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Cortical sources of resting state electroencephalographic alpha rhythms deteriorate across time in subjects with amnesic mild cognitive impairment

Claudio Babiloni [a,b,*], Claudio Del Percio [b], Roberta Lizio [b], Nicola Marzano [c], Francesco Infarinato [b], Andrea Soricelli [c,d], Elena Salvatore [e], Raffaele Ferri [f], Cinzia Bonforte [f], Gioacchino Tedeschi [g], Patrizia Montella [g], Annalisa Baglieri [h], Guido Rodriguez [i], Francesco Famà [i], Flavio Nobili [i], Fabrizio Vernieri [j], Francesca Ursini [j], Ciro Mundi [k], Giovanni B. Frisoni [l], Paolo M. Rossini [b,m]

[a] Department of Physiology and Pharmacology, University of Rome La Sapienza, Rome, Italy
[b] IRCCS San Raffaele Pisana, Roma, Italy
[c] IRCCS "SDN", Naples, Italy
[d] Department of Studies of Institutions and Territorial Systems, University of Naples Parthenope, Naples, Italy
[e] Department of Neurological Sciences, University of Naples Federico II, Naples, Italy
[f] IRCCS Oasi, Troina (Enna), Italy
[g] Department of Neurological Sciences, Second University of Naples, Napes, Italy
[h] SICILIA-IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy
[i] Service of Clinical Neurophysiology (DiNOGMI; DipTeC), IRCCS AOU S Martino-IST, Genoa, Italy
[j] Neurology, University "Campus Biomedico", Rome, Italy
[k] Department of Neuroscience, United Hospitals of Foggia, Foggia, Italy
[l] IRCCS "S. Giovanni di Dio-FBF", Brescia, Italy
[m] Department of Geriatrics, Neurosciences and Orthopedics, Catholic University "Sacro Cuore", Rome, Italy

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ABSTRACT

Cortical sources of resting state electroencephalographic (EEG) rhythms are abnormal in subjects with mild cognitive impairment (MCI). Here, we tested the hypothesis that these sources in amnesic MCI subjects further deteriorate over 1 year. To this aim, the resting state eyes-closed EEG data were recorded in 54 MCI subjects at baseline (Mini Mental State Examination I = 26.9; standard error [SE], 0.2) and at approximately 1-year follow-up (13.8 months; SE, 0.5; Mini Mental State Examination II = 25.8; SE, 0.2). As a control, EEG recordings were also performed in 45 normal elderly and in 50 mild Alzheimer's disease subjects. EEG rhythms of interest were delta (2–4 Hz), theta (4–8 Hz), alpha1 (8–10.5 Hz), alpha2 (10.5–13 Hz), beta1 (13–20 Hz), and beta2 (20–30 Hz). Cortical EEG sources were estimated using low-resolution brain electromagnetic tomography. Compared with the normal elderly and mild Alzheimer's disease subjects, the MCI subjects were characterized by an intermediate power of posterior alpha1 sources. In the MCI subjects, the follow-up EEG recordings showed a decreased power of posterior alpha1 and alpha2 sources. These results suggest that the resting state EEG alpha sources were sensitive—at least at the group level—to the cognitive decline occurring in the amnesic MCI group over 1 year, and might represent cost-effective, noninvasive and widely available markers to follow amnesic MCI populations in large clinical trials.

1. Introduction

Mild cognitive impairment (MCI) is a clinically intermediate state in elderly subjects between normal cognition and Alzheimer's disease (AD). MCI subjects show objective cognitive impairment on neuropsychological tests, but do not yet fulfill the clinical criteria for dementia (Flicker et al., 1991; Petersen et al., 1995, 2001). MCI might be considered as a precursor to AD (Arnaiz and Almkvist, 2003; Galluzzi et al., 2001), considering the high rate of progression from MCI to AD (Bachman et al., 1993; Petersen et al., 2001). In cognitively intact elderly subjects, the annual rate of transition to AD ranges from 0.17% to 3.86% (Frisoni et al., 2007; Petersen et al., 2001), but it is much higher in patients with MCI, ranging from 6% to 25% (Petersen et al., 2001). However, the transition hypothesis is partly challenged by the fact that not all MCI subjects deteriorate

* Corresponding author at: Department of Physiology and Pharmacology, University of Rome La Sapienza, P le A Moro 5, Rome I 00185, Italy. Tel.: +39 06 4991 0989; fax: +39 06 49910989 ×0917.
E-mail address: claudio.babiloni@uniroma1.it (C. Babiloni).

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over time (Bennett et al., 2002; Larrieu et al., 2002), because cumulative incidence rates for AD range from 40% to 60% after approximately 5 years (Bennett et al., 2002; Larrieu et al., 2002).

The typical dementia syndrome of AD is characterized by prominent episodic memory impairment, with secondary deficits in word-finding skills, spatial cognition, and executive functions (Karantzoulis and Galvin, 2011). For the elderly with amnestic (amnesic) MCI, who have memory impairment greater than would be expected for their age, the conversion to AD is reported to occur at a rate of 8–15% per year (Luck et al., 2007); in this line, the amnesic MCI subjects are considered at high risk to suffer from prodromal AD (Gallagher et al., 2010).

Neuropsychological markers are extremely important for the assessment of prodromal stages of AD, but there is consensus that a crucial challenge of aging research is a better understanding of the neurobiological basis of the MCI condition, to refine diagnostic procedures, and to objectively measure the efficacy of new pharmacological interventions (Albert et al., 2011; Braak and Braak, 1991; Dubois et al., 2007). In light of the recently proposed new international guidelines (Albert et al., 2011; Dubois et al., 2007), prodromal stages of AD in MCI subjects can be diagnosed according to abnormal dosages of the A beta amyloid to tau ratio in cerebrospinal fluid (CSF) and deposition of A beta amyloid in the brain, revealed using ligand-based positron emission tomography (PET). Other useful biomarkers are overt signs of neurodegeneration such as atrophy of the hippocampus on magnetic resonance imaging (MRI), or hypometabolism of the posterior cingulate/precuneus, parietal, and temporal regions, as revealed using fluorodeoxyglucose (FDG)-PET (Albert et al., 2011; Dubois et al., 2007). In 2011, the National Institute on Aging-Alzheimer's Association workgroups proposed the following 4 markers for the diagnosis of AD (Albert et al., 2011; Jack et al., 2011; McKhann et al., 2011; Sperling et al., 2011): (1) abnormal dosages of the A beta amyloid to tau ratio in CSF sampled using lumbar puncture (Tapiola et al., 2009); (2) deposition of A beta amyloid in the brain, revealed using PET-amyloid Pittsburg compound-B (PIB; Ikonomovic et al., 2008; Rowe et al., 2007); (3) hypometabolism of the posterior cingulate, precuneus, parietal, and temporal regions revealed using PET-FDG (Jagust et al., 2007); and (4) atrophy of the hippocampus revealed using structural MRI (Frisoni et al., 2010; Schuff, 2009; van de Pol et al., 2006). However, these workgroups reported neither the standard operating procedures for the extraction of the relative biomarkers nor the threshold levels for the diagnostic decision-making. Furthermore, there is a lively discussion about the sensitivity and specificity of these biomarkers because different values were reported on different international databases (Takahashi et al., 2013; Toussaint et al., 2012). Moreover, CSF markers are invasive, PET markers are costly and expose patients to radiation, and MRI markers of hippocampus volume are relatively expensive for serial screening of large elderly populations at risk for AD; therefore, they should be better devoted to a second-line screening on high-risk subjects intercepted via a first-line fully noninvasive and more cost-effective procedures. A promising approach to assess MCI subjects is the recording of resting state eyes-closed electroencephalographic (EEG) rhythms. This approach is based on low cost and relatively widely available equipment, and is fully noninvasive. It can also be used to collect serial measurements without incurring misleading effects that are solely caused by the repetition of the procedure (Rossini et al., 2007). Previous studies have successfully investigated the resting state eyes-closed EEG rhythms in MCI and AD subjects. Compared with normal elderly (Nold) subjects, AD patients showed an increase in delta (1–4 Hz) rhythms and a decrement of posterior alpha (8–12 Hz) rhythms (Dierks et al., 1993, 2000; Huang et al., 2000; Jeong, 2004; Ponomareva et al., 2003). These EEG abnormalities are associated with altered regional cerebral blood flow/metabolism and with impaired global cognitive function (Jeong, 2004; Rodriguez et al., 1998, 1999; Sloan et al., 1995). Similarly, MCI subjects show a decrease of alpha rhythms compared with Nold subjects (Huang et al., 2000; Jelic et al., 2000; Koenig et al., 2005; Zappoli et al., 1995).

