ABNORMALITIES OF RESTING STATE CORTICAL EEG RHYTHMS IN SUBJECTS WITH MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S AND LEWY BODY DISEASES

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Running title: Resting EEG markers in ADMCI and DLBMCI.

Keywords: Resting state electroencephalographic (rsEEG) rhythms; Mild cognitive impairment due to Alzheimer's disease (ADMCI); Mild cognitive impairment due to DEMENTIA WITH Lewy Body (DLBMCI); exact low resolution brain electromagnetic source tomography (eLORETA); Receiver operating characteristic (ROC) curve.

Abstract

The present study tested the hypothesis that cortical sources of resting state eyes-closed electroencephalographic (rsEEG) rhythms reveal different abnormalities in cortical neural synchronization in groups of patients with mild cognitive impairment due to Alzheimer's disease (ADMCI) and dementia with Lewy Body (DLBMCI) as compared to cognitively normal elderly (Nold) subjects. Clinical and rsEEG data in 30 ADMCI, 23 DLBMCI, and 30 Nold subjects were available in an international archive. Age, gender, and education were carefully matched in the three groups. The Mini Mental State Evaluation (MMSE) score was matched between the ADMCI and DLBMCI 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 (ROCC) classified these sources across individuals. Compared to Nold, IAF showed marked slowing in DLBMCI and moderate in ADMCI. Furthermore, the posterior alpha 2 and alpha 3 source activities were more abnormal in the ADMCI than the DLBMCI group while widespread delta source activities were more abnormal in the DLBMCI than the ADMCI group. The posterior delta and alpha sources correlated with the MMSE score and correctly classified the Nold and MCI individuals (area under the ROCC > 0.85). In conclusion, the ADMCI and DLBMCI 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 the clinical validity of these rsEEG markers.

Introduction

Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) induce a progressive cognitive impairment to death in elderly subjects as no disease-modifying treatment is available to date. The most frequent prodromal manifestation of the AD is a mild cognitive impairment (MCI) characterized by an episodic memory deficit not mitigated by cues [1]. In contrast, the most frequent prodromal manifestation of DLB includes the fluctuation of cognitive performance over time, visuospatial disabilities, and visual hallucinations several months before the appearance of motor disorders [2, 3, 4]. However, fluctuating cognition as well as mental disorders with behavioral, psychotic (e.g., auditory and visual hallucinations, delusions, depression, etc.), anxiety, and/or mood (e.g., depression) symptoms are relatively frequent in both DLBMCI and ADMCI patients [5, 6, 7]. Furthermore, the frequency of these mental disorders globally increases in DLB (40-60%) and AD (80%) patients with dementia [8, 9]. For this reason, medical regimens of DLBMCI and ADMCI patients typically include not only Acetylcholinesterase inhibitors (e.g. rivastigmine or donepezil) to improve global cognition but also classes of psychoactive drugs (e.g., low-dose antipsychotics such as quetiapine) to treat those mental disorders [4].

AD and DLB share overlapping, albeit differentially expressed, progressive neurodegenerative pathologies including abnormal accumulation of Aβ1-42 protein extracellularly and phosphorylated tau protein and α-synuclein intracellularly, which cause axonal dysfunction, neuronal loss, and brain atrophy [1, 2].

The relative differences in pathology between AD and DLB may mean that these require different disease-modifying treatments when available. Furthermore, DLB but not AD patients may have adverse effects due to neuroleptic drugs. Therefore, an important research objective is to improve the actual understanding of differential neurobiological, neuroanatomical, and neurophysiological features of MCI due to AD (ADMCI) vs. DLB (DLBMCI). Indeed, a large study [10] using data coming from 31 qualified USA academic medical centers showed that the association between clinical diagnoses and neuropathological autopsy data was moderate in DLB (sensitivity: 12.1% for AD + DLB and 32.1% for pure DLB; specificity: 95%) and Alzheimer's disease dementia (ADD; sensitivity: 85%; specificity: 51.1%), confirming previous evidence showing a relatively low sensitivity in the diagnosis of DLB with standard diagnostic protocols [10, 11].

According to the new diagnostic criteria, the diagnosis of AD can be markedly improved

by cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers of Aβ1-42 and phospho-tau [1]. A useful diagnostic biomarker of DLB probes striatal dopaminergic function by single photon emission tomography or PET [3, 4]. In this line, the understanding of neurophysiological features of ADMCI and DLBMCI, markers derived from resting state eyes-closed electroencephalographic (rsEEG) rhythms are particularly promising to further improve the instrumental assessment of those neurodegenerative diseases over aging [12, 13]. Indeed, they are cost-effective, non-invasive, non-stressful, and can be repeated several times over time without "repetition" effects.

In several rsEEG studies, AD patients with dementia (ADD) were contrasted with normal elderly (Nold) subjects as controls. Compared with groups of Nold subjects, ADD groups showed high power in delta (<4 Hz) and theta (4-7 Hz) rhythms in widespread cortical regions [14], as well as low power in alpha (8-12 Hz) and/or beta (13-20 Hz) rhythms in posterior areas [15, 16, 17]. 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 [15, 16, 17].

In a number of converging reference studies, DLB patients exhibited rsEEG features distinct from those of ADD, so these features were considered as "supportive" in authoritative international diagnostic guidelines [3, 4]. Specifically, widespread delta and theta power over the scalp were higher in DLB than ADD patients [18, 19, 20]. Furthermore, posterior beta power was greater in DLB than ADD patients [18, 19, 20].

In DLB patients, another characterizing feature was the fluctuation of global delta power over a few minutes [18, 19, 21, 22]. This fluctuation characterized most DLB patients, half of Parkinson disease with dementia patients, and a negligible amount of ADD patients [22]. This rsEEG signature was observed even in the prodromal (e.g. MCI) DLB stage, especially at occipital electrodes [23] and was reactive to treatment with Acetylcholinesterase inhibitors [24]. Furthermore, DLB and ADD patients differ in terms of posterior rsEEG dominant frequency and power variability [25].

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) [26] and its new variant called exact LORETA (eLORETA) [27]. These techniques estimate rsEEG sources in a mathematical model of the cerebral cortex. LORETA estimation demonstrated a positive

correlation between activities in the posterior cortical regional sources of low-frequency alpha rhythms (8–10.5 Hz) and the global cognitive status in Nold, ADMCI, and ADD subjects as a whole group; in contrast, the correlation with cognition was negative for occipital cortical sources of the delta rhythms [17, 28]. When compared with DLB patients, ADD patients exhibited more abnormal activity in the posterior alpha sources and less altered activity in the occipital delta sources [29].

The findings of the aforementioned reference study [29] suggest differential spatial (e.g. anterior-posterior axis) and frequency features (e.g. delta to alpha) of the rsEEG rhythms associated with ADD and DLB when compared with those reported in physiological aging. However, they did not test these features in the prodromal stage of MCI, when the interaction of psychoactive pharmacological agents and secondary effects of dementia are negligible. To address this issue, here we tested the exploratory hypothesis that a prominent abnormality of posterior delta and alpha sources might be observed even in the DLBMCI and the DADMCI condition, respectively.

Materials and Methods

Subjects

In the present retrospective exploratory study, we used the rsEEG data of an international archive, formed by clinical, neuropsychological, and electrophysiological data in 30 Nold, 30 ADMCI, and 23 DLBMCI subjects matched for relevant demographic variables. These subjects were recruited outside a formal multicenter clinical trial by the following qualified clinical recording units of the informal European 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); and, University “G. d'Annunzio” of Chieti and Pescara (Italy). General Hospital of Linz (Austria); Dokuz Eylul University (Turkey); Istanbul Medipol University (Turkey); and University of Basel (Switzerland). The three groups of subjects were carefully matched for age, gender, and education. The ADMCI and DLBMCI groups were also carefully matched for the Mini Mental State Examination (MMSE) score as a measurement of the global cognitive status [30].

Table 1 summarizes the relevant demographic and clinical (MMSE score) data of the Nold, ADMCI, and DLBMCI 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 ($H = 34.7$; $p < 0.00001$). Specifically, there was a higher MMSE score in the Nold than the ADMCI and DLBMCI groups ($p < 0.0001$). On the contrary, a statistically significant difference was found neither for the MMSE score between the ADMCI and the DLBMCI groups nor the age, gender, and education among the three groups ($p > 0.05$).

Insert here Table 1

Local institutional Ethics Committees approved data sharing for scientific purpoise. 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 (CDR) [31] score of 0.5, score on the logical memory test of 1.5 standard deviation (SD) lower than the age-adjusted mean, 15-item Geriatric Depression Scale (GDS) [32] score ≤ 5, modified Hachinski ischemia [33] score ≤ 4 and at least 5 years of education. As this retrospective study was based on data of several clinical units that did not follow a harmonized protocol, there was a jeopardized availability of the criteria of MCI status. In particular, 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: Aβ1-42/phospho-tau in the cerebrospinal fluid (CSF), Fluorodeoxyglucose PET (FDG-PET) mapping, and structural magnetic resonance imaging (MRI) [34]. Exclusion criteria were other significant neurological, systemic or psychiatric illness, enrolment in a clinical trial with experimental drugs, major depression disorders described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), 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 [30] and/or the delayed recall of a story [36]. The tests assessing language included the 1-minute verbal fluency for letters, fruits, animals or car trades [37] and/or the Token test [38]. The tests assessing executive function and attention included the Trail Making Test Part A and B [39]. Finally, the tests assessing visuoconstruction included the copy of Rey figures.

The diagnosis of the probable DLB was carried out in agreement with the consensus guidelines [3, 4]. Twenty-two out of 23 DLBMCI patients performed DaTSCAN to confirm the diagnosis of probable DLB. Concerning the detection of the core and suggestive features of DLB, the Neuropsychiatric inventory (NPI) item-2 investigated the occurrence frequency and the severity of hallucinations [40]. Frontal Assessment Battery (FAB) [41] and Clinician Assessment of Fluctuations [18, 19] were included to investigate, respectively, the severity of the frontal dysfunction and the presence and severity of the cognitive fluctuations. Unified Parkinson Disease Rating Scale-III (UPDRS-III) assessed the presence and severity of the extrapyramidal signs [42]. The presence and/or absence of rapid eye movement (REM) sleep behavior disorder (RBD) was determined according to minimal International Classification of Sleep Disorders criteria (1992) [43]. As this retrospective study was based on data of several clinical units that did not follow a harmonized protocol, the DLBMCI subjects underwent a different battery of clinical scales including the Neuropsychiatric Inventory (NPI) [40], the scale for the assessment of Behavioral and Psychological Symptoms of Dementia (BPSD), the MMSE, the Dementia Rating Scale-2 (DRS-2) [44], the Epworth Sleepiness Scale (ESS) for estimating subjective sleep disturbances, and the Alzheimer's Disease Cooperative Study for the Activities of Daily Living (ADCS-ADL). Furthermore, DLBMCI subjects underwent different battery of neuropsychological tests to evaluate the status of MCI [5]. 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).

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 [45]. As measures of severity of the motor disability, the Hoehn and Yahr stage [46] and the Unified Parkinson Disease Rating Scale-III (UPDRS-III) [42] for extrapyramidal symptoms, were used. The diagnosis of PDMCI was based on the Diagnostic Criteria for Mild Cognitive Impairment in Parkinson's Disease [47]. The inclusion criteria comprised: (1) a diagnosis of PD as based on the UK PD Brain Bank Criteria [45]; (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. On the basis of clinical features and neuroradiological findings, the exclusion criteria for PDMCI included the following forms of parkinsonism: (1) dementia with Lewy Body [3, 48, 49], (2) drug-induced parkinsonism, (3) cerebrovascular parkinsonism, and (4) atypical parkinsonism with absent or minimal responses to antiparkinsonian drugs [48, 49].

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 subjective cognitive impairment. The subjects affected by chronic systemic illnesses (e.g. diabetes mellitus) were excluded, as were the subjects receiving chronic psychoactive drugs. The 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.

