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Reactivity of Cortical Alpha Rhythms to Eye Opening in Mild Cognitive Impairment and Alzheimer's Disease: an EEG Study

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Abstract. Cortical sources of resting eyes-closed alpha rhythms are typically abnormal in mild cognitive impairment (MCI) and Alzheimer's disease (AD) subjects. Here we tested the hypothesis of a progressive impairment of cortical alpha reactivity to eye-opening across amnesic MCI and mild AD subjects, reflecting another aspect of the impairment of cortical neural synchronization. Resting electroencephalography (EEG) data were recorded in 36 normal elderly subjects (Nold), 91 amnesic MCI, and 31 mild AD subjects during eyes-closed and -open conditions. EEG sources were estimated by LORETA software. In the eye-closed condition, posterior alpha 1 (8–10.5 Hz) sources were lower in MCI and AD than Nold subjects. The opposite was true for occipital delta sources (2–4 Hz). Reactivity to the eyes-open condition showed posterior alpha 1 and alpha 2 (10.5–13 Hz) sources was high in the Nold, intermediate in the MCI, and low in the AD subjects. Furthermore, occipital alpha 1 reactivity across MCI and AD subjects was correlated to the cognitive impairment as revealed by Mini-Mental State Examination score. In conclusion, at least at group level, the continuum across amnesic MCI and mild AD status is related to an impaired reactivity of cortical neuronal synchronization to eyes opening at alpha rhythms.

Keywords: Alzheimer's disease, amnesic mild cognitive impairment, delta, theta, and alpha rhythms, electroencephalography, eyes-closed resting state, eyes-open resting state, low resolution brain electromagnetic tomography (LORETA)

INTRODUCTION

Mild cognitive impairment (MCI) is a clinical state between elderly normal cognition and dementia, featuring memory complaints and cognitive impairment on neuropsychological testing not yet fulfilling the clinical picture of dementia [1–3]. Amnesic MCI is regarded as a precursor of Alzheimer's disease (AD) [4–6] since recent studies have shown a high rate of progression to AD [3,7,8]. In cognitively intact elderly subjects, the incidence of AD ranges from 0.17 to 3.86% [3, 9], while in amnesic MCI subjects it ranges from 6 to 25% [3]. However, the "transition" hypothesis is chal-

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lenged by observations indicating that not all MCI subjects deteriorate over time [10,11], as AD cumulative incidence rates range from 40 to 60% [10–12]. These data motivate investigations aimed at understanding the neurobiological basis of MCI condition, in order to refine diagnostic/prognostic procedures and to target new pharmacological interventions [13–16].

To evaluate the general mechanisms of cortical neural synchronization in MCI and AD conditions, the power of resting-state ("resting") eyes-closed electroencephalographic (EEG) rhythms has been evaluated. When compared to healthy elderly (Nold) subjects, AD patients have been characterized by high power of delta (0–4 Hz) and theta (4–7 Hz) rhythms, and low power of posterior alpha (8–12 Hz) and/or beta (13–30 Hz) rhythms [17–23]. Furthermore, posterior alpha rhythms have shown a power decrement in MCI compared to Nold subjects [19,23–27], and have been related to the risk of progression to AD [28]. Fine topography of these rhythms has been specified by the magnetoencephalographic (MEG) counterpart of EEG activity [28,29]. However, a certain variability of resting eyes-closed brain rhythmicity in pathological aging might limit its practical utility for personalized diagnosis and prognosis, especially at earlier stages of MCI condition. For example, recent high-resolution magnetoencephalographic evidence has shown no statistically significant difference of brain rhythms in normal elderly and MCI subjects [30].

To obtain more informative data on cortical neural synchronization, resting alpha rhythms have been evaluated by comparing EEG or MEG oscillations collected in eyes-closed and -open conditions. Previous EEG studies have repeatedly reported a poor suppression (reactivity) of alpha power during eye opening in AD compared with Nold subjects [21,31–33]. This lack of reactivity has been also used to predict the long term deterioration of higher functions in subjects with cognitive decline [34]. Furthermore, MEG studies have shown that compared with Nold subjects, AD patients were characterized both by lower occipital and temporal alpha power in the eyes-closed condition and by lower reactivity of alpha rhythms during eye opening [35].

In only one previous EEG study, alpha rhythms to the eyes opening have been compared among Nold, MCI, and AD subjects [33]. The results showed statistically significant differences between Nold and AD ($p < 0.05$) but not between MCI and AD subjects [33]. MEG studies have also shown that posterior sources of alpha rhythms were lower in power during eyes-open compared with-closed conditions in Nold, MCI, and AD subjects, and that the reactivity of alpha rhythms was greater in the Nold than AD subjects; again, no difference in reactivity was observed between MCI and AD subjects [36]. This lack of difference in the mentioned EEG and MEG studies might be due to some reasons. On one hand, previous evidence might lead support to the idea that cortical neural mechanisms at the basis of eyes opening are normal in MCI subjects. On the other hand, the lack of EEG differences might be due to the use of relatively small groups and/or high inter-subjects variability of neurodegenerative processes in MCI subjects. These reasons may also explain MEG evidence showing no statistically significant difference of resting eyes-closed brain rhythms in Nold and MCI subjects [30].

To gain statistical power and sensitivity, we have recently proposed a methodological approach including the use of large groups of MCI or AD subjects, cheap digital EEG recordings, and regional source analysis of EEG rhythms by a popular called low resolution brain electromagnetic tomography (LORETA) that takes into account the head volume conduction effects and can be downloaded from Internet towards extensive clinical applications [37]. Thanks to this approach, we have shown progressive differences of resting cortical alpha rhythms along Nold, amnesic MCI, and mild AD subjects [27,28,38,39]. In the present study, we applied the methodological approach mentioned above to test the hypothesis of a progressive impairment of cortical alpha reactivity to eye opening across Nold, amnesic MCI, and AD subjects. Therefore, this study explores another aspect of the impairment of cortical neural desynchronization with respect to the mechanisms of cortical neural synchronization associated to the condition of eyes closed resting state, the latter being investigated by a bulk of previous EEG studies of the Consortium formed by the present Authors' research groups [27,28,38,39]. As a novelty, here we evaluated topographical reactivity of alpha rhythms to eyes opening among relatively large groups of Nold, amnesic MCI, and mild AD subjects, in order to conclusively ascertain if this reactivity is normal or abnormal at group level in the grey zone between preclinical and clinical stages of AD. At this early stage of the research, we focused on the group analysis as a basis of future longitudinal investigations on the practical diagnostic or prognostic utility of the present methodological approach at single subject level. Noteworthy, amnesic MCI status is not necessary the precursor of AD, and AD, with its specific neuropathological alterations, can be a qualitatively different state from the others.

METHODS

Subjects and diagnostic criteria

In this study, we recruited 91 amnesic MCI subjects and 31 AD patients. Local institutional ethics committees approved the study. All experiments were performed with the informed and overt consent of each participant or caregiver, in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the Author's Institutional Review Board.