Furthermore, the EEG abnormalities in MCI and AD subjects are related to loss of neurons and synaptic dysfunction. In this regard, it has been shown that: (1) the brain atrophy of the anterior and posterior fissure was related to alpha power in AD subjects (Frstl et al., 1996); (2) the bilateral reduction of hippocampus and/or entorhinal volumes of AD subjects was correlated with an increment of cortical delta and theta power (Fernandez et al., 2003; Grunwald et al., 2007); (3) the frontal white matter atrophy was related to frontal delta power in MCI and AD subjects (Babiloni et al., 2006f); (4) the hippocampal atrophy was related to the decline of posterior alpha power in MCI and AD subjects (Babiloni et al., 2009a; Moretti et al., 2007, 2011), and to an increase of the ratio between theta and gamma power and of the ratio between high- and low-frequency alpha power in MCI subjects (Moretti et al., 2009); (5) the gray matter atrophy in thalamus and basal ganglia was related to an increase of the power between high- and low-frequency alpha power in MCI subjects (Moretti et al., 2012); (6) the global gray matter volume was negatively correlated with global delta sources and positively correlated with the global alpha power in MCI and AD subjects (Babiloni et al., 2013). These results suggest that in MCI and AD subjects, abnormalities of resting state cortical EEG rhythms are not epiphenomena. Rather, they are strictly related to AD neurodegeneration processes revealed according to atrophy in cortical and subcortical regions.

The power of resting state EEG rhythms was related not only to brain atrophy but also to cognitive functions (i.e., attention, memory, language, and executive function) in AD and in MCI subjects (Babiloni et al., 2006c, 2007b; Roh et al., 2011). In particular, the power of alpha rhythms was positively related to global cognitive status (i.e., Mini Mental State Examination [MMSE] score), immediate memory for digits probing focused attention, and verbal memory recall (Babiloni et al., 2006c, 2007b; Roh et al., 2011). On the contrary, the power of delta and theta rhythms were negatively related to global cognition status, visuospatial immediate memory probing focused attention, memory recall, language, and executive functions (Babiloni et al., 2006c, 2007b; Roh et al., 2011; van der Hiele et al., 2007). Furthermore, an increase of beta power (13–25 Hz) was positively correlated with good performance for global cognition, attention, memory, visuospatial, and executive functions (Kim et al., 2012).

Only few longitudinal studies in relatively small groups of MCI and AD subjects have tested the hypothesis that the resting state scalp EEG rhythms can be used as marker of cognitive decline in MCI and disease progression in AD (Coben et al., 1985; Jelic et al., 2000; Soininen et al., 1989). In 1 study, 27 MCI subjects at high risk of developing AD were followed for a mean period of 21 months between baseline and follow-up EEG recordings (Jelic et al., 2000). At the follow-up examination, the MCI subjects showed a power increase of theta and delta rhythms in temporal and occipital scalp regions and a power decrease of beta rhythms (Jelic et al., 2000). In another study, a group of 40 AD patients was followed for a mean period of approximately 30 months between baseline and follow-up EEG recordings (Coben et al., 1985). At the follow-up examination, the AD patients showed a power increase of theta and delta rhythms in parietal and occipital scalp regions associated with a power reduction of alpha and beta rhythms (Coben et al., 1985). A third longitudinal study was performed in 40 patients followed for a mean period of 12 months (Soininen et al., 1989). Approximately half of them presented a power increase of theta and delta rhythms in temporal and occipital scalp regions

(Soininen et al., 1989). A methodological limitation of these studies is that the scalp topography of EEG activity is affected by reference electrode and head volume conduction effects, which prevent a precise spatial analysis of EEG rhythms (Nunez, 1995).

Cortical sources of scalp EEG rhythms have been successfully evaluated in MCI and AD subjects by single dipole sources deeply located into a spherical brain model (Dierks et al., 1993; Huang et al., 2000). An alternative approach for the cortical sources of scalp EEG rhythms is low resolution brain electromagnetic tomography (LORETA) (Pascual-Marqui and Michel, 1994; Pascual-Marqui et al., 1999, 2002). Previous LORETA studies from our group have shown that: (1) the posterior sources of dominant alpha rhythms (approximately 8–10 Hz) were abnormal in AD subjects when compared with Nold subjects, cerebrovascular dementia, and Parkinson disease subjects (Babiloni et al., 2004, 2011a); (2) the posterior sources of delta (<4 Hz) and dominant alpha rhythms were related to global cognitive status (i.e., MMSE score) in MCI and AD subjects (Babiloni et al., 2006c); (3) the atrophy of hippocampus and cortical gray matter was related to the decline of posterior cortical sources of dominant alpha rhythms in MCI and/or AD subjects (Babiloni et al., 2009a, 2012); and (4) the posterior cortical sources of the dominant alpha rhythms were related to the stability of the global cognitive status in MCI subjects (Babiloni et al., 2011b).

To our knowledge, previous longitudinal studies did not explore whether cortical sources of resting state EEG rhythms can be used as instrumental surrogate markers of the disease progression in amnesic MCI subjects. In a recent study, we have shown that cortical sources of resting state EEG rhythms in mild AD patients are sensitive to the disease progression at the early stage over 1 year (Babiloni et al., 2013). In particular, the follow-up EEG recordings have pointed to an increased power of widespread delta sources and decreased power of widespread alpha and posterior beta (13–20 Hz) sources (Babiloni et al., 2013). In the present study, we hypothesize that cortical sources of resting state EEG rhythms are sensitive to prodromic AD (MCI) state (i.e., cortical sources of resting state EEG rhythms are different among Nold, MCI, and AD subjects) and progression (i.e., cortical sources of EEG rhythms in MCI subjects deteriorate in power over 1 year) in a cohort of amnesic MCI subjects. To this aim, resting state eyes-closed EEG data were recorded in these subjects at baseline (recording I) and after a mean period of approximately 1 year (1-year follow-up; recording II). Cortical sources of the EEG rhythms were estimated using the LORETA freeware (Pascual-Marqui and Michel, 1994), following the procedures reported in the mentioned reference EEG studies (Babiloni et al., 2004, 2006c, 2006d, 2009a, 2011a, 2011b, 2012, 2013). Global cognitive status over time was indexed according to the MMSE score (Folstein et al., 1975).

2. Methods

We have extensively described in recent reports on EEG and aging most of the procedures pertinent to the current study (Babiloni et al., 2004, 2006a, 2006b, 2006c, 2006d, 2006e, 2006f, 2007a, 2007b, 2008a, 2008b, 2009a, 2009b, 2010b, 2010c, 2011a, 2011b, 2011c, 2012, 2013). It should be noted that none of the previous reports addressed the specific aim of the present study, namely the hypothesis that resting state EEG rhythms change over 1 year in amnesic MCI subjects. Of note, part of the individual data sets was used for previous physiological and pathological aging studies on EEG rhythms. Precisely, the EEG recordings of 100% of the Nold and mild AD subjects were taken from our historical EEG database, and approximately 75% of new individual EEG recordings of the amnesic MCI subjects were recorded and analyzed for the present study. Furthermore, we selected the individual data of MCI subjects from our archive based on the following criteria: (1) fitting with the mentioned inclusion/exclusion criteria; (2) availability of the EEG recordings and the MMSE scores recorded at baseline time (recording I; MMSE I) and approximately after 1 year (recording II; MMSE II) from the first recording; and (3) MMSE score at baseline >24. Furthermore, we selected the individual data sets of the Nold and mild AD subjects matched for age, sex, and education with the present MCI group.

