Journal of Alzheimer's Disease 52 (2016) 133–143
DOI 10.3233/JAD-151034
IOS Press

Searching for Primary Predictors of Conversion from Mild Cognitive Impairment to Alzheimer's Disease: A Multivariate Follow-Up Study

María Eugenia López[a,b,c,*], Agustín Turrero[c,d], Pablo Cuesta[b], David López-Sanz[b,e], Ricardo Bruña[b], Alberto Marcos[c,f], Pedro Gil[c,g], Miguel Yus[c,h], Ana Barabash[c,i], José Antonio Cabranes[c,i], Fernando Maestú[b,c,e] and Alberto Fernández[b,c,j]
[a]*Laboratory of Neuropsychology, Universitat de les Illes Balears, Palma de Mallorca, Spain*
[b]*Laboratory of Cognitive and Computational Neuroscience, Center for Biomedical Technology, Complutense University of Madrid and Technical University of Madrid, Spain*
[c]*Institute of Sanitary Investigation [IdISSC], San Carlos University Hospital, Madrid, Spain*
[d]*Department of Biostatistics and Operational Investigation, Complutense University of Madrid, Spain*
[e]*Department of Basic Psychology II, Complutense University of Madrid, Spain*
[f]*Neurology Department, San Carlos University Hospital, Madrid, Spain*
[g]*Geriatrics Department, San Carlos University Hospital, Madrid, Spain*
[h]*Radiology Department, San Carlos University Hospital, Madrid, Spain*
[i]*Laboratory of Psychoneuroendocrinology and Molecular Genetics, Biomedical Research Foundation, San Carlos University Hospital, Madrid, Spain*
[j]*Department of Psychiatry, Faculty of Medicine, Complutense University of Madrid, Spain*

Accepted 15 January 2016

Abstract. Recent proposals of diagnostic criteria within the healthy aging-Alzheimer's disease (AD) continuum stressed the role of biomarker information. More importantly, such information might be critical to predict those mild cognitive impairment (MCI) patients at a higher risk of conversion to AD. Usually, follow-up studies utilize a reduced number of potential markers although the conversion phenomenon may be deemed as multifactorial in essence. In addition, not only biological but also cognitive markers may play an important role. Considering this background, we investigated the role of cognitive reserve, cognitive performance in neuropsychological testing, hippocampal volumes, APOE genotype, and magnetoencephalography power sources to predict the conversion to AD in a sample of 33 MCI patients. MCIs were followed up during a 2-year period and divided into two subgroups according to their outcome: The "stable" MCI group (sMCI, 21 subjects) and the "progressive" MCI group (pMCI, 12 subjects). Baseline multifactorial information was submitted to a hierarchical logistic regression analysis to build a predictive model of conversion to AD. Results indicated that the combination of left hippocampal volume, occipital cortex theta power, and clock drawing copy subtest scores predicted conversion to AD with a 100% of sensitivity and 94.7% of specificity. According to these results it might be suggested that anatomical, cognitive, and neurophysiological markers may be considered as "first order" predictors of progression to AD, while APOE or cognitive reserve proxies might play a more secondary role.

Keywords: Alzheimer's disease, APOE, cognitive reserve, hippocampal volume, magnetoencephalography; mild cognitive impairment, neuropsychological tests, predictive model

*Correspondence to: María Eugenia López, Laboratory of Neuropsychology, Universitat de les Illes Balears, Carr. de Valldemossa, km 7,5, CP. 07122 Palma de Mallorca, Islas Baleares, Spain; Laboratory of Cognitive and Computational Neuroscience (UCM-UPM), Centre for Biomedical Technology (CTB), Campus de Montegancedo s/n, 28223 Pozuelo de Alarcón, Madrid, Spain; Institute of Sanitary Investigation [IdISSC], San Carlos University Hospital, Madrid, Spain. E-mail: meugenia.lopez@uib.es.

INTRODUCTION

The recent inclusion of biomarkers as supportive information in the diagnostic criteria for Alzheimer's disease (AD) has been considered an important advance in its characterization [1]. In addition, biomarkers played a key role in recognizing AD as a continuum of clinical and biological phenomena. Thereby, the National Institute on Aging-Alzheimer's Disease Association (NIA-AA) proposed three consecutive phases of the disease: preclinical, symptomatic pre-dementia or mild cognitive impairment (MCI) and AD dementia [1–3]. The combination of more precise clinical criteria and biomarkers has been decisive in increasing diagnosis and prognosis accuracy.

Although the diagnostic accuracy has certainly increased, the question of which specific MCI subject will finally develop AD still remains unanswered. A reasonable explanation for this phenomenon is to consider that during the course of the disease, pathophysiological and cognitive changes are not as linear as they were previously contemplated [4]. Predictive studies have analyzed a number of biological and cognitive factors, including cognitive reserve [5], performance in cognitive testing [6], volumetric magnetic resonance imaging (MRI) [7–9], apolipoprotein ε4 (APOE4) genotype [10], fluorodeoxyglucose and Pittsburgh compound B positron emission tomography (FGD-PET, PIB-PET) [11, 12], cerebrospinal fluid (CSF) markers [13–15], etc. Notably, most conversion studies utilized a single marker to predict progression to AD, when this phenomenon may be deemed as multifactorial in essence.

Other possible indicators, such as neurophysiological variables, have not yet been considered as putative markers of the disease. However, electroencephalography (EEG) and particularly magnetoencephalography (MEG) may provide relevant information on the progression to AD [16]. For instance, Jelic et al. [17] reported that the best predictor of future conversion to AD was an increased theta power and a decrease in alpha activity, while Huang et al. [18] showed that the best marker was the shift of alpha activity toward anterior brain areas. Rossini et al. [19] found that progressive MCI patients exhibited higher power values in delta, theta, and alpha1 bands, mainly over temporal and parietal areas, and also changes in fronto-parietal midline coherence values. Fernandez et al. [20] found that an increase in delta activity in left parietal areas was a good marker of conversion within 2 years. Thereafter, Moretti et al. [21] observed that progressive MCIs presented an increase of alpha3/alpha2 relative power ratio, being this ratio further related to hippocampal atrophy [22]. Poil et al. [23] found that multiple EEG biomarkers, mainly related to the activity in the beta-frequency range, may predict the conversion from MCI to AD. In a recent study performed by our group [9], progressive MCI subjects showed a higher synchronization in alpha band between the right anterior cingulate and temporo- occipital regions as compared with stable MCI subjects.