The use of psychoactive drugs was allowed in both ADMCI and DLBMCI subjects. Specifically, 12 out of 30 (40%) ADMCI patients and 10 out of 23 (43.48%) DLBMCI patients used psychoactive drugs. No Nold subject used psychoactive drugs. In detail, 36.67% of the ADMCI patients and 39.13% of the DLBMCI patients used antianxiety and antidepressant drugs, while 3.33% of the ADMCI patients and 17.39% of the DLBMCI patients used psychotic drugs. When given, the psychoactive drugs were suspended for about 24 hours before EEG recordings to harmonize the time of the last administration of the drug before those recordings across patients. A statistical analysis (Fisher test) was computed to evaluate the presence or absence of statistically significant differences between the ADMCI

and DLBMCI groups as the consumption of the psychoactive drugs. Furthermore, the consumption of the psychoactive drugs was used as a covariate in the main rsEEG statistical analysis, to exclude that some differences in the consumption of psychoactive drugs may influence rsEEG statistical differences between the ADMCI and the DLBMCI group.

Table 2 reports the number and the percentages of the ADMCI and DLBMCI patients assuming the psychoactive drugs for mental disorders (e.g. sedative, anxiety, antidepressant, antipsychotic), before the EEG recordings. The psychoactive drugs were categorized in two classes: the first class included anxiety and antidepressant drugs, while the second class included antipsychotic drugs. Some patients assumed more than one psychoactive drug. Furthermore, the Table 2 reports the number and the percentages of the ADMCI and DLBMCI patients who took others drugs (e.g. acetylcholinesterase inhibitors - AChEIs- and drugs for extrapyramidal symptoms and dementia). All types of drugs are reported in detail in the table 3.

Insert here Tables 2 and 3

EEG recordings

EEG data were recorded while the subjects were sitting comfortably with eyes closed in a standard resting state condition (rsEEG). At least 5 minutes of rsEEG data were recorded (128 Hz or higher sampling rate, with a bandpass between 0.01 Hz and 100 Hz) 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, and O2). Linked earlobe reference electrode was preferred, but not mandatory to respect the methodological facilities and standard internal protocols of the clinical recording units. 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 (0.3-70 Hz bandpass) were also recorded to monitor blinking and eye movements. 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.

For all Nold subjects, the clinical diagnosis (i.e. intact cognitive status) and the EEG recording were performed on the same day. Instead, the mean time from the clinical diagnosis of MCI to the EEG recording was 1.2 months (± 0.3 standard error mean, SE) in the

ADMCI patients and 19.5 months (± 4.2 SE) in the DLBMCI patients. Furthermore, the mean time from the clinical diagnosis of MCI to the last follow-up with the diagnosis of dementia or MCI was 22.9 months (± 1.4 SE) in the ADMCI patients and 49.4 months (± 7.2 SE) in the DLBMCI patients. Finally, 6 out of 30 (20%) ADMCI patients and 13 out of 23 (53.3%) DLBMCI patients converted to the dementia at the last follow-up. Statistical analyses were computed to evaluate the presence or absence of statistically significant differences between the MCI groups as the time from the clinical diagnosis of MCI to the EEG recording (T-test), the time from the clinical diagnosis to the last follow-up with the diagnosis of dementia or MCI (T-test), and the conversion from MCI to dementia (Fisher test). Statistically significant differences were found between the two MCI groups (i.e. ADMCI and DLBMCI) as the time from the clinical diagnosis of MCI to the EEG recording ($p < 0.00005$; longer time for the DLBMCI than ADMCI group), the time from the clinical diagnosis of the last follow-up with the diagnosis of dementia or MCI ($p < 0.001$; longer time for the DLBMCI than ADMCI group), and the percentage of conversion from MCI to dementia (i.e. DLB or AD; $p < 0.01$; higher converted subjects in the DLBMCI than ADMCI group). Therefore, the mentioned three variables were used as covariates in the main rsEEG statistical analyses, to minimize their effects on the statistical findings.

Preliminary analysis of the EEG data

The recorded rsEEG data were band-passed to avoid aliasing, down-sampled to 128 Hz (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, 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. The rsEEG epochs with sporadic and well-shaped blinking artifacts were corrected from the EOG activity by an autoregressive method [50]. 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 on-going increase of theta, K complex, spindles, etc.) were rejected. To

harmonize the rsEEG data collected 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

A standard digital FFT-based power spectrum analysis (Welch technique, Hanning windowing function, no phase shift) computed the power density of the 2-s rsEEG epochs with 0.5 Hz of frequency resolution. This standard FFT procedure was implemented in a software script developed under Matlab 6.5 (Mathworks Inc., Natick, MA).

According to a previous study of our group [29], 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 8 Hz (between the delta and the alpha power peak). IAF was defined as the maximum power density peak between 6 and 14 Hz. In precedence, these frequency landmarks were well described by Klimesch et al. [51, 52, 53].

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 -4 Hz to TF -2 Hz, theta from TF -2 Hz to TF, low-frequency alpha band (alpha 1 and alpha 2) from TF to IAF, and high-frequency alpha band (or alpha 3) from IAF to IAF + 2 Hz. The other bands were defined based on standard fixed frequency ranges: beta 1 from 14 to 20 Hz, beta 2 from 20 to 30 Hz, and gamma from 30 to 40 Hz. 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 tool called “exact LORETA” (eLORETA) for the linear estimation of the cortical source activity generating scalp-recorded rsEEG rhythms [27].

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 [27]. 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) [54]. The

eLORETA solves the so-called EEG inverse problem estimating "neural" current density values at any cortical voxel of the mentioned head volume conductor model. The solutions are computed rsEEG frequency bin-by-frequency bin.

The input for this estimation is the EEG spectral power density computed at 19 scalp electrodes. The output is the electrical brain source space formed by 6,239 voxels with 5 mm resolution, restricted to cortical gray matter of the head volume conductor model [37]. An equivalent current dipole is located in each voxel. For each voxel, the eLORETA package provides the Talairach coordinates, the lobe, and the Brodmann area (BA).

In line with the general low spatial resolution of the present EEG methodological approach (i.e. 19 scalp electrodes), we performed a regional analysis of the eLORETA solutions. For this purpose, we collapsed the eLORETA solutions within frontal, central, temporal, parietal, occipital, and limbic macroregions (ROIs) considered separately. Table 4 reports the list of the BAs used for the ROIs considered in the present study. Of note, the main advantage of the regional analysis of eLORETA solutions was that we could disentangle the rsEEG source activity in contiguous cortical areas. For example, the rsEEG source activity in the occipital ROI was disentangled from that estimated in the parietal and temporal ROIs, etc. This was made possible by the fact that eLORETA solves the linear inverse problem by taking into account (at least in part) the effects of the head as a volume conductor. In contrast, the solutions of rsEEG power density computed at a parietal scalp electrode reflect the contribution of source activities not only of the underlying parietal cortex but also of sorrounding occipital and temporal cortices.

For the present eLORETA cortical source estimation, a frequency resolution of 0.5 Hz was used, namely, the maximum frequency resolution allowed by the use of 2-s artifact free EEG epochs. The frequency bands of interest were delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma, which were defined subject-by-subject as described above.

Insert here Table 4

Statistical analysis of the eLORETA solutions

A statistical session was performed by the commercial tool STATISTICA 10 (StatSoft Inc., www.statsoft.com) to test the hypothesis that the rsEEG source activity as revealed by eLORETA solutions might differ between the ADMCI and DLBMCI 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, and DLBMCI), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The TF, IAF, the conversion from MCI to dementia (i.e. DLB or AD), the time from the clinical diagnosis of MCI to the EEG recording, the time from the clinical diagnosis to the last follow-up with the diagnosis of dementia or MCI, and the consumption of psychoactive drugs (antidepressant, antianxiety and antipsychotic drugs) were used as covariates. In particular, we used two different covariates concerning the use of psychoactive drugs: the first covariate included the information about the use of antidepressant and antianxiety drugs, while the second covariate included the information about the use of antipsychotic drugs. The use of two different covariates for the psychoactive drugs was motivated by the equal distribution of the antianxiety and antidepressant drugs in the ADMCI and DLBMCI (e.g. 36.67% vs 39.13%) patients before the EEG recordings and a wider use of psychotic drugs in the DLBMCI group compared with the ADMCI group (17% vs. 3%).

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 DLBMCI groups using the Nold group as a control reference. Specifically, we predicted: (1) a statistical 3-way interaction effect including the factors Group, ROI, and Band ($p < 0.05$); (2) a post-hoc test indicating statistically significant differences of the regional normalized eLORETA solutions with the pattern Nold ≠ ADMCI ≠ DLBMCI (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 DLBMCI individuals

The rsEEG sources showing 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 vs. the ADMCI individuals; (2) the Nold vs. the DLBMCI individuals; and (3) the ADMCI vs.

DLBMCI 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 [55]. The following indexes measured the classification performance of the above binary classification: (1) Sensitivity. It measures the rate of the positives who were correctly classified as positives (i.e. "true positive rate" in the signal detection theory); (2) Specificity. It 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. It is 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). The AUROC was another standard index of the global classification accuracy.

Results

Statistical analysis of the EEG cortical sources

Table 5 reports the mean values of the TF and IAF for the three groups (i.e. Nold, ADMCI, and DLBMCI), together with results of the statistical comparisons between the group pairs (ANOVA). The mean TF was 6.3 Hz (± 0.2 standard error mean, SE) in the Nold subjects, 5.4 Hz (± 0.2 SE) in the ADMCI subjects, and 4.7 Hz (± 0.2 SE) in the DLBMCI subjects. The mean IAF was 9.4 Hz (± 0.1 SE) in the Nold subjects, 8.8 Hz (± 0.3 SE) in the ADMCI patients, and 7.8 Hz (± 0.3 SE) in the DLBMCI 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 ($F = 16.6$, $p < 0.00001$) in the Nold than the ADMCI ($p < 0.005$) and DLBMCI ($p < 0.00005$) groups; it was also higher in the ADMCI than the DLBMCI group ($p < 0.01$); (2) the mean IAF was greater ($F = 16.6$, $p < 0.00001$) in the Nold than the ADMCI ($p < 0.05$) and DLBMCI ($p < 0.0005$) groups; it was also higher in the ADMCI than the DLBMCI group ($p < 0.005$). These results confirm the importance of the determination of the individual frequency bands in the comparison of rsEEG biomarkers in ADMCI and DLBMCI patients.

Insert here Table 5

Figure 1 shows the grand average of the regional eLORETA solutions for the rsEEG source estimation relative to a statistically significant ANOVA 3-way interaction effect ($F = 6.85$; $p < 0.00001$) among the factors Group (Nold, ADMCI, and DLBMCI), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal,

and limbic). 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, DLBMCI 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 testing showed that the discriminant source pattern ADMCI < DLBMCI < Nold was fitted by the occipital, temporal, and limbic alpha 2 sources as well as the occipital alpha 3 sources ($p < 0.01$ to $p < 0.000001$). Compared to the Nold group, these posterior alpha source activities showed an abnormal reduction in the ADMCI and DLBMCI groups ($p < 0.005$ to $p < 0.000001$). Furthermore, these activities they were lower in the ADMCI than the DLBMCI group ($p < 0.01$ to $p < 0.000005$). Of note, 3 ADMCI and 1 DLBMCI subjects exhibited an asymptotic rsEEG power spectra without alpha peak. On the contrary, the pattern DLBMCI > ADMCI > Nold was fitted by the frontal, parietal, and temporal delta sources ($p < 0.05$ to $p < 0.000001$). Compared to the Nold group, these delta source activities pointed to an abnormal increment in the ADMCI and DLBMCI groups ($p < 0.05$ to $p < 0.000001$). Furthermore, they were greater in the DLBMCI than the ADMCI group ($p < 0.001$ to $p < 0.00005$).

These results were confirmed in the following ANOVAs performed for control purposes. The first control analysis was performed in matched subgroups of ADMCI (N = 15) and DLBMCI (N = 13) patients who had never taken psychoactive drugs before EEG recordings. A matched Nold group (N = 17) served as a control reference (Table 6 reports all demographic data and global cognitive status as revealed by the MMSE score). The hypothesis was that the main findings of the present study may be observed even in these subgroups of ADMCI and DLBMCI patients free from the effects of psychoactive drugs.

