Neural Synchronization Abnormalities in Cognitive Impairment: A Comparative EEG Study of Alzheimer's and Parkinson's Diseases

Alessandro Bianchi, Luca Marconcini, Francesca Romana Pellegrino, Giovanni Luca Sannino

aDepartment of Neurological Sciences, University of Siena, Siena, Italy

Abstract. The aim of this retrospective and exploratory study was that the cortical sources of resting state eyes-closed electroencephalographic (rsEEG) rhythms might reveal different abnormalities in cortical neural synchronization in groups of patients with mild cognitive impairment due to Alzheimer's disease (ADMCI) and Parkinson's disease (PDMCI) as compared to healthy subjects. Clinical and rsEEG data of 75 ADMCI, 75 PDMCI, and 75 cognitively normal elderly (Nold) subjectswereavailableinaninternationalarchive.Age,gender,andeducationwerecarefullymatchedinthethreegroups.The Mini-Mental State Evaluation (MMSE) was matched between the ADMCI and PDMCI groups. Individual alpha frequency peak (IAF) was used to determine the delta, theta, alpha1, alpha2, and alpha3 frequency band ranges. Fixed beta1, beta2, and gamma bands were also considered. eLORETA estimated the rsEEG cortical sources. Receiver operating characteristic curve (ROC) classified these sources across individuals. Results showed that compared to the Nold group, the posterior alpha2 and alpha3 source activities were more abnormal in the ADMCI than the PDMCI group, while the parietal delta source activities were more abnormal in the PDMCI than the ADMCI group. The parietal delta and alpha sources correlated with MMSE score and correctly classified the Nold and diseased individuals (area under the ROC=0.77–0.79). In conclusion, the PDMCI and ADMCI patients showed different features of cortical neural synchronization at delta and alpha frequencies underpinning brain arousal and vigilance in the quiet wakefulness. Future prospective cross-validation studies will have to test these rsEEG markers for clinical applications and drug discovery.

Keywords: Exact low resolution brain electromagnetic source tomography, mild cognitive impairment due to Alzheimer's disease, mild cognitive impairment due to Parkinson's disease, receiver operating characteristic curve, resting state electroe

INTRODUCTION

Alzheimer's (AD) and Parkinson's (PD) diseases arethetwomostcommonneurodegenerativediseases of the brain inducing cognitive impairment, among other symptoms, and eventually dementia.

In the typical manifestation of PD, the disease onsetisfeaturedbymotorsymptomswithsubtlemild cognitive impairment while cognitive disorders can be observed soon after the disease onset in the majority of PD patients [1]. Cognitive deficits progress to dementia in up to 60% of PD patients [2–5]. AD and PDareduetoprogressiveneurodegenerativepathologies associated with an abnormal accumulation of proteins in the brain (i.e., $A_{1\text{-}42}$ extracellularly and phosphorylated tau protein and -synuclein intracellularly), causing axonal dysfunction, neuronal loss, and brain atrophy [6]. AD can be detected even in the prodromal stage of mild cognitive impairment (MCI) using cerebrospinal fluid (CSF) and positron emission tomography (PET) diagnostic biomarkers of $A_{1\text{-}42}$ and phospho-tau [7].

Disease monitoring of patients with MCI due to AD (ADMCI) and PD (PDMCI) is crucial since they have specific pathological causes and lesions and consequently require different treatments. This need boosts the development and validation of enhanced procedures to extract new clinical indexes and biomarkers. [8]. Among other biomarkers, resting state eyes-closed electroencephalographic (rsEEG) rhythms have extensively been studied as markers to assess the neurophysiological correlates of dementia [9–11]. These rsEEG markers are cost-effective, noninvasive, and non-stressful for patients. Although rsEEG rhythms are promising markers for a neurophysiological evaluation of the disease status and progression, they may not have an accurate diagnostic value. Indeed, rsEEG rhythms do not directly reflectthepeculiarpathophysiologicalmarkersofAD and PD. Rather, they may be part of the topographical markers, according to the definition given by Dubois and colleagues [8]. The topographic markers are not necessarily specific for the PDMCI

and ADMCI patients, but they can provide an index of the extent to which ADMCI and PDMCI patients show abnormalities in the structure and function of the brain across the disease progression and therapeutic intervention.

Several studies have investigated rsEEG rhythms as candidate topographical markers of AD and PD [12–16]. In those rsEEG studies, groups of AD and PD patients with dementia (ADD and PDD) were contrasted with normal elderly (Nold) subjects as controls. Compared to groups of Nold subjects, ADD groups showed high power in delta (<4Hz) and theta (4–7Hz)rhythmsinwidespreadcorticalregions[14], as well as low power in alpha (8–12Hz) and/or beta (13–20Hz) rhythms in posterior areas [12–14]. Furthermore, posterior alpha rhythms were markedly reduced in amplitude in ADD patients when compared with ADMCI subjects, whereas the opposite was true for slow EEG frequencies including delta and theta rhythms [12–14].

Furthermore, the PDD groups exhibited a spatial widespread slowing of the rsEEG rhythms, as represented by high delta and theta power compared to the Nold groups [15–24]. Compared with a PD group (normal cognition), the PDMCI and PDD groups exhibited lower alpha peak frequency, higher global delta and theta, and lower alpha and beta power density as surrogate markers of the cognitive status [25]. Moreover, the groups of ADD and PDD patients showed different spectral rsEEG markers. An early investigation reported similar abnormalities of posteriordeltapowerinADDandPDDsubjects[26],while the delta and the theta power averaged in the whole scalp (“global”) were greater in PDD patients than in ADD, PD, and Nold individuals [27]. It was posited that these effects were related to phosphorylation of -synuclein in the posterior cingulate cortex (hub of the default mode network), namely the higher the synuclein load, the higher the global delta, the lower the global alpha power, and the lower the frequency alpha peak [28]. Furthermore, previous rsEEG studies showed that the global delta power did fluctuate over a few minutes more in PDD than ADD patients [19, 29–31]. Moreover, the fluctuation of the occipital theta and alpha rhythms did characterize 46% of the PDD patients while it was negligible in the ADD patients [19].

To enhance the spatial analysis of the rsEEG rhythms in dementing disorders, we have recently developed and repeatedly applied an approach grounded on a freeware named low-resolution brain electromagnetic source tomography (LORETA), whichestimatesthersEEGsourcesincorticalregions of interest (ROIs). LORETA estimation unveiled a positive correlation between activities in the posterior cortical regional sources of low-frequency alpha rhythms (8–10.5Hz) and the global cognitive statusinNold,ADMCI,andADDsubjectsasawhole group; in contrast, that correlation was negative for occipital cortical sources of the delta rhythms [14, 32–34]. Compared to the groups of Nold and ADD subjects, the PPD group exhibited a higher activity in the central delta and posterior theta sources, besides a lower activity in the posterior beta sources [35]. Finally, the parieto-occipital alpha source activity was lower in the ADD than the PDD and Nold groups [35].Theseaboveresultsshoweddistinctspatial(e.g., anterior-posterior axis) and frequency features (e.g., delta to alpha) of the rsEEG rhythms associated with PDD and ADD when compared with those reported in physiological aging. However, they did not clarify if these features characterize the early stages of the diseases when the interaction of psychoactive pharmacological agents and secondary effects of dementia are negligible.

Keeping in mind the above considerations, one of the major challenges in the framework of dementing disorders is the understanding of the similarities and differences of the neurobiological and neurophysiological mechanisms underlying different neurodegenerative diseases such as AD, PD, dementia with Lewy body, frontotemporal dementia, etc. Another challenge is the understanding of the effects of the disease progression and pharmacological treatment on those particular mechanisms, particularly in theearlystagesofthediseases.Inthisvein,theaimof thisretrospectiveandexploratorystudywastotestthe hypothesis that the rsEEG (cortical) sources would disclose differences between groups of ADMCI and PDMCI patients, unveiling the spatial and frequency features of the cortical neural synchronization underlying brain arousal in the quiet wakefulness.

