Journal of Alzheimer's Disease 43 (2015) 259–273
DOI 10.3233/JAD-140633
IOS Press

Source Analysis of Spontaneous Magnetoencephalograpic Activity in Healthy Aging and Mild Cognitive Impairment: Influence of Apolipoprotein E Polymorphism

Pablo Cuesta[a,b,c], Ana Barabash[d,e], Sara Aurtenetxe[a], Pilar Garcés[a,c], María Eugenia López[a,b], Ricardo Bajo[a], Marcos Llanero-Luque[f], Inés Ancín[d,e], José Antonio Cabranes[d,e], Alberto Marcos[e,g], Miguel Sancho[c], Akinori Nakamura[h], Fernando Maestú[a,b,e] and Alberto Fernandez[a,e,i,*]
[a]*Laboratory of Cognitive and Computational Neuroscience, Center for Biomedical Technology, Complutense University of Madrid and Technical University of Madrid, Spain*
[b]*Department of Basic Psychology II, Complutense University of Madrid, Madrid, Spain*
[c]*Department of Applied Physics III, Faculty of Physics, Complutense University of Madrid, Madrid, Spain*
[d]*Laboratory of Psychoneuroendocrinology and Molecular Genetics, Biomedical Research Foundation, Clínico San Carlos Hospital, Madrid, Spain*
[e]*Institute of Sanitary Investigation [IdISSC], San Carlos University Hospital, Madrid, Spain*
[f]*Centre for Prevention of Cognitive Impairment, Ayuntamiento de Madrid, Spain*
[g]*Neurology Department, San Carlos University Hospital, Madrid, Spain*
[h]*Department of Clinical and Experimental Neuroimaging, National Center for Geriatrics and Gerontology, Obu, Japan*
[i]*Department of Psychiatry, Faculty of Medicine, Complutense University of Madrid, Madrid, Spain*

Handling Associate Editor: Susana Cid Fernández

Accepted 29 May 2014

Abstract. The apolipoprotein E (APOE) $\varepsilon 4$ allele is a genetic risk factor for the development of late-onset Alzheimer's disease (AD), which affects cholinergic system functioning. The association between reduced cholinergic levels and increase of magnetoencephalographic (MEG) low-frequency has been used to explain spectral changes found in AD patients. However, the investigation in predementia stages is scarce. We obtained MEG recordings from 25 aged controls and 36 mild cognitive impairment (MCI) patients during a resting-state condition. According to their APOE genotype, MCIs and controls were subdivided in carriers and non-carriers of the $\varepsilon 4$ allele. Sources of spectral variations in these groups were calculated through beamforming. MCI patients exhibited a significant increase of relative power within the low-frequency domain, accompanied by a power decrease within the high-frequency range. APOE$\varepsilon 4$ carriers showed an increased relative power in the 4.5–6.5 Hz frequency range over frontal lobes. The power increase observed in controls carrying $\varepsilon 4$ was significantly higher as compared

*Correspondence to: Alberto Fernández, PhD, Department of Psychiatry, Faculty of Medicine, Complutense University of Madrid and Laboratory of Cognitive and Computational Neuroscience [UCM-UPM], Centre for Biomedical Technology [CTB], Campus de Montegancedo s/n, Pozuelo de Alarcón, 28223 Madrid, Spain. Tel.: +34913942296; Fax: +34913941503; E-mail: aferlucas@med.ucm.es.

ISSN 1387-2877/15/$27.50

with MCI non-carriers, while MCI carriers exhibited the highest relative power within the 4.5–6.5 Hz range. Higher power values within the low-frequency ranges correlated with a poorer cognitive performance in MCIs and controls. Our investigation demonstrates that APOEε4 affects resting-state activity to an extent that makes it more proximate to the pattern observed in early stages of AD. Therefore, a combination of genetic and neurophysiological information might help to detect MCI patients at higher risk of conversion to AD, and asymptomatic subjects at higher risk of developing a manifest cognitive deterioration.

Keywords: Aging, APOEε4, magnetoencephalography, mild cognitive impairment, relative power, source analysis

INTRODUCTION

The human apolipoprotein E (APOE) ε4 allele is the most established genetic risk factor for the development of late-onset Alzheimer's disease (AD) [1–3]. APOE is a lipid-binding protein which is expressed in humans as three alleles, designated ε2, ε3, and ε4 [4]. Although APOEε4 is neither necessary nor sufficient to cause by itself the late-onset variant [5, 6], the risk of suffering from AD is increased for all genotypes containing the ε4 allele [7]. Several investigations tried to unveil the physiological process that underlies the relationship between APOEε4 and higher risk of developing late-onset AD. For instance, postmortem analyses revealed a significant correlation between the presence of an APOEε4 allele and a higher amyloid-β (Aβ) burden in AD patients' brains. This indicates that APOE may interact with Aβ by enhancing its deposit in form of plaques [8, 9]. The proliferation of Aβ deposits associated with APOEε4 was further supported by recent biomarker investigations [10, 11]. Additionally, some studies demonstrated that APOE regulates the effects of growth factors and oxidative processes. The APOEε3 allele promotes greater neurite outgrowth and higher neural prevention from the oxidative stress in comparison to APOEε4 [12]. What is more, APOE has been associated with the modulation of neurotransmitter release in the glutamatergic system, thus preventing excitotoxicity [13]. Animal models showed that APOE-deficient specimens exhibit decreased synaptic density in the septo-hippocampal and nucleus-basalis cholinergic pathways due to a so-called "pre-synaptic derangement" [14].

The influence of APOE on cholinergic neurotransmission is of particular importance, because nucleus-basalis projections to the cortex are believed to modulate the oscillatory neural activity reflected by modifications of the electroencephalographic (EEG) and magnetoencephalographic (MEG) spectrum [15]. Riekkinen et al. found a strong relationship among reduced cholinergic levels, increased delta power, and cognitive deterioration in AD [15–17]. Lehtovirta et al. [18] hypothesized that such a relationship might explain the significant slowing of the EEG spectrum in AD patients carrying the ε4 allele, in comparison to non-carriers. If this notion is assumed, similar results might be expected in earlier stages of the degenerative process (i.e., mild cognitive impairment, MCI) or even in asymptomatic subjects carrying the ε4 allele. Babiloni et al. [19] performed the first EEG investigation on APOEε4 including a sample of MCI patients. However, the genetic information of aged controls was not available, thus preventing a broader interpretation of ε4 effects on brain oscillations.

Considering the need of a more comprehensive research within this field, the aim of this study was to explore the influence of APOEε4 on the resting-state MEG activity of MCI patients and healthy controls. To the best of our knowledge, this is the first neurophysiological investigation where healthy aged controls carrying the ε4 allele are compared with MCI- ε4 carriers and non-carriers. Following the cholinergic hypothesis, we expect that aged controls carrying the ε4 allele would exhibit a pattern of slowing, which includes increased power within the low-frequency range, and reduced activity within the high-frequency range. According to previous results by Babiloni's group, MCI patients carrying the ε4 allele will show a reduced power within the high-frequency bands.

MATERIALS AND METHODS

Participants

MEG signals were obtained from 61 (25 controls and 36 MCI patients) right-handed [20], native Spanish speakers. MCI patients were recruited from the Geriatrics and Neurology Units of the "Hospital Universitario San Carlos", and the "Memory Decline Prevention Center", both in Madrid, Spain. Healthy volunteers were recruited from the "Seniors Center of Chamartin District", Madrid.

Table 1
Demographic description. MCI, mild cognitive impairment; M, male; F, female; MMSE, mini-mental state examination

	Control APOEε3ε3	Control APOEε3ε4	MCI APOEε3 ε3	MCI APOEε3 ε4
n	19	6	20	16
Age	70 ± 4	69 ± 4	72 ± 5	72 ± 3
Gender ratio [M/F]	7/12	4/2	8/12	8/8
MMSE score	29.4 ± 0.7	29.6 ± 0.5	27.4 ± 2.4	27.4 ± 3.0

Diagnostic criteria

All participants were screened by means of a variety of standardized diagnostic instruments that included: the Spanish version of the Mini Mental State Examination (MMSE) [21], the Global Deterioration Scale [22], the Functional assessment questionnaire [23], the Yesavage's Geriatric Depression Scale [24], the Hachinski Ischemic Score [25], the questionnaire for Instrumental Activities of Daily Living [26], and the Functional Assessment Staging [27].

MCI diagnosis was established according to Grundman et al.'s [28] criteria that includes: (a) memory complaint, corroborated by an informant; (b) abnormal memory function detected in formal testing; (c) normal general cognitive function; (d) total absence or minimal impairment in activities of daily living; and (e) not demented according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [29]. Patients and controls were free of significant medical, neurologic and/or psychiatric diseases (other than MCI) and none of them were using drugs which could affect MEG activity (including cholinesterase inhibitors).

The entire sample received an exhaustive neuropsychological assessment in order to establish their performance level in multiple cognitive domains. The neuropsychological protocol has been fully described elsewhere [30]. According to their clinical and neuropsychological profile, all MCI patients fulfilled the criteria of amnestic single-domain subtype, since they exhibited isolated memory impairment [31]. Prior to the MEG recording, all subjects signed an informed consent that explained the technical and ethical considerations of the investigation. The study was approved by the local Ethics Committee.

APOE genotype test

Genomic DNA was extracted from whole-blood samples of MCI patients and controls. APOE was determined using standard methods [32]. On the basis of such genotyping the MCI and control groups were subdivided in four genetic subgroups: 16 subjects with APOEε3 ε4 henceforth called MCI34 group; 20 subjects with APOEε3 ε3, henceforth called MCI33 group; 6 healthy subjects with APOEε3 ε4, henceforth called C34 group and 19 healthy subjects with APOEε3 ε3, henceforth called C33 group. Due to the reduced sample size (only two subjects), APOEε4 ε4 carriers were not included in the subsequent analyses. No significant differences in terms of age distribution emerged from groups' comparison (see Table 1 for demographic and genetic description).