These results were cross-validated by the following three statistical sessions performed for control purposes. In the first statistical session, the TF and IAF were compared across the ADMCI, DLBMCI, and Nold subgroups. The subgroups of ADMCI (N = 15) and DLBMCI (N = 13) patients had never taken psychoactive drugs before EEG recordings. The matched Nold subgroup (N = 17) served as a control reference. The hypothesis was that the main findings of the present study may be observed even in these subgroups of ADMCI and DLBMCI patients free from the effects of psychoactive drugs. Data analysis showed that the mean TF was 5.4 Hz (± 0.3 standard error, SE) in the ADMCI patients and 4.6 Hz (± 0.2 SE) in the DLBMCI patients. Furthermore, the mean IAF was 8.8 Hz (± 0.4 SE) in the ADMCI patients

and 7.7 Hz (± 0.4 SE) in the DLBMCI patients. In the Nold group, the mean TF and IAF were 6.4 Hz (± 0.3 SE) and 9.3 Hz (± 0.2 SE), respectively. These mean values were statistically compared between the groups by ANOVA designs ($p < 0.05$). Results showed that the pattern Nold > ADMCI and DLBMCI was confirmed with both variables, namely TF ($F= 9.38$, $p < 0.0005$) and IAF ($F = 5.75$, $p < 0.01$). These findings confirmed those observed in the main analysis performed in the whole ADMCI and DLBMCI groups including some patients assuming psychoactive drugs.

In the second statistical session, the clinical diagnosis of MCI to the EEG recording (T-test, $p < 0.05$), the time from the clinical diagnosis to the last follow-up with the diagnosis of dementia or MCI (T-test, $p < 0.05$), and the conversion from MCI to dementia (Fisher test, $p > 0.05$) were compared across the mentioned ADMCI and DLBMCI subgroups. The mean time from the clinical diagnosis of MCI to the EEG recording was 1.5 months (± 0.5 SE) in the ADMCI patients and 17 months (± 5.8 SE) in the DLBMCI patients. Furthermore, the mean time from the clinical diagnosis to the last follow-up with the diagnosis of dementia or MCI was 18.9 months (± 2.5 SE) in the ADMCI patients and 42.4 months (± 10 SE) in the DLBMCI patients. Finally, 4 out of 15 (27%) ADMCI subjects and 8 out of 13 (62 %) DLBMCI patients converted to dementia at the last follow-up. Results of the statistical comparisons between the subgroups showed no statistically significant difference between the two patients' subgroups ($p > 0.05$).

In the third statistical session, an ANOVA design compared the eLORETA source solutions in the ADMCI ($N = 15$), DLBMCI ($N = 13$), and Nold ($N = 17$) subgroups ($p < 0.05$). The ANOVA factors were Group (ADMCI, DLBMCI, Nold), Band (delta, theta, alpha 1, alpha 2, alpha 2, beta 1, beta 2, and gamma), and ROI (frontal, central, temporal, parietal, limbic, and occipital). Results showed a statistically significant 3-way interaction effect among Group, Band, and ROI ($F = 4.06$, $p = 0.00001$) as in the main statistical analysis. The Duncan planned post-hoc testing pointed to: (i) a discriminant source pattern ADMCI < DLBMCI < Nold fitted by the occipital and temporal alpha 2 sources as well as the occipital alpha 3 sources ($p < 0.05$ to $p < 0.000001$); (ii) the discriminant source pattern DLBMCI > ADMCI > Nold was fitted by the parietal and occipital delta sources ($p < 0.05$ to $p < 0.000001$). Again, these findings confirmed those observed in the main analysis performed in the whole ADMCI and DLBMCI groups including some patients assuming psychoactive drugs (see Figure 2).

The last 3 ANOVAs were performed in other subgroups of ADMCI and DLBMCI patients. In this case, the subgroups of ADMCI and DLB patients were paired as the conversion from MCI to dementia (i.e. DLB or AD), the time from the clinical diagnosis of MCI to the EEG recording, and the time from the clinical diagnosis to the last follow-up with the diagnosis of dementia or MCI. In all 3 ANOVAs, the Nold group of 30 seniors was used as a control reference.

The ANOVA in the subgroups paired as the conversion from MCI to dementia (16 ADMCI, 16 DLBMCI; 6 out of 16 ADMCI and DLBMCI patients converted to the demented patients) showed a statistically significant 3-way interaction effect among Group, Band, and ROI ($F = 12.2$, $p < 0.0001$). The Duncan planned post-hoc testing showed that: (i) the discriminant source pattern ADMCI < DLBMCI < Nold was fitted by the parietal, occipital, and limbic alpha 2 sources as well as the occipital alpha 3 sources ($p < 0.05$ to $p < 0.000001$) and (ii) the discriminant source pattern DLBMCI > ADMCI > Nold was fitted by the frontal, parietal, and temporal delta sources ($p < 0.05$ to $p < 0.000001$).

Moreover, the ANOVA in the subgroups paired as the time from the clinical diagnosis of MCI to the EEG recording (12 ADMCI, 12 DLBMCI; the mean time was 2.6 months in the ADMCI patients and 3.4 months in the DLBMCI patients) unveiled a statistically significant 3-way interaction effect among Group, Band, and ROI ($F = 8.1$, $p < 0.0001$). The Duncan planned post-hoc testing showed that: (i) the discriminant source pattern ADMCI < DLBMCI < Nold was fitted by the parietal, occipital, and limbic alpha 2 sources as well as the occipital alpha 3 sources ($p < 0.05$ to $p < 0.000005$); (ii) the discriminant source pattern DLBMCI > ADMCI > Nold was fitted by the parietal and temporal delta sources ($p < 0.05$ to $p < 0.000005$).

Finally, the ANOVA in the subgroups paired as the time from the clinical diagnosis to the last follow-up with the diagnosis of dementia or MCI (15 ADMCI, 15 DLBMCI; the mean time was 26.9 months in both ADMCI and DLBMCI patients) pointed to a statistically significant 3-way interaction effect among Group, Band, and ROI ($F = 10.1$, $p < 0.0001$). The Duncan planned post-hoc testing showed that: (i) the discriminant source pattern ADMCI < DLBMCI < Nold was fitted by the parietal, occipital, and limbic alpha 2 sources as well as the occipital alpha 3 sources ($p < 0.05$ to $p < 0.000005$) and (ii) the discriminant source pattern DLBMCI > ADMCI > Nold was fitted by the frontal, temporal, and limbic delta sources ($p < 0.05$ to $p < 0.000005$).

A control statistical analysis (Grubbs' test, $p < 0.0001$) was performed to verify that the inter-group differences in the above seven rsEEG source activities (i.e. frontal, parietal, temporal delta; occipital, temporal, and limbic alpha 2; occipital alpha 3) were not merely due to the presence of some outliers in the individual eLORETA solutions. No outlier was detected (see Figure 3), thus confirming the results of the main statistical analysis.

Insert here Figures 1, 2, 3 and Table 6

Correlation between the rsEEG source activity and MMSE

As a first analysis on the clinical relevance of the main results, Spearman test evaluated the monotonic correlation between the above seven rsEEG source activities (i.e. frontal, parietal, temporal delta; occipital, temporal, and limbic alpha 2; occipital alpha 3) and the MMSE score, as a rough index of global cognition status. The correlation analysis was performed using all Nold, ADMCI, and DLBMCI individuals as a whole group for two reasons. On the one hand, the hypothesis was that those rsEEG source activities were correlated with the global cognitive status in humans in general, namely including cases with both normal and impaired cognitive functions. On the other hand, the correlation study would have had a low statistical sensitivity if performed only in the separate groups, due to the very limited scatter of the MMSE scores within a given group (e.g. MMSE score from 30 to 28 in Nold subjects). To take into account the inflating effects of repetitive univariate tests, the statistical threshold was set at $p < 0.007$ to obtain the Bonferroni's correction at $p < 0.05$. A statistically significant negative correlation was found between the activity of the parietal delta source and the MMSE score ($r = -0.32$, $p = 0.003$). The higher the parietal delta source activity, the lower the MMSE score. A statistically significant negative correlation was found between the MMSE score and the activity of the occipital alpha 2 ($r = 0.38$, $p = 0.0003$), limbic alpha 2 ($r = 0.35$, $p = 0.001$), occipital alpha 3 ($r = 0.37$, $p = 0.0005$) sources (see Figure 4). The higher the posterior alpha source activity, the higher the MMSE score. As a control analysis, the same correlation test for any single group showed no statistically significant result, possibly because of the very limited range of the MMSE score within the single groups ($p > 0.05$).

Insert here Figure 4

The present results suggest that even if statistically significant ($p<0.005$), the absolute values of the monotonic (Spearman) correlations between rsEEG source activities and the MMSE score in the Nold, ADMCI, and DLBMCI individuals were relatively low as data variance explained ($r = 0.32–0.38$). To extend the above correlation analysis, we also computed the simple non-linear correlations between the significant rsEEG source activities (i.e. parietal delta, occipital alpha 2, limbic alpha 2, occipital alpha 3) and the MMSE score using a procedure that has been successfully used in one of our previous rsEEG studies in patients with neurodegenerative disorders [12]. Specifically, we calculated the coefficient of determination r^2 for exponential, logarithmic, and power functions as follows:

$$r^2 = 1 - (SSE/SST)$$

where

$$SSE = \sum (y_i - \hat{y}_i) \text{ and } SST = (\sum y_i^2) - ((\sum y_i)^2/n)$$

where n is the number of samples (i.e. subjects), y_i is the real value and $\hat{y}_i$ is the approximated value calculated with the following formula:

$$\hat{y}_i = c \ln x_i + b \text{ for logarithmic functions (c, b constant)}$$

$$\hat{y}_i = c e^{bx}{}_i \text{ for exponential functions (c, b constant)}$$

$$\hat{y}_i = c x_i^b \text{ for power functions (c, b constant)}$$

Table 4 reports the coefficient of determination r^2 between rsEEG source activities (i.e. parietal delta, occipital alpha 2, limbic alpha 2, occipital alpha 3) and the MMSE score using all Nold, ADMCI, and DLBMCI individuals as a whole group. Results showed that the r^2 values for the monotonic, exponential, logarithmic, and power functions were relatively low as explained data variance (i.e. $r^2 = 0.10–0.16$). However, these values exhibited statistical significance ($p < 0.005$), confirming the relevance of those rsEEG source activities for global cognition in humans. Of note, those values for the linear and non-linear functions were quite similar for the correlation between rsEEG alpha source activities and the MMSE score. Instead, the correlation between the rsEEG delta source activities and the MMSE score was characterized by a higher r^2 value for the monotonic than the exponential, logarithmic, and power functions.

Insert here Table 7

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

As a second analysis on the clinical relevance of the main results, the above seven rsEEG source activities (i.e. frontal, parietal, temporal delta; occipital, temporal, and limbic alpha 2; occipital 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 DLBMCI individuals. The results were reported in detail in Table 7 and Figure 5.

Regarding the classification of the Nold vs. ADMCI subjects, the following 4 rsEEG markers overcame the threshold of 0.7 of the AUROC curve, defined as a "moderate" classification rate (Table 8): occipital alpha 2, temporal alpha 2, limbic alpha 2, and occipital alpha 3 source activities. Among these rsEEG markers, the occipital alpha 2 source activity reached the following best classification rate (Figure 4 top): a sensitivity of 90%, a specificity of 73.3%, an accuracy of 81.7%, and 0.86 of the AUROC curve.

Concerning the classification of the Nold vs. DLBMCI subjects, the following 6 rsEEG markers overcome the threshold of 0.7 of the AUROC curve (Table 8): frontal delta, parietal delta, temporal delta, occipital alpha 2, limbic alpha 2, and occipital alpha 3 source activities. Among these rsEEG markers, the parietal delta eLORETA source activities reached the following best classification rate (Figure 4 middle): a sensitivity of 82.6%, a specificity of 80%, an accuracy of 81.3%, and 0.89 of the AUROC curve.

