

Alpha-Band Hypersynchronization in Progressive Mild Cognitive Impairment: A Magnetoencephalography Study

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People with mild cognitive impairment (MCI) show a high risk to develop Alzheimer's disease (AD; Petersen et al., 2001). Nonetheless, there is a lack of studies about how functional connectivity patterns may distinguish between progressive (pMCI) and stable (sMCI) MCI patients. To examine whether there were differences in functional connectivity between groups, MEG eyes-closed recordings from 30 sMCI and 19 pMCI subjects were compared. The average conversion time of pMCI was 1 year, so they were considered as fast converters. To this end, functional connectivity in different frequency bands was assessed with phase locking value in source space. Then the significant differences between both groups were correlated with neuropsychological scores and entorhinal, parahippocampal, and hippocampal volumes. Both groups did not differ in age, gender, or educational level. pMCI patients obtained lower scores in episodic and semantic memory and also in executive functioning. At the structural level, there were no differences in hippocampal volume, although some were found in left entorhinal volume between both groups. Additionally, pMCI patients exhibit a higher synchronization in the alpha band between the right anterior cingulate and temporo-occipital regions than sMCI subjects. This hypersynchronization was inversely correlated with cognitive performance, both hippocampal volumes, and left entorhinal volume. The increase in phase synchronization between the right anterior cingulate and temporo-occipital areas may be predictive of conversion from MCI to AD.

Key words: alpha band; anterior cingulate; functional connectivity; MEG; mild cognitive impairment; phase locking value

Introduction

Mild cognitive impairment (MCI) is an intermediate stage between the normal decline of aging and dementia (Petersen et al., 1999). MCI is considered as a pathological precursor of Alzheimer's disease (AD), because several longitudinal studies have found that the conversion rate from MCI to AD is ~10–15%/year (Petersen et al., 2001). The early identification of those MCI patients who will convert to AD is essential to initiate an early treatment to slow down the devastating effects of this neurodegenerative disorder.

AD pathology is characterized by the presence of β -amyloid (A β) plaques, tau neurofibrillary tangles, and cortical and sub-

cortical atrophy (Trzepacz et al., 2014). Today, there are different approaches, many of them already focused on biomarkers, to identify those patients who would subsequently manifest AD. From a neuropsychological point of view, the performance in episodic memory tests has been proposed as the best predictor of conversion (Albert et al., 2007). Magnetic resonance imaging (MRI) studies have observed a hippocampal and entorhinal cortex atrophy in MCI patients progressing to AD [progressive MCI (pMCI); de Toledo-Morrell et al., 2004; Devanand et al., 2007]. Meanwhile, fluoro-deoxyglucose positron emission tomography (PET) studies have shown that pMCI patients present regional hypometabolism in the temporal, parietal, and/or precuneus cortices compared with MCI patients that remain stable [stable MCI (sMCI); Hatashita and Yamasaki, 2013]. Most of the Pittsburgh compound B (PIB)–PET studies show that PIB-positive MCI patients are significantly more likely to convert to AD than PIB-negative patients (Grimmer et al., 2013). In addition, some studies describe a decreased level of A β protein in CSF in pMCI patients compared with sMCI patients (Riemenschneider et al., 2002; Hampel et al., 2004). Conversely, an increase in tau protein levels in CSF in pMCI patients has been reported in several studies (Riemenschneider et al., 2002), with its predictive power even higher than in the case of A β (Hampel et al., 2004).

The predictive power of some of these methods is very heterogeneous, and those with high values of specificity and sensitivity

Received March 11, 2014; revised July 30, 2014; accepted Aug. 2, 2014.

Author contributions: M.E.L., R.Br., S.A., A.M., and F.M. performed research; M.E.L., R.Br., and R.Ba. analyzed data; M.E.L., R.Br., and F.M. wrote the paper; M.E.L., S.A., A.M., J.A., A.I.R., P.M., and F.M. designed research; J.A.P.-P. contributed unpublished reagents/analytic tools.

This study was partially supported by Spanish Ministry of Science and Economy Grants PSI2009-14415-C03-01 and PSI2012-38375-C03-01, Ministry of Education Predoctoral Fellowships FPU AP-2008-00175 (M.E.L.) and AP2010-1317 (J.A.P.-P.), and a predoctoral fellowship from the Basque Government (S.A.). We thank Pablo Cuesta and Pilar Garcés for their help concerning the methods used in this work.

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The authors declare no competing financial interests.

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DOI:10.1523/JNEUROSCI.0964-14.2014

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are often limited by their high degree of invasiveness, reducing the likelihood of a daily clinical usage. Conversely, those methods with low invasiveness usually also obtain low classification values or do not explain the brain dynamics involved in this progression. Thus, there is a need for a non-invasive biomarker to do the following: (1) explore the brain regions that are affected in pMCI from a synchronization framework (previous functional connectivity studies with EEG/MEG were done in the sensor space; Bajo et al., 2012; Poil et al., 2013); and (2) combine information of brain damage (i.e., MR volumetry), functional network organization, and cognitive status. To the best of our knowledge, this is the first predictive resting-state MEG study in source space that combines neuropsychological, neurophysiological, and structural information to compare sMCI and pMCI patients. According to previous neurophysiological studies, we predict that pMCI patients will show a higher synchronization in high-frequency bands primarily over posterior brain areas compared with sMCI participants.