The present inclusion and exclusion criteria for amnesic MCI subjects were based on previous seminal reports [1–3,40–45]. Summarizing, the inclusion criteria were as follows: (i) objective memory impairment on neuropsychological evaluation, as defined by performances $\geqslant$ 1.5 standard deviation below the mean value of age- and education-matched controls for a battery of neuropsychological tests, to assess cognitive performance in the domains of memory (i.e., Buschke-Fuld and Memory Rey tests), language, executive function/attention, and visuo-construction [46–56]; (ii) normal activities of daily living as documented by the history and evidence of independent living [57]; and (iii) clinical dementia rating score of 0.5 [58]. The exclusion criteria included: (i) mild AD, as diagnosed by standard protocols including NINCDS-ADRDA [59]; (ii) evidence (including magnetic resonance imaging (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 the Geriatric Depression Scale (GDS; [60]) scores lower than 14 (no depression); (v) other psychiatric diseases, epilepsy, drug addiction, alcohol dependence (as revealed by a psychiatric interview), and use of psychoactive drugs including acetylcholinesterase inhibitors or other drugs enhancing brain cognitive functions; and (vi) current or previous uncontrolled or complicated systemic diseases (including diabetes mellitus) or traumatic brain injuries.

A battery of neuropsychological tests was performed to assess cognitive performance in the domains of memory, language, executive function/attention, and visuo-construction abilities in MCI and AD. The tests to assess memory were the immediate and delayed recall measure of the Rey Auditory Verbal Learning Test [48, 49], the delayed recall of Rey figures [50], the delayed recall of a 3-word list [51], and the delayed recall of a story [52]. The tests to assess language were the 1-minute verbal fluency for letters [53], the 1-minute verbal fluency for fruits, animals or car trades [53], and the Token test [52,54]. The tests to assess executive function and attention were the Trail Making Test part A and B [55], the attentive matrices [52], the Digit forward, and the Digit backward [56]. Finally, the tests to assess visuo-construction were the copy of Rey figures [50], the Raven of Progressive matrices [46], and the Clock Drawing test [47].

Probable AD was diagnosed according to NINCDS-ADRDA [59] and DSM IV criteria. The recruited AD patients underwent general medical, neurological, and psychiatric assessments. Patients were also rated with a number of standardized diagnostic and severity instruments that included Mini-Mental State Evaluation (MMSE; [61]), Clinical Dementia Rating Scale (CDR; [58]), GDS [60], Hachinski Ischemic Score (HIS, [62]), and Instrumental Activities of Daily Living scale (IADL, [57]). 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 group. Exclusion criteria included 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 [63], (iii) extra-pyramidal syndromes, (iv) reversible dementias (including pseudodementia of depression); and (v) Lewy body dementia, according to the criteria by McKeith [64].

Benzodiazepines, antidepressant, and/or antihypertensive drugs (when present) were withdrawn for about 24 h before the EEG recordings, in order to pair the period from the last assumption of the drugs and EEG recording across the MCI and AD subjects (i.e., note that the effects of drugs discontinuation are typically observed after longer periods).

For the purposes of this study, we used resting eyes-closed EEG data of 36 Nold subjects taken from a local archive. The Nold subjects were recruited mostly among non-consanguineous patients' relatives and underwent physical and neurological examinations as well as cognitive screening. Subjects affected by chronic systemic illnesses, those receiving psychoactive drugs, or with a history of neurological or psychiatric disease were excluded. All Nold subjects had a GDS score lower than 14 (no depression).

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

	Nold	MCI	AD
N	36	91	31
Age (years)	63.9 (± 2.8 SE)	70.6 (± 0.4 SE)	70.5 (± 1.8 SE)
Education (years)	9.7 (± 0.8 SE)	7.3 (± 0.4 SE)	6.5 (± 0.6 SE)
MMSE	28.24 (± 0.25 SE)	26.05 (± 0.23 SE)	21.16 (± 0.75 SE)
IAF	9.4 (± 0.19 SE)	9.4 (± 0.13 SE)	9.0 (± 0.23 SE)
Male/Female	14/22	33/59	7/24

Table 2
Results of neuropsychological tests of interest in the MCI and AD groups. The p value of the statistical ANOVA comparison is reported

	MCI	AD	MCI vs AD
Rey list immediate recall	32.72 (± 1.26 SE)	16.44 (± 1.71 SE)	$p < 0.001$
Rey list delayed recall	5.98 (± 0.44 SE)	0.83 (± 0.34 SE)	$p < 0.001$
Figure Rey list recall	9.24 (± 0.80 SE)	1.27 (± 0.57SE)	$p < 0.001$
Delayed recall of 3 words (object)	2.78 (± 0.05 SE)	1.33 (± 0.21 SE)	$p < 0.001$
Delayed recall of 3 words (place)	2.84 (± 0.06 SE)	1.62 (± 0.24 SE)	$p < 0.001$
Delayed recall of 3 words (coupling)	2.49 (± 0.11 SE)	0.91 (± 0.22 SE)	$p < 0.001$
Verbal fluency for letter	25.59 (± 1.15 SE)	19.30 (± 1.94 SE)	$p < 0.005$
Verbal fluency for category	27.07 (± 0.95 SE)	17.37 (± 1.62 SE)	$p < 0.001$
Token test	31.50 (± 0.45 SE)	27.45 (± 1.13 SE)	$p < 0.001$
Figure Rey copy	28.79 (± 0.88 SE)	15.25 (± 2.22 SE)	$p < 0.001$

Table 1 reports demographic and neuropsychological data of Nold, MCI, and AD subjects. Table 2 reports the score to some neuropsychological tests of interest in the MCI and AD groups as well as the relative statistically significant differences ($p < 0.05$). As expected, the score of the neuropsychological tests was worse in the AD group than in the MCI group.

EEG recordings

EEG recordings were performed by specialized clinical units in dimly light rooms in the late morning. During EEG recording, subjects seated on a comfortable reclined chair. EEG data were collected (0.3–70 Hz bandpass; cephalic reference) from 19 electrodes positioned according to the International 10–20 System (i.e., Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2) during standard resting state eyes-closed and eyes-open conditions. To monitor eye movements, the horizontal and vertical electrooculogram (0.3–70 Hz bandpass) was also collected. All data were digitized in a continuous recording mode (5 min of EEG eyes-closed and 5 min of EEG eyes-open; 128–256 Hz sampling rate). In order to keep constant the level of vigilance, the experimenters controlled on-line the subject and the EEG traces. Personnel of recording units were familiar with the issue of vigilance in resting state elderly subjects. Experimenters verbally alerted the subject any time that behavioral and/or EEG drowsiness appeared, especially during the eyes-closed condition.

The EEG data were analyzed and fragmented off-line in consecutive epochs of 2 s. The EEG epochs with ocular, muscular, and other types of artifact were preliminarily identified by a computerized automatic procedure. EEG epochs with sporadic blinking artifacts (less than 10% of the total) were corrected by an autoregressive method [65]. Two independent experimenters, blind to the diagnosis, manually confirmed the EEG segments accepted for further analysis.

