CORTICAL SOURCES OF RESTING STATE EEG ALPHA RHYTHMS DETERIORATE ACROSS TIME IN SUBJECTS WITH AMNESIC MILD COGNITIVE IMPAIRMENT

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Running title: Resting EEG and MCI progression

Keywords: Mild cognitive impairment (MCI), Electroencephalography (EEG), Low resolution brain electromagnetic tomography (LORETA), Disease tracking

Acknowledgments: This research was developed thank to the financial support by European Committee for the FP7-"ICT Infrastructure" project entitled "Diagnostic Enhancement of Confidence by an International Distributed Environment" ("DECIDE", Grant Agreement: RI-261593) in the framework of the validation of spectral electroencephalographic indexes of disease progression in subjects with mild cognitive impairment. Therefore, this article is presented on behalf of the DECIDE Consortium. Please find complete information about the Consortium and principal investigators at www.eu-decide.eu.

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 Evaluation, MMSE I= 26.9 ± 0.2 standard error, SE) and at approximately 1-year follow up (13.8 months ± 0.5 SE; MMSE II= 25.8 ± 0.2 SE). As a control, EEG recordings were also performed in 45 normal elderly (Nold) and in 50 mild AD 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 by low-resolution brain electromagnetic tomography (LORETA). Compared to the Nold and mild AD 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 group level- to the cognitive decline occurring in the amnesic MCI group over 1 year, and might represent cost-effective, non-invasive and widely available markers to follow amnesic MCI populations in large clinical trials.

Introduction

Mild cognitive impairment (MCI) is a clinically intermediate state between elderly subjects with normal cognition and Alzheimer's disease (AD). MCI subjects show objective cognitive impairment on neuropsychological tests, but do not yet fulfil the clinical criteria for dementia (Flicker et al., 1991; Petersen et al., 1995, 2001). MCI may be considered as a precursor to AD (Galluzzi et al., 2001; Scheltens et al., 2002; Arnaiz and Almkvist, 2003), given the high rate of progression from MCI to AD (Bachman et al., 1993; Gao et al., 1998; Petersen et al., 2001). In cognitively intact elderly subjects, the annual rate of transition to AD ranges from 0.17% to 3.86% (Petersen et al., 2001; Frisoni et al. 2007), 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 over time (Bennett et al., 2002; Larrieu et al., 2002), as cumulative incidence rates for AD range from 40 to 60% after about 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 as 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 (Braak and Braak, 1991; Rogers et al., 1996; Small et al., 1995; Nestor et al., 2004; Dubois et al., 2007; Albert et al., 2011). In the light of the recently proposed new international guidelines (Dubois et al., 2007; Albert et al., 2011), prodromal stages of AD in MCI subjects can be diagnosed by abnormal dosages of the "A beta amyloid to tau" ratio in cerebrospinal fluid (CSF) and deposition of A beta amyloid in the brain, as revealed by 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 by FDG-PET (Dubois et al., 2007; Albert et al., 2011). In 2011, the National Institute on Aging-Alzheimer's Association workgroups proposed the following four 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

cerebrospinal fluid (CSF) sampled by lumbar puncture (Tapiola et al., 2009), (2) deposition of A beta amyloid in the brain, as revealed by positron emission tomography-amyloid Pittsburg Compound B (PET-PIB; Rowe et al., 2007; Ikonomovic et al., 2008), (3) hypometabolism of the posterior cingulate, precuneus, parietal and temporal regions as revealed by positron emission tomography-fluoro-deoxy-glucose positron emission tomography (PET-FDG; Jagust et al.,2007), and (3) atrophy of the hippocampus as revealed by structural magnetic resonance imaging (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 vivid discussion about the sensitivity and specificity of these biomarkers as different values were reported on different international databases (Toussaint et al., 2012; Takahashi et al., 2013). Moreover, CSF markers are invasive, PET markers are costly and exposed to radiation, and MRI markers of hippocampus volume are ~~either invasive (and relatively reliable when comparing different laboratories) or~~ relatively expensive for serial screening of large elderly populations at risk of AD; therefore, they should be better devoted to a second line screening on high-risk subjects intercepted via a first line fully non-invasive 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, is fully non invasive. It can also be used to collect serial measurements without incurring misleading effects that are solely due to the repetition of the procedure (Rossini et al., 2007). Prior studies have successfully investigated the resting state eyes closed EEG rhythms in MCI and AD subjects. Compared to normal elderly subjects (Nold), 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; Ponomareva et al., 2003; Jeong, 2004); moreover, specific patterns of dysconnection have been identified by using dedicated software to investigate brain connectivity based on EEG/MEG rythms coherence/synchronization (see D'Amelio & Rossini for a review 2012). These EEG abnormalities are associated with altered regional cerebral blood flow/metabolism and with impaired global cognitive function as evaluated by the mini mental state examination (Sloan et al., 1995; Rodriguez et al., 1998, 1999; Jeong, 2004). Similarly, MCI subjects show a decrease of alpha rhythms compared to normal elderly subjects (Zappoli et al., 1995; Elmstahl and Rosen, 1997; Huang et al., 2000; Jelic et al., 2000; Koenig et al., 2005).