Materials and Methods

Subjects. The total sample of this experiment was recruited from the Neurology and Geriatric Departments of the University Hospital San Carlos (Madrid, Spain) and from the Centre for Prevention of Cognitive Impairment (Madrid, Spain). All the subjects were right handed (Oldfield, 1971), native Spanish speakers, and monitored over a 2 year follow-up period, with a clinical examination every 6 months.

The original sample consisted of 138 MCI patients, and after a data inspection, we selected 98 subjects with clean MEG recordings. According to their clinical follow-up, they were divided in two subgroups: sMCI ($n = 78$) and pMCI (pMCI; $n = 20$) patients. Progressive patients who developed dementias different from AD (one case of frontotemporal dementia in our sample) were discarded, resulting in a homogeneous group of AD progressive patients ($n = 19$), with a rate of conversion to AD of 19.39%.

To compare the differences between both groups with an adjusted number of the samples, we randomly selected 30 sMCI patients from the original 98. The pMCI subjects of this study can be considered as faster converters, because the conversion time to AD was ~ 1 year after their MEG recordings, MRI scans, and their clinical and neurophysiological measurements (13.16 ± 5.87 months, mean \pm SD; Okello et al., 2009). Therefore, the neurophysiological, structural, and neuropsychological comparisons made in this study between sMCI and pMCI subjects were based on the measures obtained when both groups were still MCI.

The two groups of participants were homogenized in age (mean sMCI age, 74.03 years; mean pMCI age, 76.68 years; Wilcoxon–Mann–Whitney test, $p = 0.104$), gender (sMCI, 14 males, 16 females; pMCI: 8 males, 11 females; Fisher's exact test, $p = 0.777$), and educational level (sMCI, 2.79; pMCI, 2.68; Wilcoxon–Mann–Whitney test, $p = 0.934$).

Diagnostic criteria. The Mini Mental State Examination (MMSE; Lobo et al., 1979), the Geriatric Depression Scale-Short Form (Yesavage et al., 1982), the Global Deterioration Scale (Reisberg et al., 1982), the Hachinski Ischemic Score (Rosen et al., 1980), the functional assessment questionnaire (Pfeffer et al., 1982), the questionnaire for Instrumental Activities of Daily Living (Lawton and Brody, 1969), and the Global Deterioration Scale/Functional Assessment Staging Test (Auer and Reisberg, 1997) were used to establish the global cognitive and functional status of the patients.

MCI diagnosis was established according to the National Institute on Aging–Alzheimer Association (NIA–AA) criteria (Albert et al., 2011): (1) self- or informant-reported cognitive complaint; (2) objective evidence of impairment in one or more cognitive domains; (3) preserved independence in functional abilities; and (4) not demented (McKhann et al., 2011). Besides meeting the core clinical criteria for MCI, subjects had a positive biomarker reflecting neuronal injury, which was measured by MRI. So, all of them could be categorized MCI attributable to AD-intermediate likelihood.

All subjects underwent an extensive neuropsychological assessment to evaluate their cognitive status in multiple areas with the following tests: clock drawing test (Agrell and Dehlin, 1998), direct and inverse digit span test [Wechsler Memory Scale (WMS-III); Wechsler, 1997], immediate and delayed recall (WMS-III; Wechsler, 1997), phonemic and semantic fluency (controlled oral word association test; Benton and Hamsher, 1989), ideomotor praxis of Barcelona test (Peña-Casanova, 1990), rule shift cards (behavioral assessment of the dysexecutive syndrome; Norris and Tate, 2000), visual object and space perception test (Warrington and James, 1991), Boston naming test (Kaplan et al., 1983), and trail-making tests A and B (Reitan, 1958).

According to the cognitive testing, all of them were classified as amnesic MCI patients (Petersen et al., 2001) at baseline, and those who finally fulfilled the criteria for probable AD according to the guidelines of the NIA–AA (McKhann et al., 2011) at follow-up were considered as pMCI ($n = 19$).

The whole sample of MCI subjects was free of significant neurological or psychiatric diseases (other than AD or MCI) and medical treatment that could affect MEG activity (e.g., cholinesterase inhibitors). General inclusion criteria considered an age between 65 and 85 years, a modified Hachinski score ≤ 4 , a geriatric depression scale score ≤ 5 , and a T2-weighted MRI within 12 months before MEG screening without indication of infection, infarction, or focal lesions (rated by two independent experienced radiologists; Bai et al., 2012). In addition, we performed on every participant complementary explorations (class II evidence level) to rule out possible causes of cognitive decline, such as B12 vitamin deficit, diabetes mellitus, thyroid problems, syphilis, or human immunodeficiency virus. Besides, those subjects with alcohol dependence (more than three alcoholic beverages per day) or chronic use of medication, such as anxiolytics, were not included in the experiment.

The study was approved by the local ethics committee and before the MEG recordings; a written informed consent was signed from all subjects or their legal representatives.