Finally, regarding the classification of the ADMCI vs. DLBMCI subjects, the following 2 rsEEG markers overcame the threshold of 0.7 of the AUROC curve (Table 8): parietal delta and temporal delta source activities. Among these rsEEG markers, the occipital alpha 2 source activity reached the following best classification rate (Figure 5 top): a sensitivity of 78.3%, a specificity of 66.7%, an accuracy of 72.5%, and 0.72 of the AUROC curve.

Insert here Table 5 and Figure 5

Discussion

In a previous reference study [29], we showed distinct spatial (e.g. posterior cortex) and frequency features (e.g. delta to alpha) of the rsEEG rhythms in ADD and DLB patients when compared with Nold subjects. The present retrospective study used the same methodology to test the hypothesis that these differential features might be observed even in the prodromal stage of MCI such as ADMCI and DLBMCI.

The rsEEG markers exhibiting differences between ADMCI and DLBMCI groups

As an important aspect of the present methodology, the frequency bands from delta to alpha were defined on an individual basis using the TF and IAF as landmarks (for further details see the "Methods" section). This choice allowed us to take into account the substantial differences in the IAF in the present cohorts of ADMCI and DLBMCI patients. The IAF was lower in the ADMCI (8.8 Hz) and DLBMCI (7.8 Hz) groups than the Nold group (9.4 Hz). Furthermore, it was also lower in the DLBMCI than the ADMCI group. If we were used the standard fixed alpha 1 (8-10/10.5 Hz) and alpha 2 (10-12/13 Hz) frequency sub-bands, DLBMCI would have shown low source activity in these sub-bands merely due to the slowing of the IAF.

Compared with the Nold group, the posterior source activity of the individual low-frequency alpha (i.e. alpha 2) and the occipital source activity of high-frequency alpha (i.e. alpha 3) were abnormally lower in both ADMCI and DLBMCI groups. Remarkably, this source activity was lower in the ADMCI than the DLBMCI group. Furthermore, a widespread delta source activity exhibited an abnormally higher activity in both ADMCI and DLBMCI groups. Another novel finding was that this delta source activity was higher in the DLBMCI than the ADMCI group.

The present results extend to source space and individually-determined frequency bands previous EEG evidence reported in groups of ADD and DLB patients [20, 21, 22, 23, 56, 57, 58, 59, 60]. In those previous investigations, widespread delta and theta (e.g. also termed "pre-alpha") rhythms were greater in power in DLB than ADD patients [20, 21, 22]. Finally, the present results fit previous evidence documenting more abnormal occipital delta and theta rhythms in DLB than ADD patients, even at the prodromal stage of MCI [23].

Finally, a clinically relevant evidence was that the delta and alpha source activities demonstrated a linear and non-linear correlation with the MMSE score (roughly reflecting global cognitive status) across all Nold, ADMCI, and DLBMCI subjects as a whole population. However, it should be remarked that even if statistically significant ($p < 0.005$), the absolute values of the monotonic (Spearman) and simple non-linear correlations were relatively low as variance explained (i.e. $r = 0.10–0.16$). The present findings suggest that the neurophysiological mechanisms of cortical neural synchronization underpinning brain arousal and low vigilance (as reflected in the rsEEG source solutions of this study) are only

one of the determinants of global cognitive functions in human subjects. Other relevant neurophysiological mechanisms involved in cognitive information processes may be those related to selective attention, encoding and retrieval of information in long-term memory, frontal executive functions (some assisted by internal language), and others. Therefore, future studies may measure cortical EEG rhythms not only during the resting state condition (i.e. low vigilance) but also during attention, episodic and working memory, and other cognitive tasks. The derived multiple EEG markers may be used as an input for linear (logistics regression) and non-linear (artificial neural networks or support vector machines) predictors of MMSE score as a measurement of the global status of cognitive functions in Nold subjects and patients with dementing disorders. The expected results may show high correlation values and remarkable insights about the derangement of brain functions in the evolution of dementing disorders.

The effect of ADMCI and DLBMCI on neurophysiological mechanisms generating resting state delta and alpha rhythms

Neurophysiological mechanisms underlying the above abnormalities in delta and alpha rhythms are poorly known. It can be just speculated that in the quiet wakefulness, the abnormal increase in magnitude of cortical delta rhythms in DLBMCI and (to lesser extent) ADMCI is caused by an altered interaction between thalamic and cortical pyramidal neurons. This effect might cause an abnormal functional connectivity, inducing a partial isolation of cortical delta sources [61, 62, 63]. This speculation is based on two lines of evidence in AD patients. Firstly, there is a concomitant increase of resting state delta rhythms and a decrease of regional cortical blood perfusion and metabolism [64, 65, 66, 67, 68, 69]. Secondly, there is a clear relationship between expression of these rhythms and the atrophy of cortical gray matter and hippocampus [28, 70, 71]. A new fascinating avenue is the study of the relationship between the abnormal cortical delta and alpha rhythms in those patients and the alterations of the default mode, frontoparietal attentional, and frontal executive networks as revealed by resting state functional MRI [72, 73].

Concerning the present abnormalities in patients' posterior alpha sources (prominent in ADMCI), it can be speculated that they might reflect an alteration of a complex neurophysiological network regulating the continuous sensory flow to the cortex, as well as

cortical arousal, and vigilance in the quiet wakefulness [74, 75, 76]. This speculation is based on the fact that oscillations of post-synaptic potentials at the alpha frequency control the nodes of such neurophysiological network, which spans thalamocortical high-threshold and relay-mode neurons, GABAergic interneurons, and cortical pyramidal cells in sensory areas [74, 75, 76]. As a result of those oscillations, cycles of excitation and inhibition around 70–100 ms can be observed in the local field potentials recorded in mammalian thalamic and cortical neural populations [74, 75, 76]. During the active processing of sensorimotor information, these cycles might frame perceptual events in discrete snapshots and would ensure the selectivity of that processing [74, 75, 76]. During the quiet wakefulness, they might regulate the level of general arousal in sensory, cognitive, and motor cortical areas [52, 63]. According to the above neurophysiological model, the prominent posterior alpha abnormalities in the present ADMCI and (to a less extent) DLBMCI patients might predict an alteration of visuospatial working and episodic memory processes, which may possibly relate to altered inputs from cholinergic basal forebrain to the visual cortex [77, 78, 79].

The rsEEG markers showing classification accuracy between Nold vs. patients

Another clinically relevant output of the present study was the good classification accuracy between Nold and ADMCI/DLBMCI individuals based on rsEEG sources. We found an accuracy (e.g. AUROC curve) of 86% in the classification of the Nold and the ADMCI individuals, using occipital alpha 2 source activity as an input. Furthermore, the parietal delta source activity allowed an accuracy of 89% in the classification of the Nold vs. the DLBMCI individuals. These findings build on previous variable evidence obtained from scalp rsEEG rhythms and fixed frequency bands. Discrimination accuracy has varied considerably in AD with values of 94–45% between Nold and ADD individuals, 92–78% between ADMCI vs. ADD individuals, 87–60% in the prediction of the conversion from ADMCI to ADD status [14, 16, 29, 80, 81, 82, 83, 84, 85, 86, 87, 88]. More robust discrimination accuracy of higher than 90% has been reported in the classification of Nold and DLB individuals [29, 89].

In the present study, we report just a moderate accuracy of 72% in the classification of the ADMCI vs. the DLBMCI individuals (parietal delta source activity as an input). This percentage was clearly lower than the range of classification accuracies reported in the literature about the discrimination between ADD and DLB individuals. In previous studies, a

visual analysis of rsEEG traces allowed a discrimination accuracy of 78% between DLB and ADD individuals [90]. In a more recent study, the same kind of visual analysis allowed a discrimination accuracy of 77% between DLB and ADD individuals [91]. Compared with the visual analysis of rsEEG traces, the spectral analysis returned a greater discrimination accuracy of 80-91% between DLB and ADD individuals [25, 89, 92].

At the present stage of the research, it is unclear why the discrimination accuracy is just moderate between ADMCI and DLBMCI ones. It can be speculated that at the prodromal stage, neuropathological features have more similar features in ADMCI and DLBMCI as compared to ADD and DLB status. Regarding the neuropathology factor, not only DLBMCI but also ADMCI patients may suffer from some depletion of cerebral tegmental dopamine [93] while individuals of both diseases may show a loss of basal forebrain cholinergic cells, Aβ neuritic plaques, and cortical tauopathy [94, 95]. Noteworthy, an elevated deposition of Aβ proteins in the brain was correlated with indexes of cognitive impairment in DLB patients [96]. In the same line, clusters of ADMCI and DLBMCI patients can share some progressive impairment of clinical variables such as visuospatial construction, visual conceptual reasoning, and speed of processing, even if these functions are differently impaired in the two groups [97, 98, 99]. Namely, there is greater impairment on visual tasks, speed of processing, and all-type hallucinations in DLB compared to ADD and more verbal memory impairment in ADD than DLB [97, 98, 99]. An alternative explanation is that some ADMCI and DLBMCI belonged to mixed cases of DLB-AD, thus reducing the classification accuracy between ADMCI and DLBMCI. Furthermore, another factor might be the effect of psychoactive treatment (cholinergic and/or dopaminergic) that may mitigate inter-group differences in the EEG rhythms at this stage of the disease. Future prospective studies should use appropriate structural MRI, CSF diagnostic biomarkers of AD, and DATsSCan in de-novo (i.e. no treatment) ADMCI andf DLBMCI groups of MCI patients to quantify those with mixed dementing disorders.

Methodological remarks

In the interpretation of the present findings, the following methodological limitations should be considered. The groups of ADMCI (N = 30) and DLBMCI (N = 23) patients were relatively small, so we cannot stratify them in relation to disease severity. Furthermore, this retrospective study was based on data of several clinical units that did not follow a

harmonized protocol. As a result, there was a jeopardized availability of potentially relevant genetic and neuroimaging biomarkers, clinical measurements, criteria of MCI status, and neuropsychological scores across the clinical units. 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. Furthermore, the clinical outcome of the two groups is not available for most of the ADMCI and DLBMCI patients.

Conclusions

This retrospective and exploratory study on archive data evaluated the preliminary hypothesis that cortical sources of rsEEG rhythms might characterize peculiar neurophysiological mechanisms of brain arousal in ADMCI and DLBMCI patients. Results showed that both MCI groups exhibited an IAF slower in frequency (especially the DLBMCI group) compared with the Nold group. Furthermore, both MCI groups exhibited abnormal lower posterior alpha source activities, especially the ADMCI group. Finally, they showed abnormally higher widespread delta source activities, especially the DLBMCI group. As a possible sign of clinical relevance, these rsEEG markers correlated with the MMSE score (i.e. global cognitive status) and allowed good classification accuracies (AUROC > 0.85) between the Nold and MCI individuals regardless the diagnosis. These rsEEG markers allowed just a moderate classification accuracy (AUROC > 0.7) between the ADMCI and DLBMCI individuals.

These preliminary results suggest that ADMCI and DLBMCI 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 could be also observed at the individual level.

The preliminary results of this study motivate future prospective, longitudinal, multi-center studies using harmonized protocols and hardware for a detailed evaluation of the patients' cognitive status and brain function. If cross-validated, the present rsEEG biomarkers described may have utility in clinical practice and drug discovery (e.g. patients' stratification based on abnormalities of rsEEG biomarkers).

Acknowledgements

The present study was developed based on the data of the informal European Consortium PDWAVES and European Consortium of Dementia with Lewy Body. The members and institutional affiliations of the Consortia are reported in the cover page of this manuscript. The research activities of the Unit of University of Rome "La Sapienza" were partially supported by the H2020 Marie S. Curie ITN-ETN project with the short title "BBDiag" (http://bbdiag-itn-etn.eu). We thank Mrs. Jessica Janson and Mrs. Marina Selivanova for their support to those activities in the framework of the BBDiag project.

References

[1]. Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, DeKosky ST, Gauthier S, Selkoe D, Bateman R, Cappa S, Crutch S, Engelborghs S, Frisoni GB, Fox NC, Galasko D, Habert MO, Jicha GA, Nordberg A, Pasquier F, Rabinovici G, Robert P, Rowe C, Salloway S, Sarazin M, Epelbaum S, de Souza LC, Vellas B, Visser PJ, Schneider L, Stern Y, Scheltens P, Cummings JL. (2014) Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 13, 614-629.