2.1. Subjects and diagnostic criteria

For the present multicentric study, 54 MCI subjects were enrolled, most of them being multi-domain including deficits in other cognitive domains (i.e., visuospatial, executive). The inclusion of amnesic MCI patients is justified by the fact that memory impairment is an early cognitive deficit in most of the sporadic late-onset AD patients with hippocampal atrophy, who represent most of the cases of AD (Frisoni et al., 2010; Karantzoulis and Galvin, 2011; Schuff, 2009; van de Pol et al., 2006). We also recruited 45 Nold and 50 mild AD subjects matched for age, sex, and education as control groups, matched for age, sex, and education. Local institutional ethics committees approved the recording and analysis of EEG data for scientific purposes. All experiments were performed with the informed and overt consent of each participant or caregiver, according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the author's Institutional Review Board.

The present inclusion and exclusion criteria for amnesic MCI were based on previous seminal reports (Albert et al., 1991; Flicker et al., 1991; Petersen et al., 1995, 2001; Portet et al., 2006; Zaudig, 1992). Summarizing, the inclusion criteria were as follows: (1) objective memory impairment on neuropsychological evaluation—as defined by performance 1.5 SD less than the mean value for age- and education-matched control subjects for a neuropsychological test battery of neuropsychological tests, to assess cognitive performance in the domains of memory (i.e., Busckhe-Fuld Selective Reminding or Rey Auditory Verbal Learning tests), language, executive function/attention, and visuoconstruction; (2) normal activities of daily living, documented by the history and evidence of independent living; and (3) clinical dementia rating score of 0.5.

The exclusion criteria included: (1) mild AD, diagnosed according to standard protocols including National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984); (2) evidence (including diagnostic MRI procedures) of concomitant dementia such as frontotemporal, vascular dementia, reversible dementias (including pseudodepressive dementia), marked fluctuations in cognitive performance compatible with Lewy body dementia and/or features of mixed dementias; (3) evidence of concomitant extrapyramidal symptoms; (4) clinical and indirect evidence of depression as revealed by Geriatric Depression Scale (GDS) scores >13; (5) other psychiatric diseases, epilepsy, drug addiction, alcohol dependence (revealed in a psychiatric interview), or use of psychoactive drugs including acetylcholinesterase inhibitors or other drugs enhancing cognitive functions; and (6) current or previous uncontrolled or complicated systemic diseases (including diabetes mellitus) or traumatic brain injuries.

Probable AD was diagnosed according to National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984) and *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition criteria. The mild AD patients underwent general medical, neurological, and psychiatric assessments. Patients were also rated with a number of standardized diagnostic and severity instruments that included MMSE (Folstein et al., 1975), clinical dementia rating (Hughes et al., 1982), GDS (Yesavage et al., 1982-1983), Hachinski

Ischemic Score (Rosen et al., 1980), and Instrumental Activities of Daily Living scale (Lawton and Brodie, 1969). Neuroimaging diagnostic procedures (MRI) and complete laboratory analyses were carried out to exclude other causes of progressive or reversible dementias, to have a clinically homogenous mild AD patient group. Exclusion criteria included, in particular, any evidence of: (1) frontotemporal dementia, diagnosed according to the criteria of Lund and Manchester Groups (1994); (2) vascular dementia, diagnosed according to National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences criteria (Roman et al., 1993); (3) extrapyramidal syndromes; (4) reversible dementias (including pseudodementia of depression); and (5) Lewy body dementia, according to the criteria set forth by McKeith et al. (2005). Of note, benzodiazepines, antidepressant, and/or antihypertensive medications were suspended for approximately 24 hours before EEG recordings. This did not ensure a complete washout of the drug; longer periods would have not been applicable for obvious ethical reasons, but it made the drug condition comparable across all patients.

A battery of neuropsychological tests was performed to assess general cognitive performance in the domains of memory, language, executive function/attention, and visuoconstruction abilities. The tests assessing memory included the immediate and the 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 3-words list (Chandler et al., 2004), and/or the delayed recall of a story (Spinnler and Tognoni, 1987). The tests assessing language included the 1-minute verbal fluency for letters (Novelli, 1986), the 1-minute verbal fluency for fruits, animals, or car trades (Novelli, 1986), and/or the Token test (Spinnler and Tognoni, 1987). The tests assessing executive function and attention included the Trail Making Test part A and B (Reitan, 1958), the Digit forward and/or the Digit backward (Orsini et al., 1987). Finally, the tests assessing visuoconstruction included the copy of Rey figures (Rey, 1968), the Ravens Progressive matrices (Raven, 1965), and/or the Clock Drawing test (Shulman et al., 1993).

The Nold subjects were recruited mainly among non-consanguineous relatives of MCI or mild AD subjects. All Nold subjects underwent physical and neurological examinations and cognitive screening (including MMSE and GDS). Subjects affected by chronic systemic illnesses (e.g., diabetes mellitus) were excluded, as were subjects receiving psychoactive drugs. Subjects with a history of present or previous neurological or psychiatric disease were also excluded. All Nold subjects had a GDS score <14 (no depression).

2.2. EEG recordings

Resting state eyes-closed EEG data were recorded in the Nold, MCI, and mild AD subjects by specialized clinical units, in the framework of the diagnostic phase. The EEG recordings were carried out (0.3–70 Hz bandpass) from 19 electrodes positioned according to the International 1020 System (i.e., Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). A specific kind of reference electrode was not used in all recording units, because the present preliminary data analysis and LORETA source analysis were based on a common average reference. To monitor eye movements, the horizontal and vertical electro-oculogram (EOG; 0.3-70 Hz bandpass) data were also collected. All data were digitized in continuous recording mode (5 minutes of EEG; 128,256-Hz sampling rate). It is noteworthy that in MCI subjects, the EEG data, together with the MMSE scores, were recorded at baseline (recording I; MMSE I) and approximately after 1 year (13.8 months; standard error [SE], 0.5; recording II; MMSE II).

2.3. Preliminary EEG-EOG data analysis

The recorded EEG data were analyzed and segmented off-line in consecutive epochs of 2 seconds. The EEG epochs with ocular, muscular, and other types of artifact were preliminarily identified using an automatic computerized procedure. The EEG epochs with sporadic blinking artifacts ($<10\%$ of the total) were corrected using an autoregressive method (Moretti et al., 2003). Two independent experimenters blind to the diagnosis manually confirmed the EEG segments accepted for further analysis. Finally, we rereferenced off-line artifact-free EEG data to a common average for further analysis.

2.4. Spectral analysis of the EEG data

A digital Fast Fourier Transformed (FFT)-based power spectrum analysis (Welch technique, Hanning windowing function, no phase shift) was used to compute power density of the EEG rhythms with 0.5-Hz frequency resolution. The standard frequency bands of interest were delta (24 Hz), theta (48 Hz), alpha 1 (810.5 Hz), alpha 2 (10.513 Hz), beta 1 (1320 Hz), and beta 2 (2030 Hz). It should be noted that the choice of fixed bands did not account for EEG markers such as individual alpha frequency (IAF) peak, defined as the frequency associated with the strongest EEG power at the extended alpha range (Klimesch, 1999). The mean IAF peak, for the MCI subjects, was 9.5 Hz (SE, 0.2) for recording I and 9.2 Hz (SE, 0.2) for recording II. Furthermore, the mean IAF peak was 9.5 Hz (SE, 0.2) for the Nold subjects, and 8.7 Hz (SE, 0.2) for the AD patients. Two statistical analyses (analysis of variance [ANOVA]) were performed to test possible differences in the IAF peak, the first among the Nold, MCI, and mild AD subjects (at recording I), and the second, in the MCI subjects, across 1 year. Statistically significant ANOVA differences were found using the factor, group (MCI, AD, recording I, Nold; independent variable; degrees of freedom (*df*) effect = 2; mean square (MS) effect = 9.22; *df* error = 146; MS error = 1.88; $F = 4.9$; $p < 0.01$) and using the factor, condition (recording I, recording II; dependent variable; *df* effect = 1; MS effect = 1.33; *df* error = 53; MS error = 0.29; $F = 4.5$; $p < 0.04$). To control for the residual effect of IAF on the comparison of EEG variables, the IAF peak was used as a covariate for further statistics.

