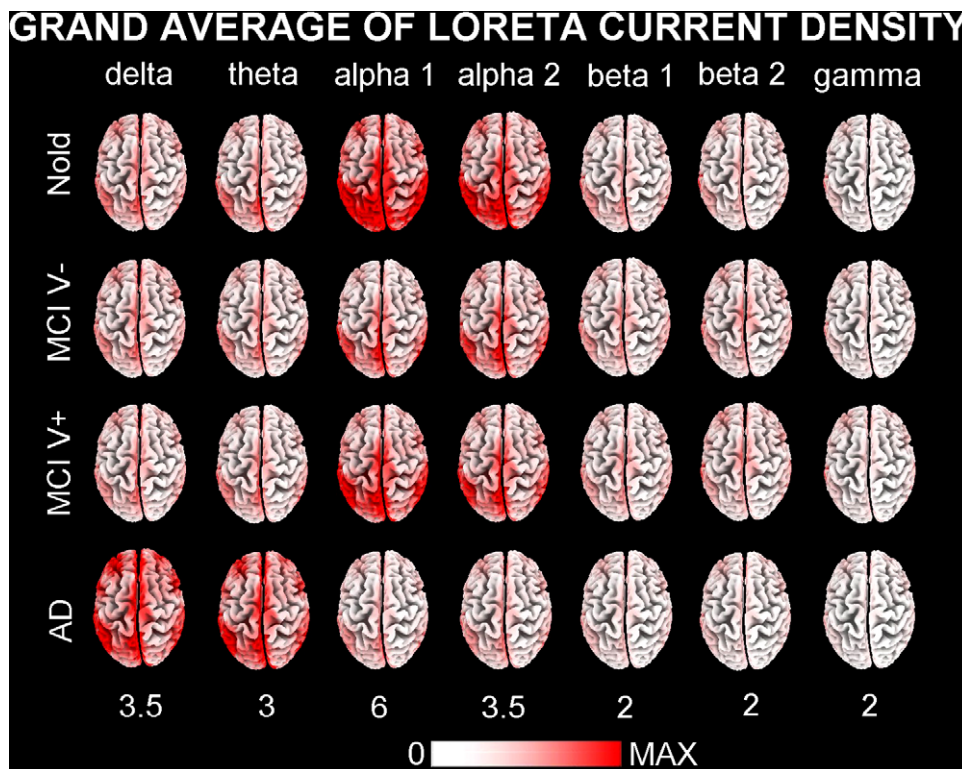

Fig. 1. Grand average of LORETA solutions (i.e. normalized relative current density at the cortical voxels) modeling the distributed EEG sources for delta, theta, alpha 1, alpha 2, beta 1, beta 2, and gamma bands in Nold, MCI V− (score of Wahlund scale <3), MCI V+ (score of Wahlund scale ≥3), and AD groups. The left side of the maps (top view) corresponds to the left hemisphere. *Legend*: LORETA, low resolution brain electromagnetic tomography. *Color scale*: All power density 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 density is reported under each column.
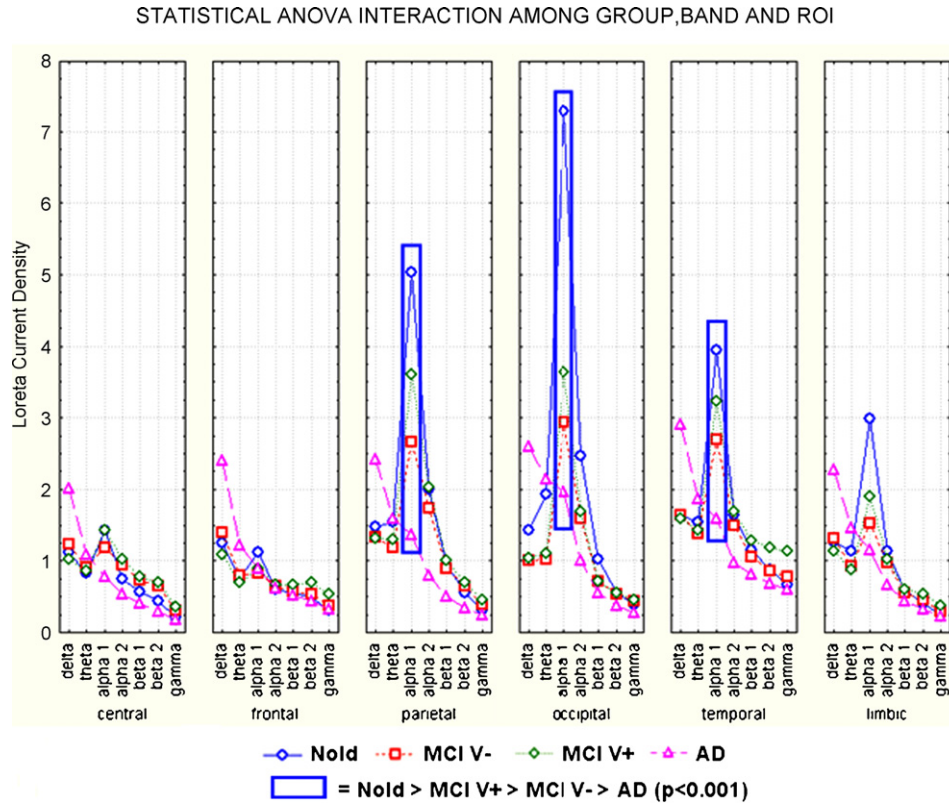
STATISTICAL ANOVA INTERACTION AMONG GROUP,BAND AND ROI