Spectral analysis of the EEG data

The digital FFT-based power spectrum analysis (Welch technique, Hanning windowing function, no phase shift) was calculated in order to establish the individual alpha frequency (IAF) peak, defined as the frequency associated to the maximum power of resting EEG rhythms at the extended alpha range of 6-14 Hz. For this purpose, we strictly followed the procedure for the computation of IAF as originally proposed by Klimesch's group, which tested such procedure in several validation studies (for a review, see [66]). Specifically, IAF peak was detected on the individual EEG power spectrum obtained averaging the EEG power spectral of all scalp electrodes [66]. Mean IAF peak was 9.4 Hz (±0.19 standard error, SE) in the Nold subjects, 9.4 Hz (±0.13 SE) in the MCI subjects, and

9.0 Hz (±0.23 SE) in the AD subjects (Table 1). No statistically significant ANOVA difference was found among the groups. Although the subjects' groups were characterized by quite similar mean IAF peaks, this value was used as a covariate (together with age, education, gender and resting eyes-closed alpha rhythms) in the statistics. This allowed the removal of any possible residual confounding effects on the cortical sources of alpha rhythms in the comparison among the Nold, MCI, and AD groups. Indeed, the IAF is a frequency of special importance, since it is associated with maximum power of resting eyes-closed EEG rhythms [66]. The above procedure minimized the possibility that small differences in the IAF peak could confound the comparisons of cortical alpha sources among the Nold, MCI, and AD groups.

The 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), in continuity with a bulk of previous studies of this Consortium on the cortical sources of resting EEG rhythms in aging [22,27,37,67–69]. The choice of the fixed EEG bands did not account for the IAF peak. However, this should not affect the results, since more than 90% of the subjects had the IAF peak within the alpha 1 band (8–10.5 Hz).

Cortical source of EEG rhythms as computed by LORETA

LORETA software as provided at http://www.unizh.ch/keyinst/NewLORETA/LORETA01.htm was used for the estimation of cortical sources of EEG rhythms [70–72]. LORETA is a functional imaging technique belonging to a family of linear inverse solution procedures [73] modeling 3D distributions of EEG sources [72], which has been successfully used in recent EEG studies on brain aging [18,22,67–69]. Of note, here we preferred LORETA to its well known evolution called standardized LORETA (sLORETA), to have results fully comparable to those obtained by using LORETA in several previous studies of this Consortium on eyes-closed resting state EEG rhythms along pathological aging [27,28,38,67–69].

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 gray matter/hippocampus of a head model co-registered to the Talairach probability brain atlas and digitized at the Brain Imaging Center of the Montreal Neurological Institute [74]. This compartment includes 2394 voxels (7 mm × 7 mm × 7 mm), each voxel containing an equivalent current dipole. Therefore, the theoretical spatial resolution of LORETA brain source volume is of 7 mm. However, the real spatial resolution is much lower for the following reasons.

Table 3
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

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

LORETA solutions consisted of voxel current density values able to predict EEG spectral power density at scalp electrodes, independently of the electrode reference used. These solutions were normalized by dividing the LORETA current density values at each voxel for the power density value obtained averaging the LORETA current density values across all frequencies (0.5–45 Hz) and 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 (for sake of brevity and clarity, we refereed to this scale as LORETA current density). This procedure reduced inter-subjects variability and fitted the LORETA solutions in a Gaussian distribution [75,76].

These solutions of the EEG inverse problem are under-determined and ill conditioned, since the number of spatial samples (electrodes) is lower than that of the unknown variables estimated by solving the EEG inverse problem (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 [70–72]; this blurring regularization reduced the theoretical spatial resolution of the source estimation to centimeters. To further take into account the low spatial resolution of the LORETA solutions, we used our MATLAB software to collapse the voxels of LORETA solutions at frontal, central, parietal, occipital, temporal, and limbic regions of the brain model coded into Talairach space. The Brodmann areas listed in Table 3 formed each of these regions of interest (ROIs). On the whole, the procedures and transformations of the present methodological approach produced a putative spatial resolution of

several centimeters, corresponding to the spatial difference among the epicenters of the mentioned cortical macroregions of interests. Such a low spatial resolution made it marginal the fact that here the EEG electrode positions were not co-registered to brain source models based on individual magnetic resonance imaging. We could not perform this co-registration, since the official LORETA package does not support the integration of the electrode positions and individual brain sources. As a main advantage, the use of the official LORETA package ideally allows to all EEG research units to replicate the present results.

Statistical analysis of the LORETA solutions

Statistical analysis was performed by ANOVAs using subjects' age, education, gender, IAF, and MMSE as covariates ($p < 0.05$). The Mauchly's test evaluated the sphericity assumption. Correction of the degrees of freedom was made with the Greenhouse–Geisser procedure. The Duncan test was used for the post-hoc testing ($p < 0.05$).

To evaluate the control hypothesis of differences in Nold, MCI, and AD subjects as cortical sources of resting eyes-closed EEG rhythms, an ANOVA used the following factors: Group (Nold, MCI, AD; independent variable), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (central, frontal, parietal, occipital, temporal). The existence of LORETA source differences among the groups would be confirmed by a statistical ANOVA effect including the factor Group.

The working hypothesis stated that Nold, MCI, and AD subjects are expected to be characterized by a different "reactivity" to eye opening of cortical sources of resting alpha rhythms. For a given frequency band, the "reactivity" was defined as the power difference of regional normalized LORETA solutions in the eyes-open condition minus eyes-closed condition For example, we computed the individual difference of the LORETA solution for occipital alpha 1 region between eyes-open condition and eyes-closed condition, and so on for the other regions, frequency bands of interest, and individuals. Negative values of this difference indexed a decrease of alpha power during the eyes opening. The power difference was used as a dependent variable for an ANOVA having the factors Group (Nold, MCI and AD; independent variable), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (central, frontal, parietal, occipital, temporal). In this ANOVA, additional covariates were the regional cortical sources of the resting eyes-closed alpha 1 and alpha 2 rhythms. The existence of LORETA alpha source differences between the groups would be confirmed by a statistical ANOVA effect including the factor Group.

Regional power differences of the normalized LORETA solutions fitting the pattern of EEG power suppression "Nold>MCI>AD" were evaluated as linear correlations with MMSE score in the MCI and AD subjects as a whole group (Pearson correlation test; Bonferroni corrected, $p < 0.05$), namely the grey zone in the continuum between preclinical and clinical stages of the disease.

RESULTS

Comparison of cortical sources of resting state eyes-closed EEG rhythms

The Nold group presented alpha 1 sources with the maximal values of amplitude distributed in parieto-occipital regions. Delta, theta, and alpha 2 sources had moderate amplitude values when compared to alpha 1 sources. Finally, beta 1 and beta 2 sources were characterized by lowest amplitude values. Compared to the Nold group, the MCI group showed a decrease in amplitude of parietal, occipital, and temporal alpha sources. With respect to the Nold and MCI groups, the AD group showed an amplitude increase of widespread delta and theta sources, along with a strong amplitude reduction of parietal, occipital, and temporal alpha sources.