2.5. Cortical source of EEG rhythms, computed using LORETA

The LORETA software as provided at: http://www.unizh.ch/keyinst/NewLORETA/LORETA01.htm was used for the estimation of cortical sources of EEG rhythms (Pascual-Marqui and Michel, 1994; Pascual-Marqui et al., 1999, 2002). LORETA is a source reconstruction technique belonging to a family of linear inverse solution procedures modeling 3-D distributions of EEG sources (Pascual-Marqui et al., 2002). It has been shown that LORETA was quite efficient when compared with other linear inverse algorithms like minimum norm solution, weighted minimum norm solution, or weighted resolution optimization (Pascual-Marqui et al., 1999; Phillips et al., 2002; Yao and He, 2001). Furthermore, it has been successfully used by independent research groups in recent EEG studies on MCI and AD using the same experimental set-up of the present study (Babiloni et al., 2004, 2006a, 2006b, 2006c, 2006d, 2006e, 2006f, 2007a, 2007b, 2008a, 2008b, 2009a, 2009b, 2010a, 2010b, 2010c, 2011a, 2011b, 2011c, 2011d, 2012, 2013; Dierks et al., 2000; Gianotti et al., 2007). LORETA computes 3-D linear solutions (LORETA solutions) for the EEG inverse problem within a 3-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 coregistered to the Talairach probability brain atlas and digitized at the Brain Imaging Center of the Montreal Neurological Institute (Talairach and

Table 1
Brodmann areas included in the cortical ROIs of the present study

ROI	Brodmann area
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

LORETA solutions were collapsed in frontal, central, parietal, occipital, and temporal ROIs.
Key: LORETA, low resolution brain electromagnetic tomography; ROI, region of interest.

Tournoux, 1988). This compartment includes 2394 voxels (7-mm resolution), each voxel containing an equivalent current dipole.

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 the 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 (0.545 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.

In line with the low spatial resolution of the adopted technique, we used our MATLAB 6.5 software to average LORETA solutions across all voxels of a given cortical macroregion of interest (ROI) such as frontal, central, parietal, occipital, and temporal regions of the brain model (Table 1 lists the ROIs in terms of Brodmann areas, defined within the LORETA source space).

2.6. Statistical analysis of the LORETA solutions

Regional normalized LORETA solutions from Nold, MCI, and mild AD subjects were used as a dependent variable for ANOVA designs using subjects' age, education, sex, and IAF peak as covariates. Mauchlys test was used to evaluate the sphericity assumption. Correction of the *df* was made using the Greenhouse-Geisser procedure. The Duncan test was used for post hoc comparisons ($p < 0.05$). In particular, 2 ANOVA designs were used to address the main scientific issues of the study.

The first ANOVA design aimed at evaluating the control hypothesis that cortical (LORETA) sources of EEG rhythms changed in power across the Nold, MCI, and mild AD groups. The regional normalized LORETA solutions from the Nold, MCI (recording I), and mild AD groups were used as an input. The ANOVA factors (levels) were: group (Nold, MCI, mild AD; independent variable), ROI (central, frontal, parietal, occipital, temporal), and band (delta, theta, alpha 1, alpha 2, beta 1, beta 2). The control hypothesis would be confirmed by the following 2 statistical results: (1) a statistical ANOVA effect including the factor, group ($p < 0.05$); and (2) a post hoc test indicating statistically significant differences of the regional normalized LORETA solutions with the patterns Nold ≠ MCI ≠ AD (Nold < MCI < mild AD or Nold > MCI > mild AD; Duncan test, $p < 0.05$).

The second ANOVA design aimed at evaluating the working hypothesis that cortical (LORETA) sources of EEG rhythms in the MCI subjects deteriorate in power over 1 year. The regional normalized LORETA solutions computed from the MCI subjects at recording I and recording II were used as an input. The ANOVA factors were: time (recording I, recording II, dependent variable), band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (central, frontal, parietal, occipital, temporal). The control hypothesis would be confirmed by the following 2 statistical results: (1) a statistical ANOVA effect including the factor, time ($p < 0.05$); and (2) a post hoc test indicating statistically significant differences of the regional normalized LORETA solutions with the patterns, recording I ≠ recording II (Duncan test, $p < 0.05$).

3. Results

3.1. Demographic and neuropsychological data

Table 2 summarizes the relevant demographic and clinical data of the present Nold, MCI, and mild AD subjects. Four ANOVAs using the factor, group (Nold, MCI, mild AD) were computed to evaluate the presence or absence of statistically significant differences among the 3 groups for MMSE, age, sex, and education. As expected, a statistically significant difference was found for MMSE (*df* effect = 2; MS effect = 543; *df* error = 146; MS error = 3.15; $F = 171$; $p < 0.001$). Duncan post hoc testing indicated the MMSE score was lower in the mild AD than in MCI and Nold subjects ($p < 0.0001$). It was also lower in the MCI than in the Nold subjects ($p < 0.0001$). On the contrary, no statistically significant difference was found for age, sex, and education ($p > 0.35$). However, the age, sex, and education values were used as covariates in the subsequent statistical analysis, to exclude that the small differences in age, sex, and education could influence the subsequent statistical analysis. To better classify the MCI and AD subjects, the mean (SE) values of Trail Making Test part A, part B, part B-A (B minus A), copy of Rey figures (Rey figures), delayed recall of Rey figures (Rey figures recall), verbal fluency for letters (letter fluency), and verbal fluency for fruits, animals, or car trades (categorical fluency) are also reported in Table 2. As expected, a statistically significant difference was found for all neuropsychological tests ($p < 0.0001$), showing a lower performance in the mild AD compared with the MCI subjects.

3.2. Topography of the EEG cortical sources estimated using LORETA

For illustrative purpose, Fig. 1 maps the grand average of the LORETA solutions (i.e., relative power current density at cortical voxels) modeling the distributed EEG cortical sources for delta, theta, alpha 1, alpha 2, beta 1, and beta 2 bands in the Nold, MCI, (recording I), and mild AD groups. The Nold group presented alpha 1 sources with the maximal values of power distributed in the

Table 2
Demographic, clinical, and neuropsychological data (mean score, SE) of the recruited Nold, MCI, and mild AD subjects

Characteristic	MCI	Mild AD	Nold	*p*
n	54	50	45	—
Age, y	72.2 (±1)	73.6 (±1)	72.2 (±1.1)	>0.55
Education, y	7.8 (±0.6)	7 (±0.5)	8.2 (±0.6)	>0.35
Sex, male/female	22/32	17/33	16/29	>0.75
MMSE I	26.9 (±0.2)	21.8 (±0.3)	28.1 (±0.2)	<0.0001
MMSE II	25.8 (±0.3)	—	—	—
TMT A	42.4 (±3.3)	132.3 (±14.7)	—	<0.00001
TMT B	129.7 (±16.5)	385.9 (±36.9)	—	<0.00001
TMT B-A	84.9 (±13.3)	274.3 (±27.6)	—	<0.00001
Rey figures	30.8 (±1)	18.2 (±1.7)	—	<0.00001
Rey figures recall	14.3 (±1.2)	6.9 (±1)	—	<0.0001
Letter fluency	31.7 (±1.4)	24.2 (±1.5)	—	<0.0005
Category fluency	34.2 (±1.1)	24.7 (±1.4)	—	<0.00001

The statistical comparison of the mean values between the 2 groups was performed ($p < 0.05$). The results are reported in the last column.
Key: AD, Alzheimer's disease; Category fluency, verbal fluency for fruits, animals or car trades; Letter fluency, verbal fluency for letters; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; Nold, normal elderly; Rey figures, copy of Rey figures; Rey figures recall, delayed recall of Rey figures; SE, standard error; TMT A, Trail Making Test part A; TMT B, Trail Making Test part B; TMT B-A, Trail Making Test part B- part A.

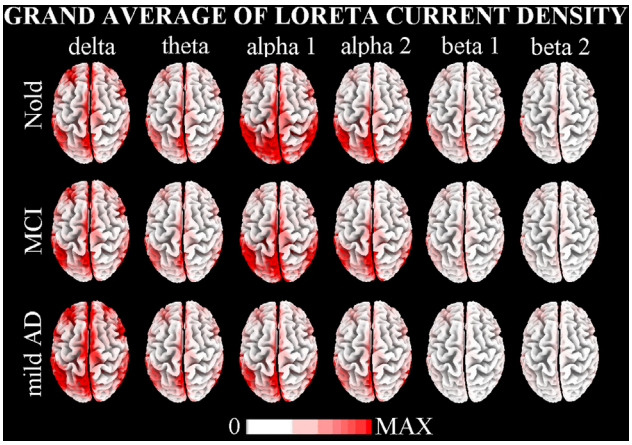

Fig. 1. Grand average of LORETA solutions (i.e., normalized relative current density at the cortical voxels) modeling the distributed EEG sources for delta, theta, alpha 1, alpha 2, beta 1, and beta 2 bands in Nold, MCI (recording I), and mild AD groups. The left side of the maps (top view) corresponds to the left hemisphere. Color scale: all power density estimates were scaled based on the averaged maximum value (i.e., alpha 1 power value of the occipital region in Nold subjects). Abbreviations: AD, Alzheimer's disease; EEG, electroencephalographic; LORETA, low resolution brain electromagnetic tomography; MCI, mild cognitive impairment; Nold, normal elderly.