[2]. Aarsland D, Litvan I, Salmon D, Galasko D, Wentzel-Larsen T, Larsen JP (2003) Performance on the dementia rating scale in Parkinson's disease with dementia and dementia with Lewy bodies: comparison with progressive supranuclear palsy and Alzheimer's disease. J Neurol Neurosurg Psychiatry 74, 1215–1220.

[3]. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Londos E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, Yamada M (2005) Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 65, 1863-1872.

[4]. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, Aarsland D, Galvin J, Attems J, Ballard CG, Bayston A, Beach TG, Blanc F, Bohnen N, Bonanni L, Bras J, Brundin P, Burn D, Chen-Plotkin A, Duda JE, El-Agnaf O, Feldman H, Ferman TJ, Ffytche D, Fujishiro H, Galasko D, Goldman JG, Gomperts SN, Graff-Radford NR, Honig LS, Iranzo A, Kantarci K, Kaufer D, Kukull W, Lee VMY, Leverenz JB, Lewis S, Lippa C, Lunde A, Masellis M, Masliah E, McLean P, Mollenhauer B, Montine TJ, Moreno E, Mori E, Murray M, O'Brien JT, Orimo S, Postuma RB, Ramaswamy S, Ross OA, Salmon DP, Singleton A, Taylor A, Thomas A, Tiraboschi P, Toledo JB, Trojanowski JQ, Tsuang D, Walker Z, Yamada M, Kosaka K. (2017) Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 89(1):88-100.

[5]. Donaghy PC, Barnett N, Olsen K, Taylor JP, McKeith IG, O'Brien JT, Thomas AJ. (2017) Symptoms associated with Lewy body disease in mild cognitive impairment. Int J Geriatr Psychiatry 32(11):1163-1171.

[6]. Sadiq D, Whitfield T, Lee L, Stevens T, Costafreda S, Walker Z. (2017) Prodromal Dementia with Lewy Bodies and Prodromal Alzheimer's Disease: A Comparison of the Cognitive and Clinical Profiles. J Alzheimers Dis. 58(2):463-470.

[7]. Ballard C, Holmes C, McKeith I, Neill D, O'Brien J, Cairns N, Lantos P, Perry E, Ince P, and Perry R. (1999) Psychiatric Morbidity in Dementia With Lewy Bodies: A Prospective Clinical and Neuropathological Comparative Study With Alzheimer's Disease American Journal of Psychiatry 156:7, 1039-1045.

[8]. Sweet RA, Nimgaonkar VL, Devlin B and Jeste DV (2003) Psychotic symptoms in Alzheimer disease: evidence for a distinct phenotype REVIEW ARTICLE. Molecular Psychiatry 8, 383–392.

[9]. Neef D and Walling (2006) A Dementia with Lewy Bodies: An Emerging Disease Am Fam Physician 73(7):1223-1229.

[10]. Nelson PT, Jicha GA, Kryscio RJ, Abner EL, Schmitt FA, Cooper G, Xu LO, Smith CD, Markesbery WR. Low sensitivity in clinical diagnoses of dementia with Lewy bodies. J Neurol. 2010 Mar;257(3):359-66.

[11]. Mok W, Chow TW, Zheng L, Mack WJ, Miller C. Clinicopathological concordance of dementia diagnoses by community versus tertiary care clinicians. Am J Alzheimers Dis Other Demen. 2004 May-Jun;19(3):161-5.

[12]. Giaquinto S, Nolfe G (1986) The EEG in the normal elderly: a contribution to the interpretation of aging and dementia. Electroencephalogr Clin Neurophysiol. 63:540-6.

[13]. Briel RC, McKeith IG, Barker WA, Hewitt Y, Perry RH, Ince PG, Fairbairn AF (1999). EEG findings in dementia with Lewy bodies and Alzheimer's disease. J Neurol Neurosurg Psychiatry 66:401-3.

[14]. Babiloni C, Triggiani AI, Lizio R, Cordone S, Tattoli G, Bevilacqua V, Soricelli A, Ferri R, Nobili F, Gesualdo L, Millán-Calenti JC, Buján A, Tortelli R, Cardinali V, Barulli MR, Giannini A, Spagnolo P, Armenise S, Buenza G, Scianatico G, Logroscino G, Frisoni GB, Del Percio C (2016) Classification of Single Normal and Alzheimer's Disease Individuals from Cortical Sources of Resting State EEG Rhythms. Front Neurosci 23;10:47.

[15]. Dierks T, Jelic V, Pascual-Marqui RD, Wahlund LO, Julin P, Linden DEJ, Maurer K, Winblad B, Nordberg A (2000) Spatial pattern of cerebral glucose metabolism (PET) correlates with localization of intracerebral EEG-generators in Alzheimer's disease. Clin Neurophysiol 111, 1817–1824.

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

[17]. 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 multi-centric study. Clin Neurophysiol 117, 252–268.

[18]. Walker MP, Ayre GA, Cummings JL, Wesnes K, McKeith IG, O'Brien JT, Ballard CG (2000a) The clinician assessment of fluctuation and the one day fluctuation assessment scale. Two methods to assess fluctuating confusion in dementia. Br. J. Psychiatry 177, 252-256.

[19]. Walker MP, Ayre GA, Perry EK, Wesnes K, McKeith IG, Tovee M, Edwardson JA, Ballard CG (2000b) Quantification and characterization of fluctuating cognition in dementia with Lewy bodies and Alzheimer's disease. Dement Geriatr Cogn Disord 11, 327-335.

[20]. Kai T, Asai Y, Sakuma K, Koeda T, Nakashima K (2005) Quantitative electroencephalogram analysis in dementia with Lewy bodies and Alzheimer's disease. J Neurol Sci 237, 89-95.

[21]. Andersson M, Hansson O, Minthon L, Rosén I, Londos E (2008) Electroencephalogram variability in dementia with lewy bodies, Alzheimer's disease and controls. Dement Geriatr Cogn Disord 26, 284-290.

[22]. Bonanni L, Thomas A, Tiraboschi P, Perfetti B, Varanese S, Onofrj M (2008) EEG comparisons in early Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease with dementia patients with a 2-year follow-up. Brain 131, 690–705.

[23]. Bonanni L, Perfetti B, Bifolchetti S, Taylor JP, Franciotti R, Parnetti L, Thomas A, Onofrj M (2015) Quantitative electroencephalogram utility in predicting conversion of mild cognitive impairment to dementia with Lewy bodies. Neurobiol Aging 36, 434-345

[24]. Onofrj M, Thomas A, Iacono D, Luciano AL, Di Iorio A. The effects of a cholinesterase inhibitor are prominent in patients with fluctuating cognition: a part 3 study of the main mechanism of cholinesterase inhibitors in dementia. Clin. Neuropharmacol. 2003;26:239–251.

[25]. Bonanni L, Franciotti R, Nobili F, Kramberger MG, Taylor JP, Garcia-Ptacek S, Falasca NW, Famá F, Cromarty R, Onofrj M, Aarsland D; E-DLB study group. EEG Markers of Dementia with Lewy Bodies: A Multicenter Cohort Study. J Alzheimers Dis. 2016 Sep 2.

[26]. Pascual-Marqui RD, Michel CM, Lehmann D (1994) Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. Int. J. Psychophysiol 18, 49–65. doi:10.1016/j.jneumeth.2006.10.023.

[27]. Pascual-Marqui, RD (2007) Discrete, 3D distributed, linear imaging methods of electric neuronal activity. Part 1: exact, zero error localization. Math Phys, 1–16.

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

[29]. Babiloni C, Del Percio C, Lizio R, Noce G, Cordone S, Lopez S, Soricelli A, Ferri R, Pascarelli MT, Nobili F, Arnaldi D, Aarsland D, Orzi F, Buttinelli C, Giubilei F, Onofrj M, Stocchi F, Stirpe P, Fuhr P, Gschwandtner U, Ransmayr G, Caravias G, Garn H, Sorpresi F, Pievani M, Frisoni GB, D'Antonio F, De Lena C, Güntekin B, Hanoğlu L, Başar E, Yener G, Emek-Savaş DD, Triggiani AI, Franciotti R, De Pandis MF, Bonanni L. Abnormalities of cortical neural synchronization mechanisms in patients with dementia due to Alzheimer's and Lewy body diseases: an EEG study. Neurobiol Aging. 2017 Jul;55:143-158

[30]. Folstein MF, Folstein SE, McHugh PR (1975) 'Mini Mental State': a practical method for grading the cognitive state of patients for clinician. J Psychiatr Res 12, 189–198.

[31]. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566-72.

[32]. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982-1983;17(1):37-49.

[33]. Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A. Pathological verification of ischemic score in differentiation of dementias. Ann Neurol 1980;7:486-8.

[34]. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, ThiesB, 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.

[35]. Rey A (1968) Reattivo della figura complessa. Organizzazioni Speciali, Firenze.

[36]. Spinnler H, Tognoni G (1987) Standardizzazione e taratura italiana di test neuropsicologici. Ital J Neurol Sci 8, 1–120.

[37]. Fuchs M., Kastner J, Wagner M, Hawes S, Ebersole J S (2002) A standardized boundary element method volume conductor model. Clin. Neurophysiol 113, 702–712.

[38]. Novelli G, Papagno C, Capitani E, Laiacona M, Vallar G, Cappa SF. (1986) Tre test clinici di ricerca e produzione lessicale. Taratura su soggetti normali. Archivio di Psicologia, Neurologia e Psichiatria 47, 477-506.

[39]. Reitan R M (1958) Validity of the Trail Making Test as an indicator of organic brain damage. Perceptual and Motor Skills 8, 271-276.

[40]. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J (1994) The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. Neurology 44, 2308–2314.

[41]. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a frontal assessment battery at bedside. Neurology 2000;55, 1621e 1626.

[42]. Fahn S, Elton R. Members of the UPDRS Development Committee (1987) Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, editors. Recent Developments in Parkinson's Disease, Vol. 2. Florham Park, NJ: Macmillan Health Care Information; 293–304.

[43]. The International Classification of Sleep disorders. Diagnostic and coding manual. American academyof sleep medicine 1992.

[44]. Jurica PJ, Leitten CL, Mattis S (2001) Dementia Rating Scale-2: professional manual. Lutz: Psychological Assessment Resources.

[45]. Gelb DJ, Oliver E, Gilman S (1999) Diagnostic criteria for Parkinson disease. Arch Neurol 56(1):33-9.

[46]. Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. Neurology 17, 427–442.

[47]. Litvan I, Aarsland D, Adler CH, Goldman JG, Kulisevsky J, Mollenhauer B, Rodriguez-Oroz MC, Tröster AI, Weintraub D (2011) MDS Task Force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. Mov Disord 26, 1814-1824

[48]. Geser F, Wenning GK, Poewe W, McKeith I (2005) How to diagnose dementia with Lewy bodies: state of the art. Mov Disord 20, S11–20.

[49]. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, Salmon DP, Lowe J, Mirra SS, Byrne EJ, Lennox G, Quinn NP, Edwardson JA, Ince PG, Bergeron C, Burns A, Miller BL, Lovestone S, Collerton D, Jansen EN, Ballard C, de Vos RA, Wilcock GK, Jellinger KA, Perry RH (1996) Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 47, 1113–1124.

[50]. Moretti DV, Babiloni F, Carducci F, Cincotti F, Remondini E, Rossini PM, Salinari S, Babiloni C (2003) Computerized processing of EEG–EOG–EMG artifacts for multicentric studies in EEG oscillations and event-related potentials. Int J Pshycophysiol 47, 199–216.

[51]. Klimesch W (1996) Memory processes, brain oscillations and EEG synchronization. Int J Psychophysiol 24, 61-100.

[52]. Klimesch W (1999) EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Research Reviews 29, 169-195.

[53]. Klimesch W, Doppelmayr M, Russegger H, Pachinger T, Schwaiger J (1998) Induced alpha band power changes in the human EEG and attention. Neurosci Lett 244, 73-76.

[54]. Mazziotta J C, Toga A , Evans, A, Fox P, Lancaster J (1995) A probabilistic atlas of the human brain: theory and rationale for its development. The International Consortium for Brain Mapping (ICBM). Neuroimage 2, 89–101.

