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Abnormalities of functional cortical source connectivity of resting-state electroencephalographic alpha rhythms are similar in patients with mild cognitive impairment due to Alzheimer's and Lewy body diseases

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ABSTRACT

Previous evidence has shown different resting-state eyes-closed electroencephalographic delta (<4 Hz) and alpha (8–10.5 Hz) source connectivity in subjects with dementia due to Alzheimer's (ADD) and Lewy body (DLB) diseases. The present study tested if the same differences may be observed in the prodromal stages of mild cognitive impairment (MCI). Here, clinical and resting-state eyes-closed

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electroencephalographic data in age-, gender-, and education-matched 30 ADMCI, 23 DLBMCI, and 30 healthy elderly (Nold) subjects were available in our international archive. Mini-Mental State Evaluation (MMSE) score was matched in the ADMCI and DLBMCI groups. The eLORETA freeware estimated delta and alpha source connectivity by the tool called lagged linear connectivity (LLC). Area under receiver operating characteristic curve (AUROCC) indexed the classification accuracy among individuals. Results showed that widespread interhemispheric and intrahemispheric LLC solutions in alpha sources were abnormally lower in both MCI groups compared with the Nold group, but with no differences were found between the 2 MCI groups. AUROCCs of LLC solutions in alpha sources exhibited significant accuracies (0.72–0.75) in the discrimination of Nold versus ADMCI-DLBMCI individuals, but not between the 2 MCI groups. These findings disclose similar abnormalities in ADMCI and DLBMCI patients as revealed by alpha source connectivity. It can be speculated that source connectivity mostly reflects common cholinergic impairment in prodromal state of both AD and DLB, before a substantial dopaminergic derangement in the dementia stage of DLB.

1. Introduction

Alzheimer's and Lewy body neurodegenerative diseases (AD and DLB) induce a progressive cognitive impairment to dementia. The most frequent prodromal manifestation of AD is an amnesic mild cognitive impairment (MCI; Dubois et al., 2014), while the most frequent prodromal manifestation of DLB includes the fluctuation of cognitive performance over time, behavioral disorders during rapid eye movement sleep, and visual hallucinations several months before the appearance of motor disorders (Aarsland et al., 2003; McKeith et al., 2005, 2017).

Prodromal and dementia stages of AD affect cortical neural synchronization and functional connectivity mechanisms underpinning brain arousal and vigilance in quiet wakefulness as revealed by resting-state eyes-closed electroencephalographic (rsEEG) rhythms (Babiloni et al., 2016b, 2017). As functional connectivity mechanisms may be especially relevant to understand the neural basis of cognitive deficits in neurodegenerative diseases (D'Amelio and Rossini, 2012; Pievani et al., 2011), we focused our short review of the rsEEG literature on this aspect in the following paragraphs.

When compared with normal elderly (Nold) subjects, patients with dementia due to Alzheimer's (ADD) pointed to lower spectral coherence (a linear measurement of interrelatedness of rsEEG activity) between electrode pairs at posterior alpha (8–12 Hz) and beta (13–20 Hz) rhythms (Adler et al., 2003; Anghinah et al., 2000; Besthorn et al., 1994a; Dunkin et al., 1994; Fonseca et al., 2011, 2013; Jelic et al., 1996, 2000; Knott et al., 2000; Leuchter et al., 1987, 1992, 1994; Locatelli et al., 1998; Pogarell et al., 2005; Sloan et al., 1994). However, these effects were topographically variable being observed in temporo-parieto-occipital electrode pairs in some studies (Adler et al., 2003; Jelic et al., 2000; Locatelli et al., 1998). By contrast, other studies reported abnormalities in frontocentral electrode leads (Besthorn et al., 1994b; Fonseca et al., 2013).

Mixed coherence results were also reported at low frequency bands such as delta (<4 Hz) and theta (4–7 Hz) rhythms between electrode pairs. Some investigations reported a decrease of rsEEG coherence at low frequencies, especially at central electrodes in the theta band (Adler et al., 2003; Knott et al., 2000). Other investigations reported increased widespread delta coherences (Babiloni et al., 2010) or a quite complex topographical pattern showing increases and decreases of coherence values at electrode pairs (Sankari et al., 2011). More recently, a measure called phase lag index has been introduced to remove the influence of zero lag coherence in the computation of interrelatedness of rsEEG rhythms at electrode pairs (Stam et al., 2007). Compared with Nold subjects, patients with ADMCI exhibited decreased phase lag index within frontal and between frontal and temporal/parietal areas at delta and theta rhythms, with more pronounced effects at 1-year follow-up (Tóth et al., 2014).

Coherence values estimate just the linear (but not nonlinear) interrelatedness of rsEEG rhythms at electrode pairs. Therefore, other studies used alternative techniques providing measures sensitive to both linear and nonlinear interrelatedness of rsEEG rhythms at electrode pairs. In this line, a study using the measure called "synchronization likelihood" showed lower interrelatedness values across all electrode pairs at beta rhythms in patients with AD than ADMCI and Nold subjects (Babiloni et al., 2004, 2006b). Other studies showed a selective reduction of "synchronization likelihood" between frontal and parietal electrodes at alpha rhythms in ADD and ADMCI patients compared with Nold subjects (Babiloni et al., 2004, 2006b). Furthermore, a similar measure called lagged phase synchronization pointed to decreased values between temporal and parietal electrodes at alpha rhythms in patients with ADD compared with Nold subjects (Canuet et al., 2012). In addition, there was an increase in lagged phase synchronization between several regions of the 2 hemispheres at low-frequency rsEEG rhythms, particularly in the theta band (Canuet et al., 2012).