An ANOVA was used to test the control hypothesis that the above differences were statistically significant ($p < 0.05$). Indeed, there was a statistically significant ANOVA interaction ($F(40,3100) = 4.67$; $p < 0.001$) among the factors Group (AD, MCI, Nold), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (central, frontal, parietal, occipital, temporal), with age, education, gender, IAF, and MMSE as covariates. In line with the control hypothesis, some EEG sources showed different amplitude across Nold, MCI, and AD subjects: namely, delta sources in frontal and temporal areas, alpha 1 sources in parietal, and occipital areas ($p < 0.001$), and alpha 2 sources in parietal, and occipital areas ($p < 0.005$ to 0.001). These results were globally in line with previous evidence [38, 67–69].

Reactivity of resting alpha EEG rhythms

For illustrative purposes, Fig. 1 plots the grand average of the LORETA solutions (i.e., normalized pow-

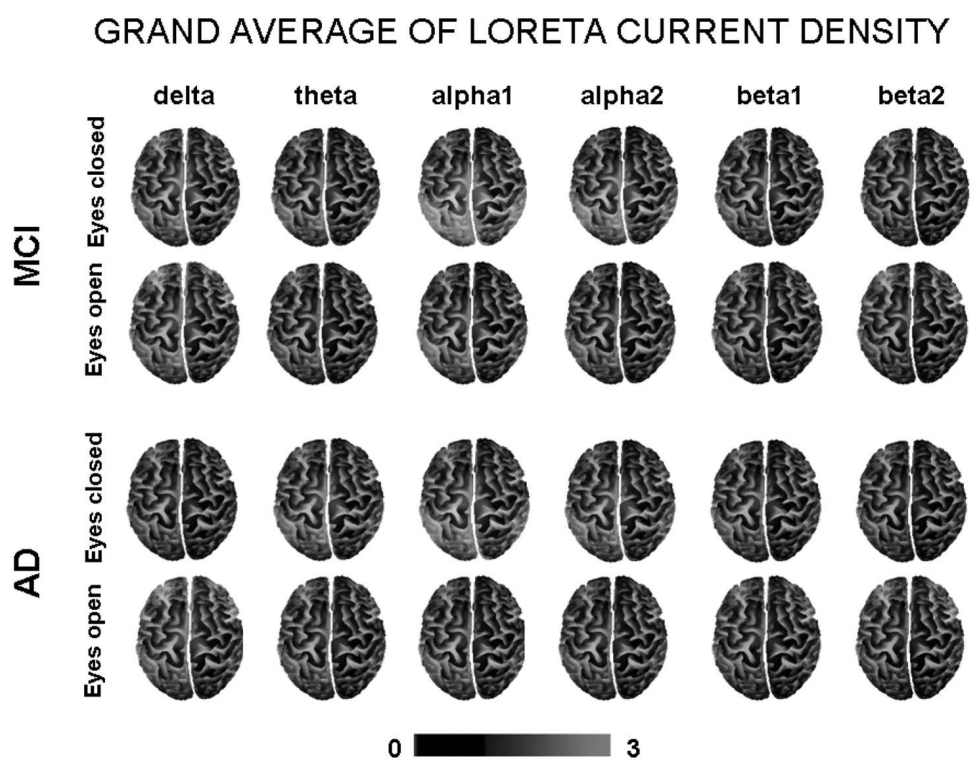

Fig. 1. Grand average of the LORETA solutions (i.e., relative power current density at cortical voxels) modeling the distributed EEG cortical sources at delta, theta, alpha 1, alpha 2, beta 1, and beta 2 bands in MCI and AD subjects for the two conditions, namely eyes-closed and eyes-open. The left side 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 MCI eyes-closed). The maximal value of power density is reported under the figure. (Colors are visible in the electronic version of this article at http://dx.doi.org/10.3233/JAD-2010-100798)

er 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 MCI and AD subjects. These solutions refer to the eyes-closed and eyes-open conditions. In both MCI and AD groups, the cortical sources of alpha 1 and alpha 2 were lower in amplitude in the eyes-open than eyes-closed condition, as an effect of the reactivity of cortical neural synchronization to the eyes-open condition. An opposite effect was observed in cortical delta sources. For control purposes, Fig. 2 plots the power difference of regional absolute LORETA solutions in the eyes-open minus eyes-closed condition modeling the distributed EEG cortical sources for delta, theta, alpha 1, alpha 2, beta 1, and beta 2 bands in the MCI and AD subjects. The figure shows a similar trend with respect to the normalized LORETA sources.

To test the statistical significance of these differences of the normalized LORETA solutions, an ANOVA was used (age, education, gender, IAF, MMSE, and resting eyes-closed alpha rhythms as covariates; $p < 0.05$). Figure 3 shows the power difference of regional normalized LORETA solutions in the eyes-open minus eyes-closed condition (i.e., "reactivity") relative to a statistical ANOVA interaction ($F(40,3100) = 3.75$; $p < 0.001$) among the factors Group (AD, MCI, Nold), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (central, frontal, parietal, occipital, temporal). The planned post-hoc testing showed that the EEG source suppression pattern Nold>MCI>AD was fitted by the following normalized regional LORETA solutions: parietal, occipital, and temporal alpha 1 sources ($p < 0.001$) as well as parietal and occipital alpha 2 sources ($p < 0.05$ to 0.001). These results were confirmed by a control ANOVA analysis probing LORETA solutions for each ROI considered separately (central, frontal, parietal, occipital, temporal). Again, the source pattern Nold>MCI>AD was fitted by the following 3 normalized regional LORETA solutions: parietal ($F(10,775) = 2.89$; $p < 0.005$), oc-