Fig. 2. Regional normalized LORETA solutions (mean across subjects) relative to a statistical MANOVA interaction among the factors Group (Nold, MCI V−, MCI V+, AD), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma), and ROI (frontal, central, parietal, occipital, temporal, limbic). This MANOVA design used the regional normalized LORETA solutions as a dependent variable. Subjects' age, education, gender and individual alpha frequency peak (IAF) were used as covariates. Regional normalized LORETA solutions modeled the EEG relative power spectra as revealed by a sort of "virtual" intracranial macro-electrodes located on the macrocortical regions of interest. *Legend*: The rectangles indicate the cortical regions and frequency bands in which LORETA solutions presented statistically significant LORETA patterns Nold ≠ MCI V− ≠ MCI V+ ≠ AD ($p < 0.05$).

V−, MCI V+, and AD groups differed across diverse cortical macro-regions, thus supporting the idea that scalp EEG rhythms are generated by a distributed pattern of cortical sources. The source pattern Nold ≠ MCI V− ≠ MCI V+ ≠ AD was fitted by the following three regional normalized LORETA solutions: parietal, occipital, and temporal alpha 1 sources ($p < 0.001$). These alpha 1 sources showed stronger amplitude in the Nold compared to the MCI V+ group ($p < 0.0001$), in the MCI V+ compared to the MCI V− group ($p < 0.001$), and in the MCI V− compared to the AD group ($p < 0.0001$). No differences between the MCI V− and MCI V+ groups in the other bands (delta, theta, alpha 2, beta 1, beta 2, gamma, $p > 0.05$) were found. Furthermore, the amplitude of delta (frontal, central, parietal, occipital, temporal and limbic areas) sources was stronger in the AD group compared to the MCI V+, MCI V−, and Nold groups ($p < 0.0001$). Moreover, the amplitude of theta sources was stronger in the AD group compared to the Nold (frontal areas, $p < 0.03$), MCI V+, and MCI V− groups (frontal, occipital, temporal and limbic areas, $p < 0.04$). Table 3 reports post hoc results for all ROIs, band, and groups. Finally, the statistical results for parietal, occipital, and temporal alpha 1 sources were also confirmed with hierarchical linear analysis ($p < 0.00006$).