[55]. DeLong ER, DeLong DM, Clarke-Pearson DL. (1988) Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 44, 837-845.

[56]. Soikkeli R, Partanen J, Soininen H, Pääkkönen A, Riekkinen Sr P (1991) Slowing of EEG in Parkinson's disease. Electroencephalogr Clin Neurophysiol 79, 159–165.

[57]. Neufeld MY, Blumen S, Aitkin I, Parmet Y, Korczyn AD (1994) EEG frequency analysis in demented and nondemented parkinsonian patients. Dementia 5, 23–28.

[58]. Tanaka H, Koenig T, Pascual-Marqui RD, Hirata K, Kochi K, Lehmann D (2000) Event-related potential and EEG measures in Parkinson's disease without and with dementia. Dement Geriatr Cogn Disord 11, 39–45.

[59]. Franciotti R, Iacono D, Della Penna S, Pizzella V, Torquati K, Onofrj M, Romani GL (2006) Cortical rhythms reactivity in AD, LBD and normal subjects: a quantitative MEG study. Neurobiol Aging 27, 1100-1109.

[60]. Stam CJ (2010) Use of magnetoencephalography (MEG) to study functional brain networks in neurodegenerative disorders. J Neurol Sci 289, 128–134.

[61]. Steriade M, Llinas RR (1988) The functional states of the thalamus and the associated neuronal interplay. Physiol Rev 68, 649–742.

[62]. Dossi RC, Nuñez A, Steriade M (1992) Electrophysiology of a slow (0.5–4 Hz) intrinsic oscillation of cat thalamocortical neurones in vivo. J Physiol 447, 215–234.

[63]. Pfurtscheller G, Lopez da Silva F (1999) Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin Neurophysiol 110, 1842–1857.

[64]. Stigsby B, Jóhannesson G, Ingvar DH (1981) Regional EEG analysis and regional cerebral blood flow in Alzheimer's and Pick's diseases. Electroencephalogr Clin Neurophysiol 51, 537–547.

[65]. Brenner RP, Ulrich RF, Spiker DG, Sclabassi RJ, Reynolds 3rd CF, Marin RS, Boller F (1986) Computerized EEG spectral analysis in elderly normal, demented and depressed subjects. Electroencephalogr Clin Neurophysiol 64, 483–492.

[66]. Rae-Grant A, Blume W, Lau C, Hachinski VC, Fisman M, Merskey H (1987) The electroencephalogram in Alzheimer-type dementia. A sequential study correlating the electroencephalogram with psychometric and quantitative pathologic data. Arch Neurol 44, 50–54.

[67]. Kwa VI, Weinstein HC, Posthumus Meyjes EF, van Royen EA, Bour LJ, Verhoeff PN, Ongerboer de Visser BW (1993) Spectral analysis of the EEG and 99m-Tc-HMPAO SPECT-scan in Alzheimer's disease. Biol Psychiatry 33, 100–107.

[68]. Passero S, Rocchi R, Vatti G, Burgalassi L, Battistini N (1995) Quantitative EEG mapping, regional cerebral blood flow, and neuropsychological function in Alzheimer's disease. Dementia 6, 148–156.

[69]. Rodriguez G, Nobili F, Copello F, Vitali P, Gianelli MV, Taddei G, Catsafados E, Mariani G (1999) 99mTc-HMPAO regional cerebral blood flow and quantitative electroencephalography in Alzheimer's disease: a correlative study. J Nucl Med 40, 522-529.

[70]. Killiany RJ, Moss MB, Albert MS, Sandor T, Tieman J, Jolesz F (1993) Temporal lobe regions on magnetic resonance imaging identify patients with early Alzheimer's disease. Arch Neurol 50, 949–954.

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

[72]. Peraza LR, Kaiser M, Firbank M, Graziadio S, Bonanni L, Onofrj M, Colloby SJ, Blamire A, O'Brien J, Taylor JP. fMRI resting state networks and their association with cognitive fluctuations in dementia with Lewy bodies. Neuroimage Clin. 2014;4:558-565.

[73]. Peraza LR, Taylor JP, Kaiser M. Divergent brain functional network alterations in dementia with Lewy bodies and Alzheimer's disease. Neurobiol Aging. 2015 Sep;36(9):2458-67.

[74]. Hughes SW, Crunelli V (2005) Thalamic mechanisms of EEG alpha rhythms and their pathological implications. Neuroscientist 11, 357-372.

[75]. Lörincz ML, Crunelli V, Hughes SW (2008) Cellular dynamics of cholinergically induced alpha (8-13 Hz) rhythms in sensory thalamic nuclei in vitro. J Neurosci 28, 660-671.

[76]. Lorincz ML, Kékesi KA, Juhász G, Crunelli V, Hughes SW (2009) Temporal framing of thalamic relay-mode firing by phasic inhibition during the alpha rhythm. Neuron 63, 683-696.

[77]. Elosúa MR, Ciudad MJ, Contreras MJ. Gender Differences in Verbal and Visuospatial Working Memory Tasks in Patients with Mild Cognitive Impairment and Alzheimer Disease. Dement Geriatr Cogn Dis Extra. 2017;7:101-108.

[78]. Mitolo M, Gardini S, Fasano F, Crisi G, Pelosi A, Pazzaglia F, Caffarra P. Visuospatial memory and neuroimaging correlates in mild cognitive impairment. J Alzheimers Dis. 2013;35:75-90.

[79]. Weintraub S, Wicklund AH, Salmon DP: The neuropsychological profile of Alzheimer disease. Cold Spring Harb Perspect Med 2012;2:a006171.

[80]. Adler G, Brassen S, Jajcevic A. (2003) EEG coherence in Alzheimer's dementia. J Neural Transm 110(9):1051-8.

[81]. Bennys K, Rondouin G, Vergnes C, Touchon J. (2001) Diagnostic value of quantitative EEG in Alzheimer disease. Neurophysiol. Clin 31, 153–160.

[82]. Claus JJ, Strijers RL, Jonkman EJ, Ongerboer de Visser BW, Jonker C, Walstra GJ, Scheltens P, van Gool WA. (1999) The diagnostic value of electroencephalography in mild senile Alzheimer's disease. Clin Neurophysiol 110, 825–832.

[83]. Brassen S, Braus DF, Weber-Fahr W, Tost H, Moritz S, Adler G. (2004) Late-onset depression with mild cognitive deficits: electrophysiological evidences for a preclinical dementia syndrome. Dement Geriatr Cogn Disord 18, 271–277.

[84]. Lehmann C, Koenig T, Jelic V, Prichep L, John RE, Wahlund LO, Dodge Y, Dierks T. (2007) Application and comparison of classification algorithms for recognition of Alzheimer's disease in electrical brain activity (EEG). J Neurosci. Methods 161, 342–350.

[85]. Missonnier P, Gold G, Herrmann FR, Fazio-Costa L, Michel JP, Deiber, MP, Michon A, Giannakopoulos P. (2006) Decreased theta event-related synchronization during working memory activation is associated with progressive mild cognitive impairment. Dement Geriatr Cogn Disord 22, 250–259.

[86]. Buscema M, Rossini P, Babiloni C, Grossi E. (2007) The IFAST model, a novel parallel nonlinear EEG analysis technique, distinguishes mild cognitive impairment and Alzheimer's disease patients with high degree of accuracy. Artif Intell Med 40(2):127-41.

[87]. Knyazeva MG, Jalili M, Brioschi A, Bourquin I, Fornari E, Hasler M, Meuli R, Maeder P, Ghika J. (2010) Topography of EEG multivariate phase synchronization in early Alzheimer's disease. Neurobiol Aging 31(7):1132-44.

[88]. Lizio R, Del Percio C, Marzano N, Soricelli A, Yener GG, Başar E, Mundi C, De Rosa S, Triggiani AI, Ferri R, Arnaldi D, Nobili FM, Cordone S, Lopez S, Carducci F, Santi G, Gesualdo L, Rossini PM, Cavedo E, Mauri M, Frisoni GB, Babiloni C (2015) Neurophysiological assessment of Alzheimer's disease individuals by a single electroencephalographic marker. J Alzheimers Dis 49(1):159-77.

[89]. Engedal K, Snaedal J, Hoegh P, Jelic V, Bo Andersen B, Naik M, Wahlund LO, Oeksengaard AR (2015) Quantitative EEG applying the statistical recognition pattern method: a useful tool in dementia diagnostic workup. Dement Geriatr Cogn Disord 40(1-2):1-12.

[90]. Roks G, Korf ES, van der Flier WM, Scheltens P, Stam CJ. The use of EEG in the diagnosis of dementia with Lewy bodies. J Neurol Neurosurg Psychiatry. 2008;79(4):377-380.

[91]. Lee H, Brekelmans GJ, Roks G. The EEG as a diagnostic tool in distinguishing between dementia with Lewy bodies and Alzheimer's disease. Clin Neurophysiol. 2015;126(9):1735-1739.

[92]. Snaedal J, Johannesson GH, Gudmundsson TE, Blin NP, Emilsdottir AL, Einarsson B, et al. Diagnostic accuracy of statistical pattern recognition of electroencephalogram registration in evaluation of cognitive impairment and dementia. Dement Geriatr Cogn Disord. 2012;34(1):51-60.

[93]. Trillo L, Das D, Hsieh W, Medina B, Moghadam S, Lin B, Dang V, Sanchez MM, De Miguel Z, Ashford JW, Salehi A. Ascending monoaminergic systems alterations in Alzheimer's disease. translating basic science into clinical care. Neurosci Biobehav Rev. 2013;37:1363-1379.

[94]. Gomperts SN, Locascio JJ, Makaretz SJ, Schultz A, Caso C, Vasdev N, Sperling R, Growdon JH, Dickerson BC, Johnson K. Tau Positron Emission Tomographic Imaging in the Lewy Body Diseases. JAMA Neurol. 2016a Nov 1;73(11):1334-1341.

[95]. Gomperts SN, Marquie M, Locascio JJ, Bayer S, Johnson KA, Growdon JH. PET Radioligands Reveal the Basis of Dementia in Parkinson's Disease and Dementia with Lewy Bodies. Neurodegener Dis. 2016b;16(1-2):118-24

[96]. Lemstra AW, de Beer MH, Teunissen CE, Schreuder C, Scheltens P, van der Flier WM, Sikkes SA. Concomitant AD pathology affects clinical manifestation and survival in dementia with Lewy bodies. J Neurol Neurosurg Psychiatry. 2017 Feb;88(2):113-118.

[97]. Gillebert CR, Schaeverbeke J, Bastin C, Neyens V, Bruffaerts R, De Weer AS, Seghers A, Sunaert S, Van Laere K, Versijpt J, Vandenbulcke M, Salmon E, Todd JT, Orban GA, Vandenberghe R. 3D Shape Perception in Posterior Cortical Atrophy: A Visual Neuroscience Perspective. J Neurosci. 2015 Sep 16;35(37):12673-92.

[98]. Peavy GM, Edland SD, Toole BM, Hansen LA, Galasko DR, Mayo AM (2016) Phenotypic differences based on staging of Alzheimer's neuropathology in autopsy-confirmed dementia with Lewy bodies. Parkinsonism Relat Disord pii: S1353-8020(16)30265-6.

[99]. Nervi A, Reitz C, Tang MX, Santana V, Piriz A, Reyes-Dumeyer D, Lantigua R, Medrano M, Jiménez-Velázquez IZ, Lee JH, Mayeux R. Comparison of clinical manifestations in Alzheimer disease and dementia with Lewy bodies. Arch Neurol. 2008 Dec;65(12):1634-9.

Table legends

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 dementia with Lewy Body (DLBMCI). Legend: MMSE = Mini Mental State Evaluation; M/F = males/females; n.s. = not significant ($p > 0.05$).

Table 2. Psychoactive drugs for mental disorders (e.g., sedatives, antianxiety, antidepressants, antipsychotics, etc.) and other drugs (acetylcholinesterase inhibitors AChEIs, drugs for extrapyramidal symptoms EPS and dementia) in the present ADMCI and DLBMCI patients. The psychoactive drugs were categorized in two classes. The first class included antianxiety and antidepressant drugs, while the second class included antipsychotic drugs. The use of those drugs is reported as number and percentage of patients chronically assuming them before EEG recordings. Some patients assumed more than one psychoactive drug.