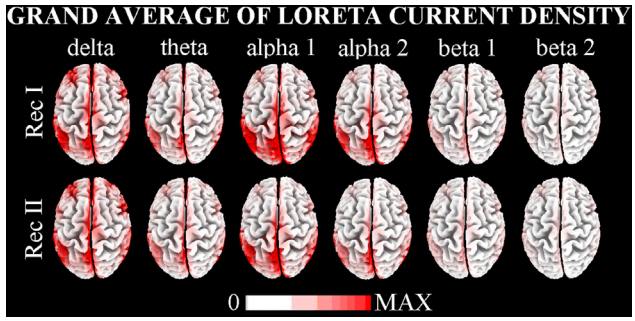

Fig. 2. Grand average of LORETA solutions (i.e., normalized relative current density at the cortical voxels) modeling the distributed EEG sources for delta, theta, alpha 1, alpha 2, beta 1, and beta 2 bands in MCI subjects during recording I and recording II. The left side of the maps (top view) corresponds to the left hemisphere. Color scale: all power density estimates were scaled based on the averaged maximum value. Abbreviations: EEG, electroencephalographic; LORETA, low resolution brain electromagnetic tomography; MCI, mild cognitive impairment; Rec, recording.

posterior regions. Delta, theta, and alpha 2 sources had moderate power values when compared with the alpha 1 sources. Furthermore, the beta 1 and beta 2 sources were characterized by the lowest power values. Compared with the Nold group, the mild AD group showed a strong power reduction of posterior alpha 1 and alpha 2 sources, along with a power increase of widespread delta sources. Compared with the Nold and mild AD groups, the MCI group was characterized by an intermediate power of posterior alpha 1 sources.

Fig. 2 maps the grand average of LORETA solutions (i.e., relative power current density at cortical voxels) modeling the distributed EEG sources for delta, theta, alpha 1, alpha 2, beta 1, and beta 2 bands in the MCI group at recordings I and II (approximately after 1 year). Compared with the recordings I, the recordings II were characterized by a decrease of posterior alpha 1 and alpha 2 sources.

3.3. Statistical comparisons

The ANOVA for the evaluation of the control hypothesis (i.e., EEG sources change in power across the Nold, MCI, and mild AD groups) showed a statistically significant interaction effect (df effect = 40; MS effect = 2.77; df error = 2920; MS error = 0.52; $F = 5.31$; $p < 0.0001$) among the factors, group (Nold, mild AD), band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (frontal, central, parietal, occipital, temporal). Fig. 3 shows the mean regional normalized LORETA solutions relative to this statistical ANOVA interaction. In the figure, the LORETA solutions had the shape of EEG relative power spectra. Notably, the profile and magnitude of these spectra in the Nold, MCI, and mild AD group differed across various cortical macroregions, thus supporting the idea that scalp EEG rhythms are generated by a distributed pattern of cortical sources. Table 3 shows the mean

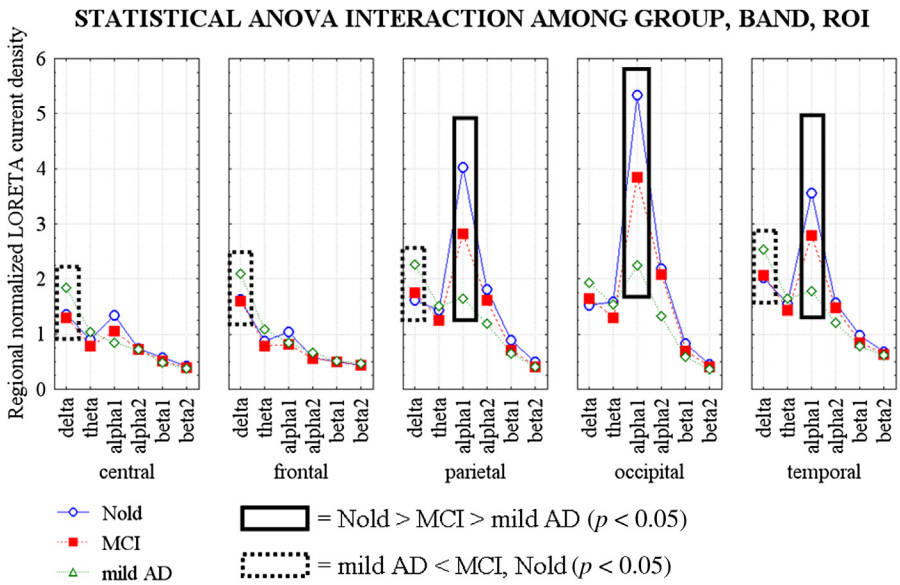

Fig. 3. Statistical ANOVA interaction ($F(40,2920) = 5.99$; $p < 0.0001$) among the factors, froup (Nold, MCI, mild AD), band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (frontal, central, parietal, occipital, temporal). Rectangles indicate the cortical regions and frequency bands in which LORETA solutions presented statistically significant LORETA patterns, Nold ≠ MCI ≠ AD (Duncan test, $p < 0.05$). Abbreviations: AD, Alzheimer's disease; ANOVA, analysis of variance; LORETA, low resolution brain electromagnetic tomography; MCI, mild cognitive impairment; Nold, normal elderly; ROI, region of interest.

Table 3
Regional normalized LORETA current densities for the Nold, MCI, and mild AD groups in the 6 bands and in the 5 ROIs

Band	Nold	MCI	Mild AD	MCI-Nold	AD-Nold
Central delta	1.36 (±0.1)	1.3 (±0.1)	1.85 (±0.1)	−0.06	0.49
Frontal delta	1.63 (±0.2)	1.6 (±0.1)	2.09 (±0.1)	−0.03	0.46
Parietal delta	1.62 (±0.1)	1.74 (±0.1)	2.27 (±0.2)	0.13	0.65
Occipital delta	1.52 (±0.1)	1.65 (±0.2)	1.93 (±0.2)	0.13	0.41
Temporal delta	2.02 (±0.1)	2.06 (±0.1)	2.53 (±0.2)	0.04	0.51
Central theta	0.9 (±0.1)	0.78 (±0.1)	1.04 (±0.1)	−0.13	0.14
Frontal theta	0.88 (±0.1)	0.79 (±0.1)	1.08 (±0.1)	−0.09	0.20
Parietal theta	1.43 (±0.2)	1.25 (±0.1)	1.51 (±0.2)	−0.18	0.07
Occipital theta	1.58 (±0.1)	1.29 (±0.1)	1.53 (±0.2)	−0.29	−0.05
Temporal theta	1.55 (±0.2)	1.43 (±0.1)	1.64 (±0.1)	−0.12	0.09
Central alpha1	1.35 (±0.1)	1.06 (±0.1)	0.85 (±0.1)	−0.29	−0.50
Frontal alpha1	1.04 (±0.1)	0.82 (±0.1)	0.84 (±0.1)	−0.22	−0.20
Parietal alpha1	4.03 (±0.5)	2.82 (±0.1)	1.65 (±0.2)	−1.21	−2.39
Occipital alpha1	5.34 (±0.8)	3.84 (±0.5)	2.24 (±0.3)	−1.49	−3.09
Temporal alpha1	3.57 (±0.4)	2.79 (±0.3)	1.78 (±0.2)	−0.78	−1.78
Central alpha2	0.74 (±0.1)	0.72 (±0.05)	0.73 (±0.1)	−0.02	−0.01
Frontal alpha2	0.57 (±0.05)	0.57 (±0.05)	0.66 (±0.1)	0.00	0.10
Parietal alpha2	1.81 (±0.2)	1.62 (±0.2)	1.19 (±0.1)	−0.20	−0.62
Occipital alpha2	2.19 (±0.3)	2.08 (±0.3)	1.32 (±0.2)	−0.12	−0.87
Temporal alpha2	1.56 (±0.1)	1.48 (±0.1)	1.21 (±0.1)	−0.08	−0.36
Central beta1	0.57 (±0.1)	0.51 (±0.1)	0.49 (±0.05)	−0.06	−0.08
Frontal beta1	0.5 (±0.05)	0.49 (±0.05)	0.52 (±0.05)	−0.01	0.02
Parietal beta1	0.89 (±0.1)	0.71 (±0.05)	0.65 (±0.1)	−0.18	−0.23
Occipital beta1	0.83 (±0.1)	0.69 (±0.1)	0.58 (±0.05)	−0.14	−0.25
Temporal beta1	0.98 (±0.1)	0.85 (±0.1)	0.79 (±0.1)	−0.13	−0.19
Central beta2	0.98 (±0.1)	0.85 (±0.1)	0.79 (±0.1)	−0.03	−0.05
Frontal beta2	0.42 (±0.05)	0.4 (±0.1)	0.37 (±0.05)	0.01	0.04
Parietal beta2	0.43 (±0.05)	0.44 (±0.05)	0.47 (±0.1)	−0.08	−0.09
Occipital beta2	0.49 (±0.05)	0.41 (±0.05)	0.41 (±0.05)	−0.04	−0.10
Temporal beta2	0.46 (±0.1)	0.42 (±0.05)	0.36 (±0.05)	−0.04	−0.06