Diverse abnormalities in the rsEEG sources at the group level would unveil different clinical neurophysiological mechanisms in the two groups of patients. To evaluate this hypothesis, we estimated and compared the rsEEG sources in groups of PDMCI and ADMCI patients matched for cognitive status and demographicvariables.AgroupofNoldsubjectswas used as a reference control.

MATERIALSANDMETHODS

Subjects

In the present retrospective exploratory study, we used the rsEEG data of an international archive, formed by clinical, neuropsychological, and electrophysiological data in 75 Nold, 75 ADMCI, and 75 PDMCI subjects matched for relevant demographic variables. These subjects were recruited outside a formalmulticenterclinicaltrialbythefollowingqualifi edclinicalrecordingunitsoftheinformalEuropean PDWAIVE Consortium: University of Rome "La Sapienza" (Italy), IRCCS Fatebenefratelli of Brescia (Italy); IRCCS SDN of Naples (Italy); IRCCS Oasi of Troina (Italy); University of Genova (Italy); Hospital San Raffaele of Cassino (Italy); IRCCS Hospital San Raffaele Pisana of Rome (Italy); University "G. d'Annunzio" of Chieti and Pescara (Italy); General Hospital of Linz (Austria); Dokuz Eylul University (Turkey); Istanbul University (Turkey); and University of Basel (Switzerland).

The three groups were carefully matched for age, gender, and education. The ADMCI and PDMCI groups were also carefully matched for the MiniMental State Examination (MMSE) score [36].

Table 1 summarizes the relevant demographic and clinical (MMSE score) data of the Nold, ADMCI, and PDMCI groups, together with the results of the statistical analyses computed to evaluate the presence or absence of statistically significant differences between the groups for the age (ANOVA), gender (Kruskal-Wallis test), education (ANOVA), and MMSE score (Kruskal-Wallis test). As expected, a statistically significant difference was found among the Nold and the other two groups for the MMSE score (H=94.8; $p<0.00001$). Specifically, there was a higher MMSE score in the Nold than the ADMCI and PDMCI groups ($p<0.00001$). On the contrary, a statistically significant difference was found neither for the MMSE score between the ADMCI and the PDMCI group nor the age, gender, and education among the three groups ($p>0.05$).

Table 1

Mean values (±standard error mean, SE) of the demographic and clinical data and results of their statistical comparisons ($p<0.05$) in the groups of normal elderly (Nold) subjects and patients with mild cognitive impairment due to Alzheimer's disease (ADMCI) and Parkinson's disease (PDMCI)

	Nold	ADMCI	PDMCI	Statistical analysis
N	75	75	75	–
Age	70.1 (±0.8 SE)	70.1 (±0.7 SE)	71.2 (±0.8 SE)	ANOVA: n.s.
Gender (M/F)	36/39	34/41	38/37	Kruskal-Wallis: n.s.
Education	10.2 (±0.5 SE)	10.9 (±0.5 SE)	10.2 (±0.6 SE)	ANOVA: n.s.
MMSE	28.5 (±0.1 SE)	25.1 (±0.3 SE)	25.7 (±0.3 SE)	Kruskal-Wallis: (Nold>ADMCI, PDMCI) H=94.8, $p<0.00001$

MMSE, Mini-Mental State Evaluation; M/F, males/females; n.s., not significant ($p>0.05$).

Local institutional Ethics Committees approved the study. All experiments were performed with the informed and overt consent of each participant or caregiver, in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the local Institutional Review Board.

Diagnostic criteria

The inclusion criteria for the enrollment of the ADMCI patients were age between 55 and 90 years, complaints of memory deficits by the patient (and

confirmed by a relative) or a relative, MMSE score≥24, overall Clinical Dementia Rating [37] score of 0.5, score on the logical memory test [38] of 1.5 standard deviation (SD) lower than the ageadjusted mean, 15-item Geriatric Depression Scale (GDS) [39] score≤5, modified Hachinski ischemia [40] score≤4, and at least 5 years of education. The MCI status could be single or multidomain. The status of ADMCI was based on the positivity to one or more of the following biomarkers: A_{1-42}/phosphotau in the CSF, fluorodeoxyglucose PET (FDG-PET) mapping, and structural magnetic resonance imaging [41]. Exclusion criteria were other significant neurological, systemic or psychiatric illness, enrolment in a clinical trial with experimental drugs, the use of antidepressantdrugswithanticholinergicsideeffects, high dose of neuroleptics or chronic sedatives or hypnotics, antiparkinsonian medication, and the use of narcotic analgesics. Of note, the use of cholinesterase inhibitors and memantine was allowed.

All ADMCI subjects underwent a battery of neuropsychological tests to evaluate the status of MCI. This battery included neuropsychological tests assessing the general cognitive performance in the domains of memory, language, executive function/attention, and visuoconstruction abilities. Specifically, the tests assessing memory included the delayed recall of Rey figures [42] and/or the delayed recall of a story [43]. The tests assessing language included the 1-min verbal fluency for letters, fruits, animals, or car trades [44], and/or the Token test [43].Thetestsassessingexecutivefunctionandattentio n included the Trail Making Test Part A and B [45]. Finally, the tests assessing visuoconstruction included the copy of Rey figures.

The diagnosis of PD was based on a standard clinical assessment of tremor, rigidity, bradykinesia, and postural instability without major cognitive deficits for 12 months [46]. As measures of severity of the motor disability, the Hoehn and Yahr stage [47], and the Unified Parkinson Disease Rating Scale-III [48] for extrapyramidal symptoms, were used. The diagnosis of PDMCI was based on the Diagnostic Criteria for Mild Cognitive Impairment in Parkinson's Disease [49]. The inclusion criteria comprised: (1) a diagnosis of PD as based on the UK PD Brain Bank Criteria [46]; (2) a gradual decline, in the context of an established PD, in the cognitive status reported by either the patient or informant, or observed by the clinicians; (3) cognitive deficits not sufficient to interfere significantly with functional independence in the activities of the daily life, although slight difficulties on complex functional tasks may be present. Onthebasisofclinicalfeaturesandneuroradiological findings, the exclusion criteria for PDMCI included the following forms of parkinsonism: (1) dementia with Lewy bodies [50–52], (2) drug-induced parkinsonism, (3) cerebrovascular parkinsonism, and (4) atypical parkinsonism with absent or minimal responses to antiparkinsonian drugs.

All PDMCI subjects underwent a battery of clinical scales including the Neuropsychiatric Inventory [53], the scale for the assessment of Behavioral and Psychological Symptoms of Dementia, the MMSE, the Dementia Rating Scale-2 [54], the Epworth Sleepiness Scale for estimating subjective sleep disturbances, and the Alzheimer's Disease Cooperative Study for the Activities of Daily Living. All PDMCI subjects also underwent a battery of neuropsychological tests to evaluate the status of MCI. This battery included neuropsychological tests assessing the general cognitive performance in the domains of memory, language, executive function/attention, and visuoconstruction abilities (some of them received the CERAD-plus battery).

All Nold subjects underwent a cognitive screening (including MMSE and GDS) as well as physical and neurological examinations to exclude any dementia or major cognitive deficit. No Nold subject referred subjectivecognitiveimpairment.Subjectsaffectedby chronic systemic illnesses (e.g., diabetes mellitus) were excluded, as were subjects receiving chronic psychoactive drugs. Subjects with a history of previous or present neurological or psychiatric disease were also excluded. All Nold subjects had a GDS score lower than the threshold of 5 (no depression) or no depression after an interview with a physician or clinical psychologist.