The three mentioned normalized regional LORETA sources (parietal, occipital, and temporal alpha 1 sources) were then used as an input for the correlation with the score of Wahlund

scale in the MCI V− and MCI V+ subjects as a single group (partial correlation analysis; age and education as confound variables). Bonferroni correction for the three regional normalized LORETA solutions gave the threshold $p < 0.017$, to obtain the Bonferroni corrected $p < 0.05$. A marginal statistical correlation was found between the parietal alpha 1 sources and the score of Wahlund scale ($r = 0.23$, $p = 0.04$). This marginal positive correlation was also confirmed at the Spearman test ($r = 0.27$, $p = 0.04$). Fig. 3 shows the scatterplot of that correlation. Of note, the mentioned correlation was not merely due to the presence of outliers as revealed by the following control analysis. In this analysis, 4 outliers out of the 79 MCI subjects were excluded; they were defined as the subjects having the extreme values within the group distribution. Without the outliers, the correlation was still statistically significant ($r = 0.26$; $p < 0.05$), confirming the main results.

3.3. Control analyses

As previously mentioned, the parietal, occipital, and temporal alpha 1 LORETA sources fitted the pattern Nold ≠ MCI V− ≠ MCI V+ ≠ AD. These three regional normalized LORETA sources were used as an input for the correlation with the score of Wahlund scale in the MCI subjects. A marginal statistical correlation was found between the parietal alpha 1

Table 3
Post hoc results for the delta, theta, alpha 1, alpha 2, beta 1, beta 2, and gamma sources

	Duncan post HOC testing (p-value)					
	Central	Frontal	Parietal	Occipital	Temporal	Limbic
delta						
Nold vs. MCI V−	0.6−	0.5−	0.9+	0.04+	0.9−	0.8−
Nold vs. MCI V+	0.6+	0.4+	0.9+	0.06+	0.8+	0.5+
Nold vs. AD	0.0001−	0.0001−	0.0001−	0.0001−	0.0001−	0.0001−
MCI V− vs. MCI V+	0.3+	0.1+	0.9+	0.8−	0.8+	0.4+
MCI V− vs. AD	0.0001−	0.0001−	0.0001−	0.0001−	0.0001−	0.0001−
MCI V+− vs. AD	0.0001−	0.0001−	0.0001−	0.0001−	0.0001−	0.0001−
theta						
Nold vs. MCI V−	0.7−	0.8−	0.9+	0.001+	0.9+	0.3+
Nold vs. MCI V+	0.8−	0.7+	0.9+	0.001+	0.6+	0.2+
Nold vs. AD	0.9−	0.03−	0.9−	0.9−	0.1−	0.1−
MCI V− vs. MCI V+	0.9+	0.6+	0.6−	0.7−	0.9−	0.8−
MCI V− vs. AD	0.1−	0.04−	0.06−	0.001−	0.02−	0.008−
alpha 1						
Nold vs. MCI V−	0.2+	0.2+	0.0001+	0.0001+	0.0001+	0.0001+
Nold vs. MCI V+	0.9+	0.3+	0.0001+	0.0001+	0.0001+	0.0001+
Nold vs. AD	0.01+	0.9+	0.0001+	0.0001+	0.0001+	0.0001+
MCI V− vs. MCI V+	0.2−	0.8−	0.0001−	0.0001−	0.001−	0.06−
MCI V− vs. AD	0.6+	0.9+	0.0001+	0.0001+	0.0001+	0.07+
MCI V + vs. AD	0.001+	0.9+	0.0001+	0.0001+	0.0001+	0.0001+
alpha 2						
Nold vs. MCI V−	0.4−	0.8−	0.2+	0.0001+	0.9+	0.4+
Nold vs. MCI V+	0.2−	0.7−	0.9−	0.0001+	0.7−	0.6+
Nold vs. AD	0.9+	0.9−	0.0001+	0.0001+	0.001+	0.02+
MCI V− vs. MCI V+	0.7−	0.9−	0.1−	0.6−	0.3−	0.8−
MCI V− vs. AD	0.6+	0.1+	0.0001+	0.003+	0.01+	0.2+
MCI V+− vs. AD	0.02+	0.9+	0.0001+	0.0005+	0.0003+	0.1+
beta 1						
Nold vs. MCI V−	0.5−	0.9−	0.7+	0.2+	0.6+	0.8+
Nold vs. MCI V+	0.3−	0.5−	0.8−	0.2+	0.5−	0.9−
Nold vs. AD	0.9+	0.9+	0.03+	0.02+	0.1+	0.9+
MCI V− vs. MCI V+	0.8−	0.6−	0.5−	0.6+	0.3−	0.8−
MCI V− vs. AD	0.1+	0.9+	0.1+	0.9+	0.9+	0.9+
MCI V+− vs. AD	0.1+	0.9+	0.02+	0.9+	0.03+	0.9+
beta 2						
Nold vs. MCI V−	0.3−	0.8−	0.6−	0.9+	0.9+	0.8−
Nold vs. MCI V+	0.2−	0.3−	0.5−	0.9+	0.1−	0.5−
Nold vs. AD	0.9+	0.5+	0.9+	0.9+	0.3+	0.8+
MCI V− vs. MCI V+	0.8−	0.5−	0.8−	0.9−	0.1−	0.7−
MCI V− vs. AD	0.1+	0.9+	0.1+	0.9+	0.9+	0.9+
MCI V+− vs. AD	0.06+	0.3+	0.1+	0.10+	0.01+	0.9+
gamma						
Nold vs. MCI V−	0.6−	0.7−	0.7−	0.8−	0.5−	0.7−
Nold vs. MCI V+	0.3−	0.5−	0.5−	0.7−	0.02−	0.5−
Nold vs. AD	0.9+	0.9−	0.7+	0.9+	0.9+	0.9+
MCI V− vs. MCI V+	0.8−	0.5−	0.7−	0.8−	0.1−	0.7−
MCI V− vs. AD	0.5+	0.9+	0.5+	0.5+	0.9+	0.7+
MCI V+− vs. AD	0.4+	0.3+	0.4+	0.4+	0.01+	0.5+