Furthermore, the EEG abnormalities in MCI and AD subjects are related to loss of neurons and synaptic dysfunction. To 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 (Förstl et al., 1994); (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 2006e); (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), as well as 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 grey 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 grey 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., 2012a). 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 as unveiled by atrophy in cortical and sub-cortical 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, language and executive function) in AD and in mild cognitive impairment (MCI) subjects (Babiloni et al., 2006a, 2007b; Roh et al., 2011). In particular, the power of alpha rhythms was positively related to global cognitive status (i.e. MMSE score), immediate memory for digits probing focused attention, and verbal memory recall (Babiloni et al., 2006a, 2007b; Roh et al., 2011). On the contrary, the power of delta and theta rhythms was negatively related to global cognition status, visuo-spatial immediate memory probing focused attention, verbal memory recall, visuo-spatial memory recall, language and executive functions (Babiloni et al., 2006a, 2007b; van der Hiele et al., 2007; Roh et al., 2011). Furthermore, an increase of beta power (13-25 Hz) was positively correlated with a good performance for global cognition, attention, memory, visuo-spatial, 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 the cognitive decline in MCI and disease progression in AD (Coben et al., 1985; Soininen et al., 1989; Jelic et al. 2000). In one 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, 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 about 30

months between baseline and follow up EEG recordings (Coben et al., 1985). At the follow up, the AD patients showed a power increase of theta and delta rhythms in parietal and occipital scalp regions associated to 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). About 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), which uses thousands of dipole sources within a 3-D brain model co-registered into Talairach space (Talairach and Tournoux, 1988). 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. LORETA is a promising technique for research in MCI and AD since (i) it is freeware, and can be freely downloaded by any research unit worldwide for the control/replication of the results and for future scientific and clinical applications; and (ii) it has been successfully used in research on MCI, AD and EEG markers by independent research groups worldwide (Dierks et al., 2000; Babiloni et al., 2004, 2006a,b,c,d,e,f, 2007a,b,c, 2008a,b, 2009a,b, 2010a,b, 2011a,b,c, 2012a,b; Gianotti et al., 2007). In particular, previous studies from our group have shown that: 1) the posterior sources of dominant alpha rhythms (about 8-10 Hz) were abnormal in AD subjects when compared to Nold, cerebrovascular dementia and Parkinson disease subjects (Babiloni et al., 2004; Babiloni et al., 2011a); 2) the posterior sources of delta (<4 Hz) and dominant alpha rhythms were related to global cognitive status (i.e. MMSE score) in both MCI and AD subjects (Babiloni et al, 2006a); 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, 2012b); 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 early stage over 1 year (Babiloni et al., 2012a). In particular, the follow-up EEG recordings have pointed to an increased power of widespread delta sources as well as decreased power of widespread alpha and posterior beta (13-20 Hz) sources (Babiloni et al., 2012a). In the present study, we hypothesize that cortical sources of resting state EEG rhythms are sensitive to both 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 about 1 year (1-year follow up; Recording II). Cortical sources of the EEG rhythms were estimated by means of the LORETA freeware (Pascual Marqui and Michel, 1994), following the procedures reported in the mentioned reference EEG studies (Babiloni et al., 2004, 2006a,b, 2009a, 2011a,b, 2012a,b). Global cognitive status over time was indexed by the mini mental state evaluation (MMSE) score (Folstein et al., 1975).