EEG recordings

EEG data were recorded while the subjects were sitting comfortably with eyes closed in a standard

resting state condition (rsEEG). At least 5min of rsEEG data were recorded (128Hz or higher sampling rate, with a bandpass between 0.01Hz and 100Hz) from a minimum number of 19 exploring scalp electrodes positioned over the whole scalp according to the 10–20 System (i.e., Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6,O1,andO2;seeFig.1).Morespecifically,18subjects out of 225 were recorded at 128Hz, 3 subjects at 200Hz,19subjectsat250Hz,122subjectsat256Hz, 31 subjects at 500Hz, 24 subjects at 512Hz, and 8 subjects at 1000Hz. Linked earlobe reference electrode was preferred, but not mandatory to respect the methodological facilities and standard internal protocols of the clinical recording units (137 subjects out of225subjectswererecordedwithlinkedearloberefere nce, while the others with cephalic reference). A ground electrode was typically located between the AFz and Fz electrodes, and electrodes impedances were kept below 5 Kohm. Horizontal and vertical electro-oculographic activities (0.3–70Hz bandpass) werealsorecordedtomonitorblinkingandeyemoveme nts. The EEG recordings were performed, in all subjects, in the late morning to minimize drowsiness. Furthermore, an operator controlled on-line the subject and the EEG traces to keep constant the level of vigilance.

Preliminary analysis of the EEG data

The recorded rsEEG data were band-passed to avoid aliasing, down-sampled to 128Hz (when recorded with higher sampling frequency), segmented in consecutive 2-s epochs, and analyzed off-line. We rejected the rsEEG epochs associated with operator's markers indicating drowsiness, verbal warnings, eyes opening, arm/hand movements, or other events (e.g., sweat, sway, head movements, etc.) disturbing the EEG recordings. Furthermore,

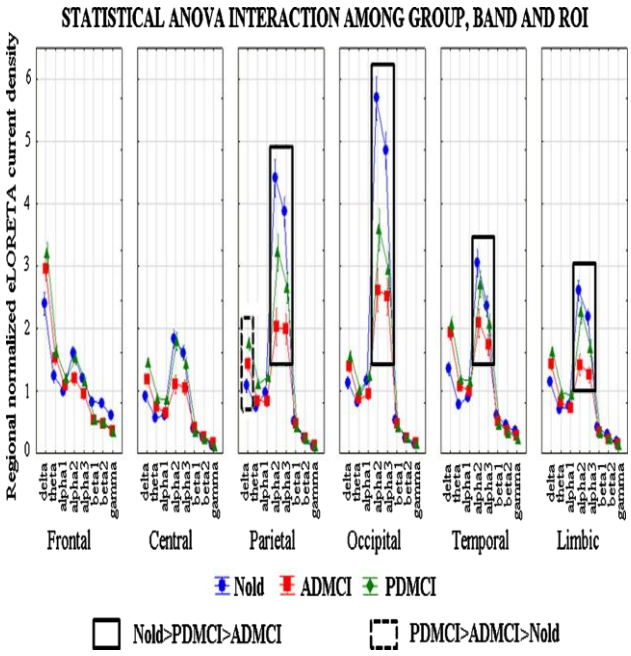

Fig. 1. Regional normalized eLORETA solutions (mean across subjects) of the interaction between the factors Group (Nold, ADMCI, PDMCI), Band (delta, the and ROI (central, frontal, parietal, occipital, temporal, limbic). This ANOVA des a dependent variable. Subjects' transition frequency (TF) and individual alpha normalized eLORETA solutions modeled the cortical sources of the rsEEG rela can be considered as a sort of "virtual" intracranial macro-electrodes located on th a definition of the TF and IAF. Legend: the rectangles indicate the cortical regior presented statistically significant eLORETA patterns as in the following: Nold =/

the rsEEG epochs with ocular (e.g., rapid eye opening despite the request to maintain the eyes closed), muscular, and other types of artifacts were preliminarily identified by an automatic computerized procedure.ThersEEGepochswithsporadicandwellsha ped blinking artifacts were corrected from the EOG activity by an autoregressive method [55]. Two independent experimenters, blind to the diagnosis at the time of the rsEEG analysis, manually revised the rsEEG epochs accepted for further analysis. The rsEEG epochs with signs of a sleep intrusion (an ongoing increase of theta, K complex, spindles, etc.) wererejected.ToharmonizethersEEGdatacollected with different reference electrodes, all artifact-free rsEEG epochs were re-referenced to the common average for further analysis.

Spectral analysis of the rsEEG epochs

AstandarddigitalFFT-basedpowerspectrumanalysis(Welchtechnique,Han

ningwindowingfunction, no phase shift) computed the power density of the 2s rsEEG epochs with 0.5Hz of frequency resolution.
This standard FFT procedure was implemented by a home-made software developed under Matlab 6.5 (Mathworks Inc., Natick, MA).

According to a previous study of our group [56], the frequency bands of interest were individually identified based on the following frequency landmarks: the transition frequency (TF) and the individual alpha frequency peak (IAF). In the EEG power density spectrum, the TF marks the transition frequency between the theta and alpha bands, defined as the minimum of the rsEEG power density between 3 and 8Hz (between the delta and the alpha power peak). Instead, the IAF is defined as the maximum power density peak between 6 and 14Hz. In precedence, these frequency landmarks were well described by Dr. Wolfgang Klimesch and his workgroup [57–59].

The TF and IAF were computed for each subject involved in the study. Based on the TF and IAF, we estimated the frequency band range for each subject as follows: delta from TF -4Hz to TF -2Hz, theta fromTF-2HztoTF,low-frequencyalphaband(alpha 1 and alpha 2) from TF to IAF, and high-frequency alpha band (or alpha 3) from IAF to IAF+2Hz. The other bands were defined based on standard fixed frequency ranges: beta 1 from 14 to 20Hz, beta 2 from 20 to 30Hz, and gamma from 30 to 40Hz. The alpha 1 and alpha 2 bands were computed for each subject as follows: alpha 1 from TF to the midpoint of the TF-IAF range and alpha 2 from this midpoint to IAF.

Cortical sources of rsEEG epochs as computed by eLORETA

We used the freeware called “exact LORETA” (eLORETA) for the linear estimation of the cortical sources activity of rsEEG rhythms [60]. It represents the improved version of the previous pieces of software called LORETA [61] and standardized LORETA [62]. Both standardized LORETA and eLORETA showed the same low spatial resolution, with zero localization error in the presence of measurement and biological noise [60, 62]. However, eLORETA exhibited a better source location in some control parameters [63].

The present implementation of eLORETA uses a head volume conductor model composed of the scalp, skull, and brain. In the scalp compartment, exploring electrodes can be virtually positioned to give EEG data as an input to the source estimation [64]. The brain model is based on a realistic cerebral shape taken from a template typically used in the neuroimaging studies, namely that of the Montreal Neurological Institute (MNI152 template) [65].

The electrical brain source space is formed by 6,239 voxels with 5mm resolution, restricted to cortical gray matter [66]. An equivalent current dipole is located in each voxel. The eLORETA solves the socalled EEG inverse problem in the mentioned head volume conductor model estimating “neural” current densityvaluesatanycorticalvoxelforeachfrequency bin. Input for this regularized inverse estimation [62] is the EEG spectral power density computed at all virtual scalp electrodes.

In line with the general low spatial resolution of the present EEG methodological approach (i.e., 19 scalp electrodes), the eLORETA solutions were averaged across all voxels in a given cortical ROI. The following six ROIs were considered: frontal, central, parietal,occipital,temporal,andlimbic.Table2specifies the Brodmann areas (BAs) included in any ROI. For the present eLORETA cortical source estimation, a frequency resolution of 0.5Hz was used, namely, the maximum frequency resolution allowed by the use of 2-s artifact free EEG epochs. The

Table 2
Regions of interest (ROIs) used for the estimation of the cortical sources of the resting state eyes-closed electroencephalographic (rsEEG) rhythms in the present study. Any ROI is defined by some Brodmannareasofthecerebralsourcespaceinthefreewareusedin this study, namely the exact low-resolution brain electromagnetic source tomography (eLORETA)

Frontal	8, 9, 10, 11, 44, 45, 46, 47
Central	1, 2, 3, 4, 6
Parietal	5, 7, 30, 39, 40, 43
Temporal	20, 21, 22, 37, 38, 41, 42
Occipital	17, 18, 19
Limbic	31, 32, 33, 34, 35, 36

frequency bands of interest were delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma, defined subject-by-subject as described above.