Due to the inherent complexity of the conversion phenomenon, it might be necessary to consider a more global perspective. To this end, we proposed a multivariate study where a sample of MCIs was followed-up during a 2-year period. The study included cognitive reserve (CR) proxies (i.e., educational level and occupational attainment), genetic risk factors (i.e., APOE genotype), cognitive performance, anatomical information (i.e., hippocampal volumes), and neurophysiological measures (i.e., source analysis of relative power by means of MEG). To the best of our knowledge, such combination of variables has never been used within this field of research.

MATERIALS AND METHODS

Participants

Thirty-three MCI patients (17 females) were recruited from the Geriatry and Neurology Units at the "Hospital Universitario San Carlos", Madrid, Spain. All of them were right-handed [24] and native Spanish speakers. Demographic and clinical data for MCI patients are shown in Table 1.

All subjects underwent a clinical evaluation, magnetic resonance (MRI), MEG scanning, and a genetic analysis. In order to evaluate the global cognitive and functional status, all participants were screened with a set of standardized tests that included: the Spanish version of the Mini-Mental State Examination (MMSE) [25], the Global Deterioration Scale (GDS) [26], the Functional assessment questionnaire (FAQ) [27], the Geriatric Depression Scale- Short Form (GDS- SF) [28], the Hachinski Ischemic Score [29], the questionnaire for Instrumental Activities of Daily Living [30], and the Functional Assessment Staging (FAST) [31]. In addition, participants underwent an extensive neuropsychological assessment to explore their cognitive functioning by using the following tests: clock drawing test [32], direct and inverse digit

Table 1
Mean values ± standard deviation of the demographics and more relevant clinical characteristics of MCI patients ($n = 33$)

	Mean ± SD & Proportions
Age	73.8 ± 6.5
Gender (male/female)	16/17
MMSE	28.3 ± 1.8
Education (years)	8.2 ± 4.7
OCC theta power	$(2.20 \pm 0.7) \times 10^{-2}$
LH_ICV	$(2.25 \pm 0.44) \times 10^{-3}$
RH_ICV	$(2.20 \pm 0.47) \times 10^{-3}$
APOE 4 (non-carrier/carrier)*	19/13

MMSE, Mini-Mental State Examination Score; OCC, occipital cortex; LH_ICV, left hippocampus normalized by total intracranial volume (ICV); RH_ICV, right hippocampus normalized by ICV; APOE, gene encoding for apolipoprotein E. Non-carrier, there is not any allele 4, and carrier: there is at least 1 allele 4. *The APOE value from one participant was missing.

Table 2
Mean values ± standard deviation of the demographics and more relevant clinical characteristics of sMCI ($n = 21$) and pMCI ($n = 12$)

	MCI Group	Mean ± SD
Age	Stable	72.7 ± 6.5
	Progressive	75.75 ± 6.2
Gender (males/females)	Stable (10/11)	
	Progressive (6/6)	
MMSE	Stable	28.48 ± 188
	Progressive	27.89 ± 1.8
Education (years)	Stable	9 ± 5.5
	Progressive	7 ± 2.7
OCC theta power	Stable	$(2.00 \pm 0.64) \times 10^{-2}$
	Progressive	$(2.56 \pm 0.82) \times 10^{-2}$
CDT copy subtest	Stable	6.63 ± 0.597
	Progressive	5.17 ± 1.467
LH_ICV	Stable	$(2.44 \pm 4.22) \times 10^{-3}$
	Progressive	$(1.93 \pm 2.82) \times 10^{-3}$
RH_ICV	Stable	$(2.36 \pm 4.05) \times 10^{-3}$
	Progressive	$(1.95 \pm 4.82) \times 10^{-3}$
APOE 4 (non-carrier/carrier)	Stable (12/9)	
	Progressive (7/4)*	

MMSE, Mini-Mental State Examination Score; OCC, occipital cortex; CDT, Clock Drawing; LH_ICV, left hippocampus normalized by total intracranial volume (ICV); RH_ICV, right hippocampus normalized by ICV; APOE, gene encoding for apolipoprotein E. Non-carrier, there is not any allele 4, and carrier: there is at least 1 allele 4. *The APOE value from one pMCI was missing.

spam test (Wechsler Memory Scale III, WMS-III) [33], immediate and delayed recall (WMS-III) [33], phonemic and semantic fluency (controlled oral word association test) [34], ideomotor praxis of Barcelona test [35], rule shift cards (behavioral assessment of the dysexecutive syndrome) [36], visual object and space perception test [37], Boston naming test [38], and trail-making test (TMT), parts A and B [39].

MCI patients were diagnosed according to the National Institute on Aging-Alzheimer Association (NIA-AA) criteria [3], and based on their cognitive profile, all of them were classified as amnestic MCI patients [40]. Besides meeting the core clinical criteria for MCI, patients also exhibited significant hippocampal atrophy according to the evaluation of an experienced neuroradiologist (M.Y.) who was blinded to the clinical outcome (see also below hippocampal volumes calculation). Consequently, patients were categorized as "MCI due to AD intermediate likelihood" [3]. A 2-year follow-up was accomplished by assessing patients' neuropsychological performance and clinical status every 6 months. MCIs were then split into two groups according to their clinical outcome: (1) The "stable" MCI group (sMCI, 21 subjects: 11 females) was composed of patients who fulfilled the diagnosis criteria of MCI at the end of follow-up; and (2) The "progressive" MCI group (pMCI, 12 subjects: 6 females) was composed of those patients who met the criteria for probable AD [1] during the follow-up period. Demographics and clinical data for sMCI and pMCI are shown in Table 2.

All MCI subjects were in good health, with no significant medical, psychiatric or neurological diseases (other than AD or MCI). General inclusion criteria considered an age between 65 and 85 years, a modified Hachinski score ≤ 4, a geriatric depression scale short-form 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) [9, 41]. Finally, those participants with medical treatment which could affect MEG activity (e.g., cholinesterase inhibitors) were required to interrupt it 48 h before the recordings.