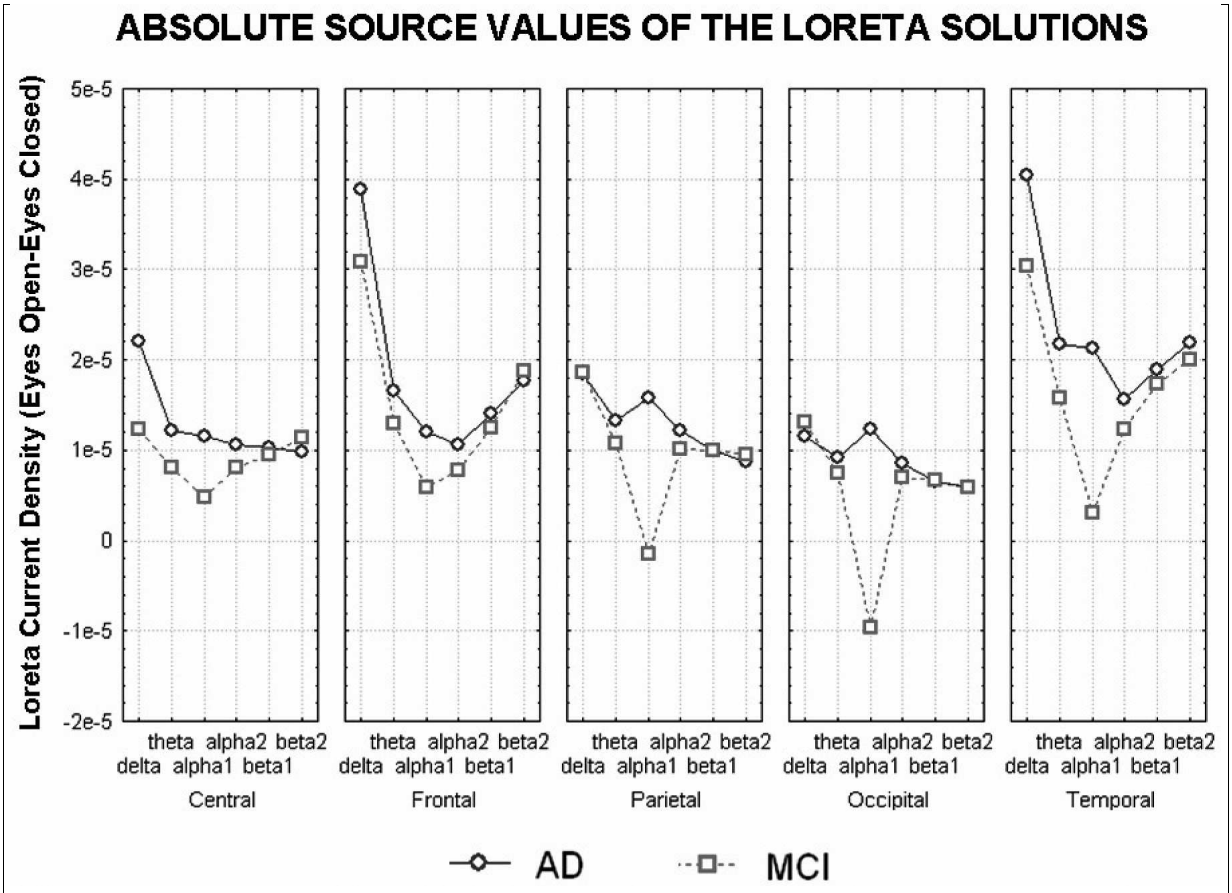

Fig. 2. Absolute source values of the LORETA solutions (eyes-open minus eyes-closed) in MCI and AD subjects for the delta, theta, alpha 1, alpha 2, beta 1, and beta 2 bands. (Colors are visible in the electronic version of this article at http://dx.doi.org/10.3233/JAD-2010-100798)

cipital (F(10,775) = 4.55; $p < 0.001$), and temporal (F(10,775) = 3.28; $p < 0.001$) alpha 1 sources. Parietal and occipital alpha 2 sources just fitted the EEG source suppression pattern AD and MCI < Nold.

The amplitude of the above statistically significant alpha 1 and alpha 2 source power differences (i.e., reactivity to eyes-open condition; $p < 0.05$ to 0.001) was correlated with the MMSE score in the MCI and AD subjects as a whole group (Pearson test, $p < 0.05$). Bonferroni correction for the five repetitions of the test set the statistical threshold to $p < 0.01$ to obtain the Bonferroni corrected $p < 0.05$. The MMSE score negatively correlated ($r = -0.24$, $p = 0.01$) with occipital alpha 1 source power difference (Fig. 4); the higher the MMSE score, the higher the source power difference as expressed by negative values. No statistically significant correlation was observed ($p > 0.01$) between the MMSE and the remaining alpha power source differences at parietal and temporal alpha 1 as well as at parietal and occipital alpha 2.

Control analyses

We performed some control analyses to ascertain if the results of the main statistical analysis were affected by relevant confounding variables.

In a first control analysis, we performed a correlation between the resting state eyes closed alpha power showing the pattern Nold>MCI>AD and the alpha reactivity to eyes opening (Pearson's test; $p < 0.05$), in order to evaluate the relationships between the cortical neural synchronization/desynchronization in the two conditions. The results showed a statistically significant correlation for parietal, occipital, and temporal alpha 1 sources as well as for parietal and occipital alpha 2 sources (r = from -0.83 to -0.95, $p < 0.001$). The higher the eyes closed alpha power, the higher the alpha reactivity to eyes opening. Of note, this correlation was quite high but unable to entirely explain the pattern Nold>MCI>AD of the alpha reactivity to eyes opening. Indeed, we obtained significant inter-groups