Statistical analysis of the eLORETA solutions

A statistical session was performed by the commercial tool STATISTICA 10 (StatSoft Inc., http://www.statsoft.com) to test the hypothesis that the rsEEG source activity as revealed by eLORETA solutions would differ between the ADMCI and PDMCI groups using the Nold group as a control reference. To this aim, an ANOVA was computed using the regional normalized eLORETA solutions (normalized current density at all voxels of a given ROI) as a dependent variable (p<0.05). The ANOVA factors were Group (Nold, ADMCI, PDMCI), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). Subjects' TF and the IAF were used as covariates. Mauchly's test evaluated the sphericity assumption. The degrees of freedom were corrected by the Greenhouse-Geisser procedure when appropriate. Duncan test was used for *post-hoc* comparisons (p<0.05).

The planned *post-hoc* testing also evaluated the above prediction about the differences in the rsEEG source solutions between the ADMCI and PDMCI groups using the Nold group as a control reference. Specifically, we predicted: (i) a statistical 3-way interaction effect including the factors Group, ROI, and Band (p<0.05); (ii) a *post-hoc* test indicating statistically significant differences of the regional normalized eLORETA solutions with the pattern Nold =/ ADMCI =/ PDMCI (Duncan test, p<0.05).

The above statistical analyses were controlled by the Grubbs test (p<0.005) for the presence of outliers in the distribution of the eLORETA source solutions.

Accuracy of the rsEEG source activity in the discrimination among the Nold, ADMCI, and PDMCI individuals

The rsEEG sources showing the highest statistically significant differences among the three groups were used as discriminant (not diagnostic as the abnormalities in those sources were not necessarily disease-specific) variables for the following classification trials: (1) the Nold versus the ADMCI individuals; (2) the Nold versus the PDMCI individuals; and (3) the ADMCI versus PDMCI individuals. The correct blind classifications of these rsEEG source activities were performed by GraphPad Prism software (GraphPad Software, Inc., California, USA) for the production of the receiver operating characteristic (ROC) curves [67]. The following indexes measured the classification performance of the above binary classification: (1) Sensitivity - measures the rate of the positives who were correctly classified as positives (i.e., "true positive rate" in the signal detection theory); (2) Specificity - measures the rate of the negatives (control) who were correctly classified as negatives (i.e., "true negative rate" in the signal detection theory); (3) Accuracy - the mean between the sensitivity and specificity (the amount of subjects in the groups was the same); and (4) Area under the ROC curve (AUROC) - another standard index of the global classification accuracy.

RESULTS

Statistical analysis of the EEG cortical sources

Table 3 reports the mean values of the TF and IAF for the three groups (i.e., Nold, ADMCI, and PDMCI), together with results of the statistical comparisons between the group pairs (ANOVA). The mean TF was 6.0Hz (±0.1 standard error mean, SE) in the Nold subjects, 5.4Hz (±0.2 SE) in the ADMCI subjects, and 5.3Hz (±0.1 SE) in the PDMCI subjects. The mean IAF was 9.3Hz (±0.1 SE) in the Nold subjects, 8.8Hz (±0.2 SE) in the ADMCI patients, and 8.3Hz (±0.2 SE) in the PDMCI patients. ANOVAs were computed to evaluate the presence or absence of statistically significant differences between the three groups for both TF and IAF (p<0.05). The results showed the following statistically significant effects: (1) the mean TF was greater (F=7.7, p<0.0005) in the Nold than the ADMCI (p<0.005) and PDMCI (p<0.0005) groups; (2) the mean IAF was greater (F=11.2, p<0.00005) in the Nold than the ADMCI (p<0.01) and PDMCI (p<0.00005) groups. It was also higher in the ADMCI than the PDMCI group

(p<0.05).

Figure 1 shows the grand average of the regional eLORETA solutions for the rsEEG source estimation relative to a statistically significant ANOVA interaction effect (F=11.9; p<0.00001) among the factors Group (Nold, ADMCI, PDMCI), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma), and ROI (frontal,central,parietal,occipital,temporal,limbic).

The TF and the IAF were used as covariates. In the figure, the eLORETA solutions had the shape of typical rsEEG relative power spectra. Notably, the profile and magnitude of the rsEEG source activity spectra in the Nold, ADMCI, PDMCI groups differed across the ROIs, supporting the idea that the scalp EEG rhythms were generated by a distinct pattern of cortical source activity in those groups. The Duncan planned*post-hoc*testingshowedthatthediscriminant source pattern ADMCI<PDMCI<Nold was fitted by the posterior (i.e., parietal, occipital, temporal, and limbic) alpha 2 and alpha 3 sources (p<0.05 to p<0.000001). Compared to the Nold group, these posterior alpha source activities showed an abnormal reduction in the ADMCI and PDMCI groups (p<0.05 to p<0.000001). Furthermore, they were lower in the ADMCI than the PDMCI group (p<0.01 to p<0.000001). Of note, 10 ADMCI and 7 PDMCI subjects exhibited an asintotic rsEEG power spectra without alpha peak. On the contrary, the pattern PDMCI>ADMCI>Nold was fitted by the parietal

Table 3

Mean values (± SE) of the transition frequency (TF) and the individual alpha frequency peak (IAF) of the rsEEG power density spectra for the three groups (i.e., Nold, ADMCI, PDMCI). The table also reports the p values of the statistical comparisons of these values between the Nold, ADMCI, PDMCI groups. See the Methods for a definition of the TF and IAF

	Nold	ADMCI	PDMCI	Statistical analysis
TF	6.0 (±0.1 SE)	5.4 (±0.2 SE)	5.3 (±0.1 SE)	F=7.7, p<0.0005 (PDMCI, ADMCI<Nold)
IAF	9.3 (±0.1 SE)	8.8 (±0.2 SE)	8.3 (±0.2 SE)	F=11.2, p<0.00005 (PDMCI<ADMCI<Nold)

Table 4

Results of the classification among Nold, ADMCI, and PDMCI individuals based on the rsEEG source activities. These source activities were those showing statistically significant differences among the three groups in the main statistical analysis (i.e., Nold, ADMCI, PDMCI). The classification rate is computed by the analysis of the area under the receiver operating characteristic (AUROC) curve. The table the classification indexes (Sensitivity, Specificity, Accuracy) for all the rsEEG source activities having a value higher than 0.70 in the AUROC curves. Highlighted in red type are the best classification results for each rsEEG source of interest

eLORETA source activity	Sensitivity	Specificity	Accuracy	AUROC
Nold versus ADMCI				
Parietal alpha 2	73.3%	65.3%	69.3%	0.75
Occipital alpha 2	72.0%	68.0%	70.0%	0.77
Limbic alpha 2	77.3%	69.3%	73.3%	0.74
Parietal alpha 3	72.0%	66.7%	69.3%	0.74
Occipital alpha 3	80.0%	58.7%	69.3%	0.74
Limbic alpha 3	73.3%	66.7%	70.0%	0.72
Parietal delta/alpha2	**70.7%**	**74.7%**	**72.7%**	**0.79**
Parietal delta/alpha 3	69.3%	69.3%	69.3%	0.77
Nold versus PDMCI				
Parietal delta	73.3%	68.0%	70.7%	0.76
Parietal delta/alpha2	77.3%	68.0%	72.7%	0.75
Parietal delta/alpha 3	**72.0%**	**73.3%**	**72.7%**	**0.77**

delta sources (p<0.05 to p<0.005). Compared to the Nold group, the parietal delta source activities pointed to an abnormal increment in the ADMCI and PDMCI groups (p<0.05 to p<0.005). Furthermore, they were greater in the PDMCI than the ADMCI group (p<0.05).