The study was approved by the Hospital Universitario San Carlos ethics committee and all subjects gave informed consent prior to their MEG recording.

Proxies of cognitive reserve

Two main proxies of cognitive reserve were considered: Educational level and occupational attainment. Educational level was measured as years of formal education (range 1 to 20 years), and obtained by questioning participants or caregivers. Occupational attainment was classified into five categories, according to the main professional activity carried out during the active life of each participant: (1) housewife/no formal employment, (2) non-qualified,

(3) qualified; (4) technical/professional; (5) highly qualified [42], see also [43].

APOE genotype

APOE genotype was extracted from blood samples of MCIs (both stable and progressive), and determined using standard methods [44]. According to the presence or absence of the $\varepsilon 4$ (APOE4) allele, participants were classified as APOE4 carriers or non-carriers (see Table 1).

MRI acquisition and hippocampal volumes

3D T1 scans were collected with a General Electric 1.5 T magnetic resonance scanner, using a high-resolution antenna and a homogenization PURE filter [Fast Spoiled Gradient Echo (FSPGR) sequence with parameters: TR/TE/TI = 11.2/4.2/450 ms; flip angle 12°; 1 mm slice thickness, 256×256 matrix; and FOV 25 cm]. T1-weighted MRI images were then processed with Freesurfer software package (version 5.1.0) and its specialized tool for automated cortical and subcortical segmentation [45], in order to obtain the hippocampal volumes. The automated Freesurfer technique is well described elsewhere (https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferMethodsCitation) and briefly, consists of an assignation of a neuroanatomical label to each voxel in an MRI volume based on probabilistic information estimated from a set of 39 training segmentations, manually labelled using the Center for Morphometric Analysis conventions. Resulting hippocampal volumes were normalized considering total intracranial volume (ICV) to account for the variability in head volume along subjects. Accordingly, two variables were created and submitted for further analysis: LH_ICV = Left Hippocampal volume/ICV; and RH_ICV = Right hippocampal volume/ICV.

MEG recordings and preprocessing

Three minutes of eyes-closed resting state MEG activity were acquired at 1000 Hz sampling rate (online bandpass anti-alias filtering at 0.1–330 Hz) with a 306-channel Vectorview system (ElektaNeuromag). 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 head-shape 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 submitted to Maxfilter software (v 2.2, correlation threshold = 0.9, time window = 10 s) in order to remove external noise with the temporal extension of the signal space separation method with movement compensation [46, 47].

Magnetometers' resting state data were automatically scanned for ocular, muscle and "jump" artifacts by means of Fieldtrip software [48], and were confirmed by a MEG expert (P.C). Then, artifact-free data were segmented in continuous 4-s fragments (trials). Only MEG recordings with at least 15 clean trials (60 s of brain activity) were kept for further analyses. In order to calculate the source reconstruction, clean trials were filtered (1.5–45 Hz) with a Finite Impulse Response filter of order 1000 designed with a Hamming window. The filter was applied using a two-pass procedure over the whole five-minute registers, in order to avoid phase distortion and edge effects.

Source reconstruction

Headmodels and beamforming

A regular grid of 2455 nodes, with 1 cm spacing, was created in the template Montreal Neurological Institute (MNI) brain. This set of nodes was transformed to the subject's space using a linear normalization between the native T1 image and a standard T1 in MNI space. The forward model was solved with the realistic single-shell model introduced by Nolte [49]. Source reconstruction was performed with a Linearly Constrained Minimum Variance beamformer [50].

Power spectra analysis

MEG power spectra of each node were computed for all artifact-free trials with a frequency-of-interest range of 0.5 Hz steps from 1.5 to 30 Hz by means of standard Fieltrip's procedure [48]. Trials were averaged across subjects, and for each node the relative power was calculated by normalizing with the total power over the 1.5–30 Hz range [17]. Finally, we defined five frequency bands: delta (1.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta1 (12–20 Hz), and beta2 (20–30 Hz).

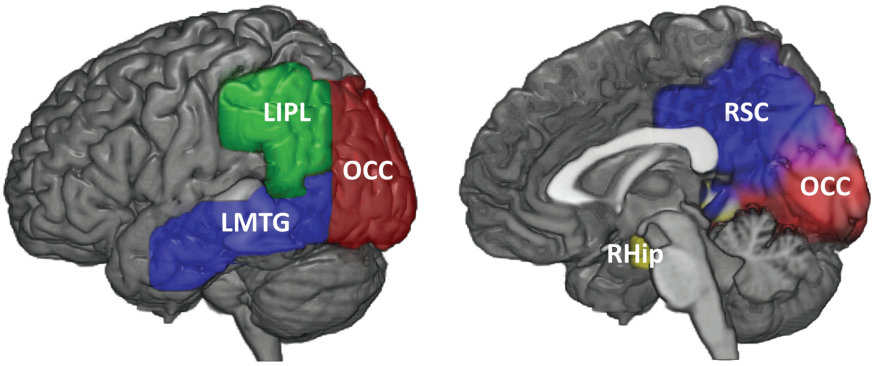

Fig. 1. Regions of interest: left inferior parietal lobe (LIPL); right inferior parietal lobe (RIPL); occipital cortex (OCC); left medial temporal gyrus (LMTG); right medial temporal gyrus (RMTG); retrosplenial cortex (RSC); left hippocampus (LHIP); and right hippocampus (RHIP).

Atlas based analysis

Anatomic labels were assigned to each node with the Harvard-Oxford probabilistic atlas [51]. We selected 8 regions of interest (ROIs) according to previous EEG and MEG AD-related literature (see Fig. 1) [20, 52–56]. Then, power values were averaged per ROIs, ending up with an 8 ROIs × 5 bands × 33 subjects matrix.