These results refer to mean regional normalized LORETA solutions (distributed EEG sources) relative to a statistical MANOVA interaction ($F(90,4650) = 7.7$; M.S.E. = 0.5; $p < 0.0001$) among the factors Group (Nold, MCI V−, MCI V+, AD), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma), and ROI (central, frontal, parietal, occipital, temporal, limbic).

sources and the score of Wahlund scale ($r = 0.23$, $p = 0.04$). A first control analysis evaluated the partial correlations between the Wahlund scale score and the amplitude of 39 regional normalized LORETA solutions (i.e. cortical regions of interest × EEG frequencies). Bonferroni correction for the 39 regional normalized LORETA solutions gave the threshold $p < 0.0001$, to obtain the Bonferroni corrected $p < 0.05$. Marginal positive correlations were found between the Wahlund scale score and the amplitude of frontal ($r = 0.29$, $p = 0.02$) or central ($r = 0.24$, $p = 0.03$) alpha 1 sources. These two correlation
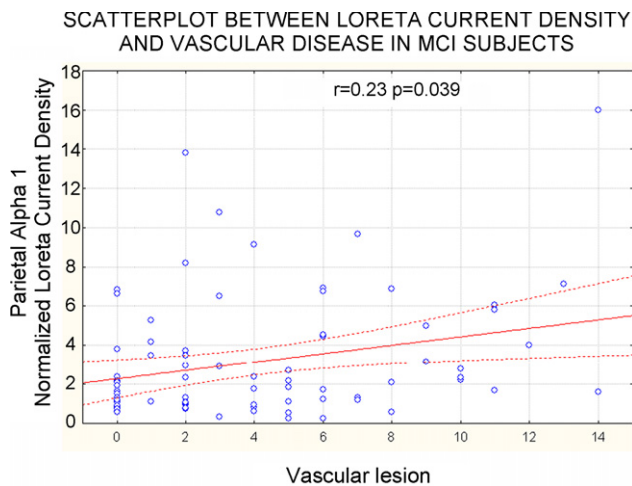
Fig. 3. Scatterplots among the parietal alpha 1 LORETA density current and the score of Wahlund scale in MCI V− and MCI V+ subjects as a single group. The *r*- and *p*-values refer to a partial correlation are reported within the diagram.

values were not confirmed with the ranking Spearman test ($p > 0.2$) and were not further considered.