Table 3. Type of psychoactive drugs, acetylcholinesterase inhibitors (AChEIs), and drugs for extrapyramidal symptoms (EPS) and dementia taken by the ADMCI and DLBMCI patients of the present study.

Table 4. 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 Brodmann areas of the cerebral source space in the freeware used in this study, namely the exact low-resolution brain electromagnetic source tomography (eLORETA).

Table 5. 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, DLBMCI). The table also reports the p values of the statistical comparisons of these values between the Nold, ADMCI, DLBMCI groups. See the Methods for a definition of the TF and IAF.

Table 6. Mean values (± SE) of the demographic and clinical data and results of their statistical comparisons ($p < 0.05$) in the groups of Nold subjects and subgroups patients with ADMCI and DLBMCI who have never taken drug before the EEG recording. Legend: MMSE = Mini Mental State Evaluation; M/F = males/females; n.s. = not significant ($p > 0.05$).

Table 7. Correlation (coefficient of determination r^2) between (eLORETA) source activity of the rsEEG rhythms and the MMSE score in the Nold, ADMCI, and DLBMCI subjects as a whole group. The r^2 value is reported for monotonic (Spearman test), exponential, logarithmic, and power functions. The values of the normalized rsEEG power density in the cortical sources considered are reported as a reference.

Table 8. Results of the classification among Nold, ADMCI, and DLBMCI 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, DLBMCI). The classification rate is computed by the analysis of the area under the receiver operating characteristic (AUROC) curve. The table reports 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.

Figure legends

Figure 1. 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, and DLBMCI), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2 and gamma), and ROI (central, frontal, parietal, occipital, temporal, and limbic). This ANOVA design used the regional normalized eLORETA solutions as a dependent variable. Subjects' transition frequency (TF) and individual alpha frequency peak (IAF) were used as covariates. Regional normalized eLORETA solutions modeled the cortical sources of the rsEEG relative power spectra at the scalp electrodes. These sources can be considered as a sort of "virtual" intracranial macro-electrodes located on the macro-cortical regions of interest. See the Methods for a definition of the TF and IAF. Legend: the rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions presented statistically significant eLORETA patterns as in the following: Nold ≠ ADMCI ≠ DLBMCI (Duncan post hoc test, $p < 0.05$).

Figure 2. Regional normalized eLORETA solutions (mean across subjects) of the rsEEG rhythms relative to a statistical 3-way ANOVA interaction between the factors Group (17 Nold, 15 ADMCI, and 13 DLBMCI, who had never taken drugs before EEG recordings), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2 and gamma), and ROI (central, frontal, parietal, occipital, temporal, and limbic). Legend: the rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions presented statistically significant eLORETA patterns as in the following: Nold ≠ ADMCI ≠ DLBMCI (Duncan post hoc test, $p < 0.05$).

Figure 3. Individual values of the eLORETA cortical source activity showing statistically significant ($p < 0.05$) differences between the Nold, ADMCI, and DLBMCI groups in the main statistical analysis (i.e. frontal, parietal, and temporal delta; occipital, temporal, and limbic alpha 2; occipital alpha 2; see Figure 1 for the specific rsEEG source activities showing statistical significant results). Noteworthy, the Grubbs' test showed no outliers from those individual values of the eLORETA solutions (arbitrary threshold of $p < 0.0001$).

Figure 4. Scatterplots showing the correlation between (eLORETA) source activity of the rsEEG rhythms and the MMSE score in the Nold, ADMCI, and DLBMCI subjects as a whole group. The Spearman test evaluated the hypothesis of a correlation these rsEEG and MMSE variables (Bonferronio corrected $p < 0.05$). The r and p values are reported within the diagram.

Figure 5. (Top): Receiver operating characteristic (ROC) curves illustrating the classification of the ADMCI and Nold individuals based on the occipital alpha 2 (eLORETA) source activity. The area under the ROC (AUROC) curve was 0.86 indicating a good classification accuracy of the ADMCI and Nold individuals. (Middle): ROC curves illustrating the classification of the DLBMCI and Nold individuals based on the parietal delta (eLORETA) source activity. The AUROC curve was 0.89 indicating a good classification accuracy of the DLBMCI and Nold individuals. (Bottom): ROC curves illustrating the classification of the DLBMCI and ADMCI individuals based on the parietal delta (eLORETA) source activity. The

AUROC curve was 0.72 indicating a moderate classification accuracy of the DLBMCI and Nold individuals.

Table 1

MEAN VALUES (± SE) OF DEMOGRAPHIC DATA AND GLOBAL COGNITIVE STATUS (MMSE score)				
	Nold	**ADMCI**	**DLBMCI**	**Statistical analysis**
N	30	30	23	-
Age	74.7 (± 0.8)	74.2 (± 0.6)	75.7 (± 1.4)	ANOVA: n.s.
Gender (M/F)	18/12	16/14	14/9	Kruskal-Wallis: n.s.
Education	9.7 (± 0.7)	9.8 (± 0.8)	9.0 (± 0.9)	ANOVA: n.s.
MMSE	28.5 (± 0.2)	25.6 (± 0.4)	25.7 (± 0.4)	Kruskal-Wallis: $H = 34.7$, $p < 0.00001$ (Nold > ADMCI,DLBMCI)

Table 2

DRUGS ASSUMED BEFORE EEG RECORDING										
Drugs for anxiety and depression disorders			**Antipsychotic drugs**		**ALL PSYCHOACTIVE DRUGS**		**AChEI, EPS and dementia drugs**		**ALL DRUGS**	
	ADMCI	**DLBMCI**	**ADMCI**	**DLBMCI**	**ADMCI**	**DLBMCI**	**ADMCI**	**DLBMCI**	**ADMCI**	**DLBMCI**
(N)	11	8	1	4	12	10	4	4	16	14
%	36.67	34.78	3.33	17.39	40.00	43.48	13.33	17.39	53.33	60.87

Table 3

	Sedative, anxiety and antidepressant drugs (barbiturate, benzodiazepine..)	**Antipsychotic drugs**	**Other drugs (AChEI, EPS, dementia)**
ADMCI	Citalopram, pasaden, venlafaxine, seroplex, stilnox, xarax, cymbalta, cipralex, sereupin, entact, efexor, percital, seropram, trittico	Pipamperon	Donepezil, memantina, nicetile
DLBMCI	Circadin, lendormin, lorazepam, seripnol, cymbalta, cipralex, sertralina, selegilina, trittico,zoloft	Depakin, quetiapina, neuleptil, nozinan	Donepezil, rivastigmina, madopar, selegilina, memantina

Table 4

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

Table 5

MEAN VALUES (± SE) OF TRANSITION FREQUENCY (TF) AND INDIVIDUAL ALPHA FREQUENCY PEAK (IAF)				
	Nold	**ADMCI**	**DLBMCI**	**Statistical analysis**
TF	6.3 (± 0.2)	5.4 (± 0.2)	4.7 (± 0.2)	$F = 16.6$, $p < 0.00001$ (DLBMCI < ADMCI < Nold)
IAF	9.4 (± 0.1)	8.8 (± 0.3)	7.8 (± 0.3)	$F = 10.5$, $p < 0.0001$ (DLBMCI < ADMCI, Nold)

Table 6

MEAN VALUES (± SE) OF DEMOGRAPHIC DATA AND GLOBAL COGNITIVE STATUS (MMSE score)				
	Nold	**ADMCI**	**DLBMCI**	**Statistical analysis**
N	17	15	13	-
Age	76.6 (± 0.7)	74.8 (± 0.8)	77.8 (± 1.5)	ANOVA: n.s.
Gender (M/F)	11/6	8/7	10/3	Kruskal-Wallis: n.s.
Education	9.1 (± 0.9)	11.1 (± 1.1)	9.6 (± 1.4)	ANOVA: n.s.
MMSE	28.6 (± 0.2)	25.1 (± 0.6)	24.7 (± 0.4)	Kruskal-Wallis: H = 26.9 p = 0.00001 (Nold > ADMCI, DLBMCI)

Table 7

CORRELATION BETWEEN (eLORETA) SOURCE ACTIVITY AND THE MMSE SCORE (COEFFICIENT OF DETERMINATION R^2)				
	Monotonic (Spearman)	**Exponential**	**Logarithmic**	**Power**
Parietal delta	0.102	0.053	0.055	0.05
Occipital alpha 2	0.144	0.143	0.166	0.145
Limbic alpha 2	0.126	0.105	0.132	0.106
Occipital alpha 3	0.137	0.142	0.135	0.146

Table 8

CLASSIFICATION BETWEEN Nold, ADMCI, AND DLBMCI INDIVIDUALS BASED ON eLORETA SOURCES OF rsEEG RHYTHMS				
Nold vs. ADMCI				
eLORETA source activity	**Sensitivity**	**Specificity**	**Accuracy**	**AUROC**
Occipital alpha 2	**90.0%**	**73.3%**	**81.7%**	**0.86**
Temporal alpha 2	70.0%	66.7%	68.3%	0.73
Limbic alpha 2	90.0%	83.3%	86.7%	0.84
Occipital alpha 3	86.7%	73.3%	80.0%	0.85
Temporal delta/alpha 2	63.3%	86.7%	75.0%	0.78
Nold vs. DLBMCI				
eLORETA source activity	**Sensitivity**	**Specificity**	**Accuracy**	**AUROC**
Frontal delta	69.6%	86.7%	78.1%	0.80
Parietal delta	**82.6%**	**80.0%**	**81.3%**	**0.89**
Temporal delta	100.0%	60.0%	80.0%	0.87
Occipital alpha 2	87.0%	66.7%	76.8%	0.79
Limbic alpha 2	65.2%	80.0%	72.6%	0.73
Occipital alpha 3	73.9%	76.7%	75.3%	0.79
ADMCI vs. DLBMCI				
eLORETA source activity	**Sensitivity**	**Specificity**	**Accuracy**	**AUROC**
Parietal delta	**78.3%**	**66.75%**	**72.5%**	**0.72**
Temporal delta	95.7%	43.3%	69.5%	0.71

Figure 1

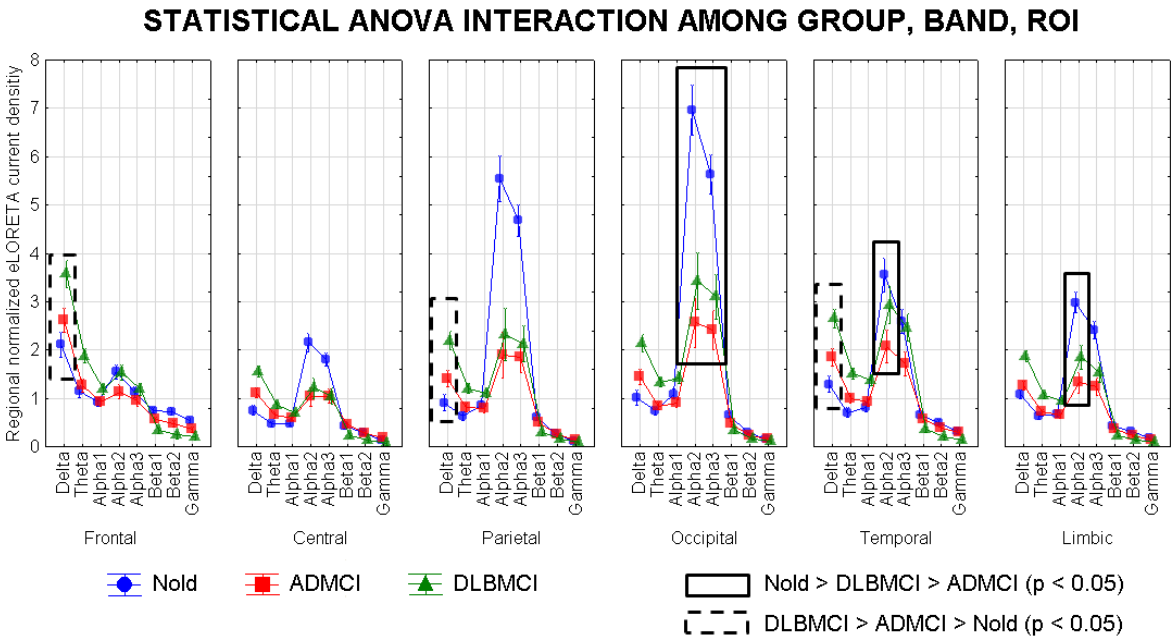

STATISTICAL ANOVA INTERACTION AMONG GROUP, BAND, ROI
Regional normalized eLORETA current density
0
1
2
3
4
5
6
7
8
Delta
Theta
Alpha1
Alpha2
Alpha3
Beta1
Beta2
Gamma
Frontal
Central
Parietal
Occipital
Temporal
Limbic
Nold
ADMCI
DLBMCI
Nold > DLBMCI > ADMCI (p < 0.05)
DLBMCI > ADMCI > Nold (p < 0.05)