Statistical analyses

In order to identify those factors related with outcome, stability, or progression to AD, and to retrospectively assess the predictive capability of each one of them, we performed an analysis of each set of factors, separately by blocks that contain information of different nature or level of aggregation. Factors included in the analysis and evaluated at entry were: 1) Demographic variables (age, gender and cognitive reserve proxies); 2) APOE genotype; 3) Neuropsychological testing scores; 4) MEG power data on each ROI; and 5) Hippocampal volumes. In each block two-sample *t*-tests and Chi-square tests of homogeneity were applied to evaluate group differences in quantitative and categorical variables, respectively. Once the candidate variables of each block were selected, hierarchical logistic regression analyses were applied in order to obtain a model that might allow the discrimination of stable and progressive MCI patients. The motivation for using the hierarchical logistic regression model was to control or take into account the impact of each block of variables on outcome. As in previous studies of our group [20, 55], the variable selection paradigm described in Hosmer et al. [57] has been used in each block; this includes the use of a stepwise method in those blocks that contain a large number of significant variables. The change in the Block Chi-square allows evaluating how much predictive power was added to the model by the addition of another block. The accuracy of the final fitted model was then assessed by means of R^2 statistics such as Cox-Snell and Nagelkerke statistics as well as using the ROC curve analysis. Finally, a complementary split-sample validation analysis, in particular a 75-25 cross-validation was employed. Thus, the sample containing all cases was randomly divided into two subsamples, a training sample containing 75% of the cases and a holdout sample containing the remaining 25% of the cases. The final fitted logistic model was refitted to the training sample, and the holdout sample was classified using the coefficients based on the training sample.

Statistical analyses were performed using SPSS 22 statistical package.

RESULTS

Stable versus progressive MCIs analyses

As described in the Methods section, after a two-year follow-up 12 of 33 MCI (36%) patients met the criteria for probable AD.

Demographic variables

None of the demographic variables showed statistically differences between groups: gender ($\chi^2_1 = 0.017$, $p = 0.895$), occupational attainment ($\chi^2_1 = 1.954$, $p = 0.162$), years of education ($t_{31} = 1.382$, $p = 0.178$) and age ($t_{31} = -1.335$, $p = 0.192$) (see Table 2).

APOE4

The proportion of APOE4 carriers was homogeneously distributed in sMCI and pMCI groups ($\chi^2_1 = 0.126$, $p = 0.722$) (see Table 2).

MEG variables

T-tests showed statistically significant differences for all ROIs within theta and beta2 frequency ranges (all $p < 0.04$). pMCIs showed higher theta and lower beta2 power values as compared with sMCIs. The strong correlation among theta values (all $r > 0.94$) and among beta2 values (all $r > 0.79$), as well as the significant inverse correlation between both sets of values (all $r < –0.69$) allows to anticipate a considerable reduction in the number of MEG variables when multivariate analysis is undertaken. The differences were not statistically significant for beta1 (all $p > 0.20$), alpha (all $p > 0.20$) and delta bands (all $p > 0.67$).

Neuropsychological testing

Among the neuropsychological variables, *t*-tests showed that only Clock Drawing (CDT) copy subtest ($p = 0.009$), CDT order subtest ($p = 0.025$), and Delayed Recall of the WMS-III ($p = 0.009$) showed significant differences between sMCIs and pMCIs. pMCIs exhibited reduced scores in the three tests. Also, TMT-B Hits ($p = 0.052$), TMT-B Time ($p = 0.073$), and Immediate Recall of the WMS-III ($p = 0.069$) showed close-to-significant differences. Results indicated that MMSE scores were homogeneously distributed in sMCI and pMCI groups at baseline ($p = 0.418$).

Hippocampal volumes

pMCIs showed significantly reduced LH_ICV ($p = 0.001$) and RH_ICV ($p = 0.014$) as compared with sMCIs (see Table 2).

Hierarchical logistic regression analyses

We conducted a hierarchical logistic regression analysis with the selected variables in each of three significant blocks, to study potential predictors of conversion to AD. A stepwise procedure was applied separately by blocks. Only CDT copy subtest ($p = 0.01$), OCC theta ($p = 0.05$), and LH_ICV ($p = 0.009$) demonstrated a predictive power in the multivariate model. The model-building process continued by ascertaining the correct scale in the logit for the three variables. The analysis showed evidence of linearity in three cases (all $p > 0.4$). Finally, we searched for interactions between these three variables. No interaction was found (all $p > 0.15$). Therefore, the model including CDT copy subtest, OCC theta, and LH_ICV was selected as the best model for stable versus progressive MCIs discrimination (see Fig. 2).

The Nagelkerke R^2 goodness of fit statistic was 0.82, indicating that an 82% of the "variation" in the diagnosis (stable vs. progressive) was explained by the logistic model. The Cox-Snell R^2 was 0.61. The estimated sensitivity and specificity of model, from the classification table, was 100% and 94.7 %, respectively when a 0.50 cut-off point is adopted (one misclassified subject). Notably, sensitivity/specificity percentages remain stable for a cut-off point's interval between 0.36 and 0.65, thus indicating the robustness of the model. Also, results of a 75-25 cross-validation analysis confirmed the goodness of fit. The accuracy rate for the training sample was 95.5% while the same rate for the holdout sample was 100%. Both global significance test and the corresponding tests for each of the predictors in the training sample were significant ($p < 0.001$ and all $p < 0.04$ respectively). These results support the predictive capability of the model and consequently its usefulness.

The estimated relative risk of conversion to AD decreases by 84.8% for an increase of 1 point in CDT copy subtest score. This relative risk of conversion increases by 62.5% for an increase of 0.01 units in OCC theta. The estimated relative risk of conversion to AD decreases by 71.5% when the "ratio of volumes" LH_ICV increases 0.0001. Finally, The AUROC for this model was of 0.97 (95% CI = 0.91; 1.00).