Hippocampal, parahippocampal, and entorhinal volumes. Hippocampal, parahippocampal, and entorhinal volumes were measured as anatomical evidences of brain atrophy characteristic for MCI and AD (Albert et al., 2011; McKhann et al., 2011). In addition, these measures have shown previously its predictive power in AD progression (Jack et al., 1999; deToledo-Morrell et al., 2004; Devanand et al., 2007). For most of the subjects included in this paper (23 sMCI and 14 pMCI), a T1-weighted MRI was available, acquired in a GE Healthcare 1.5 Tesla magnetic resonance scanner, using a high-resolution antenna and a homogenization pure filter (fast spoiled gradient echo sequence; repetition time, 11.2 ms; echo time, 4.2 ms; inversion time, 450 ms; flip angle, 12°; 1 mm slice thickness; 256×256 matrix; and field of view, 25 cm). These MRI images were processed with Freesurfer software (version 5.1.0) and its specialized tool for automated cortical and subcortical segmentation (Fischl et al., 2002) to obtain the volume of several brain areas. Finally, volumes were normalized with respect to the overall intracranial volume to account for differences in head volume over subjects.

MEG recordings. Neurophysiological data was acquired by using a 306 channel (102 magnetometers, 204 planar gradiometers) Vectorview MEG system (Elekta), placed in a magnetically shielded room (Vacuum-Schmelze) at the Laboratory of Cognitive and Computational Neuroscience (Madrid, Spain). All recordings were obtained in the morning while subjects were sat comfortably, resting with eyes closed but awake. Three minutes of MEG signal was acquired for each subject.

Head shape was obtained by using a three-dimensional Fastrak digitizer (Polhemus) by acquiring three fiducial points (nasion and left and right preauricular points) and at least 300 points of the surface of the scalp. In addition, four head position indication (HPI) coils were placed in the subjects' head: two in the mastoids and two in the forehead. The position of the HPI coils was also acquired using the Fastrak device to provide continuous head position estimation during the recording. Finally, a vertical electrooculogram was placed near the left eye of the subjects to capture the blinks and eye movements.

MEG data were acquired using a sampling rate of 1000 Hz using an online anti-alias filter between 0.1 and 330 Hz. Recordings were filtered offline using a tempo-spatial filtering algorithm (correlation window,

0.9; time window, 10 s; Taulu and Kajola, 2005; Taulu and Simola, 2006) to subtract the sources of noise placed outside the head, and the head movements were corrected using the same algorithm.

The signal coming from the planar gradiometers was discarded, and only magnetometers were used in the subsequent analysis. Ocular, muscular, and jump artifacts were identified using an automatic procedure from the Fieldtrip package (Oostenveld et al., 2011) and were confirmed by an MEG expert. The remaining data were segmented in 4 s epochs of artifact-free activity. Only subjects with at least 15 segments were selected for additional analysis (27.23 ± 5.99 epochs in the sMCI group, 26.11 ± 6.73 epochs in the pMCI group, mean \pm SD). In addition, an independent component analysis-based procedure was used to remove the electrocardiographic artifact when it was easily identified.

Artifact-free epochs were filtered in six frequency bands: delta (2–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta 1 (12–20 Hz), beta 2 (20–30 Hz), and gamma (30–45 Hz), using a 1500 order finite impulse response filter with Hamming window and a two-pass filtering procedure. The segments were padded with 1.75 s of real signal from both sides (1750 samples) to prevent edge effects inside the data.

Source reconstruction. A source reconstruction analysis was performed independently for each band, using a linearly constrained minimum variance beam former (Van Veen et al., 1997). Because we did not have a T1 MRI for all subjects, a 1 mm resolution template of healthy adults (52 subjects, aged 69.9 ± 4.4 years, mean \pm SD) normalized to the Montreal Neurological Institute (MNI) 1 mm voxel size template was used to place the sources inside the brain. T1 images were coregistered to the MNI T1 template (available in SPM5, <http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>) using linear affine registration with normalized mutual information as fitness function (Collignon and Maes, 1995). The registered images were normalized to the MNI template using a nonlinear registration algorithm (Ashburner, 2007) and then smoothed with a Gaussian kernel with full-width half-maximum of 4 mm. The resulting normalized images were averaged across subjects to obtain a template, which was used to define a homogeneous grid of 1 cm. Then both the template and grid were linearly transformed to fit the head shape of each subject.

The lead fields were defined using a local spheres approach to fit the head shape of each subject in the vicinity of each sensor. Spatial filter coefficients were estimated for each subject using the computed lead field and an average of the covariance matrix for all the segments. Thereafter, this filter was used to compute the source time series separately for each segment and source location.

Sources were grouped according to the 96-area Harvard–Oxford cortical map, assigning each source location to the most probable area given its position. From the original 3431 source locations, only those 1681 labeled as belonging to an area defined in the atlas were considered in the following steps. The other 1750 sources were placed in areas not defined in the atlas (i.e., white matter, CSF, or subcortical regions) and therefore cannot be source generators of MEG signals (Hämäläinen et al., 1993).

Connectivity analysis. The analysis of the connectivity was performed using the hypothesis of phase synchronization (Rosenblum et al., 2001) evaluated by means of the phase locking value (PLV; Lachaux et al., 1999). Phase synchronization measures are based on the hypothesis that the difference of phases between two phase-locked systems must be non-uniform, and so the degree of non-uniformity must be a good estimator of the coupling level.