MEG acquisition

Three minutes of resting state with eyes closed were recorded at 1000 Hz sampling rate (online bandpass filtering at 0.1–330 Hz) with a 306-channel Vectorview system (ElektaNeuromag) which combines two orthogonal, planar gradiometers, and one magnetometer. Only magnetometers information was submitted to source and statistical analyses. The MEG system was placed in a magnetically shielded room (VacuumSchmelze GmbH, Hanua, Germany) at the "Laboratorio UPM-UCM de Neurociencia Cognitiva y Computacional" (Madrid, Spain).

The head movement was controlled by means of four head-position indicator (HPI) coils attached to the scalp. The position of HPI coils and subject's headshape relative to three anatomical locations (nasion and both preauricular points) were defined using a 3D digitizer (FastrakPolhemus). Ocular movements were monitored by two bipolar electrodes. Recordings were offline filtered and corrected for head movements with a temporal signal space separation filter (Maxfilter Software 2.2) [33].

MRI acquisition

3D T1 weighted anatomical brain MRI scans were collected with a General Electric 1.5T MRI scanner, using a high-resolution antenna and a homogenization PURE filter (Fast Spoiled Gradient Echo) sequence with parameters: TR/TE/TI = 11.2/4.2/450 ms; flip angle 12°; 1 mm slice thickness, a 256×256 matrix and FOV 25 cm).

Source analysis

Data analysis was done using both Fieldtrip software [34] and custom-made scripts.

MEG preprocessing

Magnetometers' resting state data were automatically scanned for ocular, muscle, and jump artifacts. Then artifact-free data were segmented in continuous 4-second fragments (trials) and MEG power spectra (1.5–30 Hz) were computed for all trials. An experienced technician blinded to the subjects' diagnosis made a visual inspection of these spectra. Those trials with an aberrant power spectra profile were dismissed. Finally, only MEG recordings with at least 15 clean trials (one minute of brain activity) were kept for further analyses. The number of clean trials did not differ significantly ($p < 0.05$) among groups. In order to calculate the source reconstruction, clean trials were filtered (1.5–30 Hz) with a Finite Impulse Response filter of order 1000 using the whole three-minute register to avoid edge effects.

Headmodels

Firstly, a regular grid of 302 nodes with 2 cm spacing was created in the template Montreal Neurological Institute (MNI) brain. This set of nodes was transformed to subject's space using a non-linear normalization between the native T1 image (whose coordinate system was previously transformed to match the MEG coordinate system) and a standard T1 in MNI space with 2 mm resolution. This grid constituted the source locations. The forward model was solved with the realistic single-shell model introduced by Nolte [35].

Beamforming

Source reconstruction was performed with a Linearly Constrained Minimum Variance beamformer [36]. For each subject, the covariance matrix was first averaged over all trials to compute the spatial filter's coefficients, and then these coefficients were applied to individual trials, obtaining a time series per segment and source location.

Power spectra

MEG power spectra were computed at each node for all non-artifacted trials. A frequency-of-interest range of 0.5 Hz steps from 1.5 to 30 Hz was employed. In order to obtain the average frequency-content of each trial we applied a multitaper method (mtmfft) with discrete prolate spheroidal sequences (dpss) as windowing function and 1 Hz smoothing. Trials were averaged across subjects, obtaining a matrix with dimension: 302 nodes × 58 frequency steps × 61 subjects. For each node the relative power was calculated by normalizing with the total power over the 1–30 Hz range [37].

Atlas based analysis

For the subsequent analysis, we selected 30 regions of interest (ROIs) including relevant regions in the resting state networks literature and Aβ deposition: cingulate cortex, precuneus, hippocampus, occipital cortex, parietal cortex, temporal cortex, and prefrontal cortex [38–41]. Anatomical labels were assigned to each of the 302 nodes with the Harvard-Oxford probabilistic atlas [42]. In order to obtain a balance between specificity and reliability, all ROIs used in this study had to have at least two nodes within them. In addition, each node had to have a minimum 15% of probability to belong to the corresponding ROI and was assigned to the ROI which had higher probability to belong to (see Tables 2a, b). Finally, power values were averaged per ROIs and the original 302 × 58 × 61 matrices were transformed into 30 × 58 × 61 matrices.

Statistics

Similarly to previous works [30, 43], we accomplished a data-driven comparison among groups that did not use pre-established and conventional frequency bands. Thereby, we followed a method adapted from Maris and Oostenveld [44]. Firstly, values were transformed with $x = \log\left({}^{x}/_{1\_x}\right)$ to obtain a normal distribution. Secondly, to examine power differences due to APOE genotype and diagnosis, power values were subjected to an exploratory two-way ANOVA test per each frequency step, which includes "Diagnosis" and "Genotype" as factors. In order to perform such analyses, a criterion of frequency adjacency was applied by considering significant ROIs to those whose differences remain significant during at least a 2 Hz-interval. Relative power on each significant ROI was averaged across the corresponding frequency range and inspected by means of pairwise *t*-tests. *Post hoc* pairwise comparisons involved the analysis of main and interaction effects (Diagnosis and Genotype). The relationship between power values

Table 2a
Regions of Interest (ROIs). ROIs' names and number of nodes per ROI are listed in the first two columns. Central ROIs coordinates denotes the average coordinates of all nodes within the corresponding ROI. Maximum/minimum radius show the maximum/minimum Euclidean distance between each node and the central position of the corresponding ROI

Region of interest	# Nodes	Central MNI coordinates [mm]	*r* max [mm]	*r* min [mm]
Occipital Pole	6	[0 −100 10]	22	10
Left Lateral Inferior Occipital Cortex	3	[−47 −73 −7]	20	12
Right Lateral Inferior Occipital Cortex	3	[47 −73 −7]	20	12
Left Lateral Superior Occipital Cortex	7	[−29 −71 40]	25	13
Right Lateral Superior Occipital Cortex	7	[29 −71 40]	25	13
Left Angular Gyrus	3	[−47 −60 27]	15	10
Right Angular Gyrus	3	[47 −60 27]	15	10
Left Supramarginal Gyrus	4	[−55 −35 35]	17	9
Right Supramarginal Gyrus	4	[55 −35 35]	17	9
Left Superior Temporal Gyrus	3	[−60 −20 0]	20	0
Right Superior Temporal Gyrus	3	[60 −20 0]	20	0
Left Precentral Gyrus	7	[−43 −9 46]	32	11
Right Precentral Gyrus	7	[43 −9 46]	32	11
Left Poscentral Gyrus	3	[−27 −40 67]	15	10
Right Poscentral Gyrus	3	[27 −40 67]	15	10
Left Frontal Orbital Cortex	2	[−30 20 −20]	10	10
Right Frontal Orbital Cortex	2	[30 20 −20]	10	10

Table 2b

Region of interest	# Nodes	Central MNI coordinates [mm]	*r* max [mm]	*r* min [mm]
Left Temporal Pole	2	[−40 10 −40]	10	10
Right Temporal Pole	2	[40 10 −40]	10	10
Left Inferior Temporal Gyrus	3	[−60 −40 −20]	20	0
Right Inferior Temporal Gyrus	3	[60 −40 −20]	20	0
Posterior Cingulate Cortex	3	[0 −33 33]	15	10
Anterior Cingulate Cortex	5	[0 24 24]	29	6
Precuneus	7	[0 −60 37]	30	3
Left Hippocampus	2	[−20 −30 −10]	14	14
Right Hippocampus	2	[20 −30 −10]	14	14
Superior Frontal Gyrus	8	[0 23 53]	31	8
Left Prefrontal Cortex	8	[−30 50 −3]	27	14
Right Prefrontal Cortex	8	[30 50 −3]	27	14
Medial Prefrontal Cortex	4	[0 55 −5]	25	7

and neuropsychological performance was assessed through Pearson correlation tests in the whole sample (MCIs + Controls). The analyses were performed by correlating the average power of each significant ROI within the corresponding frequency ranges and the scores on each neuropsychological test. To control the family-wise error due to multiple comparisons, a permutation test procedure was utilized [45] for *t*-tests and correlations. This procedure has been fully described elsewhere [30]. Moreover, all *t*-test comparisons involving the C34 group underwent an additional correction due to the limited number of subjects in this group. Ten subjects from the other groups were randomly selected and a new *t*-test was performed. This procedure was repeated 2000 times and only results that remained significant in the 85% of the tests were reported.

Finally, the effect sizes were calculated through the following expression: $\Delta = \frac{\bar{X}_1 - \bar{X}_2}{\sigma}$. The symbol σ was the standard deviation of the control group (all controls in the case of diagnosis main effect results, and all the APOE3 population in the case of the APOE genotype main effect).