DISCUSSION

During the last two decades, the detection of those subjects with an increased risk of conversion to AD became a crucial goal for basic and clinical neuroscience. In this vein, most studies tried to demonstrate that a particular marker (i.e., demographic, cognitive, biological, etc.) was sensitive enough to predict progression to AD. However, relatively few investigations compared the specific contribution of different kinds of markers and their conjoint predictive capability. When such investigations were carried out (see below) a new perspective emerged, and two key ideas

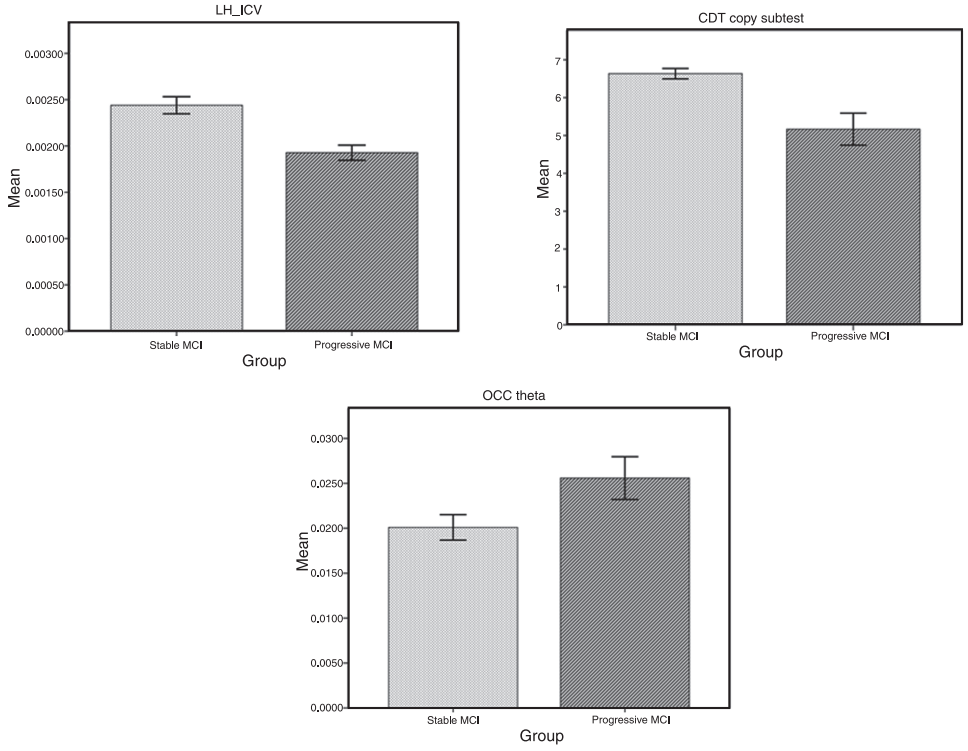

Fig. 2. Graph of the mean values of the three variables statistically significant between Stable and Progressive MCI groups: CDT copy subset, LH_ICV, and Occipital theta in Stable and Progressive MCI groups. Error bars indicate Standard errors.

were stated: 1) The combination of markers yields a radical increase in the predictive capability of the models; and 2) Several markers, typically associated with cognitive deterioration, fail to demonstrate a significant contribution as predictors of conversion when they are tested in multivariate models. The latter affirmation is of special relevance, since it might suggest the existence of "first order" and "second order" predictors of conversion to AD. First order predictors would be those markers that survive in a systematic selection process when they are merged with other markers, since they provide basic and non-redundant information about MCI outcome. Second order predictors may be defined as those markers that do not survive in a systematic selection process since they provide information that is better addressed by first order predictors.

Our results support both ideas. Several investigations proved that APOE4 is a risk factor for late-onset AD, which is associated with a faster rate of cognitive decline and with a decrease in the age at onset of dementia [10]. However, APOE4 sensitivity and specificity are low when the marker is used alone, and some studies showed no association between APOE4 and progression to dementia [58–60]. Supporting our results, the meta-analysis carried out by Modrego [61] indicated that APOE4 is not a strong predictor of conversion to AD.

Regarding CR proxies, our results indicated that they made no significant contribution to the prediction of conversion to AD. Undoubtedly, the interaction between cognitive enrichment and brain plasticity may produce a reserve against late-life insults [62]. Nevertheless, the actual influence of CR proxies on cognition might be biased by the strong relationship between those proxies and performance in tests utilized for MCI or AD diagnosis. This problem was noted by Stern [63], and has been considered in subsequent studies [43, 64, 65]. Thereby, Amieva et al. [64] pointed out that recent investigations showed a positive effect of education on cognitive performance but a lack of association with rates of cognitive decline. A potential explanation could be due to the difference in premorbid level of performance. Authors put forward that, as higher-educated subjects achieve higher premorbid levels of cognitive performance, the delay in reaching dementia threshold would be longer but education per se might have no particular effect on the rate of decline. Similarly, Serra et al. [65] found no differences in the percentage

of conversion to AD between MCI patients with high and low CR, and posed that such results were in accordance with Stern's theory of reserve [62] which hypothesizes that cognitive enrichment does not protect against disease progression itself.

Considering this background, it might be affirmed that APOE4 and CR proxies could be examples of second order predictors of conversion to AD. On the contrary, our results strongly suggest the notion that hippocampal volumetry and MEG source analysis of low-frequency activity may be examples of first order predictors. A cognitive marker was also included in our final predictive model but this fact deserves further comment. Although very recent studies stressed the predictive capability of cognitive markers [66], the actual role of these markers has been questioned. Some authors stated that since AD and MCI diagnosis are based on the severity of cognitive dysfunction, the use of neuropsychological performance as a predictor of conversion is circular [67]. According to this, Heister and colleagues [67] claimed that neuropsychological tests might be better conceptualized as severity measures rather than "predictors". Notwithstanding, very recent studies that combined demographic, cognitive, and biological markers pointed out that some cognitive tests, specially delayed episodic memory and screening measures such as the CDT, survive in an exhaustive process of markers selection [67–69]. Interestingly, in three of these four studies [67, 69, 70] the combination of mesial temporal atrophy and cognitive performance were best predictors of progression to AD, while CR or APOE4 made no contribution.

Findings presented in this work are totally in line with the above cited investigations. First, our results indicated that left hippocampal volume is the marker showing the strongest association with conversion, thus supporting the overwhelming evidence that left hippocampal atrophy represents a cornerstone in the predictive models of progression to AD [71, 72]. Second, our findings confirmed that screening tests such as the CDT, probably less influenced by educational factors as compared with the MMSE, are also reliable severity measures [67, 70, 73]. Our results also confirmed that when an additional, non-redundant marker is included (see, for example, Devanant et al. [68]), the model's sensitivity increases. In this case the additional marker was theta power in posterior (i.e. occipital cortex) brain regions.