Methods

We have extensively described in recent papers on EEG and aging most of the procedures (subjects recruitment procedures, EEG recordings, LORETA analysis, statistics) pertinent to the current study (Babiloni et al., 2004, 2006a,b,c,d,e,f, 2007a,b,c, 2008a,b, 2009a,b, 2010a,b, 2011a,b,c, 2012a,b). Those papers described the results of an international multi-centric EEG study on pathological aging, involving several neurological research units. It should be remarked that none of the previous papers 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 was taken from our "historical" EEG database. On the other hand, about 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 on the basis of the following criteria: (i) fitting with the mentioned inclusion/exclusion criteria; (ii) 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 (iii) MMSE score at baseline higher than 24. Furthermore, we selected the individual data sets of the Nold and mild AD subjects matched for age, gender and education with the present MCI group.

Subjects and diagnostic criteria

For the present multi-centric study, 54 MCI subjects were enrolled, most of them being multi-domain including deficits in other cognitive domains (i.e. visuo-spatial, 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 are the vast majority of the cases of AD (Karantzoulis and Galvin, 2011, Frisoni et al., 2010; Schuff, 2009; van de Pol et al., 2006). We also recruited 45 Nold and 50 mild AD subjects matched for age, gender and education as control groups, matched for age, gender 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, in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the Author's Institutional Review Board.

The present inclusion and exclusion criteria for amnesic MCI were based on previous seminal reports (Albert et al., 1991; Flicker et al., 1991; Petersen et al., 1995, 2001; Rubin et al., 1989; Zaudig, 1992; Portet et al., 2006). Summarizing, the inclusion criteria were as follows: (i) objective memory impairment on neuropsychological evaluation - as defined by performances $\geq$1.5 standard deviations below the mean value for age- and education-matched controls 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 visuo-construction; (ii) normal activities of daily living as documented by the history and evidence of independent living; and (iii) clinical dementia rating (CDR) score of 0.5.

The exclusion criteria included: (i) mild AD, as diagnosed by standard protocols including NINCDS-ADRDA (McKhann et al., 1984); (ii) evidence (including diagnostic MRI procedures) of concomitant dementia such as frontotemporal, vascular dementia, reversible dementias (including pseudo-depressive dementia), marked fluctuations in cognitive performance compatible with Lewy body dementia 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 (GDS) scores higher than 13; (v) other psychiatric diseases, epilepsy, drug addiction, alcohol dependence (as revealed by a psychiatric interview) or use of psychoactive drugs including acetylcholinesterase inhibitors or other drugs enhancing cognitive functions; and (vi) current or previous uncontrolled or complicated systemic diseases (including diabetes mellitus) or traumatic brain injuries.

Probable AD was diagnosed according to NINCDS-ADRDA (McKhann et al., 1984) and DSM IV 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), CDR (Hughes et al., 1982), GDS (Yesavage et al., 1983), Hachinski Ischemic Score (HIS, Rosen et al., 1980), and Instrumental Activities of Daily Living scale (IADL, Lawton and Brodie, 1969). Neuroimaging diagnostic procedures (MRI) and complete laboratory analyses were carried out to exclude other causes of progressive or reversible dementias, in order to have a clinically homogenous mild AD patient group. Exclusion criteria included, in particular, any evidence of (i) frontotemporal dementia, diagnosed according to criteria of Lund and Manchester Groups (1994), (ii) vascular dementia, diagnosed according to NINDS-AIREN criteria (Roman et al., 1993), (iii) extra-pyramidal syndromes, (iv) reversible dementias (including pseudodementia of depression); and (v) Lewy body dementia, according to the criteria by McKeith (2005). Of note, benzodiazepines, antidepressant and/or antihypertensive were suspended for about 24 h before EEG recordings. This did not insure a complete washout of the drug –longer periods would had not been applicable for obvious ethical reasons- but made it comparable the drug condition across the patients.

A battery of neuropsychological tests was performed to assess general cognitive performance in the domains of memory, language, executive function/attention, and visuo-construction abilities. The tests assessing memory included the immediate and the delayed recall measure of the Rey Auditory Verbal Learning Test (Rey, 1958; Carlesimo, 1996), the delayed recall of Rey figures (Rey, 1968), the delayed recall of a 3-words list (Chandler, 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 e 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 1987). Finally, the tests assessing visuo-construction included the copy of Rey figures (Rey, 1968), the Raven's Progressive matrices (Raven, 1965), and/or the Clock Drawing test (Shulman, 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 as well as 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 lower than 14 (no depression).