RESULTS

Diagnosis effects

The MCI group showed a significant power increase within a 6–9 Hz frequency range as compared with healthy controls (see Fig. 1) in 29 of the 30 ROIs. Only the superior frontal gyrus (SFG) did not show that effect. Within the alpha range (10–14 Hz) the right frontal orbital cortex (rFOC) and left temporal pole (lTP) showed a significant decrease in relative power in MCI group when compared with healthy controls (see Fig. 2). As it can be observed in Fig. 2, relative power values in both regions exhibited a progressive decrease,

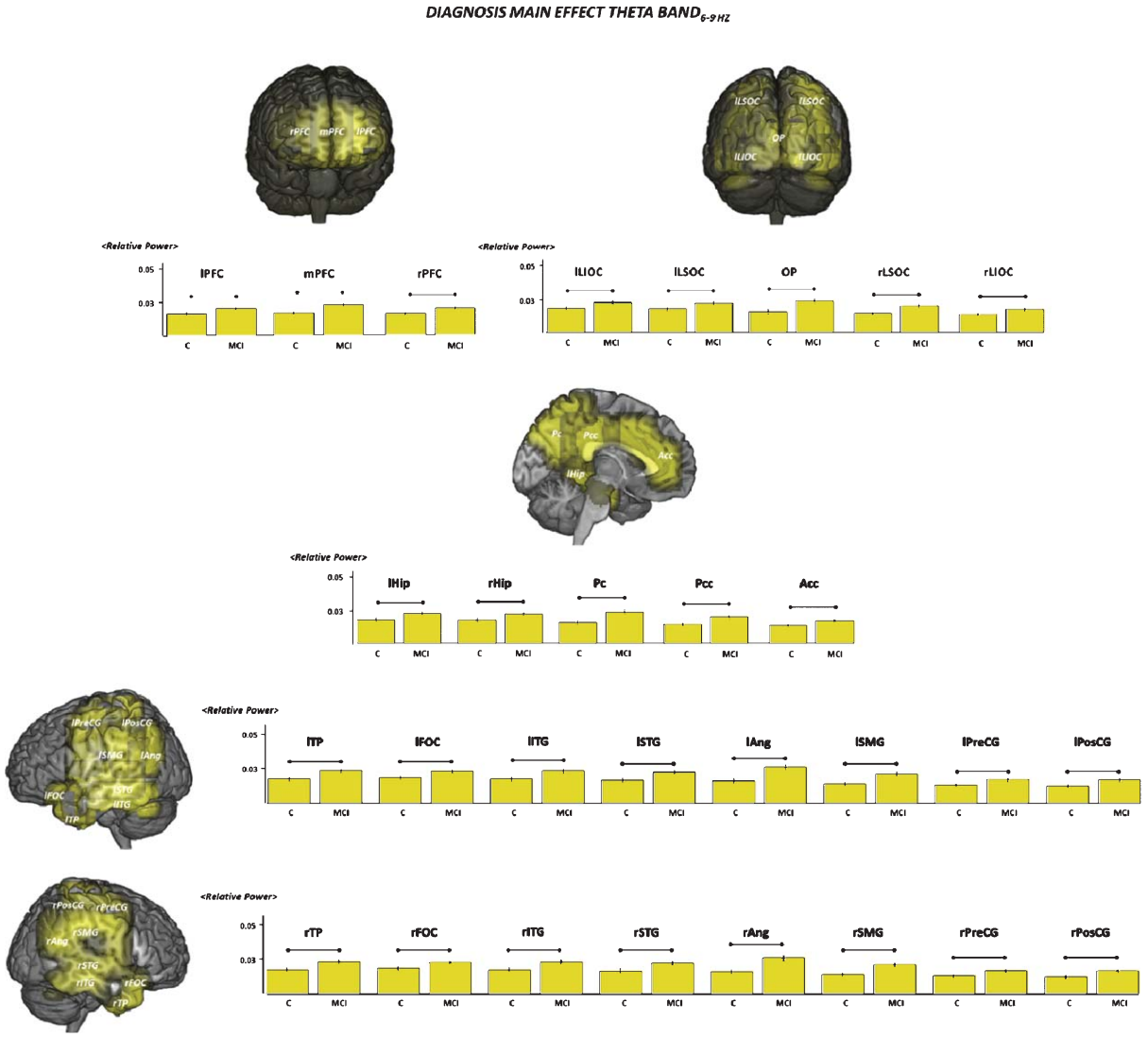

Fig. 1. Main effect of diagnosis within the 6–9 Hz frequency range. ROIs in yellow display significant differences ($p < 0.05$) in relative power between controls and MCI patients. Yellow-bar graphs show the corresponding ROI's average relative power for each group. The horizontal bars on top indicate the significant power differences ($p < 0.05$) due to diagnosis main effect and pairwise t-test comparisons among groups. The average value of the corresponding effect size values is 0.91 ± 0.17 (minimum 0.69 maximum 1.29).

with C33 group showing the highest values and MCI34 group showing the lowest values. Finally, within beta range (19–22 Hz) Diagnosis exerted a significant effect on four ROIs: left angular gyrus (lAng), left lateral inferior occipital cortex (lLIOC), right LIOC (rLIOC), and occipital pole (OP). All of them showed a decrease in the relative power within MCI group as compared with healthy controls (see Fig. 3).

Genotype effects

APOE Genotype exerted a significant effect on SFG power values. Overall, APOEε3 ε4 carriers exhibited a significantly increased relative power within a "low" theta range (4.5–6.5 Hz) when compared with APOEε3 ε3 carriers (see Fig. 4). APOEε3 ε4 carriers showed higher power values both within MCI and control groups. Thereby, the comparison between MCI34 versus MCI33, and C34 versus C33 was significant in both cases. Of note, the distribution of power values across groups suggested a combined influence of Genotype and Diagnosis effects. C34 subjects exhibited significantly higher relative power within the 4.5–6.5 Hz frequency range when compared with MCI33 patients, while MCI34 patients showed the highest power values within this particular range.

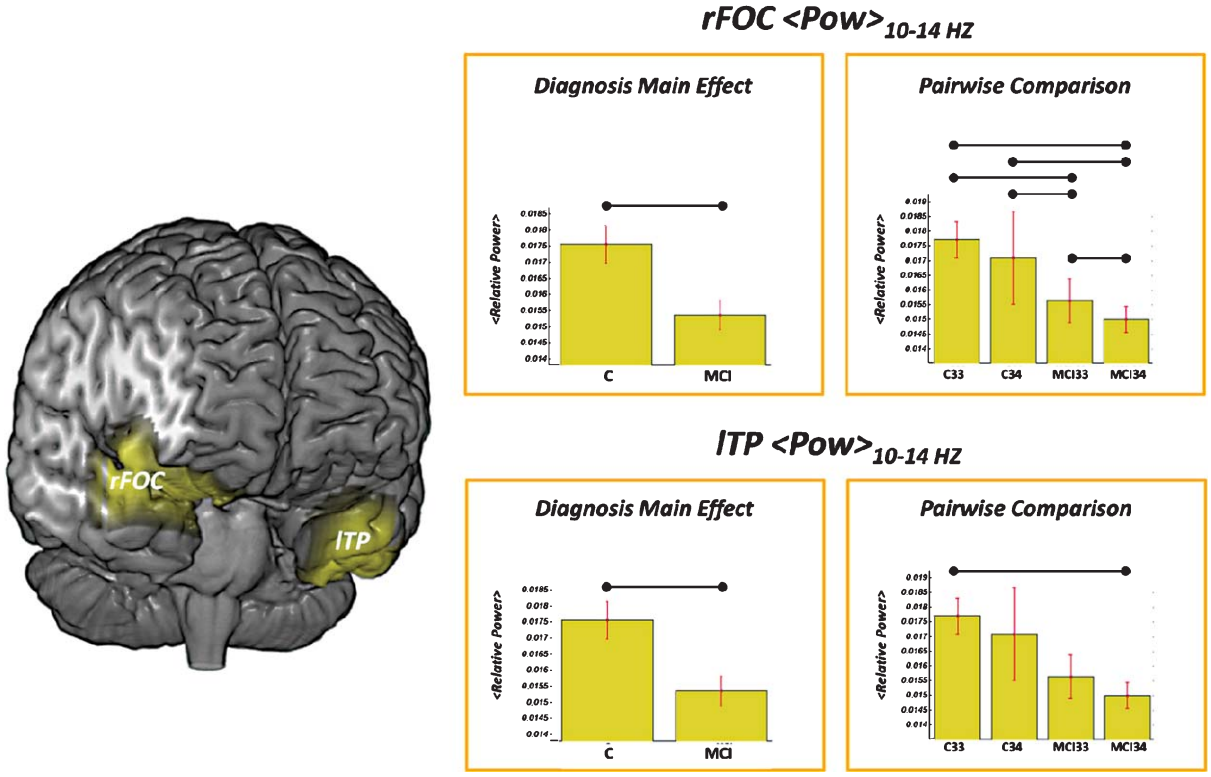

Fig. 2. Main effect of diagnosis within the 10–14 Hz frequency range. ROIs in yellow display significant differences ($p < 0.05$) in relative power between controls and MCI patients. Yellow-bar graphs show the corresponding ROI's average relative power for each group. The horizontal bars on top indicate the significant power differences ($p < 0.05$) due to diagnosis main effect and pairwise *t*-test comparisons among groups. The effects size value for the relative power comparison between controls and MCI subjects in rFOC is −0.7, 1 while in lTP is −0.63.

Importantly, no significant differences emerged from the comparison of MCI33 and C33 groups.

Power-neuropsychology correlation

4.5–6.5 Hz frequency range

This frequency range emerged as significant in the analysis of genotype effects. SFG power values correlated negatively with MMSE scores, indicating that an increased relative power within this region is associated with a more important cognitive decline (see Table 3).

6–9 Hz frequency range

As it was previously described, the significant increase of relative power within this frequency range in MCIs almost comprises all anatomical regions. Such a "massive" effect correlated inversely with MMSE, Immediate and Delayed Recall, Boston Naming Test, Trail Making Test (TMT)-B accuracy, and Inverse Digit Span. On the other hand, there were positive correlations between relative power values on most of the ROIs and TMT-B time. Finally, there existed a slight direct correlation between power in both SMGs, lSTG, and TMT-A Time scores. These results indicate that higher relative power values in these ROIs are associated with lower cognitive status in different domains (see Tables 4a–c).