This evidence represents a new confirmation of MEG low-frequency activity as a crucial factor to estimate the risk of progression to AD. The predictive value of neurophysiological techniques was highlighted in EEG studies [17] but they were limited by a poor spatial resolution. Previous investigations by our group using MEG source analysis, demonstrated that an increased low-frequency activity in posterior cortex correlated with genetic risk profiles, elevated the risk of conversion by a factor of 3.5, and was involved in the transition from healthy aging to MCI, and from MCI to AD [20, 55, 74, 75]. Specifically, an increased delta activity on the occipital cortex was involved in the transition from healthy aging to MCI [55]. These observations coincide with several EEG/MEG studies on AD that demonstrated a slowing of the dominant oscillatory brain activity over posterior brain regions with progression to more anterior regions during the evolution of the disease [76–79]. According to this process, the dominant alpha activity over occipital cortex is progressively substituted by a rhythm within the low-frequency range [79]. Chiaramonti et al. [80] calculated the centroid of the conventional EEG bands in a group of mild and moderate AD patients, and reported that such "substitution" process was associated with disease severity (for more information on the implication of occipital pathology in AD see McKee et al. [81]). Now we prove that OCC theta power survived in a hierarchical selection process where multiple markers were included, suggesting that it provided with information that significantly improved the sensitivity of the model. The final model including LH_ICV, CDT copy subtest and OCC theta power reached 100% and 94.4% of sensibility and specificity, respectively, values that may be considered within the top rank reported in the literature (see [67]).

The results obtained in this study were limited by the small sample size, especially in the case of pMCIs. Notwithstanding, it still demonstrated that a combination of cognitive, structural and neurophysiological markers was predictive of progression to AD in a MCI population. In addition, our results showed that other markers such as APOE4 genotype or CR proxies might play a secondary role. Finally, these results represent an additional corroboration for the importance of MEG as a biomarker within the healthy aging-AD continuum.

ACKNOWLEDGMENTS

This study was supported by two projects from the Spanish Ministry of Economy and Competitiveness (PSI2009-14415-C03-01 and PSI2012-38375-C03

-01), a postdoctoral fellowship to María Eugenia López (FJCI-2014-22730) and a predoctoral fellowship to López-Sanz (BES-2013-063772), both from the Spanish Ministry of Economy and Competitiveness.

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/15-1034r2).

REFERENCES

[1] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263-269.

[2] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH (2011) Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 280-292.

[3] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 270-279.

[4] Jack CR, Wiste HJ, Knopman DS, Vemuri P, Mielke MM, Weigand SD, Senjem ML, Gunter JL, Lowe V, Gregg BE, Pankratz VS, Petersen RC (2014) Rates of β-amyloid accumulation are independent of hippocampal neurodegeneration. *Neurology* **82**, 1605-1612.

[5] Valenzuela MJ, Sachdev P (2006) Brain reserve and dementia: A systematic review. *Psychol Med* **36**, 441-454.

[6] Albert M, Moss M, Blacker D (2007) Longitudinal change in cognitive performance among individuals with mild cognitive impairment. *Neuropsychology* **21**, 158-169.

[7] Devanand DP, Pradhaban G, Liu X, Khandji A, De Santi S, Segal S, Rusinek H, Pelton GH, Honig LS, Mayeux R, Stern Y, Tabert MH, de Leon MJ (2007) Hippocampal and entorhinal atrophy in mild cognitive impairment: Prediction of Alzheimer disease. *Neurology* **68**, 828-836.

[8] Clerx L, van Rossum IA, Burns L, Knol DL, Scheltens P, Verhey F, Aalten P, Lapuerta P, van de Pol L, van Schijndel R, de Jong R, Barkhof F, Wolz R, Rueckert D, Bocchetta M, Tsolaki M, Nobili F, Wahlund L-O, Minthon L, Frölich L, Hampel H, Soininen H, Visser PJ (2013) Measurements of medial temporal lobe atrophy for prediction of Alzheimer's disease in subjects with mild cognitive impairment. *Neurobiol Aging* **34**, 2003-2013.

[9] López ME, Bruña R, Aurtenetxe S, Pineda-Pardo JÁ, Marcos A, Arrazola J, Reinoso AI, Montejo P, Bajo R, Maestú F (2014) Alpha-band hypersynchronization in progressive mild cognitive impairment: A magnetoencephalography study. *J Neurosci* **34**, 14551-14559.

[10] 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.

[11] Hatashita S, Yamasaki H (2013) Diagnosed mild cognitive impairment due to Alzheimer's disease with PET biomarkers of beta amyloid and neuronal dysfunction. *PLoS One* **8**, e66877.

[12] Grimmer T, Wutz C, Drzezga A, Förster S, Förstl H, Ortner M, Perneczky R, Kurz A (2013) The usefulness of amyloid imaging in predicting the clinical outcome after two years in subjects with mild cognitive impairment. *Curr. Alzheimer Res* **10**, 82-85.

[13] Buchhave P, Minthon L, Zetterberg H, Wallin AK, Blennow K, Hansson O (2012) Cerebrospinal fluid levels of β-amyloid 1-42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia. *Arch Gen Psychiatry* **69**, 98-106.

[14] van Rossum I, a, Vos SJB, Burns L, Knol DL, Scheltens P, Soininen H, Wahlund L-O, Hampel H, Tsolaki M, Minthon L, L'italien G, van der Flier WM, Teunissen CE, Blennow K, Barkhof F, Rueckert D, Wolz R, Verhey F, Visser PJ (2012) Injury markers predict time to dementia in subjects with MCI and amyloid pathology. *Neurology* **79**, 1809-1816.

[15] Canuet L, Pusil S, Lopez ME, Bajo R, Pineda-Pardo JA, Cuesta P, Galvez G, Gaztelu JM, Lourido D, Garcia-Ribas G, Maestu F (2015) Network disruption and cerebrospinal fluid amyloid-beta and phospho-tau levels in mild cognitive impairment. *J Neurosci* **35**, 10325-10330.