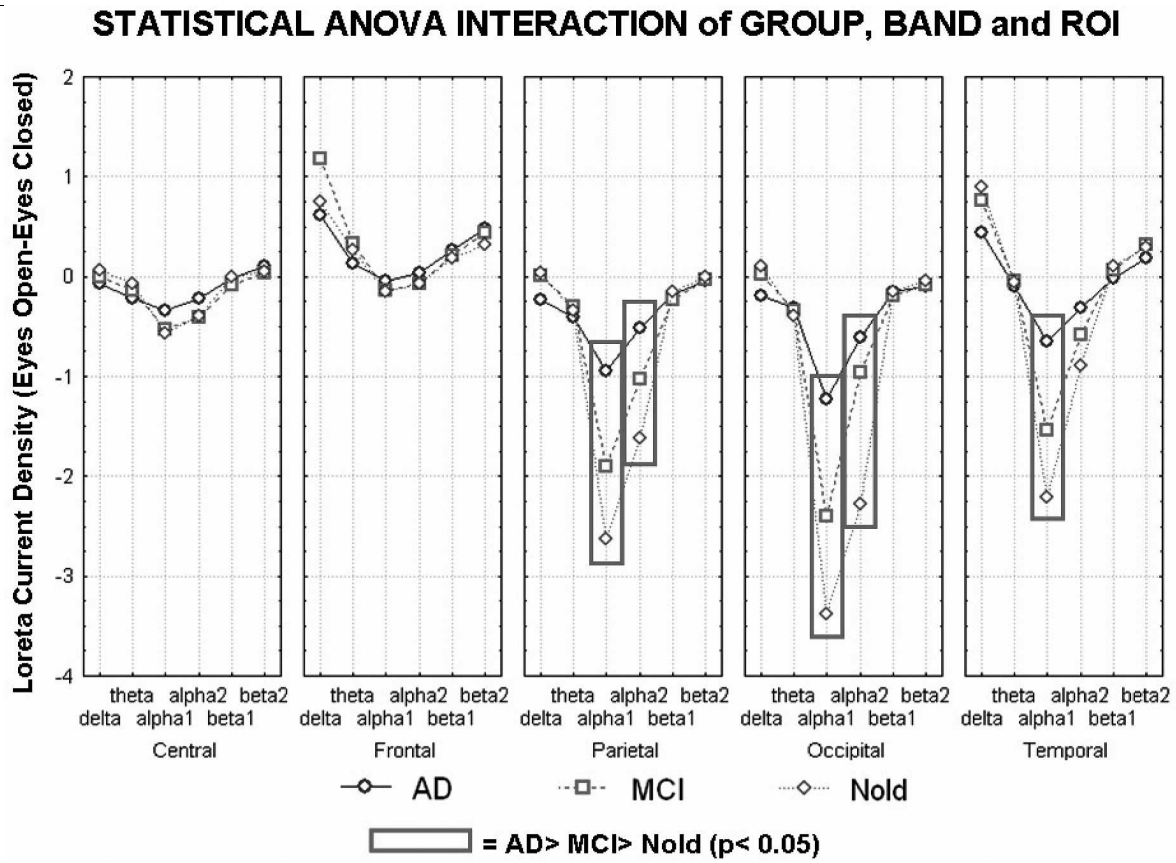

Fig. 3. Normalized power differences at the regional normalized LORETA solutions (eyes-open minus eyes-closed) relative to a statistical ANOVA interaction ($F(40,3100) = 3.75$; $p < 0.001$) among the factors Group (AD, MCI, Nold), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (central, frontal, parietal, occipital, temporal). Subjects' age, education, gender, IAF, MMSE and resting alpha Loreta Current Density eyes closed were used as covariates. The planned post-hoc testing showed that the source pattern eyes-closed > eyes-open was fitted by the following 5 normalized regional LORETA solutions: parietal, occipital and temporal alpha 1 sources ($p < 0.005$ to 0.001) as well as parietal and occipital alpha 2 sources ($p < 0.05$ to 0.001). Legend: the rectangles indicate the cortical regions and frequency bands in which LORETA solutions presented statistically significant LORETA patterns ($p < 0.05$). (Colors are visible in the electronic version of this article at http://dx.doi.org/10.3233/JAD-2010-100798)

effects of alpha reactivity to eyes opening although resting state eyes closed alpha power at relevant sources was used as a covariate in the statistical model.

In a second control analysis, we performed an ANOVA using the power difference of regional absolute (as opposed to normalized) LORETA solutions in the eyes-open minus eyes-closed condition as a dependent variable. The ANOVA factors were Group (AD, MCI, Nold), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (central, frontal, parietal, occipital, temporal). Subjects' age, education, gender, IAF, and MMSE served as covariates. In contrast to the ANOVA using the regional relative LORETA solutions, the control analysis showed no statistically significant interaction among the factors ($p > 0.05$). These control results confirmed that with respect to relative EEG power, absolute EEG power depends on (irrelevant) properties of conductibility of subjects' skull, and may be less sensitive to the changes due to brain neural synchronization.

In a third control analysis, we performed an ANOVA using the LORETA solutions relative to a low-frequency alpha sub-band of 7–9 Hz in the eyes-open minus eyes-closed condition as a dependent variable. This sub-band was lower than mean IAF (i.e., around 9 Hz), to control that the results were not affected by high alpha frequencies. The ANOVA factors were Group (AD, MCI, Nold) and ROI (central, frontal, parietal, occipital, temporal). Subjects' age, education, gender, IAF, and MMSE served as covariates. There was a statistically significant interaction between the factors ($F(8,620) = 2.39$; $p < 0.01$). Post-hoc testing indicated that parietal, occipital and temporal alpha re-

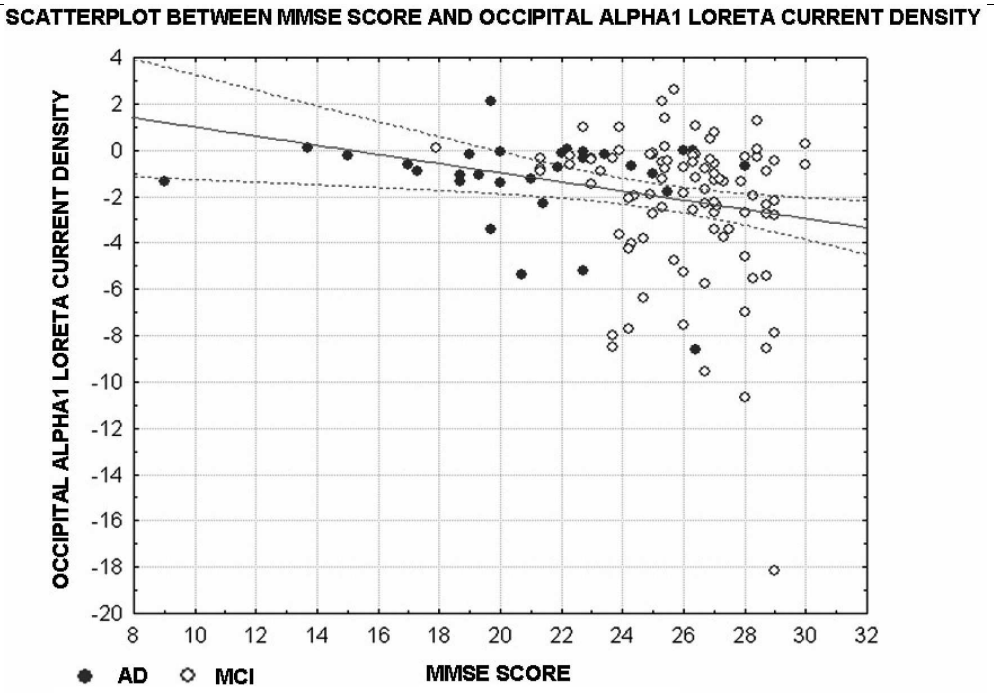

Fig. 4. Scatter plots relative to the results of a correlation analysis between MMSE and occipital alpha 1 sources of EEG rhythms (eyes-open minus eyes-closed) in the MCI and AD subjects as a whole group. (Colors are visible in the electronic version of this article at http://dx.doi.org/10.3233/JAD-2010-100798)

activity to the eyes opening showed differences among the AD and the Nold and MCI subjects ($p < 0.01$), in line with the results of the main statistical analysis.

In a fourth control analysis, we performed an ANOVA including sub-groups of subjects that were carefully matched as number (31 AD, 31 MCI, and 31 Nold subjects), mean age (AD = 70.5 years; MCI = 70.2 years; Nold = 66.0 years), and mean education (AD = 6.5, MCI = 6.7, and Nold = 7.3 years). This allowed a good control of the inter-groups variability. The dependent variable was the normalized LORETA solution in eyes-open minus eyes-closed condition. The ANOVA design was the same of the main analysis. There was a statistical ANOVA interaction ($F(40,1800) = 3.68$; $p < 0.0001$) among the factors Group (AD, MCI, Nold), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (central, frontal, parietal, occipital, temporal). The planned post-hoc testing substantially confirmed the results of the main analysis, showing that the EEG source suppression pattern Nold>MCI>AD was fitted by parietal, occipital, and temporal alpha 1 sources ($p < 0.05$).