10–14 Hz frequency range

Relative power values within this frequency range in rFOC and lTP were positively correlated with MMSE, Immediate and Delayed Recall. Accordingly, the higher the relative power in these ROIs the better the global cognitive status and the performance in memory scores (see Table 5).

19–22 Hz frequency range

OP, lAng, lLIOC, and rLIOC power values were positively correlated with MMSE, Immediate and Delayed Recall, TMT-B Accuracy, Boston Naming Test, and Inverse Digit Span. TMT-B Time was inversely correlated with power values in the four ROIs. TMT-A Time

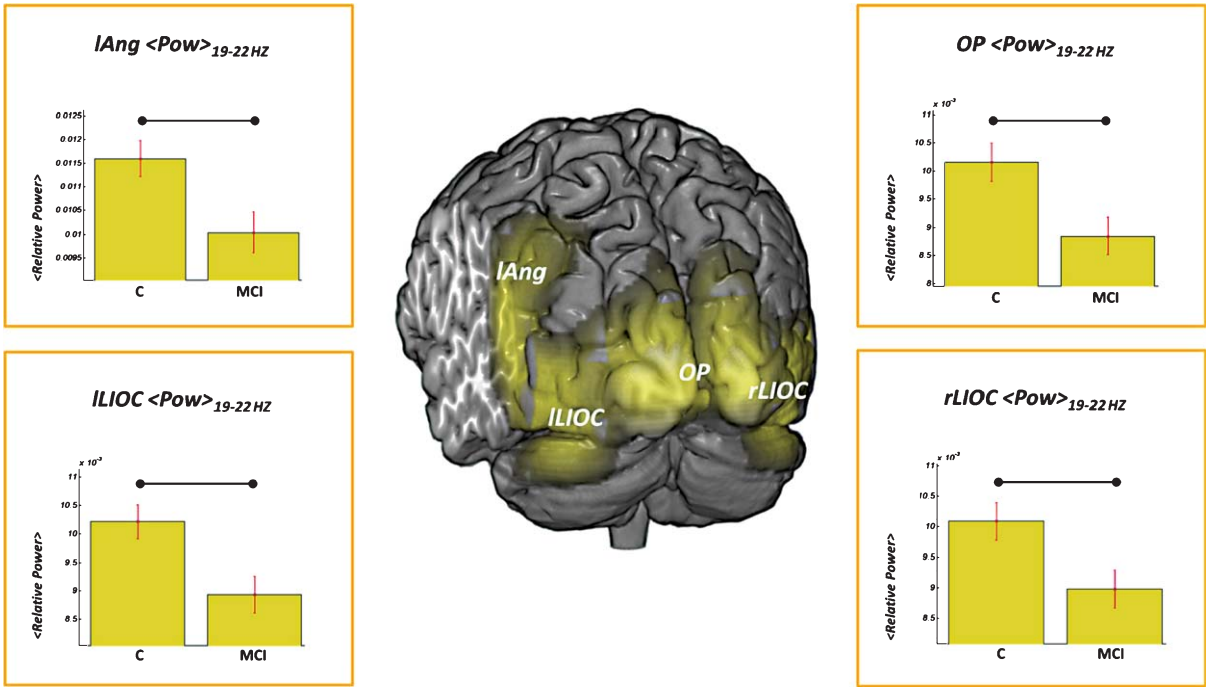

Fig. 3. Main effect of diagnosis within the 19–22 Hz frequency range. ROIs in yellow display significant differences ($p < 0.05$) in relative power between controls and MCI patients. Yellow-bar graphs show the corresponding ROI's average relative power for each group. The horizontal bars on top indicate the significant power differences ($p < 0.05$) due to diagnosis main effect and pairwise t-test comparisons among groups. The effects size for the relative power comparison between controls and MCI subjects in lAng, lLIOC, OP, and rLIOC are −0.74, −0.83, −0.69, and −0.78 respectively.

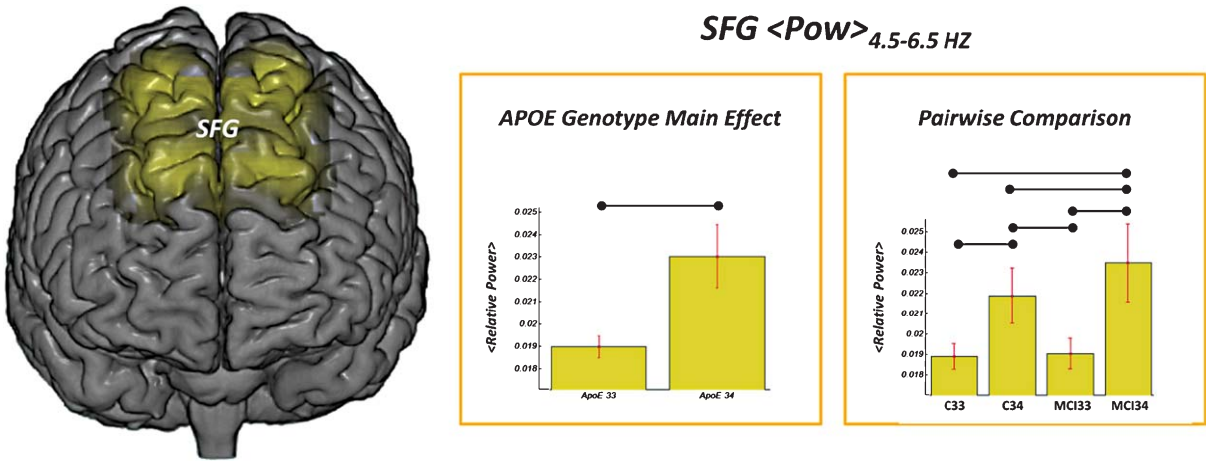

Fig. 4. Main effect of APOE genotype within the 4.5–6.5 Hz frequency range. ROIs in yellow display significant differences ($p < 0.05$) in relative power between controls and MCI patients. Yellow-bar graphs show the corresponding ROI's average relative power for each group. The horizontal bars on top indicate the significant power differences ($p < 0.05$) due to APOE main effect and pairwise t-test comparisons among groups. The effects size for the relative power comparison between $\varepsilon 4$ carriers and non-carriers in SFG is 1.41.

followed the same tendency but only with lAng and lLIOC ROIs. So, mirroring the 10–14 Hz frequency range, increased high-frequency values are associated with a better cognitive performance (see Table 5).

DISCUSSION

The results presented in this report add further information on the influence of APOE genotype in

Table 3
Pearson's "*r*" and "*p*" values of all significant correlation among neuropsychological test and relative power values within the 4.5–6.5 frequency range. MMSE, Mini-Mental State Examination; TMT, Trail Making Test; n.s., not significant

Test	MMSE	Inverse digit span	Immediate recall	Delayed recall	TMT A [acc.]	TMT A [time]	TMT B [acc.]	TMT B [time]	Boston naming test
4.5–6.5 Hz Frequency Range									
Superior frontal gyrus	$p = 0.0014$ $r = -0.41$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Table 4a
Pearson's "*r*" and "*p*" values of all significant correlation among neuropsychological test and relative power values within the 6–9 Hz frequency range. MMSE, Mini-Mental State Examination; TMT, Trail Making Test, n.s., not significant; OP, occipital pole; lLIOC, left lateral inferior occipital cortex; rLIOC, right lateral inferior occipital cortex; lLSOC, left lateral superior occipital cortex; rLSOC, right lateral superior occipital cortex; lAng, left angular gyrus; rAng, right angular gyrus; lSMG, left supramarginal gyrus; rSMG, right supramarginal gyrus; lSTG, left superior temporal gyrus; rSTG, right superior temporal gyrus; lPreCG, left precentral gyrus; rPreCG, right precentral gyrus; lPosCG, left poscentral gyrus; rPosCG, right poscentral gyrus; lFOC, left frontal orbital cortex; rFOC, right frontal orbital cortex; lTP, left temporal pole; rTP, right temporal pole; lITG, left inferior temporal gyrus; rITG, right inferior temporal gyrus; Pcc, posterior cingulate cortex; Acc, anterior cingulate cortex; Pc, precuneus; lHip, left hippocampus; rHip, right hippocampus; lPFC, left prefrontal cortex; rPFC, right prefrontal cortex; mPFC, medial prefrontal cortex