[16] Maestú F, Peña J-M, Garcés P, González S, Bajo R, Bagic A, Cuesta P, Funke M, Mäkelä JP, Menasalvas E, Nakamura A, Parkkonen L, López ME, del Pozo F, Sudre G, Zamrini E, Pekkonen E, Henson RN, Becker JT (2015) A multicenter study of the early detection of synaptic dysfunction in mild cognitive impairment using magnetoencephalography-derived functional connectivity. *Neuroimage Clin* **9**, 103-109.

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

[18] Huang C, Wahlund L-O, Dierks T, Julin P, Winblad B, Jelic V (2000) Discrimination of Alzheimer's disease and mild cognitive impairment by equivalent EEG sources: A cross-sectional and longitudinal study. *Clin Neurophysiol* **111**, 1961-1967.

[19] 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.

[20] Fernández A, Turrero A, Zuluaga P, Gil P, Maestú F, Campo P, Ortiz T (63) (2006) Magnetoencephalographic parietal delta dipole density in mild cognitive impairment. *Arch Neurol* **63**, 427-430.

[21] Moretti DV, Frisoni GB, Fracassi C, Pievani M, Geroldi C, Binetti G, Rossini PM, Zanetti O (2011) MCI patients' EEGs show group differences between those who progress and those who do not progress to AD. *Neurobiol Aging* **32**, 563-571.

[22] Moretti DV, Miniussi C, Frisoni GB, Geroldi C, Zanetti O, Binetti G, Rossini PM (2007) Hippocampal atrophy and EEG markers in subjects with mild cognitive impairment. *Clin Neurophysiol* **118**, 2716-2729.

[23] Poil S-S, de Haan W, van der Flier WM, Mansvelder HD, Scheltens P, Linkenkaer-Hansen K (2013) Integrative EEG biomarkers predict progression to Alzheimer's disease at the MCI stage. *Front Aging Neurosci* **5**, 58.

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

[25] 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.

[26] 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.

[27] 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.

[28] 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.

[29] Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A (1980) Pathological verification of ischemic score in differentiation of dementias. *Ann Neurol* **7**, 486-468.

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

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

[32] Agrell B, Dehlin O (1998) The clock-drawing test. *Age Ageing* **27**, 399-403.

[33] Wechsler D (1997) *Wechsler Memory Scale- Third Edition manual*.

[34] Benton A, Hamsher K (1989) *Multilingual Aphasia Examination*. Iowa City.

[35] Peña-Casanova J (1990) *Programa Integrado de Exploración Neuropsicológica- Test Barcelona. Protocolo*, Masson SA, Barcelona.

[36] Norris G, Tate RL (2000) The Behavioural Assessment of the Dysexecutive Syndrome (BADS): Ecological, concurrent and construct validity. *Neuropsychol Rehabil* **10**, 33-45.

[37] Warrington E, James M (1991) *The Visual Object and Space Perception Battery*, Thames Valley Test Company, Bury St. Edmunds, UK.

[38] Kaplan E, Goodglass H, Weintraub S (1983) *The Boston Naming Test*, Lea and Febiger, Philadelphia.

[39] Reitan R (1958) Validity of the Trail Making test as an indicator of organic brain damage. *Percept Mot Ski* **8**, 271-276.

[40] Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B (2001) Current concepts in mild cognitive impairment. *Arch Neurol* **58**, 1985-1992.

[41] Bai F, Shu N, Yuan Y, Shi Y, Yu H, Wu D, Wang J, Xia M, He Y, Zhang Z (2012) Topologically convergent and divergent structural connectivity patterns between patients with remitted geriatric depression and amnestic mild cognitive impairment. *J Neurosci* **32**, 4307-4318.

[42] López ME, Aurtenetxe S, Pereda E, Cuesta P, Castellanos NP, Bruña R, Niso G, Maestú F, Bajo R (2014) Cognitive reserve is associated with the functional organization of the brain in healthy aging: A MEG study. *Front Aging Neurosci* **6**, 125.

[43] Garibotto V, Borroni B, Sorbi S, Cappa SF, Padovani A, Perani D (2012) Education and occupation provide reserve in both ApoE ε4 carrier and noncarrier patients with probable Alzheimer's disease. *Neurol Sci* **33**, 1037-1042.

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

[45] Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM (2002) Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron* **33**, 341-355.

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

[47] Taulu S, Simola J (2006) Spatiotemporal signal space separation method for rejecting nearby interference in MEG measurements. *Phys Med Biol* **51**, 1759-1768.

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

[49] 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.

[50] 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.

[51] Desikan RS, Ségonne 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.

[52] Babiloni C, Binetti G, Cassetta E, Cerboneschi D, Dal Forno G, Del Percio C, Ferreri F, Ferri R, Lanuzza B, Miniussi C, Moretti DV, Nobili F, Pascual-Marqui RD, Rodriguez G, Romani GL, Salinari S, Tecchio F, Vitali P, Zanetti O, Zappasodi F, Rossini PM (2004) Mapping distributed sources of cortical rhythms in mild Alzheimer's disease. *A Multicentric EEG Study Neuroimage* **22**, 57-67.

[53] Babiloni C, Binetti G, Cassetta E, Dal Forno G, Del Percio C, Ferreri F, Ferri R, Frisoni G, Hirata K, Lanuzza B, Miniussi C, Moretti DV, Nobili F, Rodriguez G, Romani GL, Salinari S, 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.

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

[55] Fernández A, Turrero A, Zuluaga P, Gil-Gregorio P, del Pozo F, Maestu F, Moratti S (2013) MEG delta mapping along the healthy aging-Alzheimer's disease continuum: Diagnostic implications. *J Alzheimers Dis* **35**, 495-507.

[56] Garcés P, Vicente R, Wibral M, Pineda-Pardo JÁ, López ME, Aurtenetxe S, Marcos A, de Andrés ME, Yus M, Sancho M, Maestú F, Fernández A (2013) Brain-wide slowing of spontaneous alpha rhythms in mild cognitive impairment. *Front Aging Neurosci* **5**, 1-7.