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 10–20 System (i.e. Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2). A specific kind of reference electrode was not used in all recording units, given that the present preliminary data analysis and LORETA source analysis were based on common average reference. To monitor eye movements, the horizontal and vertical electro-oculogram (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). 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 ± 0.5 standard error, SE; Recording II; MMSE II). All 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 or the subject opened the eyes.

Duration and all other technical characteristics of the EEG recording (5 min) allowed the comparison of the present results with several previous MCI and AD studies using either EEG recording periods shorter than 5 min (Babiloni et al., 2004, 2006a,b,c,d,e,f, 2007a,b,c, 2008a,b, 2009a,b, 2010a,b, 2011a,b,c, 2012a,b; Buchan et al., 1997; Pucci et al., 1999; Rodriguez et al., 2002; Szelies et al., 1999) or about 1 min (Dierks et al., 1993, 2000); longer epochs would have reduced data variability but increased risks for dropping vigilance and arousal.

Preliminary EEG-EOG data analysis

The recorded EEG data were analyzed and segmented off-line in consecutive epochs of 2 s. The EEG epochs with ocular, muscular, and other types of artifact were preliminary identified by a computerized automatic procedure. The EEG epochs with sporadic blinking artifacts (less than 10% of the total) were corrected by an autoregressive method (Moretti et al., 2003). Two independent experimenters blind to the diagnosis manually confirmed the EEG segments accepted for further analysis. Of note, special attention was devoted to avoid the inclusion of EEG segments and individual data sets with EEG signs of drowsiness or pre-sleep stages. Finally, we re-referenced off-line artifact free EEG data to common average for further analysis.

Spectral analysis of the EEG data

A digital FFT-based power spectrum analysis (Welch technique, Hanning windowing function, no phase shift) computed power density of the EEG rhythms with 0.5 Hz frequency resolution. The standard frequency bands 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). These frequency bands were chosen averaging those used in previous relevant EEG studies on dementia (Besthorn et al., 1997; Chiaramonti et al., 1997; Jelic et al., 1996; Leuchter et al., 1993; Rodriguez et al., 1999; Babiloni et al., 2004, 2006a,b,c,d,e,f, 2007a,b,c, 2008a,b, 2009a,b, 2010a,b, 2011a,b,c, 2012a,b). Sharing of a frequency bin by two contiguous bands is a widely accepted procedure (Besthorn et al., 1997; Holschneider et al., 1999; Jelic et al., 1996; Kolev et al., 2002; Nobili et al., 1998; Pucci et al., 1997). Furthermore, this fits the theoretical consideration that near EEG rhythms may overlap at their frequency borders (Babiloni et al., 2004, 2006a,b,c,d,e,f, 2007a,b,c, 2008a,b, 2009a,b, 2010a,b, 2011a,b,c, 2012a,b; Klimesch, 1996, 1999; Klimesch et al., 1997, 1998). This choice made more significant the source differences at a given band but not at the contiguous ones. However, 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 (±0.2 SE) for the Recording I and 9.2 Hz (±0.2 SE) for the Recording II. Furthermore, the mean IAF peak was 9.5 Hz (±0.2 SE) for the Nold subjects, and 8.7 Hz (±0.2 SE) for the AD patients. Two statistical analyses (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 one year. Statistically significant ANOVA differences were found both using the factor Group (MCI, AD- Recording I, Nold; independent variable; df Effect=2; 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 (together with age, gender and education) for further statistics.

We could not use narrow frequency bands for beta 1 (13–20 Hz) and beta 2 (20–30 Hz) bands because of the variability of beta peaks in the power spectra. Therefore, LORETA results for the beta bands could suffer from the limitations as sensitivity of EEG spectral analyses for large bands (Szava et al., 1994).