Test	MMSE	Inverse digit span	Immediate recall	Delayed recall	TMT A [acc.]	TMT A [time]	TMT B [acc.]	TMT B [time]	Boston naming test
6–9 Hz Frequency Range									
OP	$p = 0.0141$	n.s.	$p = 0.0048$	$p = 0.0016$	n.s.	n.s.	n.s.	n.s.	n.s.
	$r = -0.32$		$r = -0.36$	$r = -0.41$					
lLIOC	$p = 0.0004$	n.s.	$p = 0.0002$	$p = 3e\text{-}05$	n.s.	n.s.	$p = 0.0116$	$p = 0.0153$	$p = 0.0157$
	$r = -0.45$		$r = -0.46$	$r = -0.52$			$r = -0.33$	$r = 0.31$	$r = -0.31$
rLIOC	$p = 0.0008$	n.s.	$p = 0.0009$	$p = 0.0002$	n.s.	n.s.	$p = 0.0063$	$p = 0.0111$	$p = 0.0130$
	$r = -0.43$		$r = -0.41$	$r = -0.47$			$r = -0.35$	$r = 0.33$	$r = -0.32$
lLSOC	$p = 0.0008$	$p = 0.0159$	$p = 0.0005$	$p = 5e\text{-}05$	n.s.	n.s.	$p = 0.0041$	$p = 0.0046$	$p = 0.0046$
	$r = -0.43$	$r = -0.31$	$r = -0.43$	$r = -0.51$			$r = -0.37$	$r = 0.36$	$r = -0.36$
rLSOC	$p = 0.0008$	n.s.	$p = 0.0007$	$p = 8e\text{-}05$	n.s.	n.s.	$p = 0.0037$	$p = 0.0050$	$p = 0.0040$
	$r = -0.43$		$r = -0.42$	$r = -0.49$			$r = -0.37$	$r = 0.36$	$r = -0.37$
lAng	$p = 0.0008$	n.s.	$p = 0.0003$	$p = 1e\text{-}05$	n.s.	n.s.	$p = 0.0046$	$p = 0.0049$	$p = 0.0113$
	$r = -0.43$		$r = -0.44$	$r = -0.54$			$r = -0.36$	$r = 0.36$	$r = -0.33$
rAng	$p = 0.0005$	$p = 0.0097$	$p = 0.0003$	$p = 5e\text{-}05$	n.s.	n.s.	$p = 0.0039$	$p = 0.0050$	$p = 0.0051$
	$r = -0.44$	$r = -0.33$	$r = -0.44$	$r = -0.51$			$r = -0.37$	$r = 0.36$	$r = -0.36$
lSMG	$p = 0.0001$	$p = 0.0020$	$p = 6e\text{-}05$	$p = 7e\text{-}06$	n.s.	$p = 0.0086$	$p = 0.0008$	$p = 0.0017$	$p = 0.0005$
	$r = -0.49$	$r = -0.39$	$r = -0.49$	$r = -0.55$		$r = 0.33$	$r = -0.42$	$r = 0.40$	$r = -0.44$
rSMG	$p = 5e\text{-}05$	$p = 0.0020$	$p = 0.0001$	$p = 1e\text{-}05$	n.s.	$p = 0.0087$	$p = 0.0004$	$p = 0.0008$	$p = 0.0004$
	$r = -0.51$	$r = -0.39$	$r = -0.48$	$r = -0.54$		$r = 0.33$	$r = -0.44$	$r = 0.42$	$r = -0.44$
lSTG	$p = 0.0002$	$p = 0.0105$	$p = 0.0004$	$p = 0.0004$	n.s.	$p = 0.0144$	$p = 0.0018$	$p = 0.0059$	$p = 0.0020$
	$r = -0.47$	$r = -0.33$	$r = -0.41$	$r = -0.45$		$r = 0.31$	$r = -0.40$	$r = 0.35$	$r = -0.39$
rSTG	$p = 0.0006$	$p = 0.0063$	$p = 0.0002$	$p = 0.0002$	n.s.	n.s.	$p = 0.0016$	$p = 0.0032$	$p = 0.0059$
	$r = -0.44$	$r = -0.35$	$r = -0.41$	$r = -0.47$			$r = -0.40$	$r = 0.37$	$r = -0.35$

the resting-state neurophysiological activity of MCI patients and healthy aged controls. As expected, MCI patients exhibited a significant increase in relative power within the low-frequency domain, accompanied by a power decrease within the alpha and "high" beta frequency ranges. More importantly, APOEε3 ε4 carriers showed a significant increase in relative power within a 4.5–6.5 Hz frequency range in the SFG. This increase appeared in MCIs and healthy controls, indicating that the presence of an ε4 allele produces a pattern of "slowing" of the MEG background activity. This slowing was prominent enough to cause a significant increase of relative power within the C34 group as compared with the C33 group but also with the MCI33 group. In addition, the MCI34 patients exhibited the highest relative power within the 4.5–6.5 Hz range. Contrary to our prediction based on previous studies, no differences emerged within the high-frequency range related to APOE effects. Finally, higher power values within the low-frequency ranges were associated with a poorer cognitive performance in MCIs and controls, and increased power within higher frequency ranges were associated with a better cognitive status.

The pattern of slowing observed in MEG activity of MCI patients has been seen in several neurophysiological investigations (see, [46–49]). In a recent study, López et al. [30] reported in a sensor-domain study that MCI patients showed a generalized increase of

Table 4b

Test	MMSE	Inverse digit span	Immediate recall	Delayed recall	TMT A [acc.]	TMT A [time]	TMT B [acc.]	TMT B [time]	Boston naming test
6–9 Hz Frequency Range									
lPreCG	$p=0.0068$	$p=0.0186$	$p=0.0003$	$p=0.0003$	n.s.	n.s.	$p=0.0040$	n.s.	$p=0.0064$
	$r=-0.35$	$r=-0.30$	$r=-0.38$	$r=-0.46$			$r=-0.37$		$r=-0.35$
rPreCG	$p=0.0028$	$p=0.0120$	$p=0.0004$	$p=0.0004$	n.s.	n.s.	$p=0.0007$	$p=0.0070$	$p=0.0008$
	$r=-0.38$	$r=-0.32$	$r=-0.38$	$r=-0.45$			$r=-0.43$	$r=0.34$	$r=-0.42$
lPosCG	$p=0.0027$	$p=0.0153$	$p=0.0003$	$p=0.0003$	n.s.	n.s.	$p=0.0039$	n.s.	$p=0.0036$
	$r=-0.39$	$r=-0.31$	$r=-0.39$	$r=-0.46$			$r=-0.37$		$r=-0.37$
rPosCG	$p=0.0018$	n.s.	$p=0.0002$	$p=0.0002$	n.s.	n.s.	$p=0.0094$	n.s.	$p=0.0029$
	$r=-0.40$		$r=-0.40$	$r=-0.47$			$r=-0.33$		$r=-0.38$
lFOC	$p=0.0046$	n.s.	$p=0.0032$	$p=0.0014$	n.s.	n.s.	$p=0.0085$	n.s.	n.s.
	$r=-0.37$		$r=-0.37$	$r=-0.41$			$r=-0.34$		
rFOC	$p=0.0033$	n.s.	$p=0.0051$	$p=0.0016$	n.s.	n.s.	$p=0.0112$	n.s.	n.s.
	$r=-0.38$		$r=-0.35$	$r=-0.41$			$r=-0.33$		
lTP	$p=0.0024$	n.s.	$p=0.0004$	$p=4e\text{-}05$	n.s.	n.s.	$p=0.0091$	n.s.	$p=0.0080$
	$r=-0.39$		$r=-0.44$	$r=-0.51$			$r=-0.34$		$r=-0.34$
rTP	$p=0.0015$	n.s.	$p=0.0025$	$p=0.0006$	n.s.	n.s.	$p=0.0066$	n.s.	$p=0.0056$
	$r=-0.41$		$r=-0.38$	$r=-0.44$			$r=-0.35$		$r=-0.35$
lITG	$p=0.0001$	n.s.	$p=0.0019$	$p=0.0001$	n.s.	n.s.	n.s.	n.s.	n.s.
	$r=-0.47$		$r=-0.39$	$r=-0.48$					
rITG	$p=4e.05$	n.s.	$p=0.0006$	$p=4e\text{-}05$	n.s.	n.s.	$p=0.0010$	$p=0.0048$	$p=0.0053$
	$r=-0.51$		$r=-0.42$	$r=-0.51$			$r=-0.42$	$r=0.36$	$r=-0.36$

Table 4c

Test	MMSE	Inverse digit span	Immediate recall	Delayed recall	TMT A [acc.]	TMT A [time]	TMT B [acc.]	TMT B [time]	Boston naming test
6–9 Hz Frequency Range									
Pcc	$p=0.0011$	$p=0.0097$	$p=0.0011$	$p=0.0003$	n.s.	n.s.	$p=0.0009$	$p=0.0031$	$p=0.0021$
	$r=-0.42$	$r=-0.33$	$r=-0.41$	$r=-0.46$			$r=-0.42$	$r=0.38$	$r=-0.39$
Acc	$p=0.0005$	$p=0.0081$	$p=0.0011$	$p=0.0002$	n.s.	n.s.	$p=0.0004$	$p=0.0065$	$p=0.0008$
	$r=-0.45$	$r=-0.34$	$r=-0.41$	$r=-0.47$			$r=-0.44$	$r=0.35$	$r=-0.42$
Pc	$p=0.0011$	$p=0.0156$	$p=0.0005$	$p=6e\text{-}05$	n.s.	n.s.	$p=0.0014$	$p=0.0029$	$p=0.0037$
	$r=-0.42$	$r=-0.31$	$r=-0.43$	$r=-0.50$			$r=-0.41$	$r=0.38$	$r=-0.37$
lHip	$p=0.0033$	n.s.	$p=0.0061$	$p=0.0005$	n.s.	n.s.	$p=0.0120$	$p=0.0145$	$p=0.0173$
	$r=-0.38$		$r=-0.35$	$r=-0.44$			$r=-0.33$	$r=0.31$	$r=-0.31$
rHip	$p=0.0040$	n.s.	$p=0.0051$	$p=0.0005$	n.s.	n.s.	$p=0.0069$	$p=0.0090$	$p=0.0078$
	$r=-0.37$		$r=-0.35$	$r=-0.44$			$r=-0.35$	$r=0.33$	$r=-0.34$
lPFC	$p=0.0011$	n.s.	$p=0.0042$	$p=0.0006$	n.s.	n.s.	$p=0.0023$	$p=0.0154$	$p=0.0099$
	$r=-0.42$		$r=-0.36$	$r=-0.44$			$r=-0.39$	$r=0.31$	$r=-0.33$
rPFC	$p=0.0006$	n.s.	$p=0.0020$	$p=0.0002$	n.s.	n.s.	$p=0.0034$	$p=0.0127$	$p=0.0069$
	$r=-0.44$		$r=-0.39$	$r=-0.47$			$r=-0.37$	$r=0.32$	$r=-0.35$
mPFC	$p=7e\text{-}05$	$p=0.0161$	$p=0.0002$	$p=3e\text{-}05$	n.s.	n.s.	$p=0.0044$	$p=0.0080$	$p=0.0017$
	$r=-0.49$	$r=-0.31$	$r=-0.45$	$r=-0.52$			$r=-0.37$	$r=0.34$	$r=-0.40$

theta activity. This was accompanied by a decrease in the alpha and beta frequency ranges that was localized in occipital, temporo-parietal, and frontal regions. The importance of alpha activity sources that extend beyond the traditional posterior sites in MCI patients has also been stressed in source-domain investigations [50]. With respect to the correlation analyses, our results support previous studies [51–53]. The MCI group showed higher power values within the 6–9 Hz frequency range in a large number of brain regions, including both hippocampi. This increase was related to lower performance in several cognitive functions such as executive functioning, memory or language. In addition, the decreased power within high frequency ranges was directly correlated with the performance in neuropsychological tests and functional status. For instance, within 10–14 Hz range, lower activity in frontal and temporal areas leads to a poorer performance in the episodic memory tests (i.e., Immediate and Delayed Recall) and cognitive functioning (i.e., MMSE).