Data are presented as mean values (standard error). The differences of regional normalized LORETA current density between MCI and Nold (MCI-Nold) and between AD and Nold (AD-Nold) groups are also reported.
Key: AD, Alzheimer's disease; LORETA, low resolution brain electromagnetic tomography; MCI, mild cognitive impairment; Nold, normal elderly; ROI, region of interest.

values (SE) of the regional normalized LORETA current density for the Nold, MCI, and mild AD groups in the 6 bands (delta, theta, alpha 1, alpha 2, beta 1, beta 2) and in the 5 ROIs (central, frontal, parietal, occipital, temporal). The differences of the regional normalized LORETA current density between MCI and Nold and between AD and Nold groups are also reported. The planned post hoc testing showed that the source pattern Nold > MCI > mild AD was fitted by parietal, occipital, and temporal alpha 1 sources ($p < 0.00001$). Furthermore, the frontal, central, parietal, and temporal delta sources were lower in power in the mild AD than in the Nold and MCI groups ($p < 0.002$). Table 4 shows p values (Duncan post hoc) and effect sizes (Cohen's d) for the 5 cortical regions and frequency bands in which LORETA solutions presented statistically significant source patterns Nold ≠ MCI ≠ mild AD and mild AD ≠ Nold and MCI ($p < 0.05$). These results were in line with previous EEG evidence from our group, showing that the cortical sources of the resting state low-frequency alpha rhythms change across Nold, MCI and AD subjects as a function of the global cognitive level (Babiloni et al., 2006b, 2006c, 2007a, 2007b, 2008a).

Table 4
p values (Duncan post hoc) and effect sizes (Cohen's d) for the cortical regions and frequency bands in which LORETA solutions presented statistically significant source patterns, Nold ≠ MCI ≠ mild AD, and mild AD ≠ Nold and MCI ($p < 0.05$)

LORETA current density	Nold versus MCI	Nold versus AD	MCI versus AD
Central delta	NS	0.005, −0.57	0.002, −0.68
Frontal delta	NS	0.007, −0.51	0.005, −0.6
Parietal delta	NS	0.00007, −0.54	0.001, −0.43
Temporal delta	NS	0.002, −0.48	0.004, −0.44
Parietal alpha 1	0.000003, 0.45	0.000002, 1.03	0.000002, 0.65
Occipital alpha 1	0.00001, 0.35	0.000001, 0.78	0.000004, 0.56
Temporal alpha 1	0.00001, 0.34	0.000002, 0.94	0.000002, 0.58

Key: AD, Alzheimer's disease; LORETA, low resolution brain electromagnetic tomography; MCI, mild cognitive impairment; Nold, normal elderly; NS, not significant.

The ANOVA for the evaluation of the working hypothesis (i.e., EEG sources in MCI subjects deteriorate in power over time) showed a statistically significant interaction effect (df effect = 20; MS effect = 0.82; df error = 1060; MS error = 0.19; $F = 4.25$; $p < 0.0001$) among the factors, time (recording I, recording II), band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (central, frontal, parietal, occipital, temporal). Fig. 4 shows the mean regional normalized LORETA solutions relative to this statistical ANOVA interaction. Table 5 shows the mean values (SE) of the regional normalized LORETA current density for the MCI group in the 6 bands (delta, theta, alpha 1, alpha 2, beta 1, beta 2) and in the 5 ROIs (central, frontal, parietal, occipital, temporal) for the 2 EEG recordings (recording I, recording II). The differences of the regional normalized LORETA current density between recording II and recording I are also reported. The Duncan planned post hoc testing showed that compared with recording I, recording II was characterized by lower power of the parietal, occipital and temporal alpha 1 ($p < 0.000005$) and alpha 2 ($p < 0.05$) sources. Table 6 shows p values (Duncan post hoc) and effect sizes (Cohen's d) for the cortical regions and frequency bands in which LORETA solutions presented statistically significant different values in recording I with respect to recording II ($p < 0.05$).

3.4. Additional analyses

As a first analysis, the LORETA source solutions of recording I were correlated with the MMSE score (as an index of the subjects global cognitive status) across all Nold, MCI, and mild AD patients as a single group (Pearson test, $p < 0.05$). The LORETA source solutions were those showing statistically significant post hoc differences

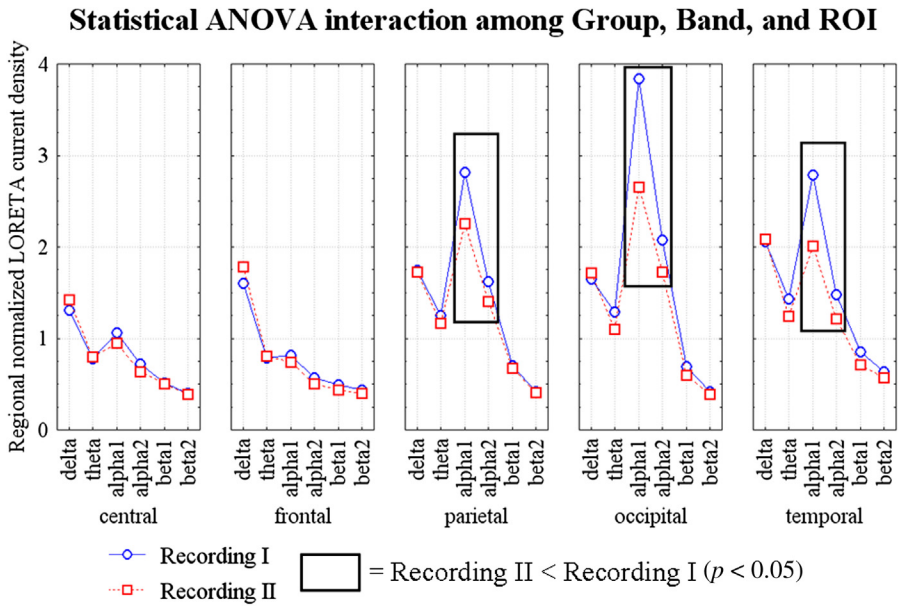

Fig. 4. Statistical ANOVA interaction ($F(20,1060) = 4.25$; $p < 0.00001$) among the factors, time (recording I, recording II), band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (frontal, central, parietal, occipital, temporal). Rectangles indicate the cortical regions and frequency bands in which LORETA solutions presented statistically significant LORETA patterns, recording I ≠ recording II (Duncan test, $p < 0.05$). Abbreviations: ANOVA, analysis of variance; LORETA, low resolution brain electromagnetic tomography; ROI, region of interest.

among the Nold, MCI, and mild AD groups ($p < 0.05$). Results showed that the correlation was positive between the alpha 1 sources and the MMSE score. The significant correlations were observed with the parietal ($r = 0.27$, $p = 0.0007$), occipital ($r = 0.26$, $p = 0.001$), and temporal alpha 1 ($r = 0.28$, $p = 0.0006$).