In a fifth control analysis, we performed a control data analysis to cross-validate the present LORETA results with an analysis of EEG spectral power density computed at the scalp electrodes. We strictly followed the general methodological approach used for the analysis of the LORETA solutions. The EEG spectral power density at each electrode was normalized to the EEG spectral power density averaged across all frequencies (0.5–45 Hz) and the electrodes, which were representative of the following scalp regions: (i) Fp1, Fp2, F7, F3, Fz, F4, and F8 electrodes for the frontal region; (ii) C3, Cz and C4 electrodes for the central region; (iii) P3, Pz and P4 electrodes for the parietal region; (iv) T3, T4, T5, and T6 electrodes for the temporal region; (v) O1 and O2 electrodes for the occipital region. For a given region, the regional power density for the eyes-closed (eyes-open) condition was defined as the power density averaged across all electrodes of that region. The reactivity of regional EEG power density to the eyes opening and the statistical comparisons were computed according to the procedures used for the analysis of the LORETA solutions. The relative ANOVA used the power difference of regional scalp solutions in the eyes-open minus eyes-closed condition as a dependent variable. The ANOVA factors were Group (AD, MCI, Nold), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and Scalp ROI (central, frontal, parietal, occipital, temporal). Subjects' age, education,

gender, IAF, and MMSE served as covariates. Results showed a statistical ANOVA interaction ($F(40,3100) = 7.14$; $p < 0.001$) among the factors Group (AD, MCI, Nold), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and Scalp ROI (central, frontal, parietal, occipital, temporal). The planned post-hoc testing showed that the scalp EEG reactivity pattern Nold>MCI>AD was fitted by the following normalized regional scalp solutions: parietal, occipital, and temporal alpha 1 ($p <$ 0.05 to 0.001) as well as parietal and occipital alpha 2 ($p <$ 0.05 to 0.001). The amplitude of the above statistically significant alpha 1 and alpha 2 scalp solutions (i.e., reactivity to eyes-open condition; $p <$ 0.05 to 0.001) was correlated with the MMSE score in the MCI and AD subjects as a whole group (Pearson test, $p <$ 0.05). Bonferroni correction for the 5 repetitions of the test set the statistical threshold to $p < 0.01$ to obtain the Bonferroni corrected $p < 0.05$. No statistically significant correlation was observed ($p > 0.01$) between the MMSE and the mentioned alpha scalp solutions in the MCI and AD subjects as a whole. Summarizing, the results showed that in good accordance with the LORETA solutions reported above, posterior scalp alpha reactivity to the eyes opening showed differences between the Nold and MCI subjects and between the MCI and AD subjects. However, in contrast with the LORETA solutions reported above, the occipital scalp alpha 1 reactivity was not correlated to the MMSE score.

DISCUSSION

This study tested the hypothesis of a progressive impairment of cortical alpha reactivity to the eyes-open compared with eyes-closed condition across Nold, amnesic MCI and AD subjects, reflecting the functional impairment of cortical neural desynchronization in the grey zone of the continuum between preclinical and clinical stages of AD. This issue represents the step forward of the present study with respect to previous studies of this Consortium (i.e., Authors' research groups) focused on the mechanisms of cortical neural synchronization associated to the condition of eyes closed resting state [27,28,38,67,68]. With respect to the EEG literature [30,33,36] the novelty of the present EEG study is to focus on topographical reactivity of alpha rhythms to eyes opening and to use relatively large groups of Nold, amnesic MCI, and mild AD subjects, to better take into account for head volume conduction effects and inter-groups variability of resting state EEG rhythms.

In the control eye-closed condition, posterior cortical sources of alpha rhythms were lower in power in the MCI and AD subjects than in the normal elderly subjects. Furthermore, the opposite was true for frontal and temporal cortical sources of delta rhythms. These control results were in line with previous EEG evidence of our Consortium showing progressive differences of resting eyes-closed cortical alpha rhythms along the shadow line across Nold, amnesic MCI, and mild AD subjects [27,28,38,67,68].

With respect to the eyes-closed condition, the eyes-open condition induced a suppression of posterior alpha sources that was greater in the Nold than MCI subjects and in the MCI than AD subjects. In the occipital low-frequency alpha sources, this reactivity was proportional to the subjects' global cognitive function as revealed by MMSE score across MCI and AD individuals (i.e., the grey zone of the disease).

Notably, the eyes-closed alpha power and alpha reactivity to eyes opening pointed to a remarkable correlation and to a similar source pattern in the MCI and AD subjects. However, these variables provided at least in part independent physiological information, since the inter-groups differences in alpha reactivity were still significant when the eyes closed alpha sources were used as covariate in the statistical model. On the whole, it can be speculated that the synchronizing neural circuits at the basis of eyes closed alpha rhythms largely corresponded to the neural circuits that desynchronized during eyes opening.

The present results agree with previous EEG and MEG studies showing that alpha power during eye opening is suppressed more in Nold than in AD subjects, as a reflection of impaired cortical neural desynchronization in visual systems of the patients [21,31–33,35,36]. They also agree with previous suggestion that alpha reactivity to eye opening might predict the deterioration of higher functions in subjects with cognitive decline [33]. Since some of previous EEG and MEG studies have shown that differences between MCI and AD subjects at resting state are not ever discernible [30,33,36], we suggest that ideally, EEG and MEG techniques are used in a combined way to better understand neurophysiology of brain rhythms in amnesic MCI and AD subjects for basic research and clinical applications. High spatial resolution MEG techniques would be effective in the fine topographical estimation of tangentially-oriented cortical sources of brain rhythms, while the present low-resolution EEG approach would be sensitive to the global activity of both tangentially- and radially-oriented cortical sources. Of

course, this scenario may come true when MEG technology could be largely accessible, and automation of the data analysis procedures could reduce time and costs for the production of clinical reports.

An open issue of the present study is whether the present methodological approach for the evaluation of resting state EEG rhythms be used alone for personalized diagnosis and prognosis of individual MCI subjects, given the intrinsic variability of alpha rhythms [30,77]. We think that the present methodological approach is promising for future clinical applications. Indeed, it represents a simple, quick and cheap experimental model to probe the relationships between aging and mechanisms of cortical neural synchronization/desynchronization in two complementary modes of resting state (i.e., presence/absence of visual stimulus processing), without the confounding effects of anxiety, fatigue, boring, and task complexity. Indeed, these mechanisms reflect the integrity of neural populations and synapses as well as the efficiency of functional connectivity and brain reactivity. Such experimental model can be used with elderly individuals ranging from full cognitive performance to severe cognitive impairment, and is not affected by meta-learning and effects of the repetition of the experimental recordings over time. The present results suggest that at least at group level, AD progression is related to an impaired reactivity of the mechanisms desynchronizing posterior cortical neurons at alpha rhythms during eyes opening. This conclusion represents a first important step for understanding the relationship between early stages of AD neurodegeneration and mechanisms of cortical neural synchronization/desynchronization. It also represents an important motivation to ascertain the clinical relevance of the present results (i.e., early diagnosis, prognosis, therapy monitoring) by future longitudinal studies. In this regard, we are aware that the high intrinsic inter-subjects variability of EEG reactivity to eyes opening might prevent its practical clinical use for early diagnosis/prognosis of AD in single MCI individuals. However, we think that there are promising perspectives for the combined used of this EEG marker together with other EEG (i.e., resting state eyes closed), neuroimaging (MRI, PET-FDG, MEG), and biological (CSF, blood) markers. Of special interest the coregistration of resting state EEG rhythms and functional MRI (fMRI). fMRI reflects the ratio between deoxyhemoglobin and oxyhemoglobin blood (BOLD), has a low temporal resolution (> 1 s) and a very high spatial resolution (< 1 cm), and is especially suitable to investigate spatial details of both cortical and subcortical activation [78]. The resting state fMRI represents an indirect measurement of the functional connectivity among brain regions, and perfectly complements the properties of resting state EEG rhythms [79].