With regards to APOE effects, Lehtovirta et al. [18] reported that AD patients showed higher theta and lower beta amplitude, with $\varepsilon 4$ carriers showing an "extra" slowing. After a follow-up period of three years, differences between AD-$\varepsilon 4$ carriers and non-

Table 5
Pearson's "r" and "p" values of all significant correlation among neuropsychological test and relative power values within the 10-14, and 19-22 Hz frequency ranges. rFOC, right frontal orbital cortex; lTP, left temporal pole; OP, occipital pole; lLIOC, left lateral inferior occipital cortex; rLIOC, right lateral inferior occipital cortex; lAng, left angular gyrus; MMSE, Mini-Mental State Examination; TMT, Trail Making Test, n.s., not significant

Test	MMSE	Inverse digit span	Immediate recall	Delayed recall	TMT A [acc.]	TMT A [time]	TMT B [acc.]	TMT B [time]	Boston naming test
10–14 Hz Frequency Range									
rFOC	$p=0.0025$	n.s.	$p=0.0074$	$p=0.0083$	n.s.	n.s.	n.s.	n.s.	n.s.
	$r=0.39$		$r=0.34$	$r=0.34$					
lTP	$p=0.0100$	n.s.	$p=0.0110$	$p=0.0087$	n.s.	n.s.	n.s.	n.s.	n.s.
	$r=0.34$		$r=0.32$	$r=0.34$					
19–22 Hz Frequency Range									
OP	$p=0.0007$	$p=0.0073$	$p=0.0015$	$p=7e\text{-}05$	n.s.	n.s.	$p=0.0087$	$p=0.0004$	$p=0.0042$
	$r=0.43$	$r=0.34$	$r=0.40$	$r=0.50$			$r=0.34$	$r=-0.44$	$r=0.36$
lLIOC	$p=0.0001$	$p=0.0146$	$p=0.0013$	$p=3e\text{-}05$	n.s.	$p=0.0201$	$p=0.0107$	$p=0.0008$	$p=0.0026$
	$r=0.48$	$r=0.31$	$r=0.40$	$r=0.52$		$r=-0.30$	$r=0.33$	$r=-0.42$	$r=0.38$
rLIOC	$p=0.0002$	$p=0.0033$	$p=0.0030$	$p=0.0003$	n.s.	n.s.	$p=0.0122$	$p=0.0006$	$p=0.0014$
	$r=0.46$	$r=0.37$	$r=0.38$	$r=0.46$			$r=0.32$	$r=-0.43$	$r=0.40$
LAng	$p=0.0002$	$p=0.0208$	$p=0.0085$	$p=0.0001$	n.s.	$p=0.0032$	$p=0.0143$	$p=0.0006$	$p=0.0004$
	$r=0.46$	$r=0.30$	$r=0.34$	$r=0.48$		$r=-0.37$	$r=0.32$	$r=-0.43$	$r=0.44$

carriers disappeared [54]. Jelic et al. [55] confirmed this trend, since AD patients showed a pronounced slowing of their background activity when compared to aged controls. However, the APOE genotype did not exert any influence on this pattern. Authors interpreted this finding as a confirmation of the reduced influence of APOE on EEG activity once the dementia is fully established. Babiloni et al. [19] found that MCI and AD patients carrying the $\varepsilon 4$ allele showed lower alpha 1 and alpha 2 amplitudes in occipital, temporal, and limbic areas. Ponomareva et al. [56] investigated EEG patterns in AD patients and their unaffected relatives who were divided into carriers and non-carriers of the $\varepsilon 4$ allele. During the resting state condition, AD-$\varepsilon 4$ carriers showed lower alpha power, and no differences were found in the relatives group. When relatives $\varepsilon 4$ carriers underwent hyperventilation, 60% of the sample exhibited EEG signs such as high-voltage delta and theta activity, sharp waves, etc. Recently, Waal et al. [57] showed that controls carrying the $\varepsilon 4$ allele present a different distribution of alpha activity with less frontal and central power than non-carriers.

Most of the above-cited EEG studies utilized the cholinergic-deficit hypothesis associated with APOE$\varepsilon 4$ as a way of explaining the increased low-frequency power observed in $\varepsilon 4$ carriers. The previously mentioned investigation by Chapman et al. [14] offered an animal model for this deficit but prior post-mortem studies in humans had reported similar findings [58, 59]. According to this evidence, and considering the well-known relationship between cholinergic-system deficits and low-frequency activity, a pattern of increased delta and/or theta power should be expected in $\varepsilon 4$ carriers. Furthermore, the effect of $\varepsilon 4$ allele should be visible in the earlier stages of the degenerative process. Our results fully support this perspective. First, MCI patients showed increased MEG theta activity but APOE$\varepsilon 4$ carriers exhibited the same "extra" slowing observed by Lehtovirta et al. [18] in the EEG resting state recordings of their AD patient. Additionally, control $\varepsilon 4$ carriers presented an increased low-frequency activity in the SFG when compared to the C33 group but, more interestingly, also when compared to the MCI34 group.

This modification of the spectral patterns associated with APOE$\varepsilon 4$ may be related to variations in the neural network functionality. These changes affect low-frequencies to a greater extent in our sample. Usually, it is assumed that low-frequencies modulate activity over large spatial regions in long temporal windows, while high-frequencies modulate activity over small regions and short temporal windows [60]. In this vein, neurophysiological studies on aging and AD-related disorders have confirmed a change in the dominant oscillatory neural network. This change might be produced by a progressive impairment of thalamo-cortical and cortico-cortical systems (i.e., long distance connections) [61]. Gloor et al. [62] demonstrated that white matter, thalamic, and reticular formation lesions are major sources of low-frequency activity in the brain. The power increase within the low-frequency domain is usually accompanied by a decrease in the high-frequency ranges that is not observed in our results. This is a limitation of our investigation that will be further discussed below.

Regarding to APOE influence on white matter, Honea et al. [63] demonstrated that APOEε4-positive non-demented subjects had lower fractional anisotropy values. These values correlated with a poorer cognitive performance and hippocampal atrophy. Mirroring these results, Bagepally et al. [64] found lower fractional anisotropy scores in AD patients and healthy aged controls carrying APOEε4. Importantly, the reduction of white matter integrity in ε4 carriers might be explained by a possible major role of APOE in myelin sheath building [65]. Such a role is of particular importance because white matter participates in the speed control of impulse conduction, and as a consequence in the synchronization among cortical regions [66]. Synchronization among brain regions is a basic mechanism that explains the frequencies' variability observed in EEG/MEG signals [67].

Fractional anisotropy studies of APOE and our own results share a common finding: asymptomatic controls seem to exhibit some kind of change in their physiological response which apparently is not associated with any overt clinical manifestation. Similarly, FDG-PET studies of young and middle-aged APOEε4 carriers [68–71] consistently found a pattern of hypometabolism in some regions such as the precuneus, posterior cingulate, and posterior parietal areas that are considered key structures in AD. Even more intriguing results were found in recent investigations of cerebrospinal fluid, PET-PIB, and PET-florbetapir imaging in aged asymptomatic ε4 carriers [11, 72, 73]. Overall, these studies revealed that asymptomatic ε4 carriers have significant Aβ deposition in their brains. In some cases [72, 73], the levels of deposition may be even higher than in ADs that do not carry the ε4 allele. Mirroring these findings, our C34 sample presented a more pronounced slowing of their MEG background activity than diagnosed MCI patients. This is traditionally associated with cognitive deterioration [74, 75]. Such association is supported by the significant negative correlation between frontal power within the 4.5–6.5 frequency range and MMSE scores. This suggests that the presence of the ε4 allele does not have a negative influence on specific cognitive areas. On the other hand, it does negatively affect the global cognitive ability, which seems to highlight its involvement in the earlier onset of the dementia.

Our investigation demonstrates that APOEε4 affects normal resting-state activity in MCI patients and controls, to such an extent that it makes it more proximate to the typical pattern observed in the early stages of AD. Taking this into account, a combination of genetic and neurophysiological information might help to detect MCI patients at higher risk of conversion to AD (see for example [76]), and asymptomatic subjects at higher risk of developing a manifest cognitive deterioration. Notwithstanding, the results obtained in our research should be treated with caution as they have some limitations. First of all, our sample size is relatively small and this problem affects C34 group to a greater extent. As we described in the Statistics section, all comparisons where this group was involved were treated with a very restrictive strategy in order to avoid the appearance of Type I errors. Unfortunately, we cannot state with complete confidence that Type II errors were totally avoided, and some significant differences might have been missed (i.e., APOE effects on high-frequency ranges). On the other hand, MCIs and controls were not followed-up for this particular investigation, and information about a potential progression was not yet available. Nevertheless, we believe that this research offers valuable knowledge about the interaction of neurophysiological and genetic variables in aging and cognitive deterioration.