As a second control analysis, we performed an ANOVA design to confirm the expected decline of the MMSE score in the whole MCI group at 1-year follow-up. As expected, the analysis showed a statistically significant higher value of the MMSE score in the baseline (i.e., MMSE I) than in the 1-year follow-up (i.e., MMSE II; *df* effect = 1; MS effect = 34.3; *df* error = 53; MS error = 1.82; $F = 18.7$; $p < 0.0001$).

A third control analysis tested the hypothesis that the power of the parietal, occipital, and temporal alpha 1 sources (i.e., posterior alpha 1 sources presented a higher difference in the comparison among the Nold, MCI, and mild AD subjects) allows a correct blind classification of the Nold, MCI, and mild AD subjects. To this aim, we used MedCalc software (Mariakerke, Belgium; http://www.medcalc.org), which is a user-friendly software for the production of receiver operating characteristic curves (DeLong et al., 1988). For the AD subjects, we considered the values of posterior alpha 1 sources relative not only to the baseline recording (data shown) but also to the resting state eyes-closed EEG recording performed at approximately 1-year follow-up (recording II; data not shown). Results showed that the posterior alpha 1 sources allowed a moderate classification of the Nold versus AD subjects at recording I (area under the curve [AUC] from 075 to 0.76). The AUC increased in the comparison of the Nold and AD subjects at recording II (0.81 to 0.84), reasonably reflecting the cognitive decline of the AD subjects along 1 year. Furthermore, the posterior alpha 1 sources allowed a modest classification of the Nold versus MCI and of the AD versus MCI subjects at recording I (AUC from 0.6 to 0.65). The AUC increased in the comparison of the Nold and AD subjects at recording II (0.69 to 0.71), reasonably reflecting the cognitive decline of the AD subjects along 1 year. Fig. 5 shows the receiver operating characteristic curves illustrating these results.

These results with $n = 54$ MCI subjects raises a crucial question on the sample size of MCI subjects that must be used to study the MCI state or progression in clinical trials. The sample size used in a study is determined based on the previous data collection, and the need to have sufficient statistical power. Here, we evaluated the sample size required to yield a statistical power $p < 0.05$ using the previously mentioned EEG results on 54 MCI, 50 mild AD, and 40 Nold subjects. For this purpose, we used EEG results on posterior alpha 1 sources that presented a higher difference in the comparison among the Nold, MCI, and mild AD subjects (MCI state markers). These sources showed higher differences in the comparison between recording I and recording II in the mild AD patients (MCI progression markers). Sample size was calculated using Cohens' tables (Cohen, 1977). To this aim, we used free software for calculating the sample sizes considering the anticipated effect size, the probability level, and the desired statistical power level (http://www.danielsoper.com/statcalc3/calc.aspx?id=47). Table 7 reports the sample sizes required to yield a probability level at $p = 0.05$ and desired statistical power level at $p = 0.8$. We used EEG data of parietal, occipital, and temporal alpha 1 sources. Such findings suggest that an ideal sample size of approximately 90 subjects per group allows the use of the present EEG markers for the study of the MCI status when 2 MCI and Nold groups are compared. Furthermore, an ideal sample size of approximately 35 subjects per group allows the study of the MCI state according to these EEG markers when MCI and AD groups are compared. Finally, an ideal sample size of approximately 80 amnesic MCI subjects allows the use of the present EEG markers for the study of the disease progression at 1-year follow-up.

4. Discussion

In this study, we tested the hypothesis that the cortical sources of resting state EEG rhythms were sensitive to prodromal AD (amnesic MCI) state and disease progression in a cohort of amnesic MCI subjects. As a first step of the study, the EEG source markers of the disease state were extracted from the MCI subjects baseline EEG recordings. The parietal, occipital, and temporal low-frequency alpha sources showed intermediate values in power in the MCI compared with the Nold and AD subjects (Babiloni et al., 2006b, 2006c, 2007a, 2007b, 2008a).

Table 5
Regional normalized LORETA current density

Region	MCI (recording I)	MCI (recording II)	Recording II − recording I
Central delta	1.3 (±0.1)	1.42 (±0.1)	0.12
Frontal delta	1.6 (±0.1)	1.78 (±0.1)	0.18
Parietal delta	1.74 (±0.1)	1.72 (±0.2)	−0.02
Occipital delta	1.65 (±0.2)	1.71 (±0.3)	0.07
Temporal delta	2.06 (±0.1)	2.09 (±0.1)	0.03
Central theta	0.78 (±0.1)	0.8 (±0.1)	0.02
Frontal theta	0.79 (±0.1)	0.81 (±0.1)	0.02
Parietal theta	1.25 (±0.1)	1.17 (±0.2)	−0.08
Occipital theta	1.29 (±0.1)	1.1 (±0.1)	−0.20
Temporal theta	1.43 (±0.1)	1.24 (±0.1)	−0.19
Central alpha1	1.06 (±0.1)	0.95 (±0.1)	−0.11
Frontal alpha1	0.82 (±0.1)	0.74 (±0.1)	−0.08
Parietal alpha1	2.82 (±0.1)	2.25 (±0.3)	−0.56
Occipital alpha1	3.84 (±0.5)	2.65 (±0.3)	−1.19
Temporal alpha1	2.79 (±0.3)	2.01 (±0.2)	−0.78
Central alpha2	0.72 (±0.05)	0.64 (±0.1)	−0.08
Frontal alpha2	0.57 (±0.05)	0.51 (±0.05)	−0.06
Parietal alpha2	1.62 (±0.2)	1.41 (±0.3)	−0.21
Occipital alpha2	2.08 (±0.3)	1.72 (±0.3)	−0.36
Temporal alpha2	1.48 (±0.1)	1.22 (±0.1)	−0.26
Central beta1	0.51 (±0.1)	0.51 (±0.1)	0.00
Frontal beta1	0.49 (±0.05)	0.44 (±0.05)	−0.05
Parietal beta1	0.71 (±0.05)	0.68 (±0.1)	−0.03
Occipital beta1	0.69 (±0.1)	0.59 (±0.1)	−0.10
Temporal beta1	0.85 (±0.1)	0.71 (±0.1)	−0.14
Central beta2	0.85 (±0.1)	0.39 (±0.05)	−0.01
Frontal beta2	0.4 (±0.1)	0.40 (±0.05)	−0.04
Parietal beta2	0.44 (±0.05)	0.40 (±0.05)	−0.01
Occipital beta2	0.41 (±0.05)	0.39 (±0.1)	−0.03
Temporal beta2	0.42 (±0.05)	0.57 (±0.1)	−0.07

Mean values (SE) of the relative LORETA current density for the MCI group in the 6 bands (delta, theta, alpha 1, alpha 2, beta 1, beta 2) and in the 5 ROIs (central, frontal, parietal, occipital, temporal) for the 2 EEG recordings (recording I, recording II). The differences of regional normalized LORETA current density between recording II and recording I are also reported.
Key: EEG, electroencephalographic; LORETA, low resolution brain electromagnetic tomography; MCI, mild cognitive impairment; ROI, region of interest; SE, standard error.

As a second step of the study, the EEG source markers of MCI progression were obtained using the comparison between the baseline and the 1-year follow-up EEG recordings. In the current MCI group, the parietal, occipital, and temporal alpha sources at low- and high-frequency decreased in power in the 1-year follow-up compared with baseline. These alpha source solutions were used as input for the power analysis at $p < 0.05$ of the sample size required to test drugs against AD symptoms and/or disease in future clinical trials. This was done calculating Cohens' d values (Cohen, 1977). Results showed that an ideal sample size of approximately 80 amnesic MCI subjects allows the use of the posterior low-frequency alpha source markers for the study of the disease progression at 1-year follow-up. These results extend to the spatial source domain previous evidence of longitudinal EEG studies showing that at approximately 2-year follow-up, MCI patients were characterized by a power increase of delta and theta rhythms in temporal and occipital scalp regions associated with a power reduction of beta rhythms (Jelic et al., 2000). In the same line, previous studies have shown that AD patients present a power increase of delta and theta rhythms in temporal, parietal and/or occipital scalp regions when tested at 1- to 3-year follow-up (Coben et al., 1985; Soininen et al., 1989).