As second control analysis, the partial correlation between white-matter vascular lesion and parietal, occipital, and temporal alpha LORETA sources in the MCI V− and MCI V+ subjects as separate groups was performed. Bonferroni correction for three sources × two groups gave the threshold $p < 0.008$ to obtain the Bonferroni corrected $p < 0.05$. No statistically significant result was found, probably due to the fact that the correlation analysis on each single group reduced the degrees of freedom, the range of the values to be correlated, and then the sensitivity of the statistical computation.

Furthermore, one may argue that the above-mentioned results could be merely due to different results to the neuropsychological tests between the MCI V− and MCI V+ groups. To address this issue, a third control analysis was performed. Eighteen ANOVAs (one for each neuropsychological test) using the factor Group (MCI V−, MCI V+) were computed to evaluate the presence or absence of statistically significant different results between the MCI V− and MCI V+ groups to the neuropsychological tests. No statistically significant difference for the test for memory ($p > 0.5$), language ($p > 0.15$), executive function/attention ($p > 0.4$), and visuo-construction tests ($p > 0.1$) was found.

As a fourth control analysis, the amplitude of parietal alpha 1 sources and the score of Wahlund scale were correlated to neuropsychological measures in MCI V− and MCI V+ subjects as a whole group. Bonferroni correction for 18 tests gave the threshold $p < 0.0026$ to obtain the Bonferroni corrected $p < 0.05$. No statistically significant correlation was found between the score of Wahlund scale and the neuropsychological measures. Instead, marginal positive correlations were observed between the amplitude of parietal alpha 1 sources and the scores of Token test ($r = 0.25$, $p = 0.03$), Raven's Progressive Matrices ($r = 0.25$, $p = 0.03$), and Trail Making part B ($r = -0.3$, $p = 0.008$).

As fifth control analysis, a MANOVA tested the hypothesis that the differences of regional normalized LORETA solutions

among MCI V−, MCI V+, and mild AD groups were not due to the subjects' age, education, gender, and MMSE. We considered two sub-groups of the MCI V− ($N = 17$) and MCI V+ ($N = 17$) subjects having practically equal age (MCI V−: 70.5 years; MCI V+−: 70.8 years), education (MCI V−: 7.6 years; MCI V+−: 7.2 years), ratios of gender (MCI V−: 41% male; MCI V+−: 43% male), and MMSE (MCI V−: 26.5; MCI V+−: 26.2). The regional normalized LORETA solutions were used as a dependent variable. The MANOVA factors (levels) were Group (MCI V−, MCI V+; independent analysis), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma), and ROI (frontal, central, parietal, occipital, temporal, limbic). There was a statistical interaction ($F(30,1860) = 1.6$; M.S.E. = 0.37; $p < 0.02$) among the factors Group, Band, and ROI. The Duncan planned post-hoc testing showed that the regional normalized LORETA solutions were higher in amplitude in the MCI V+ than MCI V− group at alpha 1 (parietal, occipital, temporal, limbic areas; $p < 0.00003$) and alpha 2 (parietal, occipital, temporal areas; $p < 0.02$) bands. The results globally confirmed those obtained with the larger groups. Therefore, the differences of the LORETA solutions between the full MCI V− and MCI V+ groups were not substantially affected by the subjects' age, education, gender and MMSE.

4. Discussion

4.1. Methodological remarks

In the present study, the duration of the EEG recordings (5 min) allowed the comparison of the present results with several previous AD studies using either EEG recordings with a global duration shorter than 5 min (Babiloni, Binetti, et al., 2004; Babiloni, Benussi, Binetti, Bosco, et al., 2006; Babiloni, Benussi, Binetti, Cassetta, et al., 2006; Babiloni, Binetti, Cassarino, et al., 2006; Babiloni, Binetti, Cassetta, et al., 2006; Buchan et al., 1997; Pucci, Belardinelli, Cacchio, Signorino, & Angeleri, 1999; Rodriguez et al., 2002; Szelies, Mielke, Kessler, & Heiss, 1999) or about 1 min (Dierks et al., 1993, 2000). Longer EEG recordings would have reduced data variability but increased risks for dropping vigilance and arousal.