Cortical source of EEG rhythms as computed by 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 3D distributions of EEG sources (Pascual-Marqui et al., 2002). It has been shown that LORETA was quite efficient when compared to 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). LORETA can be used from EEG data collected by low spatial sampling of 19-electrodes 10-20 system montage, when cortical sources are estimated from resting EEG rhythms (Anderer et al., 2003, 2004; Babiloni et al., 2004, 2006a,b,c,d,e,f, 2007a,b,c, 2008a,b, 2009a,b, 2010a,b, 2011a,b,c, 2012a,b; Laufer and Pratt, 2003; Mulert et al., 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 one (Dierks et al., 2000; Babiloni et al., 2004, 2006a,b,c,d,e,f, 2007a,b,c, 2008a,b, 2009a,b, 2010a,b, 2011a,b,c, 2012a,b; Gianotti et al., 2007). Noteworthy, this electrode montage is considered as an adequate EEG spatial sampling for the estimation of cortical sources of eyes closed resting state EEG rhythms, since these rhythms are widely represented across all human cerebral cortex in contrast to the circumscribed functional topography of event-related EEG changes (especially at high frequencies) in response to specific sensory or motor events. Therefore, eyes closed resting state EEG rhythms can be properly sampled with a relatively low amount of electrodes, as opposed to the higher spatial sampling required to take into account to the detailed functional topography of event-related EEG activity. This relatively low-spatial sampling of EEG rhythms is in line with the fact that LORETA solutions are intrinsically maximally smoothed at source space, due to its regularization procedure (Pascual-Marqui and Michel, 1994). LORETA computes 3D 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 grey 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 and Tournoux, 1988). This compartment includes 2394 voxels (7 mm resolution), each voxel containing an equivalent current dipole. Of note, EEG electrode positions were not co-registered to individual brain source models; unfortunately, the official LORETA package did not include

software to do so and we could not obtain the digitalization of the electrode position from our clinical units.

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. The general procedure fitted the LORETA solutions in a Gaussian distribution and reduced inter-subject variability (Leuchter et al., 1993; Nuwer, 1988). Of note, other methods of normalization using the principal component analysis are effective for estimating the subjective global factor scale of the EEG data (Hernàndez et al., 1994). These methods are not available in the LORETA package, so they were not used in this study.

Solutions of the EEG inverse problem are under-determined and ill conditioned when the number of spatial samples (electrodes) is lower than the number of the unknown samples (current density at each voxel). In order to properly address this problem, the cortical LORETA solutions predicting scalp EEG spectral power density were regularized to estimate distributed rather than punctual EEG source patterns (Pascual-Marqui and Michel, 1994, Pascual-Marqui et al., 1999, 2002). In line with the low spatial resolution of the adopted technique, we used our MATLAB software to average LORETA solutions across all voxels of a given cortical macroregion of interest (ROI) such frontal, central, parietal, occipital, and temporal regions of the brain model (Table 1 lists the ROIs in terms of Brodmann areas as defined within the LORETA source space). This methodological option may minimize the effects of poor LORETA estimates in deep voxels (i.e. including those of the limbic region) at which the estimation of EEG sources could be imprecise, especially using an EEG spatial sampling from 19 electrodes (10-20 system).

Finally, the main advantage of the regional analysis of LORETA solutions was that our modeling could disentangle rhythms of contiguous cortical areas. For example, the rhythms of the occipital source were disentangled with respect to those of the contiguous parietal and temporal sources etc. This was made possible by the fact that LORETA solves the linear inverse problem by taking into account the well-known effects of the head as a volume conductor. With respect to other procedures of data reduction, this type of regional approach may represent an important reference for multimodal comparisons with structural and functional neuroimaging methods (SPECT, PET, surface EEG/MEG topography). Finally, it can be stated that the present approach

represents a clear methodological improvement compared to EEG spectral analyses surface electrodes. Indeed, the EEG potentials collected at each scalp electrode may be strongly affected by head volume conductor effects. For example, occipital electrodes collect scalp potentials generated not only from the occipital cortex but also influenced (at a lower extent) from parietal and temporal cortices due to head volume conductor effects.

Insert here Table 1

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, gender, and IAF peak as covariates. Mauchly's test evaluated the sphericity assumption. Correction of the degrees of freedom was made with the Greenhouse-Geisser procedure. Duncan test was used for post-hoc comparisons ($p<0.05$). In particular, two 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), Region of Interest (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 two statistical results: (i) a statistical ANOVA effect including the factor Group ($p<0.05$); (ii) a post-hoc test indicating statistically significant differences of the regional normalized LORETA solutions with the patterns Nold $\neq$ MCI $\neq$ 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 two statistical results: (i) a statistical ANOVA effect including the factor Time ($p<0.05$); (ii) a post-hoc test indicating statistically significant differences of the regional normalized LORETA solutions with the patterns Recording I $\neq$ Recording II (Duncan test, $p<0.05$).