Figure 2

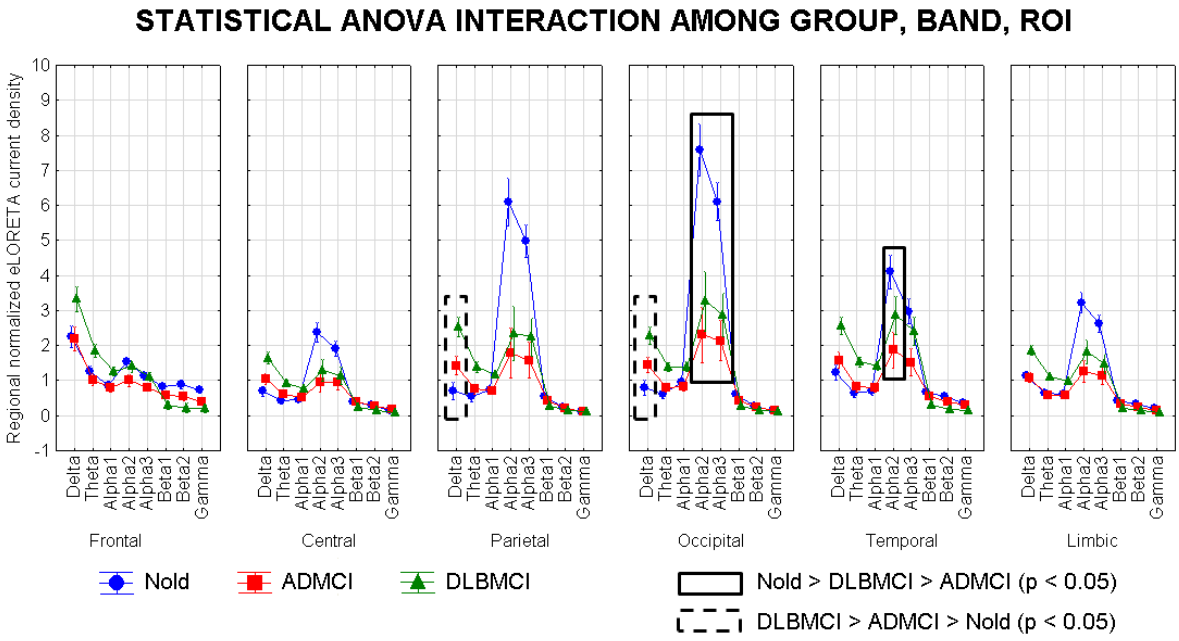

STATISTICAL ANOVA INTERACTION AMONG GROUP, BAND, ROI
Regional normalized eLORETA current density
10
9
8
7
6
5
4
3
2
1
0
-1
Delta
Theta
Alpha1
Alpha2
Alpha3
Beta1
Beta2
Gamma
Frontal
Central
Parietal
Occipital
Temporal
Limbic
Nold
ADMCI
DLBMCI
Nold > DLBMCI > ADMCI (p < 0.05)
DLBMCI > ADMCI > Nold (p < 0.05)

Figure 3

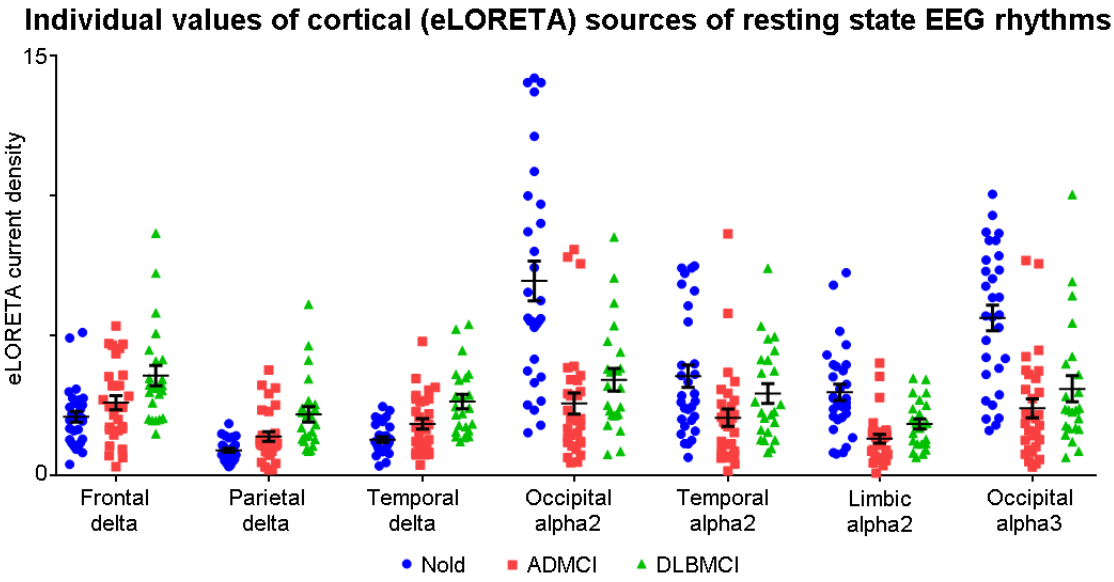

Individual values of cortical (eLORETA) sources of resting state EEG rhythms
eLORETA current density
15
0
Frontal delta
Parietal delta
Temporal delta
Occipital alpha2
Temporal alpha2
Limbic alpha2
Occipital alpha3
NoId
ADMCI
DLBMCI

Figure 4

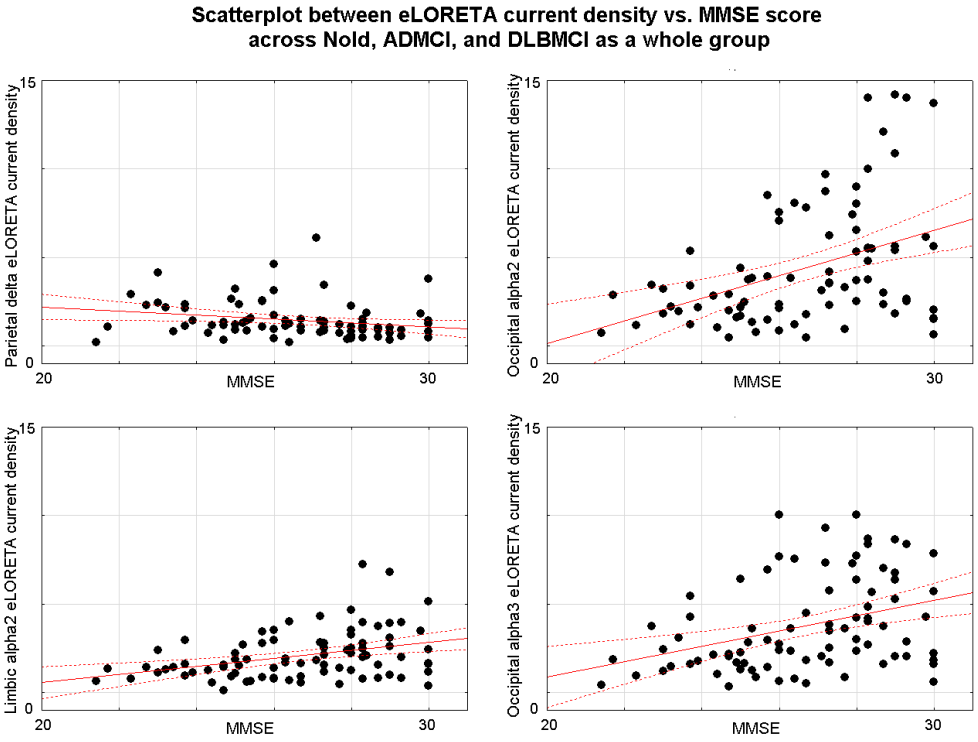
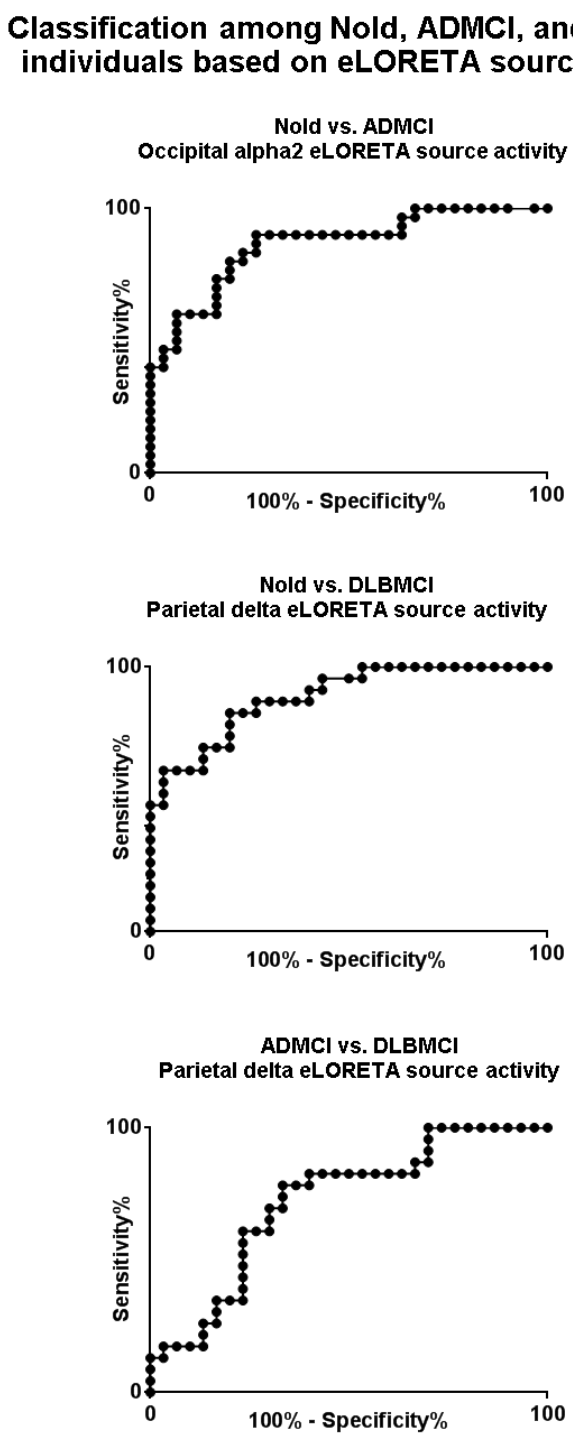

Scatterplot between eLORETA current density vs. MMSE score
across NoId, ADMCI, and DLBMCI as a whole group
Parietal delta eLORETA current density
Occipital alpha2 eLORETA current density
Limbic alpha2 eLORETA current density
Occipital alpha3 eLORETA current density
MMSE
15
0
20
30

Figure 5


Classification among Nold, ADMCI, and DLBMCI individuals based on eLORETA source activity
Nold vs. ADMCI
Occipital alpha2 eLORETA source activity
Sensitivity%
100% - Specificity%
0
100
Nold vs. DLBMCI
Parietal delta eLORETA source activity
Sensitivity%
100% - Specificity%
0
100
ADMCI vs. DLBMCI
Parietal delta eLORETA source activity
Sensitivity%
100% - Specificity%
0
100