In the PLV, the degree of non-uniformity is calculated by defining as many vectors as temporal points, each one with unity norm and phase equal to the difference of phases of both systems for this temporal point. The norm of the mean vector is the PLV, ranging from 0, when the differences of phases are uniformly distributed, to values near 1, when the phases are concentrated in a small portion of the available range. The formal definition for the PLV between two systems, i and j , with instantaneous phases $\varphi_i(t)$ and $\varphi_j(t)$, is (Lachaux et al., 1999) as follows:

$$PLV_{i,j} = \left| \frac{1}{T} \sum_t e^{2\pi j(\varphi_i(t) - \varphi_j(t))} \right|.$$

To reduce the dimensionality of the information, we estimated the synchronization between each pair of areas of the Harvard–Oxford cortical

atlas. We can consider each area as a system and each source position inside the area as a noise-contaminated realization of the system. For each pair of areas, area i with M_i sources and area j with M_j sources, we can create M_i by M_j combinations of sources for each segment, leading to M_i by M_j repetitions of the experiment. All these repetitions are time locked; thus, the total synchronization can be obtained as the norm of the mean vector for all the repetitions.

Conversely, different segments are not time locked, because in the resting state, there is no triggering event that resets the phases (Lachaux et al., 1999). We can then average the synchronization value of all the K segments for each pair of areas, obtaining a consistent indicator of the level of coupling between the areas. Formally, this PLV index between the areas i and j is calculated as follows:

$$PLV_{i,j} = \frac{1}{K} \sum_k \left| \frac{1}{M_i \times M_j \times T} \sum_{M_i} \sum_{M_j} \sum_T e^{2\pi j(\varphi_{m_i}(t,k) - \varphi_{m_j}(t,k))} \right|,$$

where $\varphi_m(t,k)$ represents the instantaneous phase the time series i of the area m for the instant t of the segment k . In this work, the instantaneous phase of the signal in each band was calculated from the phase of the analytic signal of the narrow band data, obtained using the Hilbert transform (Pereda et al., 2005).

Statistical analysis. To assess the significant differences in functional connectivity measures, we performed a Mann–Whitney U nonparametric test using the PLVs estimated for each pair of areas. To correct the multiple comparisons problem, we first performed a nonparametric permutation test, keeping the size of the groups but randomly permuting their members (10,000 permutations). The p value obtained in this step represents the portion of permutations in which the U statistic was greater than that in the original dataset.

Then a false discovery rate (FDR; Benjamini and Hochberg, 1995) with $q = 0.1$ (a 10% false-positive probability) was used to reduce the portion of false positives in the obtained p value distribution. Only the links that survived the FDR are reported in Results. In addition, a Spearman's correlated test was performed between connectivity values in these links and neuropsychological and structural data to better understand its significance.

Finally, a classification analysis was performed using the variables that showed significant differences between both groups by using a logistic regression analysis with the leave-one-out cross-validation procedure. Results are described in terms of accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Accuracy value represents the fraction of subjects classified correctly. Sensitivity and specificity values represent the fractions of pMCI and sMCI patients correctly classified, respectively. Finally, PPVs and NPVs represent the fraction of patients classified as pMCI that were really pMCI and the fraction of patients classified as sMCI that were really sMCI, respectively. When reporting accuracy values, the information is completed with a confidence interval (CI) for the statistic, calculated using the β approach (Clopper and Pearson, 1937).

Results

Because the clinical criteria of AD, according to the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association, are based on cognitive or behavioral symptoms, our first approach was to evaluate the predictive capacity of the functional and cognitive measures to discriminate between sMCI and pMCI. Table 1 shows the statistical values associated with each cognitive measurement and with volumes of the temporal region. MMSE scores showed no differences between groups. In contrast, both groups of patients did differ in immediate ($p = 3.26 \times 10^{-6}$) and delayed ($p = 7.18 \times 10^{-5}$) recall, rule shift cards ($p = 0.028$), and semantic fluency ($p = 0.041$). The values obtained by each group in these four neuropsychological measures are depicted in Figure 1. A classification analysis was performed for each one of the two most significant, achieving classification rates

Table 1. Demographic, anatomical, and neuropsychological information

	sMCI patients (n = 30)	pMCI patients (n = 19)	p values
Age (years)	74.0 ± 5.3	76.7 ± 5.3	0.104
Gender (males/females)	14/16	8/11	0.777
Educational level	2.8 ± 1.3	2.7 ± 1.0	0.934
MMSE score	27.9 ± 1.9	27.4 ± 2.0	0.455
GDS	3.0 ± 0.0	3.0 ± 0.0	1.000
FAQ	1.9 ± 1.8	1.8 ± 2.8	0.501
GDS-SF	3.8 ± 3.1	3.5 ± 3.8	0.647
Immediate recall	20.7 ± 8.2	10.0 ± 5.0	3.26 × 10 ⁻⁶ *
Delayed recall	8.6 ± 7.4	1.8 ± 2.2	7.18 × 10 ⁻⁵ *
Rule shift cards	2.4 ± 1.3	1.6 ± 1.2	0.028*
Semantic fluency	13.0 ± 2.8	11.6 ± 4.4	0.041*
Phonemic fluency	10.8 ± 4.2	8.8 ± 4.1	0.119
BNT	50.4 ± 10.7	46.3 ± 9.4	0.510
Clock drawing test (copy)	7.6 ± 2.6	8.0 ± 4.2	0.600
Clock drawing test (order)	6.4 ± 2.6	7.4 ± 3.6	0.615
Direct digit spam	6.7 ± 1.6	6.4 ± 1.5	0.413
Inverse digit spam	4.7 ± 1.3	4.0 ± 1.4	0.103
VOSP	6.7 ± 3.5	7.2 ± 3.1	0.593
TMTA (time)	78.7 ± 36.0	82.8 ± 33.6	0.580
TMTA (accuracy)	24.0 ± 0.6	23.8 ± 1.8	0.401
TMTB (time)	223.2 ± 107.8	258.4 ± 121.7	0.329
TMTB (accuracy)	20.1 ± 4.8	15.2 ± 8.6	0.050
Ideomotor praxis	7.3 ± 1.7	7.2 ± 1.1	0.374
Left hippocampal volume	0.002217 ± 0.000508	0.001992 ± 0.000254	0.056
Right hippocampal volume	0.002197 ± 0.000466	0.001965 ± 0.000388	0.063
Left entorhinal volume	0.000527 ± 0.000100	0.000452 ± 0.000106	0.038*
Right entorhinal volume	0.000481 ± 0.000072	0.000452 ± 0.000155	0.954
Left parahippocampal volume	0.000663 ± 0.000072	0.000596 ± 0.000169	0.153
Right parahippocampal volume	0.000645 ± 0.000113	0.000604 ± 0.000175	0.864