Results

Demographic and neuropsychological data

Table 2 summarizes the relevant demographic and clinical data of the present Nold, MCI and mild AD subjects. Four analyses of variance (ANOVA) using the factor Group (Nold, MCI, mild AD) were computed to evaluate the presence or absence of statistically significant differences among the three groups for MMSE, age, gender, 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 MCI and Nold subjects ($p<0.0001$). It was also lower in the MCI than Nold subjects ($p<0.0001$). On the contrary, no statistically significant difference was found for age, gender and education ($p>0.35$). However, the age, gender and education values were used as covariates in the subsequent statistical analysis, to exclude that the small differences in age, gender and education could influence the subsequent statistical analysis. In order to better classify the MCI and AD subjects, the mean (±SE) values of Trail Making Test part A (TMT A), part B (TMT B), part B-A (TMT B-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 reported in Table 3. As expected, a statistically significant difference was found for all neuropsychological tests (t test; $p<0.0001$), showing a lower performance in the mild AD compared to the MCI subjects.

Insert here Table 2 and Table 3

Topography of the EEG cortical sources as estimated by LORETA

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

Insert here Figure 1

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 one year).

Compared to the Recordings I, the Recordings II was characterized by a decrease of posterior alpha 1 and alpha 2 sources.

Insert here Figure 2

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). Figure 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 macro-regions, thus supporting the idea that scalp EEG rhythms are generated by a distributed pattern of cortical sources. Table 4 reports the mean 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 as well as 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 Nold and MCI groups ($p<0.002$). Table 5 reports p values (Duncan post hoc) and effect sizes (Cohen's d) for the above mentioned 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 of 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., 2006a,d 2007a,b, 2008a).

Insert here Figure 3, Table 4 and Table 5

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). Figure 4 shows the mean regional normalized LORETA solutions relative to this statistical ANOVA interaction. Table 6 reports 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 two 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 to the Recording I, the 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 7 reports 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 ($p<0.05$)

Insert here Figure 4,Table 6 and Table 7

Additional analyses

As a first analysis, the LORETA source solutions of the 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 single group (Pearson test, $p<0.05$). The LORETA source solutions were those showing statistically significant post-hoc differences among the Nold, MCI and the 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, occipital, and temporal alpha 1 ($p<0.05$). Table 8 reports the r and p values of the statistically significant correlations between the LORETA source solutions of the Recording I and the MMSE score ($p<0.05$).

Insert here Table 8

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 the1-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 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 (ROC) curves (DeLong et al., 1988). Table 9 reports the values of sensitivity, specificity, and area under the ROC curve relative to individual parietal, occipital

and temporal alpha 1 sources for the blind classification of the EEG datasets of the following groups: Nold vs. AD (Recording I), Nold vs. MCI (Recording I), MCI (Recording I) vs. AD (Recording I), Nold vs. AD (Recording II), and Nold vs. MCI (Recording II). 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 vs. 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 vs. MCI and of the AD vs. 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. Figure 5 o 6 shows the ROC curves illustrating the above results.

Insert here Fig. 6 and Table 9

The above mentioned results with N=54 MCI subjects opens a crucial question on the sample size of MCI subjects that must be used to study 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 above 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 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 the Recording I and the Recording II in the mild AD patients (MCI progression markers). Sample size was calculated by Cohen's tables (Cohen et al., 1977). To this aim, we used a free software for calculating the sample sizes given the anticipated effect size, the probability level, and the desired statistical power level (http://www.danielsoper.com/statcalc3/calc.aspx?id=47). Table 10 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 about 90 subjects per group allows the use of the present EEG markers for the study of the MCI status when two MCI and Nold groups are compared. Furthermore, an ideal sample size of about 35 subjects per group allows the study of the MCI state by these EEG markers when MCI and AD groups are compared. Finally, an ideal sample size of about 80

amnesic MCI subjects allows the use of the present EEG markers for the study of the disease progression at 1-year follow up.

Insert here Table 10

Discussion

Here we tested the hypothesis that the cortical sources of resting state EEG rhythms were sensitive to both 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 to the Nold and AD subjects. These results extend previous EEG evidence 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., 2006a,d 2007a,b, 2008a).

As a second step of the study, the EEG source markers of MCI progression were obtained by 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 compared to 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 Cohen's d values (Cohen et al., 1977). Results showed that an ideal sample size of about 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 about 2-years follow up, MCI patients were characterized by a power increase of delta and theta rhythms in temporal and occipital scalp regions associated to 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 1-3 years follow up (Coben et al., 1985; Soininen et al., 1989).