[57] Hosmer D, Lemeshow S, Sturdivant R (2013) *Applied Logistic Regression* 3rd Edition.

[58] Riley KP, Snowdon DA, Markesbery WR (2002) Alzheimer's neurofibrillary pathology and the spectrum of cognitive function: Findings from the Nun Study. *Ann Neurol* **51**, 567-577.

[59] Tyas SL, Salazar JC, Snowdon DA, Desrosiers MF, Riley KP, Mendiondo MS, Kryscio RJ (2007) Transitions to mild cognitive impairments, dementia, and death: Findings from the Nun Study. *Am J Epidemiol* **165**, 1231-1238.

[60] Barabash A, Marcos A, Ancín I, Vázquez-Alvarez B, de Ugarte C, Gil P, Fernández C, Encinas M, López-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.

[61] Modrego PJ (2006) Predictors of conversion to dementia of probable Alzheimer type in patients with mild cognitive impairment. *Curr Alzheimer Res* **3**, 161-170.

[62] Stern Y (2009) Cognitive reserve. *Neuropsychologia* **47**, 2015-2028.

[63] Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R (1994) Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA* **271**, 1004-1010.

[64] Amieva H, Letenneur L, Dartigues J-F, Rouch-Leroyer I, Sourgen C, D'Alchée-Birée F, Dib M, Barberger-Gateau P, Orgogozo J-M, Fabrigoule C (2004) Annual rate and predictors of conversion to dementia in subjects presenting mild cognitive impairment criteria defined according to a population-based study. *Dement Geriatr Cogn Disord* **18**, 87-93.

[65] Serra L, Musicco M, Cercignani M, Torso M, Spanò B, Mastropasqua C, Giulietti G, Marra C, Bruno G, Koch G, Caltagirone C, Bozzali M (2015) Cognitive reserve and the risk for Alzheimer's disease: A longitudinal study. *Neurobiol Aging* **36**, 592-600.

[66] Snyder PJ (2013) The retooling of old cognitive tests as an interim step on the path to validating a next generation of neuropsychological paradigms and assays. *Alzheimers Dement* **9**, S1-S3.

[67] Heister D, Brewer JB, Magda S, Blennow K, McEvoy LK (2011) Predicting MCI outcome with clinically available MRI and CSF biomarkers. *Neurology* **77**, 1619-1628.

[68] Devanand DP, Liu X, Tabert MH, Pradhaban G, Cuasay K, Bell K, de Leon MJ, Doty RL, Stern Y, Pelton GH (2008) Combining early markers strongly predicts conversion from mild cognitive impairment to Alzheimer's disease. *Biol Psychiatry* **64**, 871-879.

[69] Gomar JJ, Bobes-Bascaran T, Conejero-goldberg C, Davies P, Goldberg TE, Initiative for the ADN (2011) Utility of combninations of biomarkers, cognitive markers, and risk factors to predict convresion from Mild cognitive impairment to Alzheimer disease in patients in the Alzheimer's disease neuroimaging initiative. *Arch Gen Psychiatry* **68**, 961-969.

[70] Gomar JJ, Conejero-goldberg C, Davies P, Goldberg TE (2014) Extension and refinement of the predictive value of different classes of markers in ADNI: Four-year follow-up data. *Alzheimers Dement* **10**, 704-712.

[71] Ferreira LK, Diniz BS, Forlenza OV, Busatto GF, Zanetti MV (2011) Neurostructural predictors of Alzheimer's disease: A meta-analysis of VBM studies. *Neurobiol Aging* **32**, 1733-1741.

[72] Thompson PM, Moussai J, Zohoori S, Goldkorn A, Khan AA, Mega MS, Small GW, Cummings JL, Toga AW (1998) Cortical variability and asymmetry in normal aging and Alzheimer's disease. *Cereb Cortex* **8**, 492-509.

[73] Amodeo S, Mainland BJ, Herrmann N, Shulman KI (2015) The times they are a-changin': Clock drawing and prediction of dementia. *J Geriatr Psychiatry Neurol* **28**, 145-155.

[74] Cuesta P, Garc P, Aurtenetxe S, Bajo R, Pineda-Pardo A, Bru R, Garc A (2015) Influence of the APOEε (4 allele and mild cognitive impairment diagnosis in the disruption of the MEG resting state functional connectivity in sources space. *J Alzheimers Dis* **44**, 493-505.

[75] Cuesta P, Barabash A, Aurtenetxe S, Garcés P, López ME, Bajo R, Llanero-Luque M, Ancín I, Cabranes JA, Marcos A, Sancho M, Nakamura A, Maestú F, Fernandez A (2015) Source analysis of spontaneous magnetoencephalograpic activity in healthy aging and mild cognitive impairment: Influence of apolipoprotein E polymorphism. *J Alzheimers Dis* **43**, 259-273.

[76] Jeong J (2004) EEG dynamics in patients with Alzheimer's disease. *Clin Neurophysiol* **115**, 1490-1505.

[77] de Haan W, Stam CJ, Jones BF, Zuiderwijk IM, van Dijk BW, Scheltens P (2008) Resting-state oscillatory brain dynamics in Alzheimer disease. *J Clin Neurophysiol* **25**, 187-193.

[78] Berendse H, Verbunt JP, Scheltens P, van Dijk B, Jonkman E (2000) Magnetoencephalographic analysis of cortical activity in Alzheimer's disease: A pilot study. *Clin Neurophysiol* **111**, 604-612.

[79] Osipova D, Ahveninen J, Jensen O, Ylikoski A, Pekkonen E (2005) Altered generation of spontaneous oscillations in Alzheimer's disease. *Neuroimage* **27**, 835-841.

[80] Chiaramonti R, Muscas GC, Paganini M, Müller TJ, Fallgatter AJ, Versari A, Strik WK (1997) Correlations of topographical EEG features with clinical severity in mild and moderate dementia of Alzheimer type. *Neuropsychobiology* **36**, 153-158.

[81] McKee AC, Au R, Cabral HJ, Kowall NW, Seshadri S, Kubilus CA, Drake J, Wolf PA (2006) Visual association pathology in preclinical Alzheimer disease. *J Neuropathol Exp Neurol* **65**, 621-630.