Mean ± SD values of the demographic and clinical characteristics of the sMCI and pMCI patients. MMSE, Mini Mental State Examination; GDS, Global Deterioration Scale; FAQ, Functional Activity Questionnaire; GDS-SF, Geriatric Depression Scale-Short Form; BNT, Boston Naming Test; VOSP, Visual Object and Space Perception Battery; TMTA, Trail-Making Test part A; TMTB, Trail-Making Test part B. Educational level was grouped into five levels: 1, illiterate; 2, primary studies; 3, elemental studies; 4, high school studies; 5, university studies. *p* values for between-groups differences were introduced, and **p* < 0.05. Wilcoxon–Mann–Whitney test was used for continuous variables (age, educational level, MMSE, or immediate and delayed recall) and Fisher's exact test for gender differences.

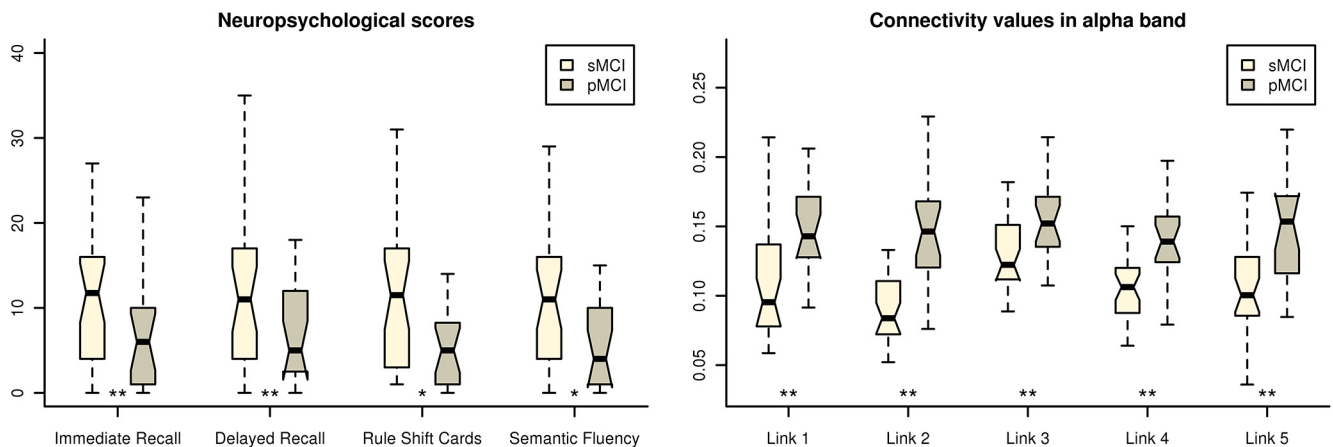


Figure 1. Box plots depicting the behavior of the subjects for each group. Left, Scores achieved by the subjects in the four statistically significant neuropsychological tests. Right, Connectivity values for the subjects in the five statistically significant links. **p* < 0.05, ***p* < 0.001.

of 79.6% for immediate recall (95% CI = 65.7–89.8%, 84.2% sensitivity, 76.7% specificity, 69.6% PPV, 88.5% NPV) and 77.6% for delayed recall (95% CI = 63.4–88.2%, 78.9% sensitivity, 76.7% specificity, 68.2% PPV, 85.2% NPV). Conversely, the pMCI group exhibited lower left entorhinal volume than the sMCI group (*p* = 0.038), but no differences were found in either the parahippocampal or hippocampal volumes (*p* > 0.05).