As 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 upon the following

theoretical considerations. In the condition of awake resting state eyes-closed condition, dominant low-frequency alpha rhythms (about 8–10 Hz) would denote the synchronization of diffuse neural networks regulating the fluctuation of subject's global awake and conscious states, whereas high-frequency alpha rhythms (about 10-12 Hz) would denote the synchronization of more selective neural networks specialized in the processing of modal specific or semantic information (Klimesch, 1999; Pfurscheller 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. "de-synchronization or blocking") and are replaced by fast EEG oscillations at high-frequency beta (about 20-30 Hz) and gamma (>30 Hz) rhythms (Pfurscheller 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; Pfurscheller and Lopes da Silva, 1999). In the MCI progression, this abnormality would be associated to 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 de-synchronization of the resting state alpha rhythms, as a reflection of a tonic and unselective cortical excitation, would be associated to an abnormal brain function and predicts cognitive deficits in humans. Indeed, effective cognitive processing is expected to stem upon the selectivity and flexibility of the excitation and inhibition across brain neural networks during both resting state condition and task demands (see for example the concept of "neural efficiency"; Vernon, 1993, Haier et al., 1988, 2004, Rypma et al., 2006).

The present results motivate further investigations aimed at testing hypotheses crucial for the eventual clinical application of the present EEG markers. Firstly, 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 as unveiled by the combination of the mentioned biomarkers. Secondly, future investigations should develop a careful evaluation of the changes of the EEG markers in Nold subjects at 1 year follow up, in order 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 (ANNs) or Bayesian predictors (i.e. Bayesian) to test the hypothesis that the present EEG markers can reflect and predict cognitive decline in single amnesic MCI individuals for a personalized clinical management. For the assessment of the cognitive functions, the use of ADAS-cog would allow a better characterization of the MCI and AD patients with reference to that 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 group level- to the cognitive decline 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 amount of amnesic MCI subjects required to show the effects of the disease progression (about N=80) on the basis of the present power analysis at $p<0.05$.

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Table legends

Table 1. Brodmann areas included in the cortical regions of interest (ROIs) of the present study. LORETA solutions were collapsed in frontal, central, parietal, occipital, temporal ROIs.

Table 2. Demographic and clinical data of the recruited normal elderly controls (Nold), mild cognitive impairment and mild Alzheimer's disease (mild AD)subjects.

Table 3. Mean score (± standard error, SE) reported by the MCI and mild AD subjects to the neuropsychological tests used in the present study. Legend: TMT A= Trail Making Test part A; TMT B= Trail Making Test part B; TMT B-A= Trail Making Test part B- part A, Rey figures= copy of Rey figures; Rey figures recall= delayed recall of Rey figures; letter fluency= verbal fluency for letters; categorical fluency= verbal fluency for fruits, animals or car trades. The statistical comparison of the mean values between the two groups was performed by t test ($p<0.05$). The results are reported in the last column.

Table 4. Mean values (±SE) of the relative 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 regional normalized LORETA current density between MCI and Nold as well as between AD and Nold groups are also reported.

Table 5. 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 ($p<0.05$).

Table 6. 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 two EEG recordings (Recording I, Recording II). The differences of regional normalized LORETA current density between Recording II and Recording I are also reported.

Table 7. 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 ($p<0.05$).

Table 8. The r and p values of all statistically significant correlations between the LORETA source solutions of the Recording I and the MMSE score across the Nold, MCI and mild AD subjects as a single group ($p<0.05$). Of note, only the regional normalized LORETA solutions fitting the pattern Nold ≠ MCI ≠ mild AD were considered for that correlation analysis.

Table 9. Values of sensitivity, specificity, and area under the receiver operating characteristic (ROC) curve using individual parietal, occipital and temporal alpha 1 for the blind classification of the EEG datasets of Nold vs. AD (Recording I), Nold vs. MCI (Recording I), MCI (Recording I) vs. AD (Recording I), Nold vs. AD (Recording II), and Nold vs. MCI subjects (Recording II).

Table 10. Sample sizes required to yield a statistical power $p<0.05$ 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.

Figure legends

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. 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).

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. Legend: LORETA, low resolution brain electromagnetic tomography. Color scale: all power density estimates were scaled based on the averaged maximum value.