A control statistical analysis (Grubbs' test, p<0.005) was performed to verify that the intergroup differences in the above nine rsEEG source activities (i.e., parietal delta; parietal, occipital, temporal, and limbic alpha 2; parietal, occipital, temporal, and limbic alpha 3) were not merely due to the presenceofsomeoutliersintheindividualeLORETA solutions. No outlier was detected (see Fig. 2), thus confirming the results of the main statistical analysis.

Correlation between the rsEEG source activity and MMSE

As a first analysis on the clinical relevance of the main results, Spearman test evaluated the correlation between the above nine rsEEG source activities (i.e., parietaldelta;parietal,occipital,temporal,andlimbic alpha2;parietal,occipital,temporal,andlimbicalpha 3) and the MMSE score across all Nold, ADMCI, and PDMCI individuals as a whole group (p<0.05). A statistically significant negative correlation was found between the activity of the parietal delta source and the MMSE score (r=–0.18, p<0.005; Fig. 3). Thehighertheparietaldeltasourceactivity,thelower the MMSE score. Furthermore, a statistically significant positive correlation was found between the activity of the parietal alpha 2 (r=0.24, p<0.0005), occipital alpha 2 (r=0.30, p<0.000005), temporal alpha 2 (r=0.17, p<0.01), limbic alpha 2 (r=0.23, p<0.001),theparietalalpha3(r=0.28,p<0.00001), occipital alpha 3 (r=0.32, p<0.000001), temporal alpha 3 (r=0.19, p<0.005), limbic alpha 3 (r=0.26, p<0.0001).

Classification among Nold, ADMCI, and PDMCI individuals based on rsEEG source activity

As a second analysis on the clinical relevance of the main results, the above nine rsEEG source activities (i.e., parietal delta; parietal, occipital, temporal, and limbic alpha 2; parietal, occipital, temporal, and limbic alpha 3) served as discriminant input variables for the computation of the AUROC curves. These AUROC curves aimed at indexing the classification accuracy in the discrimination among the Nold, ADMCI, and PDMCI individuals. Additional discriminant variables were obtained by computing the ratio between (1) the parietal delta and alpha 2 source activity and (2) the parietal delta and alpha 3 source activity. The results were reported in detail in Table 4 and Fig. 4.

Regarding the classification of the Nold versus ADMCI subjects, the following 8 rsEEG markers overcome the threshold of 0.7 of the AUROC curve, defined as a "moderate" classification rate (Table 4): parietal alpha 2, occipital alpha 2, limbic alpha 2, parietalalpha3,occipitalalpha3,limbicalpha3,parietal delta/alpha 2, and parietal delta/alpha 3 source activities. Among these rsEEG markers, the parietal delta/alpha 2 source activity reached the following best classification rate (Fig. 4 top): a sensitivity of 70.7%, a specificity of 74.7%, an accuracy of 72.7%, and 0.79 of the AUROC curve.

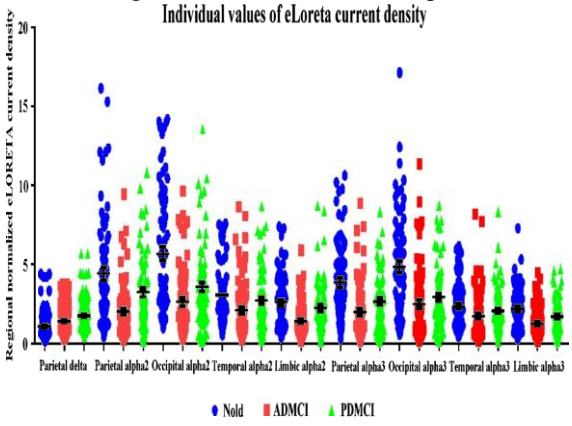

Fig. 2. Individual values of the eLORETA cortical source activity showing statist
ADMCI, and PDMCI groups in the main statistical analysis (i.e., parietal delta; p
sources; see Fig. 1 for the specific rsEEG source activities showing statistical sig
no outliers from those individual values of the eLORETA solutions (arbitrary thr

Concerning the classification of the Nold versus PDMCI subjects, the following 3 rsEEG markers overcome the threshold of 0.7 of the AUROC curve (Table 4): parietal delta, parietal delta/alpha 2, and parietal delta/alpha 3 source activities. Among these rsEEG markers, the parietal delta/alpha 3 eLORETA source activities reached the following best classification rate (Fig. 4 bottom): the sensitivity of 72%, the specificity of 73.3%, the accuracy of 72.7%, and 0.77 of the AUROC curve.

Unfortunately, these rsEEG markers did not produce a substantial classification accuracy (>0.7 of the
AUROC curve) between the ADMCI and PDMCI subjects.

Control analysis

As previously reported, we defined the frequency bands from delta to alpha on an individual basis using the TF and IAF as landmarks. This determination of the individual frequency bands allowed taking into account the fact that the mean IAF was slower in frequency: (i) in the current ADMCI (8.8Hz) and PDMCI (8.3Hz) groups than the Nold (9.3Hz) group and (ii) in the PDMCI than the ADMCI group. The impact of this methodological option was tested with a control analysis aimed at evaluating the difference of the rsEEG source activity (eLORETA solutions) among the Nold, ADMCI, and PDMCIgroupsusingstandardfixedfrequencybands.
The procedure is reported in the following. Firstly, we selected the standard fixed frequency bands in line with previous field studies of our research group [14, 32–35], namely delta (2–4Hz), theta (4–8Hz), alpha1 (8.5–10Hz), alpha2 (10.5–13Hz), beta1 (13.5–20Hz), beta2 (20–30Hz), and gamma (30–40Hz). Secondly, eLORETA solutions using the following fixed frequency bands were computed. Thirdly,anANOVAwascomputedusingtheregional normalized eLORETA solutions as a dependent variable (p<0.05). The ANOVA factors were Group (Nold, ADMCI, PDMCI), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). Results of this analysis are reported inFig.5illustratingastatisticallysignificantANOVA interaction effect among the factors Group, Band, and ROI (F=9.1; p<0.00001). The Duncan planned *post-hoc* testing showed that the discriminant source pattern ADMCI<PDMCI<Nold was fitted by the parietal and limbic alpha 2 sources (p<0.0005). Furthermore, these sources were lower in the ADMCI than the PDMCI group (p<0.01). Moreover, compared to the Nold and ADMCI groups, the PDMCI group was characterized by an abnormal increase of the parietal theta sources (p<0.02). Keeping in mind that the PDMCI group was characterized by a more apparent slowing of the IAF compared to the Nold and ADMCI groups (p<0.01), a reasonable explanation is that the above abnormal increase of the theta sources in the PDMCI group was due to the frequency slowing of the alpha rhythms. When