A crucial question is then: "What is the functional meaning of a reduced alpha reactivity to eye opening along MCI and AD subjects?" During slow-wave sleep, corticofugal slow oscillations (< 1 Hz) are effective in grouping thalamic-generated delta rhythms (1–4 Hz) and spindling activity (7–14 Hz) rhythms [80]. Delta would dominate EEG rhythms and alpha (about 8–12 Hz) would be low in amplitude. In the case of brain arousal, spindles, high and low components of the delta rhythms are blocked by the inhibition of reticulothalamic (7–14 Hz), thalamo-cortical (1–4 Hz), and intracortical (< 1 Hz) oscillators. These rhythms are replaced by fast oscillations (beta and gamma) induced by forebrain (nucleus basalis) cholinergic inputs to hippocampus and cortex as well as by thalamocortical projections [80,81]. In the condition of waking rest, 8–10 Hz alpha oscillations represent the dominant resting rhythms of human brain [82–85], and have been linked to intelligence quotient, memory, and cognition [66]. Alpha rhythms are mainly generated by the coordinated interplay between cortico-cortical and thalamocortical dynamics, as suggested by studies in higher mammals (lower mammals show negligible or absent alpha rhythms; for a review see [86]. Given that primary visual cortex seems not to be seriously affected in the prodromal stages of AD, it can be speculated that the link between the present results (impairment of cortical desynchronization mechanisms underlying EEG alpha reactivity) and neuropathological events or lesions characterizing AD may rely upon abnormal postsynaptic potentials generated in large pyramidal neurons of occipital-parietal cortical regions and in the neurons conveying signals from parietal nodes of attention networks to visual cortex. This may be due to synaptic and neural loss associated to AD neurodegenerative processes occurring initially and predominantly in the medial temporal lobe structures including hippocampus and amygdala [13]. Hippocampal and amygdalar atrophy in AD have been documented, although thalamic degeneration in the early stages of the disease is an open issue [13,87–90]. The hippocampus connects directly with the anterior thalamus via the fornix and mammillary bodies as well as with the pulvinar via the temporopulvinar tract. Integrity of these connections is essential for episodic memory [91], which is specifically impaired in AD [92]. Keeping in mind this premises, it should be methodologically remarked that estimation

of EEG sources by LORETA directly modeled cortical but not thalamic generators of alpha rhythms. Indeed, LORETA software uses dipole source into a volume fitting cortical grey matter but not thalamus, basal ganglia and other sub-cortical structures. Therefore, cortical sources of alpha rhythms can be affected by altered inputs from thalamus but LORETA is not able to directly model thalamic abnormalities. An abnormal interplay between human thalamic and cortical neural populations can be investigated by combined recordings of EEG and PET-FDG or fMRI. To this regard, it has been shown that alpha power is positively correlated with the cerebral blood flow, glucose metabolism, and BOLD signals in the thalamus, whereas it is negatively correlated with these measurements in visual areas [93–96].

In this theoretical framework, the role of cholinergic systems is still poorly known. On one hand, there is no evidence of the participation of the basal forebrain, via its cholinergic innervation to the cortex, in the generation of alpha rhythms in higher mammals. In cholinergic basal forebrain, lesion and stimulation of nucleus basalis of Meynert mainly affect fast cortical oscillations in the range of gamma rhythms [97]. Furthermore, human occipital cortex (peristriate areas, BA 19) receives a relatively scarce density of cholinergic axons from the intermediate Ch4 subdivision [98]. On the other hand, it has been emphasized the role of parallel cholinergic tracts from basal forebrain to human hippocampus-amygdala, thalamus, and cerebral cortex in the selection/modulation of cortical excitability for attention and visual processes and consciousness [99, 100], which are typically related to alpha rhythms [66]. These cholinergic tracts would be targeted by AD neurodegenerative processes [101–105], especially in AD patients not responding to long term cholinergic therapy [106]. Instead, brainstem cholinergic innervation of the thalamus would be relatively spared [103,107–110]. Furthermore it has been reported that scopolamine (a cholinergic antagonist) mimicked in healthy subjects the typical pattern of alpha and theta rhythms observed in AD patients [77], and the loss of cholinergic connections to cerebral cortex has been shown to reduce the power of resting posterior alpha sources in amnesic MCI subjects [111,112]. Moreover, it has been shown that posterior sources of resting delta and alpha rhythms were especially impaired in AD patients not responding to cholinergic therapy at 1-year follow up [113]. Finally, recent MEG data have pointed to a complex interaction of several resting state EEG rhythms as the reflection of the balance of different neuromodulation systems [114].

Keeping in mind these data, progressive impairment of the alpha reactivity to eye opening in the continuum along amnesic MCI and mild AD conditions might reflect the synaptic and neural loss of large cortical pyramidal neurons including those convey signals through white-matter to visual cortex, in order to modulate arousal-attention and, hence, the transmission and processing of information [115,116]. Future studies should clarify the role played by cholinergic, monoaminergic and glutamatergic systems in the modulation of cortical excitability and alpha rhythms in amnesic MCI and AD subjects [117,118]. In this framework, an intriguing working hypothesis for these future studies is that cholinergic systems play a remarkable role in the desynchronization of posterior alpha rhythms during eyes opening (and mental activity), whereas cortico-cortical and thalamo-cortical interactions rhythms play a remarkable role in the synchronization of posterior alpha rhythms in the condition of eyes closed resting state.

In conclusion, the novelty of present study was to test the hypothesis of a progressive impairment of cortical alpha reactivity to eye opening among relatively large groups of Nold, amnesic MCI and AD subjects, possibly reflecting the functional impairment of cortical neural desynchronization in the grey zone between preclinical and clinical stages of AD. Compared with the eyes–closed condition, the eyes-open condition showed a power reduction of posterior alpha 1 and 2 sources that was greater in the Nold than in MCI subjects and in the MCI than AD subjects. In the occipital alpha 1 sources, this reduction was proportional to the subjects' global cognitive function as revealed by MMSE score across MCI and AD individuals. The present results suggest that at least in its early stages and at group level, AD progression is related to an impaired reactivity of the mechanisms desynchronizing cortical neurons at alpha rhythms during background visual information processing. This conclusion represents a first important step for understanding the relationship between early stages of AD neurodegeneration and mechanisms of cortical neural desynchronization as a reflection of functional brain connectivity and physiological reactivity. However, despite their important heuristic value, the present results are valid at group level and are not conclusive about the utility of the present methodological approach for diagnostic/prognostic purposes in single amnesic MCI subjects. Future longitudinal "follow up" studies should evaluate the clinical relevance of the present results towards practical clinical applications.

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