The functional connectivity analysis exhibited no significant differences between groups after the FDR in delta, theta, beta 1, beta 2, or gamma bands. In contrast, FDR analysis in the alpha

band showed five significant links between the right anterior cingulate gyrus and right middle temporal gyrus and occipital regions, mainly in the right hemisphere. In all these links, pMCI patients showed significantly greater connectivity values than sMCI patients (*p* < 10⁻³). Figure 1 represents the connectivity values obtained for each group, Figure 2 depicts the position and size of all six regions implied in these links, and Table 2 shows the *p* value of each one of the five significant links. Afterward, a classification analysis was performed individually for each link, achieving a maximal classification rate in link 2 (right lateral

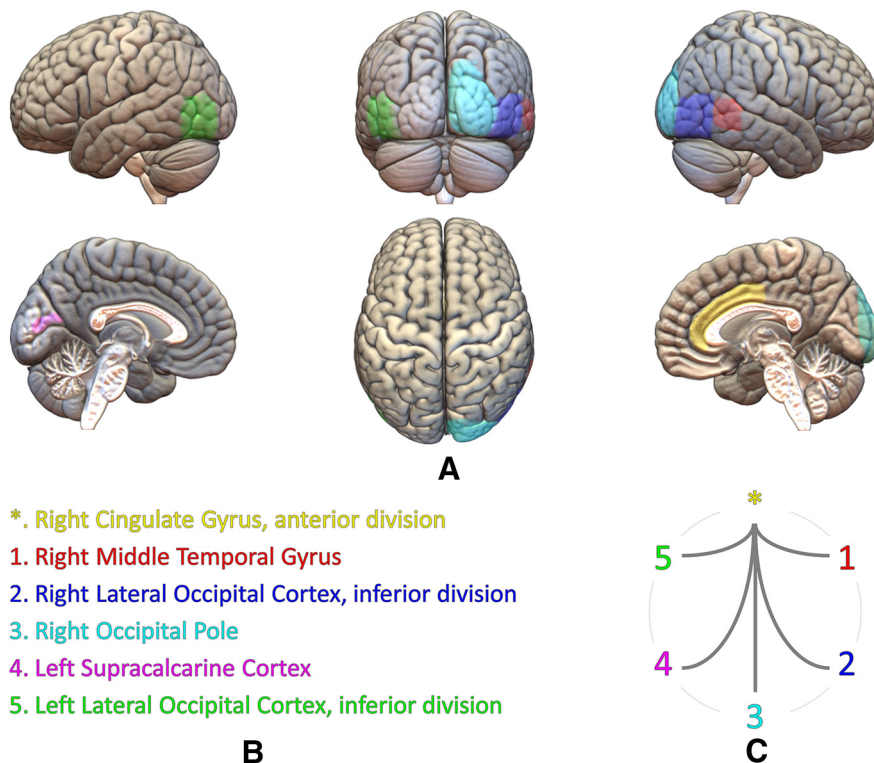


Figure 2. Cortical areas implied in the five connectivity links that showed significant differences between groups. **A**, Different views of the brain based on the MNI template and Harvard–Oxford cortical areas involved in those links. **B**, Relation of areas, numbers, and colors. **C**, Significant connectivity links established between those areas.

occipital cortex, inferior division, with right cingulate gyrus, anterior division) with an accuracy of 81.6% (95% CI = 68.0–91.2%, 84.2% sensitivity, 80.0% specificity, 72.7% PPV, 88.9% NPV). All classification statistics are also shown in Table 2.

To better describe our functional connectivity findings, we performed a Spearman's correlation test between connectivity values in those links, neuropsychological punctuations, and volumetric data. We found an inverse significant correlation ($p < 0.05$) between some of these links and MMSE, immediate recall, and semantic fluency scores. Moreover, we observed inverse significant correlations ($p < 0.05$) between several links, both hippocampus volumes and left entorhinal volume. Table 3 details all these findings along with their significance level.

Finally, with the aim of evaluating the combined predictive power of both neuropsychological and neurophysiological data in terms of conversion, we performed a classification analysis using as variables those with higher classification statistics: immediate recall scores and link 2 connectivity values. The accuracy achieved combining both measures was 89.8% (95% CI = 77.8–96.6%, 89.5% sensitivity, 90.0% specificity, 85.0% PPV, 93.1% NPV), greater than if these two variables were considered separately.

Discussion

This study provides a specific pattern of functional network organization in resting state in those MCI patients who developed dementia. pMCI patients showed an increase in functional connectivity values in the alpha band between the anterior and posterior brain areas and more specifically between the right anterior cingulate and temporo-occipital areas.

Previous resting state EEG studies found different markers of progression to AD. Jelic et al. (2000) reported that the best pre-

dictor of future conversion from MCI to AD was an increased theta power and a decrease in alpha activity, whereas Huang et al. (2000) evidenced that the best predictor was the shift of alpha activity toward anterior brain. Rossini et al. (2006) found that pMCI patients exhibit higher power values in the delta, theta, and alpha 1 bands, mainly over temporal and parietal areas, and also changes in fronto-parietal midline coherence values. More recently, Moretti et al. (2011) observed that those MCI patients who convert to AD presented an increase in the alpha3/alpha2 relative power ratio, with this ratio further related to hippocampal atrophy (Moretti et al., 2007). Poil et al. (2013) reported that multiple EEG biomarkers were mainly related to activity in the beta-frequency range, which was higher in the pMCI group than in the sMCI group.

Surprisingly, there are very few MEG studies about the MCI progression to AD. A resting-state MEG study by Fernández et al. (2006) found that an increase in delta activity in the left parietal areas was a good marker of conversion within 2 years. Furthermore, Maestú et al. (2011) observed that, during the performance of a short-term memory task, pMCI patients showed higher activity in the ventral and dorsal pathways than sMCI subjects. Afterward, and under the same memory paradigm, Bajo et al. (2012) described that pMCI patients exhibited higher values of synchronization over parieto-occipital sensors in the alpha and beta 1 bands than sMCI patients.