SCATTERPLOT BETWEEN eLORETA SOURCE ACTIVITY VS. MMSE SCORE ACROSS ALL SUBJECTS

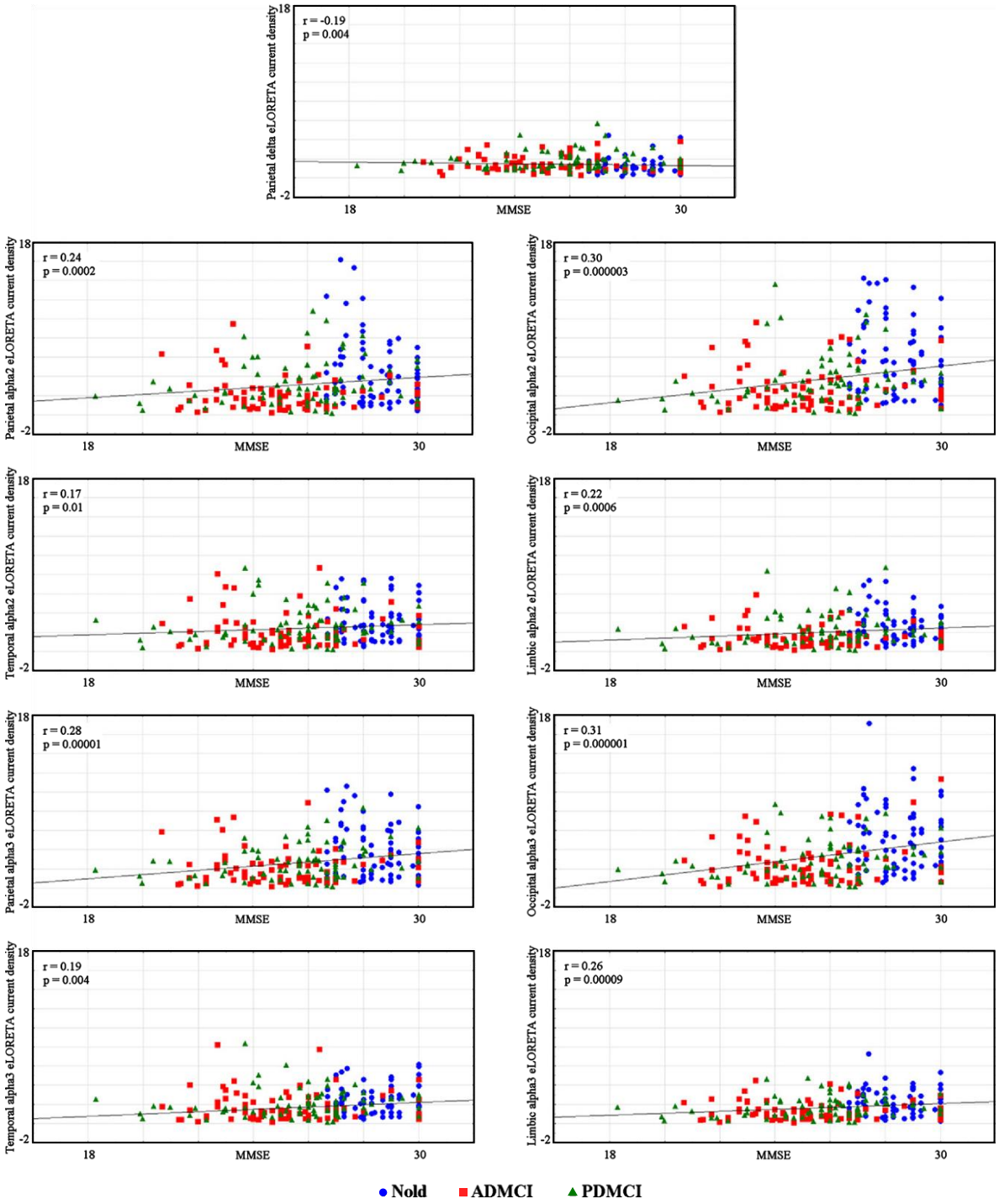

Fig. 3. Scatterplots showing the correlation between (eLORETA) source activity of the rsEEG rhythms and the MMSE score in the Nold, ADMCI, and PDMCI subjects as a whole group. The Spearman test evaluated the hypothesis of a correlation these rsEEG and MMSE variables (p<0.05). The r and p values are reported within the diagram.

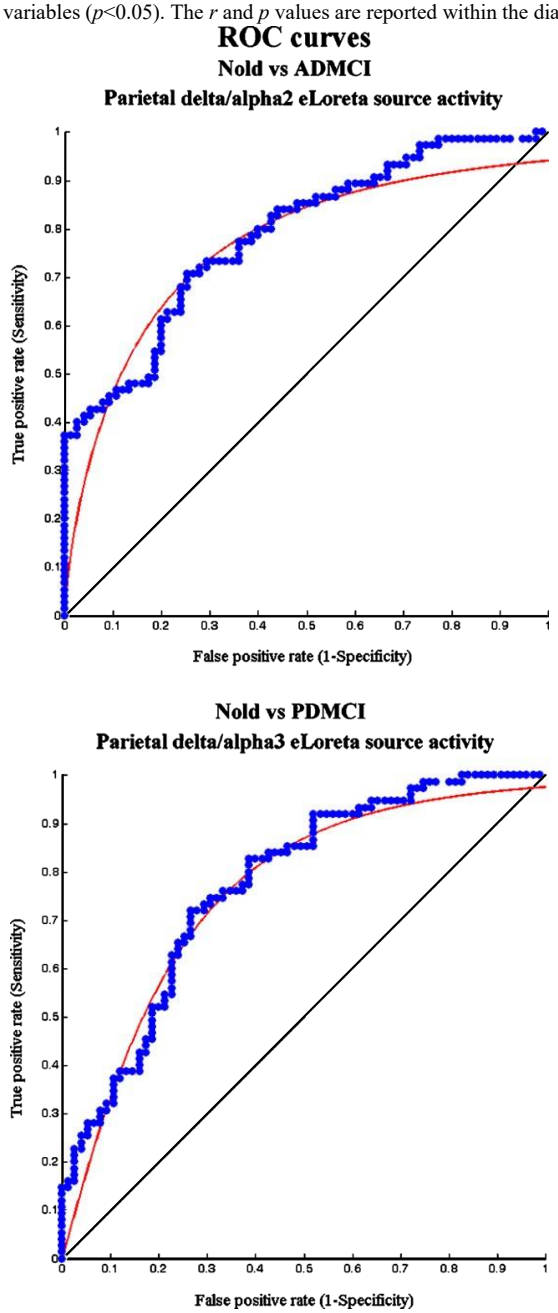

Fig. 4. (Top): Receiver operating characteristic (ROC) curves illustrating the classification of the ADMCI and Nold individuals based on the parietal delta/alpha 2 (eLORETA) source activity. The area under the ROC (AUROC) curve was 0.79 indicating a moderate classification accuracy of the ADMCI and Nold individuals. (Bottom): ROC curves illustrating the classification of the PDMCI and Nold individuals based on the parietal delta/alpha 3 (eLORETA) source activity. The AUROC curve was 0.77 indicating a moderate classification accuracy of the PDMCI and Nold individuals. Of note, the true positive rate shows the probability of the correct classification of the MCI subjects (sensitivity), whereas the false positive rate indicates the probability of the incorrect classification of the Nold individuals (1-specificity).

this slowing was taken into account by the individual frequency bands (see the main data analysis of this study), the ADMCI group did not show the abnormal increaseofthethetasources.Theresultsofthepresent control analysis lead support to the use of individual frequency bands in the comparison of the rsEEG sources between the present PDMCI and ADMCI groups.

DISCUSSION

Thisretrospectiveandexploratorystudyonarchive data preliminarily tested the hypothesis that the rsEEG source mapping would unveil different spatial and frequency features of the cortical neural synchronization in two major neurodegenerative dementing disorders at the prodromal stage of MCI such as ADMCI and PDMCI. To evaluate this exploratory hypothesis, we compared cortical rsEEG sources in two groups of ADMCI and PDMCI patients matched for cognitive status (MMSE score) and demographic variables. Furthermore, a group of Nold subjects served as a control group. An assumption is that diverse abnormalities in the rsEEG sources at the grouplevelwouldunveildifferentclinicalneurophysiol ogical mechanisms in the two groups of patients. As a methodological advancement, we defined the frequency bands from delta to alpha on an individual basis using the TF and IAF as landmarks (see Methods for further details). The individual TF allowed marking the transition between the theta and alpha bands in the individual rsEEG source spectra while IAF did define the transition between the lowand high-frequency sub-bands of the alpha rhythms [56–59]. This determination of the individual frequency bands allowed taking into account the fact that on average, the IAF was slower in frequency: (i) in the current ADMCI (8.8Hz) and

PDMCI (8.3Hz) groups than the Nold (9.3Hz) group and (ii) in the PDMCI than the ADMCI group. In this case, the use of the standard alpha 1 (8–10/10.5Hz) and alpha 2 (10–12/13Hz) sub-bands would have produced differences in the source activity between the ADMCI and PDMCI groups merely due to the slowing of the IAF in the latter group. Of note, the low-frequency alpha (alpha 1 and alpha 2) rhythms would be mainly related to a subject's global attentional readiness, whereas the high-frequency alpha (alpha 3) rhythms would reflect the oscillation of specific neural systems for the elaboration of sensorimotor or semantic information [57–59].

lower in the ADMCI group than the PDMCI group. In the same vein, the parietal delta source activity showedaninterestingdifferenceamongthosegroups. About the Nold group, the ADMCI and PDMCI groups exhibited an abnormally higher activity in those sources. As another novel finding, this source activity was greater in the PDMCI group than the ADMCI group. Noteworthy, a clinically relevant evidence was that these source activities exhibited a correlation with the MMSE score (roughly reflecting global cognitive status) across all Nold, ADMCI, and PDMCI subjects as a whole population.