Fig. 3. Statistical ANOVA interaction ($F(40,2920)=5.99$; $p<0.0001$) among the factors Group (Nold, MCI, mild AD), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (frontal, central, parietal, occipital, temporal). Legend: rectangles indicate the cortical regions and frequency bands in which LORETA solutions presented statistically significant LORETA patterns Nold $\neq$ MCI $\neq$ AD (Duncan test, $p<0.05$).

Fig. 4. Statistical ANOVA interaction ($F(20,1060)=4.25$; $p<.00001$) 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). Legend: rectangles indicate the cortical regions and frequency bands in which LORETA solutions presented statistically significant LORETA patterns Recording I $\neq$ Recording II (Duncan test, $p<0.05$).

Fig. 5. Mean receiver operating characteristic (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 vs. AD (Recording I), Nold vs. MCI (Recording I), MCI (Recording I) vs. AD (Recording I), Nold vs. AD (Recording II), and Nold vs. MCI subjects (Recording II).

Table 1

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

Table 2

	MCI	mild AD	Nold	p value
N	54	50	45	
Age (years)	72.2 (±1 SE)	73.6 (±1 SE)	72.2 (±1.1 SE)	>0.55
Education (years)	7.8 (±0.6 SE)	7 (±0.5 SE)	8.2 (±0.6 SE)	>0.35
Gender (M/F)	22/32	17/33	16/29	>0.75
MMSE I	26.9 (±0.2 SE)	21.8 (±0.3 SE)	28.1 (±0.2 SE)	<0.0001
MMSE II	25.8 (±0.3 SE)	-	-	-

Table 3

	MCI	mild AD	t-test
TMT A	42.4 (± 3.3)	132.3 (± 14.7)	p<0.00001
TMT B	129.7 (± 16.5)	385.9 (± 36.9)	p<0.00001
TMT B-A	84.9 (± 13.3)	274.3 (± 27.6)	p<0.00001
Rey figures	30.8 (± 1)	18.2 (± 1.7)	p<0.00001
Rey figures recall	14.3 (± 1.2)	6.9 (± 1)	p<0.0001
Letter fluency	31.7 (± 1.4)	24.2 (± 1.5)	p<0.0005
Category fluency	34.2 (± 1.1)	24.7 (± 1.4)	p<0.00001

Table 4

Regional normalized LORETA current density					
	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

Table 5

p values and effect sizes (Cohen's d)			
LORETA current density	**Nold vs MCI**	**Nold vs AD**	**MCI vs AD**
Central delta	N.S.	0.005, -0.57	0.002, -0.68
Frontal delta	N.S.	0.007, -0.51	0.005, -0.6
Parietal delta	N.S.	0.00007, -0.54	0.001, -0.43
Temporal delta	N.S.	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

Table 6

Regional normalized LORETA current density			
	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

Table 7

p values and effect sizes (Cohen's d)	
LORETA current density	**Recording II vs 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

Table 8

Correlation between LORETA current density and MMSE score (r, p value)	
Parietal alpha 1 vs MMSE	r= 0.27, p=0.0007
Occipital alpha 1 vs MMSE	r= 0.26, p=0.001
Temporal alpha 1 vs MMSE	r= 0.28, p=0.0006

Table 9

	Parietal alpha 1			Occipital alpha 1			Temporal alpha 1		
	Sens.	***Spec.***	***AUC***	***Sens.***	***Spec.***	***AUC***	***Sens.***	***Spec.***	***AUC***
Nold vs AD (Rec I)	78	68.9	0.76	66	80	0.75	84	64.8	0.75
Nold vs MCI (Rec I)	51.9	71.1	0.62	37	84.4	0.6	55.6	64.4	0.6
MCI (Rec I) vs AD (Rec I)	84	44.4	0.65	68	61.1	0.66	82	50	0.65
Nold vs AD (Rec II)	90	71.1	0.81	84	80	0.84	94	64.4	0.82
Nold vs MCI (Rec II)	63	71	0.69	61.1	73.3	0.71	75.9	60	0.71

Table 10

Sample size required to yield p<0.05			
	MCI state (MCI vs Nold)	**MCI state (MCI vs mild AD)**	**MCI progression**
Parietal alpha 1	62	30	97
Occipital alpha 1	102	41	78
Temporal alpha 1	108	38	68