Our connectivity results seem to be in agreement with those obtained by Rossini et al. (2006) and Bajo et al. (2012), because they reported an increase in connectivity measures in the pMCI subjects compared with the sMCI group. Although the increase in synchronization observed in MCIs has been interpreted usually as a compensatory mechanism, the negative correlations found in this study with neuropsychological performance and temporal brain volumes could lead us to consider two possible hypotheses about this hypersynchronization: (1) it could be an unsuccessful compensation: the right anterior cingulate along with temporal and occipital regions try to assume the functions of other brain circuits that are more impaired (i.e., involving the posterior cingulate) but in an inefficient way; or (2) it could be the result of an inhibitory deficit: the loss of GABAergic synapses caused by the accumulation of $A\beta$ plaques (García-Marín et al., 2009) leads it to establish aberrant relationships between areas that start to be affected as the disease progresses.

The anterior cingulate is a region of the medial frontal circuit that has been related to conflict monitoring, decision making, and affective behavior, among other functions (Devinsky et al., 1995). A relationship between its alteration in AD patients and inhibition disabilities, unawareness of deficits, and apathy has been found (Amanzio et al., 2011; Mori et al., 2014). The executive and inhibitory deficits found even in pure amnesic MCI patients may also be attributable to the damage of this brain structure (Kramer et al., 2006; Johns et al., 2012). In addition, some MRI, single-photon emission computed tomography, and

Table 2. The five significant links in the alpha band between sMCI and pMCI patients were obtained with a Mann–Whitney *U* test after the FDR

	sMCI patients (<i>n</i> = 30)	pMCI patients (<i>n</i> = 19)	<i>p</i> values	Classification statistics (%)				
				ACC (95% CI)	SEN	SPE	PPV	NPV
Link 1	0.11 ± 0.03	0.14 ± 0.02	2.04 × 10 ⁻⁴	77.6 (63.4–88.2)	78.9	76.7	68.2	85.2
Link 2	0.10 ± 0.03	0.14 ± 0.03	3.40 × 10 ⁻⁵	81.6 (68.0–91.2)	84.2	80.0	72.7	88.9
Link 3	0.10 ± 0.02	0.13 ± 0.03	1.73 × 10 ⁻⁴	77.6 (63.4–88.2)	73.7	80.0	70.0	82.8
Link 4	0.14 ± 0.03	0.18 ± 0.03	1.35 × 10 ⁻⁴	77.6 (63.4–88.2)	78.9	76.7	68.2	85.2
Link 5	0.10 ± 0.03	0.14 ± 0.03	2.81 × 10 ⁻⁴	69.4 (54.6–81.7)	68.4	70.0	59.1	77.8

Link 1, right cingulate gyrus, anterior division, with right middle temporal gyrus, temporo-occipital part; Link 2, right cingulate gyrus, anterior division, with right lateral occipital cortex, inferior division; Link 3, right cingulate gyrus, anterior division, with right occipital pole; Link 4, right cingulate gyrus, anterior division, with left supracalcarine cortex; Link 5, right cingulate gyrus, anterior division, with left lateral occipital cortex, inferior division; ACC, accuracy; SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value; 95% CI, 95% confidence interval.

Table 3. Spearman's correlation analyses of the five significant links obtained in the alpha band with neuropsychological test scores and hippocampal volumes in the whole sample

	Link 1	Link 2	Link 3	Link 4	Link 5
MMSE	<i>r</i> = -0.195 n.s.	<i>r</i> = -0.300 <i>p</i> = 0.047	<i>r</i> = -0.207 n.s.	<i>r</i> = -0.143 n.s.	<i>r</i> = -0.097 n.s.
Immediate recall	<i>r</i> = -0.268 n.s.	<i>r</i> = -0.394 <i>p</i> = 0.005	<i>r</i> = -0.366 <i>p</i> = 0.010	<i>r</i> = -0.300 <i>p</i> = 0.036	<i>r</i> = -0.350 <i>p</i> = 0.014
Semantic fluency	<i>r</i> = -0.172 n.s.	<i>r</i> = -0.286 <i>p</i> = 0.047	<i>r</i> = -0.264 n.s.	<i>r</i> = -0.145 n.s.	<i>r</i> = -0.135 n.s.
Left hippocampal volume	<i>r</i> = -0.322 <i>p</i> = 0.046	<i>r</i> = -0.370 <i>p</i> = 0.020	<i>r</i> = -0.170 n.s.	<i>r</i> = -0.336 <i>p</i> = 0.036	<i>r</i> = -0.213 n.s.
Right hippocampal volume	<i>r</i> = -0.223 n.s.	<i>r</i> = -0.302 n.s.	<i>r</i> = -0.342 <i>p</i> = 0.033	<i>r</i> = -0.368 <i>p</i> = 0.021	<i>r</i> = -0.431 <i>p</i> = 0.006
Left entorhinal volume	<i>r</i> = -0.374 <i>p</i> = 0.021	<i>r</i> = -0.411 <i>p</i> = 0.010	<i>r</i> = -0.209 n.s.	<i>r</i> = -0.475 <i>p</i> = 0.003	<i>r</i> = -0.318 n.s.