4.2. Sources of delta and alpha rhythms change across Nold, MCI, and AD subjects

When compared to the Nold subjects, EEG rhythms in MCI and AD subjects were characterized by a marked power decrease of alpha 1 sources in parieto-occipital and temporal areas. In AD subjects, these rhythms were also characterized by a marked power increase of frontal, parieto-occipital, and temporal delta sources in line with previous EEG studies (Babiloni, Binetti, et al., 2004; Babiloni, Benussi, Binetti, Bosco, et al., 2006; Babiloni, Benussi, Binetti, Cassetta, et al., 2006; Babiloni, Binetti, Cassarino, et al., 2006; Babiloni, Binetti, Cassetta, et al., 2006; Babiloni, Frisoni, et al., 2006; Rodriguez, Copello, et al., 1999; Rodriguez, Nobili, et al., 1999; Wolf, Jelic, & Gertz, 2003).

4.3. White-matter vascular lesion and alpha EEG sources positively correlate in MCI

As novel results, the power of temporal, parietal and occipital low-frequency alpha sources (8–12.5 Hz) was higher in the MCI V+ than in the MCI V− group. Furthermore, a weak statistical correlation was found between the parietal alpha 1 sources and the score of Wahlund scale across all MCI subjects ($p = 0.04$). Such a linear correlation was relatively low ($r = 0.23$), thus pointing to a complex relationship between white-matter vascular lesions and cortical sources of alpha rhythms in MCI subjects. Future studies using non-linear procedures and neural artificial networks should investigate that complex relationship.

The present results confirm the hypothesis that posterior cortical alpha rhythms are more preserved in the MCI subjects in whom the global cognitive status is impaired more for the white-matter vascular lesions than for the neurodegenerative processes. In this sense, they suggest that posterior cortical alpha rhythms might be a marker of neurodegenerative processes rather than a marker of white-matter vascular lesions, in line with previous evidence showing that posterior cortical alpha rhythms are more affected in AD patients than in subjects with sub-cortical vascular dementia (Babiloni, Binetti, et al., 2004).

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 & Jansen, 2006). The above cholinergic-vascular explanation fits the evidence showing that the relationships between cholinergic tone and neurodegenerative processes in AD may be non-linear (Babiloni, Binetti, Cassarino, et al., 2006) and might depend on vasomotor reactivity of cerebral circulation (Claassen & Jansen, 2006; Silvestrini et al., 2006). Indeed, two studies have suggested that cognitive deficits in MCI and early AD 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 early 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). Keeping in mind these data, present results allow a specification of cholinergic-vascular hypothesis in AD. Health of cholinergic systems as revealed by alpha power was not negatively correlated with diffuse white-matter vascular lesion in MCI (i.e. higher alpha power, lower white-matter vascular lesion). In contrast, as explained above, the correlation was positive (i.e. higher alpha power, higher white-matter vascular lesion), showing a minor effect of cerebrovascular impairment on cholinergic systems at the level of amnesic MCI.

The present results fully support with original EEG evidence on amnesic MCI subjects the notion that cerebrovascular and AD lesions represent additive or synergistic factors in the development of cognitive impairment across AD (Regan et al., 2006; Snowdon et al., 1997; Zekry et al., 2002).

5. Conclusions

It is an open issue if vascular and AD lesions represent additive factors in the development of MCI, as a preclinical stage of AD at group level. In the present study, we tested the hypothesis that EEG alpha rhythms, which are affected (i.e. decreased in amplitude) by AD processes, are relatively preserved in MCI subjects in whom the cognitive decline is mainly explained by white-matter vascular load. As novel results, the amplitude of parietal, occipital, and temporal alpha 1 sources was higher in the MCI V+ (high vascular load; $N = 42$; MMSE = 26) than MCI V− group (low vascular load; $N = 37$; MMSE = 26.7). Furthermore, a weak but significant ($p < 0.05$) positive statistical correlation was found between the parietal alpha 1 sources and the score of Wahlund scale across all MCI subjects (i.e. the more severe white-matter lesions, the higher parietal alpha source power). These results are in line with the additive model of cognitive impairment postulating that this arises as the sum of neurodegenerative and cerebrovascular lesions.

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