The present results extend to source space and

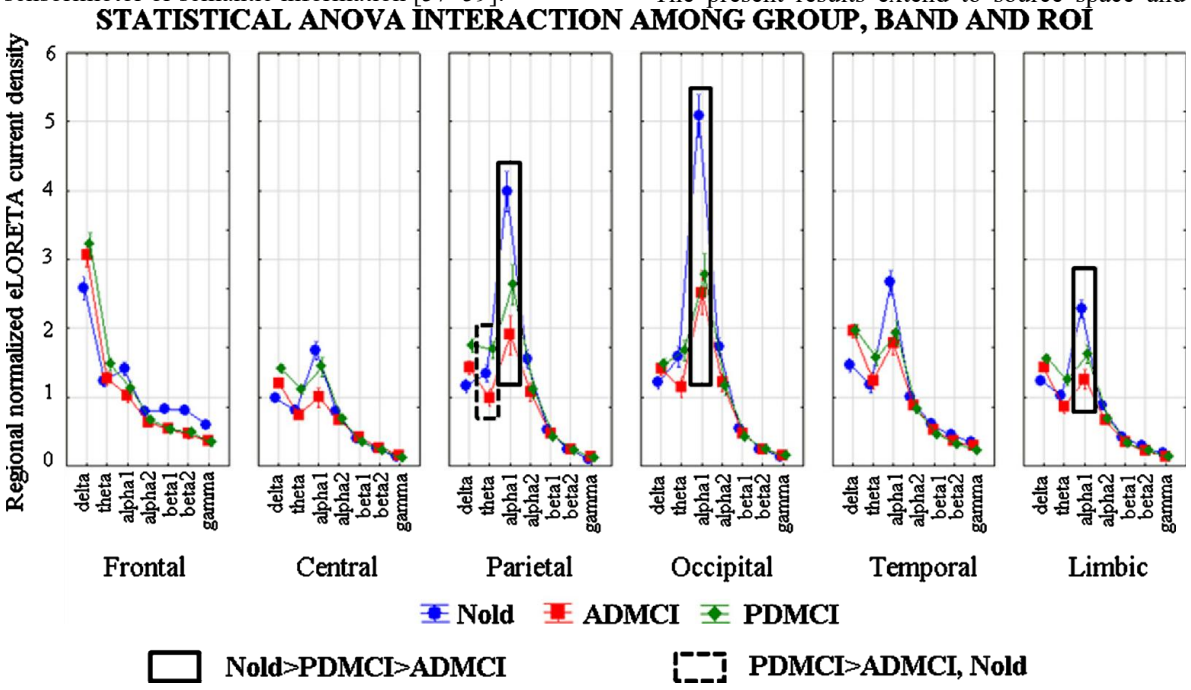

Fig. 5. Regional normalized eLORETA solutions (mean across subjects) of the rsEEG rhythms relative to a statistical 3-way ANOVA interaction between the factors Group (Nold, ADMCI, PDMCI), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2 and gamma), and ROI (central, frontal, parietal, occipital, temporal, limbic). The following standard fixed frequency bands were considered: delta (2–4 Hz), theta (4–8 Hz), alpha1 (8.5–10 Hz), alpha2 (10.5–13 Hz), beta1 (13.5–20 Hz), beta2 (20–30 Hz), and gamma (30–40 Hz). This ANOVA design used the regional normalized eLORETA solutions as a dependent variable. Legend: the rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions presented statistically significant eLORETA patterns (Duncan *post hoc* test, $p<0.05$) as in the following: Nold =/ ADMCI =/ PDMCI; Nold, ADMCI =/ PDMCI.

The rsEEG markers showing differences between the Nold, ADMCI, and PDMCI groups

ComparedwiththeNoldgroup,theposterior(parietal , occipital, temporal and limbic) source activity of the individual low-frequency alpha (i.e., alpha 2) and high-frequency alpha (i.e., alpha 3) rhythms was abnormally lower in both the ADMCI and PDMCI groups. As a novel finding, this source activity was

individually-determined frequency bands previous EEG evidence reported in groups of ADD and PDD patients [15, 16, 20, 68–72]. It has been shown a greater power in the posterior delta and theta rsEEG rhythms in groups of PDD patients when compared with those of ADD individuals [29, 73]. This effect was also described as an occipital "pre-alpha" peak in the rsEEG power spectrum [20]. Furthermore, previous EEG and MEG findings reported a greater

power in the delta and theta rhythms and a lower alpha and beta power in groups of PDD than those of non-demented PD patients [15, 16, 74]. However, an increment of the delta and theta power was found in PD patients with no dementia as well, so that these rsEEG features could be partially unspecific in the explanation of the cognitive decline along the disease evolution [35, 75]. Finally, the present findings complement those of Bonanni and colleagues [19] unveiling more fluctuation in the occipital delta and theta rhythms in PDD patients than the ADD individuals, even at the MCI stage [71].

What are the neurophysiological mechanisms underlying these rsEEG abnormalities in the groups of ADMCI and PDMCI patients? It can be speculated that in the quiet wakefulness, the abnormal increase in magnitude of cortical delta rhythms is caused by an altered interaction between cortical pyramidal and thalamic neural populations, which could induce a dysfunctional connectivity and partial isolation of cortical generators of these rhythms [58, 76, 77]. The relationship between such a functional isolation and the increase of delta rhythms in AD patients would be suggested by a concomitant reduction of regional cortical blood perfusion and metabolism [78–86], as well as the atrophy of the cortical gray matter and the hippocampus [34, 87, 88]. Keeping in mind the above data and considerations, the present findings in the delta cortical sources would suggest a frontal and parietal localization of these abnormalities in the early stages of both AD and PD with cognitive deficits.

Concerning the present patients' abnormalities in theposterioralphasources,wecanspeculatethatthey reflect an alteration of a complex neurophysiological network regulating the cortical arousal, the generation of alpha rhythms, and the vigilance in the quiet wakefulness [89–91]. In physiological conditions, this network controls the interplay of thalamocortical high-threshold and relay-mode neurons, GABAergic interneurons, and cortical pyramidal cells [89–91]. The main role of that network may be the production of cycles of excitation and inhibition around 70–100ms in thalamic and cortical neurons [89–91]. During the active processing of sensorimotor information,thesecyclesmightframeperceptualevents in discrete snapshots and would ensure the selectivity of that processing [89–91]. According to that neurophysiological model, the prominent occipital and parietal localization of the alpha abnormalities in the present ADMCI and PDMCI subjects would predict an alteration of visuospatial attentional processes, may be related to altered inputs from cholinergic basal forebrain to the visual cortex.