Shown are the *r* (correlation index) and *p* values that were significant (*p* < 0.05). MMSE, Mini Mental State Examination.

PIB–PET studies pointed out that this densely connected region might be key during the evolution of AD. Peters et al. (2014) found that one of the best predictors of the conversion from MCI to AD after 2 years was the cortical thinning in the right anterior cingulate. Johnson et al. (2007) reported an more increased perfusion in pMCI patients than in sMCI patients within a 5 year follow-up period in the rostral anterior cingulate. Recently, Okello et al. (2009) found that faster converters (average of 1 year, as our patients) showed a higher amyloid deposition in the anterior cingulate than slow converters. These findings would be in agreement with the idea that the hyperactivation observed in this brain region is attributable to the loss of inhibitory synapses, caused by the accumulation of Aβ (Garcia-Marin et al., 2009).

One of the main finding in AD studies is the decrease in synchronization in high-frequency bands, especially in alpha (Locatelli et al., 1998; Berendse et al., 2000), so the hypersynchronization usually observed in pMCI patients seems to be paradoxical. However, the synaptic disruption produced in the cholinergic system (Requena et al., 2006; Schliebs and Arendt, 2006) and the loss of inhibitory neurons caused by the accumulation of neuritic plaques (Garcia-Marin et al., 2009) may produce the increase in synchronization in high oscillations in these patients. The synchronization found in the alpha band over the occipital cortex is consistent with the eyes-closed resting-state condition. The occipital lobe has usually been considered less impaired or not prominently involved until the last stages of the AD, but there is evidence of amyloid pathology in MCI patients and even in healthy subjects (McKee et al., 2006; Uhlhaas et al., 2008). Thus, our results suggest that the occipital lobe appears to be part of a disrupted network in which pMCI patients present a higher amyloid pathology than sMCI subjects.

Several studies have also described an increase of synchronization in the alpha band in MCI subjects while performing a cognitive task compared with controls (Pijnenburg et al., 2004;

Jiang and Zheng, 2006; Bajo et al., 2010). Therefore, we speculated that, as the disease progresses, the hypersynchronization observed in MCI patients would lead to neuronal death, causing the disruption observed in more advance stages of the AD (Locatelli et al., 1998; Koenig et al., 2005; Stam et al., 2009).

In line with previous studies, pMCI patients showed a worse performance in episodic memory, which was the cognitive area with higher classification rates (Albert et al., 2007), but also in semantic memory and executive functioning. These findings suggest that extra-memory cognitive impairments may also have a role in the prediction of the progression from MCI to AD (Chapman et al., 2011). In addition, the hypersynchronization exhibited by pMCI patients was inversely correlated with different neuropsychological scores, indicating that it has a negative effect on memory and general cognitive status of patients.

At the structural level, there were no differences in either parahippocampal or hippocampal volumes between sMCI and pMCI patients (Peters et al., 2014), although the left hippocampus was slightly smaller in the pMCI patients, which is in accordance with previous studies (Douaud et al., 2013). However, pMCI patients exhibited a significant reduction of the left entorhinal volume. It is considered that, in this brain structure, the AD pathology begins (Khan et al., 2014) and that it is the interface between the hippocampus and the neocortex that has a critical role in memory (Takehara-Nishiuchi, 2014). Therefore, the differences obtained in verbal memory between both groups may be explained by the higher atrophy observed in the pMCI group, although it is important to note that the deficits in executive functioning exhibited by this group may influence verbal memory performance (Brooks et al., 2006; Chang et al., 2010). Notwithstanding that hippocampal atrophy is one of the anatomical changes that better predicts the subsequent conversion to AD (Jack et al., 1999), our anatomical results seem to be consistent with the role of the entorhinal cortex at the onset of AD, because our pMCI patients

were faster converters and there was greater involvement of the entorhinal than the parahippocampal cortex in predicting the conversion to AD (Devanand et al., 2007). The increase in synchronization showed by pMCI subjects was negatively related to both hippocampal volumes and left entorhinal volume, indicating that this increment reflect higher atrophy of these brain structures, which are more vulnerable to AD.

Finally, the higher classification scores obtained in the hypersynchronized links separately or combined with neuropsychological information are similar, or even better, than those obtained previously (Poil et al., 2013; Belleville et al., 2014; Peters et al., 2014). These findings suggest that MEG functional network organization is able to detect the functional changes caused by synaptic disruption that precede the structural ones.

Together, this work shows MEG as a promising biomarker of synaptic disruption in the prediction of the AD and the importance of combining it with other measures (Lehmann et al., 2007; Poil et al., 2013) to development a predictive model of AD (Antila et al., 2013). Forthcoming studies should go further and focus on predicting future cognitive decline in healthy subjects with and without subjective memory complaints (Pritchep et al., 2006) to initiate preventive treatments at the earliest possible time.

The study of brain connectivity is allowing us a better understanding of how our mind works to achieve a good cognitive performance (Hampson et al., 2006) and how the disease causes its disruption to affect the cognitive status of the patients (de Haan et al., 2012). Therefore, the present work provides a new perspective in addressing the evolution of AD and reinforces the MEG as an important biomarker to evaluate AD progression.

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