ACKNOWLEDGMENTS

This study was supported by two projects, PSI2009-14415-C03-01 and PSI2012-38375-C03-01, from the Spanish Ministry of Science and Economy, one project from the National Institute of Health Carlos III PI10/01585. A Predoctoral fellowship from the Ministry of Education [FPU AP-2008-00175], a predoctoral fellowship from the Spanish Ministry of Science and Innovation [BES-2010-036469], a PICATA predoctoral fellowship of the Moncloa Campus of International Excellence [UCM-UPM], and a predoctoral fellow from the Basque Government.

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=2374).

REFERENCES

[1] Mayeux R, Small SA, Tang M, Tycko B, Stern Y (2001) Memory performance in healthy elderly without Alzheimer's disease: Effects of time and apolipoprotein-E. *Neurobiol Aging* **22**, 683-689.

[2] Reitz C, Mayeux R (2010) Use of genetic variation as biomarkers for mild cognitive impairment and progression of mild cognitive impairment to dementia. *J Alzheimers Dis* **19**, 229-251.

[3] Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE (2007) Systematic meta-analyses of Alzheimer disease genetic association studies: The AlzGene database. *Nat Genet* **39**, 17-23.

[4] Anoop S, Misra A, Meena K, Luthra K (2010) Apolipoprotein E polymorphism in cerebrovascular & coronary heart diseases. *Indian J Med Res* **132**, 363-378.

[5] Saunders AM, Hulette O, Welsh-Bohmer KA, Schmechel DE, Crain B, Burke JR, Alberts MJ, Strittmatter WJ, Breitner JC, Rosenberg C (1996) Specificity, sensitivity, and predictive value of apolipoprotein-E genotyping for sporadic Alzheimer's disease. *Lancet* **348**, 90-93.

[6] Mayeux R, Saunders AM, Shea S, Mirra S, Evans D, Roses AD, Hyman B, Crain B, Tang MX, Phelps CH (1998) Utility of the apolipoprotein E genotype in the diagnosis of Alzheimer's disease. Alzheimer's Disease Centers Consortium on Apolipoprotein E and Alzheimer's Disease. *N Engl J Med* **338**, 506-511.

[7] Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM (1997) Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA* **278**, 1349-1356.

[8] Rebeck GW, Reiter JS, Strickland DK, Hyman BT (1993) Apolipoprotein E in sporadic Alzheimer's disease: Allelic variation and receptor interactions. *Neuron* **11**, 575-580.

[9] Schmechel DE, Saunders AM, Strittmatter WJ, Crain BJ, Hulette CM, Joo SH, Pericak-Vance MA, Goldgaber D, Roses AD (1993) Increased amyloid beta-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease. *Proc Natl Acad Sci U S A* **90**, 9649-9653.

[10] Tosun D, Schuff N, Truran-Sacrey D, Shaw LM, Trojanowski JQ, Aisen P, Peterson R, Weiner MW (2010) Relations between brain tissue loss, CSF biomarkers, and the ApoE genetic profile: A longitudinal MRI study. *Neurobiol Aging* **31**, 1340-1354.

[11] Morris JC, Roe CM, Xiong C, Fagan AM, Goate AM, Holtzman DM, Mintun MA (2010) APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Ann Neurol* **67**, 122-131.

[12] Curtiss LK, Boisvert WA (2000) Apolipoprotein E and atherosclerosis. *Curr Opin Lipidol* **11**, 243-251.

[13] Aono M, Lee Y, Grant ER, Zivin RA, Pearlstein RD, Warner DS, Bennett ER, Laskowitz DT (2002) Apolipoprotein E protects against NMDA excitotoxicity. *Neurobiol Dis* **11**, 214-220.

[14] Chapman S, Michaelson DM (1998) Specific neurochemical derangements of brain projecting neurons in apolipoprotein E-deficient mice. *J Neurochem* **70**, 708-714.

[15] Riekkinen P, Buzsaki G, Riekkinen P Jr, Soininen H, Partanen J (1991) The cholinergic system and EEG slow waves. *Electroencephalogr Clin Neurophysiol* **78**, 89-96.

[16] Riekkinen P Jr, Sirvio J, Riekkinen P (1990) Relationship between the cortical choline acetyltransferase content and EEG delta-power. *Neurosci Res* **8**, 12-20.

[17] Soininen H, Partanen J, Laulumaa V, Helkala EL, Laakso M, Riekkinen PJ (1989) Longitudinal EEG spectral analysis in early stage of Alzheimer's disease. *Electroencephalogr Clin Neurophysiol* **72**, 290-297.

[18] Lehtovirta M, Partanen J, Kononen M, Soininen H, Helisalmi S, Mannermaa A, Ryynanen M, Hartikainen P, Riekkinen P (1996) Spectral analysis of EEG in Alzheimer's disease: Relation to apolipoprotein E polymorphism. *Neurobiol Aging* **17**, 523-526.

[19] Babiloni C, Benussi L, Binetti G, Cassetta E, Dal Forno G, Del Percio C, Ferreri F, Ferri R, Frisoni G, Ghidoni R, Miniussi C, Rodriguez G, Romani GL, Squitti R, Ventriglia MC, Rossini PM (2006) Apolipoprotein E and alpha brain rhythms in mild cognitive impairment: A multicentric electroencephalogram study. *Ann Neurol* **59**, 323-334.

[20] Oldfield RC (1971) The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia* **9**, 97-113.

[21] Lobo A, Ezquerra J, Gómez Burgada F, Sala JM, Seva Díaz A (1979) Cognocitive mini-test: A simple practical test to detect intellectual changes in medical patients. *Actas Luso Esp Neurol Psiquiatr Cienc Afines* **7**, 189-202.

[22] Reisberg B, Ferris SH, de Leon MJ, Crook T (1982) The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry* **139**, 1136-1139.

[23] Pfeffer RI, Kurosaki TT, Harrah CH, Chance JM, Filos S (1982) Measurement of functional activities in older adults in the community. *J Gerontol* **37**, 323-329.

[24] Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO (1982) Development and validation of a geriatric depression screening scale: A preliminary report. *J Psychiatr Res* **17**, 37-49.

[25] Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A (1980) Pathological verification of ischemic score in differentiation of dementias. *Ann Neurol* **7**, 486-488.

[26] Lawton MP, Brody EM (1969) Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist* **9**, 179-186.

[27] Auer S, Reisberg B (1997) The GDS/FAST staging system. *Int Psychogeriatrics* **9**(Suppl 1), 167-171.

[28] Grundman M, Petersen RC, Ferris SH, Thomas RG, Aisen PS, Bennett Da, Foster NL, Jack CR, Galasko DR, Doody R, Kaye J, Sano M, Mohs R, Gauthier Serge, Kim HT, Jin S, Schultz AN, Schafer K, Mulnard R, van Dyck CH, Mintzer J, Zamrini EY, Cahn-Weiner D, Thal LJ (2004) Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. *Arch Neurol* **61**, 59-66.

[29] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-944.

[30] López ME, Cuesta P, Garcés P, Castellanos PN, Aurtenetxe S, Bajo R, Marcos A, Delgado ML, Montejo P, López- Pantoja JL, Maestú F, Fernández A (2014) MEG spectral analysis in subtypes of mild cognitive impairment. *AGE* **36**, 9624.

[31] Petersen RC (2004) Mild cognitive impairment as a diagnostic entity. *J Intern Med* **256**, 183-194.

[32] Hixson JE, Vernier DT (1990) Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *J Lipid Res* **31**, 545-548.

[33] Taulu S, Kajola M (2005) Presentation of electromagnetic multichannel data: The signal space separation method. *J Appl Phys* **97**, 124905.

[34] Oostenveld R, Fries P, Maris E, Schoffelen JM (2011) FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Comput Intell Neurosci* **2011**, 156869.

[35] Nolte G (2003) The magnetic lead field theorem in the quasi-static approximation and its use for magnetoencephalography forward calculation in realistic volume conductors. *Phys Med Biol* **48**, 3637-3652.

[36] Van Veen BD, van Drongelen W, Yuchtman M, Suzuki A (1997) Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *IEEE Trans Biomed Eng* **44**, 867-880.

[37] Jelic V, Johansson SE, Almkvist O, Shigeta M, Julin P, Nordberg A, Winblad B, Wahlund LO (2000) Quantitative electroencephalography in mild cognitive impairment: Longitudinal changes and possible prediction of Alzheimer's disease. *Neurobiol Aging* **21**, 533-540.

[38] Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF (2006) Consistent resting-state networks across healthy subjects. *Proc Natl Acad Sci U S A* **103**, 13848-13853.

[39] Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. *Proc Natl Acad Sci U S A* **98**, 676-682.

[40] Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD (2007) Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* **27**, 2349-2356.

[41] Brier MR, Thomas JB, Snyder AZ, Benzinger TL, Zhang D, Raichle ME, Holtzman DM, Morris JC, Ances BM (2012) Loss of intranetwork and internetwork resting state functional connections with Alzheimer's disease progression. *J Neurosci* **32**, 8890-8899.

[42] Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ (2006) An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* **31**, 968-980.

[43] Fernandez A, Hornero R, Mayo A, Poza J, Maestu F, Ortiz Alonso T (2006) Quantitative magnetoencephalography of spontaneous brain activity in Alzheimer disease: An exhaustive frequency analysis. *Alzheimer Dis Assoc Disord* **20**, 153-159.

[44] Maris E, Oostenveld R (2007) Nonparametric statistical testing of EEG- and MEG-data. *J Neurosci Methods* **164**, 177-190.

[45] Ernst MD (2004) Permutation methods: A basis for exact inference. *Stat Sci* **19**, 676-685.