As for novelty, the present study compared the EEG source markers of the MCI (prodromic stage of AD) status and of the disease progression in the mentioned MCI group. Common EEG source markers of the MCI state and progression were observed at parietal, occipital, and temporal low-frequency alpha rhythms. On the other hand, peculiar EEG source markers of the MCI progression were observed at parietal, occipital, and temporal high-frequency alpha rhythms. A neurophysiologic explanation of the present results stems on the following theoretical considerations. In the condition of awake resting state eyes-closed condition, dominant low-frequency alpha rhythms (approximately 8–10 Hz) would denote the synchronization of diffuse neural networks regulating the fluctuation of the subject's global awake and conscious states, whereas high-frequency alpha rhythms (approximately 10–12 Hz) would denote the synchronization of more selective neural networks specialized in the processing of modal specific or semantic information (Klimesch, 1999; Pfurtscheller and Lopes da Silva, 1999). When the subject is engaged in sensorimotor or cognitive tasks, alpha and low-frequency beta rhythms reduce in power (i.e., desynchronization or blocking) and are replaced by fast EEG oscillations at high-frequency beta (approximately 20–30 Hz) and gamma (>30 Hz) rhythms (Pfurtscheller and Lopes da Silva, 1999).

Keeping in mind these theoretical considerations, it can be speculated that in the resting state eyes-closed condition, the EEG source markers of amnesic MCI condition and of the disease progression along 1 year would reflect an abnormal tonic desynchronization of the cortical low-frequency alpha rhythms, suggesting an exaggerated and unselective activation of brain networks underlying cortical arousal (Klimesch, 1999; Pfurtscheller and Lopes da Silva, 1999). In the MCI progression, this abnormality would be associated with an abnormal tonic desynchronization of the cortical high-frequency alpha rhythms indicating a worsening of the selective neural networks specialized in the processing of modal specific or semantic information (Klimesch, 1999). The tonic desynchronization of the resting state alpha rhythms, as a reflection of a tonic and unselective cortical excitation, would be associated with an abnormal brain function and predicts cognitive deficits in humans. Indeed, effective cognitive processing is expected to stem on the selectivity and flexibility of the excitation and inhibition across brain neural networks during the resting state condition and task demands (see for example the concept of neural efficiency; Haier et al., 2004; Rypma et al., 2006; Vernon, 1993).

The present results motivate further investigations aimed at testing hypotheses crucial for the eventual clinical application of the present EEG markers. First, future investigations should stratify a larger population of amnesic MCI subjects as prodromal AD at different stages of the disease on the basis of the biomarkers mentioned on the recent international guidelines such as CSF, MRI, or PET markers (Albert et al., 2011; Jack et al., 2011; McKhann et al., 2011; Sperling et al., 2011). It is expected that the present EEG markers of disease progression show a steeper decline at 1-year follow-up in the amnesic MCI subjects with more evident signs of neurodegeneration, unveiled using the combination of the mentioned biomarkers. Second, future investigations should

Table 6
p values (Duncan post hoc) and effect sizes (Cohen's d) for the cortical regions and frequency bands in which LORETA solutions presented statistically significant source patterns, recording II ≠ recording I in MCI subjects ($p < 0.05$)

Region	Recording II versus recording I
Parietal alpha 1	0.000003, −0.36
Occipital alpha 1	0.000003, −0.4
Temporal alpha 1	0.000004, −0.43
Parietal alpha 2	0.02, −0.19
Occipital alpha 2	0.00007, −0.18
Temporal alpha 2	0.006, −0.29

Key: LORETA, low resolution brain electromagnetic tomography; MCI, mild cognitive impairment.

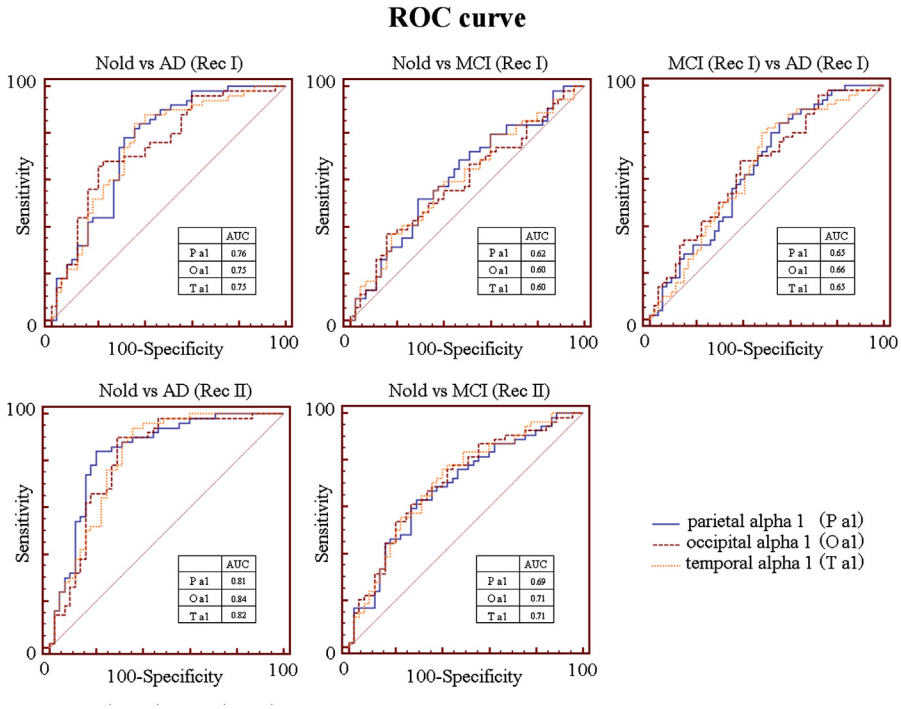

Fig. 5. Mean ROC curves illustrating the performance of the classifier using individual parietal, occipital, and temporal alpha 1 sources for the blind classification of the EEG datasets of Nold versus AD (recording I), Nold versus MCI (recording I), MCI (recording I) versus AD (recording I), Nold versus AD (recording II), and Nold versus MCI subjects (recording II). Abbreviations: AD, Alzheimer's disease; EEG, electroencephalographic; MCI, mild cognitive impairment; Nold, normal elderly; ROC, receiver operating characteristic.

develop a careful evaluation of the changes of the EEG markers in Nold subjects at 1-year follow-up, to correct for the deterioration of the resting state EEG rhythms along physiological aging. Finally, future studies should use more advanced classifiers such as using artificial neural networks or Bayesian predictors to test the hypothesis that the present EEG markers can reflect and predict cognitive decline in single amnesic MCI individuals for personalized clinical management. For the assessment of cognitive functions, the use of ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale) would allow a better characterization of the MCI and AD patients with reference to those of the main clinical studies on AD.

In conclusion, the results of the present study suggest that the cortical sources of resting state low- and high-frequency alpha rhythms seem to be sensitive—at least at the group level—to the cognitive decline that occurred in the amnesic MCI group over 1 year. The use of these cost-effective alpha source markers in future clinical trials is encouraged by the relatively low number of amnesic MCI subjects required to show the effects of the disease progression (approximately 80) on the basis of the present power analysis at $p < 0.05$.

Table 7
Sample sizes required to yield a statistical power of $p < 0.05$

Region	MCI state		MCI progression
	(MCI vs. Nold)	(MCI vs. mild AD)	
Parietal alpha 1	62	30	97
Occipital alpha 1	102	41	78
Temporal alpha 1	108	38	68

Sample sizes required to yield a statistical power of $p < 0.05$ using EEG data of parietal, occipital, and temporal alpha 1 sources of MCI ($n = 54$), mild AD ($n = 50$), and Nold ($n = 45$) subjects. Sample size was calculated using Cohen's tables.
Key: AD, Alzheimer's disease; EEG, electroencephalographic; MCI, mild cognitive impairment; Nold, normal elderly.

Disclosure statement

The authors declare that they have no conflicts of interest in the research.

Local institutional ethics committees approved the recording and analysis of EEG data for scientific purposes. All experiments were performed with the informed and overt consent of each participant or caregiver, according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the author's Institutional Review Board.

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