The rsEEG markers showing accurate classifications between Nold versus ADMCI and PDMCI individuals

Another clinically relevant evidence of the present study was the moderate classification accuracy of the individual patients with MCI based on rsEEG sources. Here we reported an accuracy (e.g., AUROC curve) of 79% in the classification of the Nold versus the ADMCI individuals, based on the ratio between the parietal delta and alpha 2 source activity. Furthermore, the ratio between the parietal delta and alpha 3 source activity allowed an accuracy of 77% in the classification of the Nold versus the PDMCI individuals. Concerning the classification of Nold versus ADD and PDD individuals, the present discrimination with 77–79% of success was intermediate when compared with previous field studies classifying Nold versus ADD and PDD individuals. The discrimination of Nold versus ADD individuals was 94–45%, that of ADMCI versus ADD individuals was 92–78%, and the conversion from ADMCI to ADD status showed 87–60% of accuracy [13, 92–102]. The discrimination of Nold versus PDD individuals was 90–95% [102, 103].

In the present study, the classification accuracy was not substantial between the ADMCI and PDMCI patients. At the present stage of the research, we can only conclude that the present topographical rsEEG markers are able to capture some differences at the group level in specific frequency pattern between ADMCI and PDMCI. Instead, the picture is more complex about the individual level of the analysis. These topographical rsEEG markers are able to detect neurophysiological abnormalities in ADMCI and PDMCI individuals when contrasted to Nold subjects. However, these abnormalities were not so different at the individual level to discriminate across the individuals of the two pathological

groups. A tentative explanation of this failure is the relatively high variance of the present rsEEG variables in the ADMCI and PDMCI patients, possibly related to some common neuropathological and clinical features in the two neurodegenerative disorders [52]. Regarding the neuropathology factor, not only PDMCI but also ADMCI patients may suffer from somedepletionofcerebraltegmentaldopaminewhile individuals of both diseases may show a loss of basal forebrain cholinergic cells and A neuritic plaques [104]. Noteworthy, an elevated deposition of A proteins in the brain was correlated with indexes of cognitive impairment in PD patients [105]. In the same line, clusters of ADMCI and PDMCI patients can share some progressive impairment of clinical variables such as visuospatial construction, visual conceptualreasoning,visualhallucination,andspeed of processing [52, 106], possibly related to an abnormal brain cholinergic connectivity [107–110].

Methodological remarks

In the interpretation of the present findings, the following methodological limitations should be considered.

First, the relatively small number of the patients in the ADMCI and PDMCI groups (N=75) did not permit their stratification based on the pharmacological regimens (e.g., cholinergic, dopaminergic, serotoninergic), the severity of dementia and motor symptoms, and the disease duration.

Second, the data were collected in all clinical units without a single experimental protocol. As a result, some interesting biomarkers, clinical measurements, and neuropsychological scores were not available in all subjects, e.g., APOE genotyping, DAT scan, and ADAS-Cog as a measurement of the global cognitive status. Indeed, the only measurement of the global cognitive status common to all subjects was the MMSE score and the evaluation of functioning in the daily life activities. The MMSE measurement is widelyusedfortheassessmentoftheglobalcognitive functions in elderly subjects, with special attention to the area of memory. However, it may be not equally sensitive to global cognitive deficits in all neurodegenerative dementing disorders.

Third, the cognitive deficits of the current PDMCI group were more heterogeneous than those of the ADMCI group were. Indeed, all present ADMCI patients showed the amnesic deficit, while the MCI status of the current PDMCI patients was related to amnesic or non-amnesic deficits. Keeping in mind these differences, the results of the present study motivateafutureresearchonextendedpopulationsof ADMCIandPDMCIpatientsallowingastratification of the patients in the statistical design based on a fine manipulation of the clinical and neuropsychological features.

Fourth, the subjects were not given the identical instructionsinallclinicalunits,andtheexperimenters did not receive the same qualification training to set the environmental conditions for the rsEEG recording. However, we think that these aspects were minor sources of variance as they are very standard in the practice of the expert clinical units of the E-DLB and PDWAIVE Consortia.

Fifth, the lack of groups of patients with de-novo (i.e.,noanti-dementiapharmacologicaltherapy)MCI due to AD and PD prevented a better understanding of the earlier relationships among cortical rsEEG rhythms, motor, and cognitive functions.

Sixth,thersEEGdatawererecordedfromdifferent hardware systems and various recording parameters (i.e., frequency sampling, antialiasing passband, and reference electrode) in the clinical units. To mitigate these potential sources of variability, we performed the following steps of a centralized and well-standardized procedure of data analysis: (i) a common antialiasing bandpass filtering and downsampling to 128Hz; (ii) a re-referencing of all rsEEG data to the common average reference; (iii) and a normalization of the eLORETA rsEEG sources to removing the effects of the local amplifier gain and electrode resistance.

Seventh, it should be remarked that cognitive abnormalities may appear at different stages in the progression of the AD and PD. The status of MCI could occur at an earlier stage in the AD than the PD (in the PD patients, it typically occurs several years after the manifestation of the characterizing motor symptoms). Unfortunately, the clinical outcome of the two groups is not available for most of the ADMCI and PDMCI patients of this spontaneous, retrospective multicentric study. Therefore, while most of the ADMCI patients are supposed to develop

dementing disorders over time, less clear is the clinical/behavioral outcome in the present PDMCI patients. Keeping in mind this limitation, the results of the present study motivate a future research on populations of ADMCI and PDMCI patients followed over time to address that issue.

Conclusions

Thisretrospectiveandexploratorystudyonarchive data evaluated the preliminary hypothesis that cortical sources of rsEEG rhythms would characterize peculiar neurophysiological mechanisms of brain arousal in ADMCI and PDMCI patients with a main focus on the group level. To test the hypothesis, the cortical rsEEG rhythms were analyzed in groups of ADMCI, PDMCI, and Nold subjects carefully matched as for age, gender, and education. The MMSE score was also matched between the two groups of the patients. Compared to the Nold group, all patients' groups exhibited a slower IAF, especially the PDMCI group. Furthermore, all patients' groups showed lower posterior alpha 2 and alpha 3 source activities, especially the ADD group. Finally, they showed higher parietal delta source activities, especially the PDD group. As a possible sign of clinical relevance, these rsEEG markers correlated with the MMSE score (i.e., global cognitive status) and allowed moderate classification accuracies (about 0-77-0.79%) between the Nold versus diseased individuals with ADMCI and PDMCI. These rsEEG markers were not able to discriminate the ADMCI versus PDMCI individuals.

ThesepreliminaryresultssuggestthatADMCIand PDMCI patients might be characterized by different spatial and frequency features of the rsEEG sources at the group level, possibly reflecting cortical neural synchronization underpinning brain arousal in quiet wakefulness. The abnormalities of these neural synchronization mechanisms can be observed at the individual level in those ADMCI and PDMCI patients even if the information lacks specificity for the disease. This limitation does not preclude the possible use of those EEG biomarkers in the clinical practice as a reliable differential diagnosis of MCI due to AD and PD can be done by the clinical phenotype (e.g., an early onset of the cognitive over motor deficits would indicate AD and vice versa). Most importantly, the information of the neurophysiological abnormality at individual level might be of clinical interest for the monitoring of the disease over time. The preliminary results of this study motivate future prospective, multi-center studies using a detailed evaluation of the patients' cognitive status, harmonized EEG hardware systems, and unique data collection protocols. The aim of those studies will be tocross-validateandextendthepresentresultsaswell as support the following main predictions. Firstly, cortical sources of the rsEEG rhythms would reflect different abnormalities of the core neurophysiological mechanisms underlying brain arousal in quiet wakefulness and low vigilance in groups of ADMCI andPDMCIpatients.Secondly,thementionedrsEEG markers would be clinically useful in the disease staging of those patients (even if not for differential diagnostic purposes), monitoring over time, and drug discovery. Diagnosis of MCI due to AD or PD being equal, a patient with abnormal rsEEG markers would reflect abnormalities in the brain arousal in quiet wakefulness and be a candidate to a quick progression of the disease and a critical clinical management.

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