[46] Babiloni C, Binetti G, Cassetta E, Dal Forno G, Del Percio C, Ferreri F, Ferri R, Frisoni G, Galderisi S, Hirata K, Lanuzza B, Miniussi C, Mucci A, Nobili F, Rodriguez G, Romani GL, Rossini PM (2006) Sources of cortical rhythms change as a function of cognitive impairment in pathological aging: A multicenter study. *Clin Neurophysiol* **117**, 252-268.

[47] Babiloni C, Carducci F, Lizio R, Vecchio F, Baglieri A, Bernardini S, Cavedo E, Bozzao A, Buttinelli C, Esposito F, Giubilei F, Guizzaro A, Marino S, Montella P, Quattrocchi CC, Redolfi A, Soricelli A, Tedeschi G, Ferri R, Rossi-Fedele G, Ursini F, Scrascia F, Vernieri F, Pedersen TJ, Hardemark HG, Rossini PM, Frisoni GB (2013) Resting state cortical electroencephalographic rhythms are related to gray matter volume in subjects with mild cognitive impairment and Alzheimer's disease. *Hum Brain Mapp* **34**, 1427-1446.

[48] Rossini PM, Del Percio C, Pasqualetti P, Cassetta E, Binetti G, Dal Forno G, Ferreri F, Frisoni G, Chiovenda P, Miniussi C, Parisi L, Tombini M, Vecchio F, Babiloni C (2006) Conversion from mild cognitive impairment to Alzheimer's disease is predicted by sources and coherence of brain electroencephalography rhythms. *Neuroscience* **143**, 793-803.

[49] Fernandez A, Hornero R, Mayo A, Poza J, Gil-Gregorio P, Ortiz T (2006) MEG spectral profile in Alzheimer's disease and mild cognitive impairment. *Clin Neurophysiol* **117**, 306-314.

[50] Garces P, Vicente R, Wibral M, Pineda-Pardo JA, Lopez ME, Aurtenetxe S, Marcos A, de Andres ME, Yus M, Sancho M, Maestu F, Fernandez A (2014) Brain-wide slowing of spontaneous alpha rhythms in mild cognitive impairment. *Front Aging Neurosci* **5**, 100.

[51] Jelic V, Shigeta M, Julin P, Almkvist O, Winblad B, Wahlund LO (1996) Quantitative electroencephalography power and coherence in Alzheimer's disease and mild cognitive impairment. *Dementia* **7**, 314-323.

[52] van der Hiele K, Vein AA, Reijntjes RH, Westendorp RG, Bollen EL, van Buchem MA, van Dijk JG, Middelkoop HA (2007) EEG correlates in the spectrum of cognitive decline. *Clin Neurophysiol* **118**, 1931-1939.

[53] Babiloni C, Visser PJ, Frisoni G, De Deyn PP, Bresciani L, Jelic V, Nagels G, Rodriguez G, Rossini PM, Vecchio F, Colombo D, Verhey F, Wahlund LO, Nobili F (2010) Cortical sources of resting EEG rhythms in mild cognitive impairment and subjective memory complaint. *Neurobiol Aging* **31**, 1787-1798.

[54] Lehtovirta M, Partanen J, Kononen M, Hiltunen J, Helisalmi S, Hartikainen P, Riekkinen P, Soininen H (2000) A longitudinal quantitative EEG study of Alzheimer's disease: Relation to apolipoprotein E polymorphism. *Dement Geriatr Cogn Disord* **11**, 29-35.

[55] Jelic V, Julin P, Shigeta M, Nordberg A, Lannfelt L, Winblad B, Wahlund LO (1997) Apolipoprotein E epsilon4 allele decreases functional connectivity in Alzheimer's disease as measured by EEG coherence. *J Neurol Neurosurg Psychiatry* **63**, 59-65.

[56] Ponomareva NV, Goltsov AY, Kunijeva SS, Scheglova NS, Malina DD, Mitrofanov AA, Boikova TI, Rogaev EI (2008) Age- and genotype-related neurophysiologic reactivity to oxidative stress in healthy adults. *Neurobiol Aging* **33**, 839.e11-e21.

[57] de Waal H, Stam CJ, de Haan W, van Straaten EC, Blankenstein MA, Scheltens P, van der Flier VM (2013) Alzheimer's disease patients not carrying the apolipoprotein E epsilon4 allele show more severe slowing of oscillatory brain activity. *Neurobiol Aging* **34**, 2158-2163.

[58] Soininen H, Kosunen O, Helisalmi S, Mannermaa A, Paljarvi L, Talasniemi S, Ryynanen M, Riekkinen P (1995) A severe loss of choline acetyltransferase in the frontal cortex of Alzheimer patients carrying apolipoprotein epsilon 4 allele. *Neurosci Lett* **187**, 79-82.

[59] Poirier J, Delisle MC, Quirion R, Aubert I, Farlow M, Lahiri D, Hui S, Bertrand P, Nalbantoglu J, Gilfix B, Gauthier S (1995) Apolipoprotein E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer disease. *Proc Natl Acad Sci U S A* **92**, 12260-12264.

[60] Canolty RT, Knight RT (2010) The functional role of cross-frequency coupling. *Trends Cogn Sci* **14**, 506-515.

[61] Lizio R, Vecchio F, Frisoni GB, Ferri R, Rodriguez G, Babiloni C (2011) Electroencephalographic rhythms in Alzheimer's disease. *Int J Alzheimers Dis* **2011**, 927573.

[62] Gloor P, Ball G, Schaul N (1977) Brain lesions that produce delta waves in the EEG. *Neurology* **27**, 326-333.

[63] Honea RA, Vidoni E, Harsha A, Burns JM (2009) Impact of APOE on the healthy aging brain: A voxel-based MRI and DTI study. *J Alzheimers Dis* **18**, 553-564.

[64] Bagepally BS, Halahalli HN, John JP, Kota L, Purushottam M, Mukherjee O, Sivakumar PT, Bharath S, Jain S, Varghese M (2012) Apolipoprotein E4 and brain white matter integrity in Alzheimer's disease: Tract-based spatial statistics study under 3-Tesla MRI. *Neurodegener Dis* **10**, 145-148.

[65] Han X (2007) Potential mechanisms contributing to sulfatide depletion at the earliest clinically recognizable stage of Alzheimer's disease: A tale of shotgun lipidomics. *J Neurochem* **103**(Suppl 1), 171-179.

[66] Fields RD (2008) White matter in learning, cognition and psychiatric disorders. *Trends Neurosci* **31**, 361-370.

[67] Lutzenberger W, Preissl H, Pulvermuller F (1995) Fractal dimension of electroencephalographic time series and underlying brain processes. *Biol Cybern* **73**, 477-482.

[68] Langbaum JB, Chen K, Caselli RJ, Lee W, Reschke C, Bandy D, Alexander GE, Burns CM, Kaszniak AW, Reeder SA, Corneveaux JJ, Allen AN, Pruzin J, Huentelman MJ, Fleisher AS, Reiman EM (2010) Hypometabolism in Alzheimer-affected brain regions in cognitively healthy Latino individuals carrying the apolipoprotein E epsilon4 allele. *Arch Neurol* **67**, 462-468.

[69] Chen K, Reiman EM, Alexander GE, Caselli RJ, Gerkin R, Bandy D, Domb A, Osborne D, Fox N, Crum WR, Saunders AM, Hardy J (2007) Correlations between apolipoprotein E epsilon4 gene dose and whole brain atrophy rates. *Am J Psychiatry* **164**, 916-921.

[70] Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, Saunders AM, Hardy J (2004) Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. *Proc Natl Acad Sci U S A* **101**, 284-289.

[71] Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, Saunders AM, Hardy J (2005) Correlations between apolipoprotein E epsilon4 gene dose and brain-imaging measurements of regional hypometabolism. *Proc Natl Acad Sci U S A* **102**, 8299-8302.

[72] Fleisher AS, Chen K, Liu X, Ayutyanont N, Roontiva A, Thiyyagura P, Protas H, Joshi AD, Sabbagh M, Sadowsky CH, Sperling RA, Clark CM, Mintun MA, Pontecorvo MJ, Coleman RE, Doraiswamy PM, Johnson KA, Carpenter AP, Skovronsky DM, Reiman EM (2013) Apolipoprotein E epsilon4 and age effects on florbetapir positron emission tomography in healthy aging and Alzheimer disease. *Neurobiol Aging* **34**, 1-12.

[73] Murphy KR, Landau SM, Choudhury KR, Hostage CA, Shpanskaya KS, Sair HI, Petrella JR, Wong TZ, Doraiswamy PM (2013) Mapping the effects of ApoE4, age and cognitive status on 18F-florbetapir PET measured regional cortical patterns of beta-amyloid density and growth. *Neuroimage* **78**, 474-480.

[74] Fernandez A, Maestu F, Amo C, Gil P, Fehr T, Wienbruch C, Rockstroh B, Elbert T, Ortiz T (2002) Focal temporoparietal slow activity in Alzheimer's disease revealed by magnetoencephalography. *Biol Psychiatry* **52**, 764-770.

[75] Fernandez A, Arrazola J, Maestu F, Amo C, Gil-Gregorio P, Wienbruch C, Ortiz T (2003) Correlations of hippocampal atrophy and focal low-frequency magnetic activity in Alzheimer disease: Volumetric MR imaging-magnetoencephalographic study. *AJNR Am J Neuroradiol* **24**, 481-487.

[76] Barabash A, Marcos A, Ancin I, Vazquez-Alvarez B, de Ugarte C, Gil P, Fernandez C, Encinas M, Lopez-Ibor JJ, Cabranes JA (2009) APOE, ACT and CHRNA7 genes in the conversion from amnestic mild cognitive impairment to Alzheimer's disease. *Neurobiol Aging* **30** 1254-1264.