The aforementioned techniques do not provide an estimation of the directionality of driving forces inducing the functional cortical connectivity derived from rsEEG rhythms at electrode pairs, namely the directionality from one electrode to the other. In this line, results exhibited a lower directionality from parietal to frontal electrodes in the directed transfer function of alpha and beta rhythms estimated in ADD and ADMCI patients when compared with Nold subjects (Babiloni et al., 2009; Dauwels et al., 2009, 2010).

Measurements of interrelatedness of rsEEG rhythms between electrodes showed some differences in patients with ADD versus patients with DLB at the group level but with contrasting findings in different studies. Compared with Nold and ADD subjects, patients with DLB exhibited higher coherence at delta rhythms and lower coherence at alpha rhythms, computed averaging the values across all pairs of electrodes (Andersson et al., 2008). In the same line, intrahemispheric coherence values computed between temporo-fronto-central electrode pairs at delta and theta frequencies were higher in patients with DLB than patients with ADD, whereas occipital-temporo-centro-parietal beta (but not alpha) coherence values were lower in the former than the latter (Kai et al., 2005). By contrast, another study found the differences between groups using global alpha phase lag index, again computed averaging the values across all pairs of electrodes; this index was lower in DLB than both Nold and ADD subjects (van Dellen et al., 2015). Finally, phase transfer entropy measured directionality of rsEEG coupling at electrode pairs with the following results: (1) posterior-to-anterior directionality of rsEEG activity was observed in Nold subjects at theta, alpha, and beta rhythms; (2) this directionality was absent in patients with DLB at alpha rhythms and was more deranged in patients with ADD than patients with DLB at beta rhythms (Dauwan et al., 2016b).

Measurements of interrelatedness of rsEEG rhythms between electrodes showed some differences in patients with ADD versus patients with DLB at the group level but with contrasting findings in different studies. Compared with Nold and ADD subjects, patients with DLB exhibited higher coherence at delta and lower coherence at alpha rhythms, computed averaging the values across all pairs of electrodes (Andersson et al., 2008). In the same line, another study using global alpha phase lag index, computed averaging the values across all pairs of electrodes, manifested a decrease of this index in DLB compared with both Nold and ADD subjects (van Dellen et al., 2015). In addition, intrahemispheric coherence values computed at temporo-fronto-central electrode pairs at delta and theta rhythms were higher in patients with DLB than patients with ADD. By contrast, occipital-temporo-centro-parietal beta (but not alpha) coherence values were lower in DLB than both Nold and ADD subjects (Kai et al., 2005). Finally, phase transfer entropy measured directionality of rsEEG coupling at electrode pairs with the following results: (1) posterior-to-anterior directionality of rsEEG activity was observed in Nold subjects at theta, alpha, and beta rhythms; (2) this directionality was absent in patients with DLB in alpha rhythms and was more deranged in patients with ADD than patients with DLB in beta rhythms (Dauwan et al., 2016b).

The mentioned results provide contrasting evidence about the inter-relatedness of delta, theta, alpha, and beta rhythms at electrode pairs in patients with AD compared with patients with DLB, thus not providing a consistent representation of cortical functional connectivity in the 2 groups neither at the dementia stage nor in the MCI status. Specifically, the previous results on rsEEG rhythms were unclear if delta and theta (i.e., one or both) oscillatory activities may pathologically increase or decrease in DLBMCI compared with ADMCI subjects, and if intrahemispheric and interhemispheric functional connectivity values (i.e., one or both) may be altered or not. These doubts are relevant for the neurophysiological meaning of the abnormalities in functional cortical connectivity observed in the early stages of those neurodegenerative disorders.

To improve the spatial and frequency details of such analysis, we recently proposed a procedure combining the estimation of cortical sources of rsEEG rhythms by exact low-resolution brain electromagnetic tomography (Pascual-Marqui, 2007a) and the use of alpha frequency peak (IAF) in the determination of personalized delta, theta, and alpha frequency bands (Klimesch, 1999; Klimesch et al., 1996, 1998). With this procedure, we unveiled differences in delta and alpha source activation, as markers of cortical neural synchronization/desynchronization, in ADMCI and DLBMCI patients compared with Nold subjects (Babiloni et al., 2018a, b). Both ADMCI and DLBMCI groups exhibited an IAF slower in frequency (especially the DLBMCI group) compared with the Nold group subjects (Babiloni et al., 2018b). Furthermore, both MCI groups exhibited abnormal widespread delta (especially the DLBMCI group) and posterior alpha (especially the ADMCI group) source activities (Babiloni et al., 2018b). Moreover, this advanced procedure showed that compared with Nold and DLB patients, patients with ADD were characterized by increased delta and decreased alpha source connectivity (Babiloni et al., 2018a). Keeping in mind these findings, this study evaluated the hypothesis that compared with Nold subjects, ADMCI and DLBMCI patients may show abnormal delta (ADMCI) and alpha (ADMCI and DLBMCI) cortical source connectivity. To facilitate the comparison with our previous results (Babiloni et al., 2018a, b), the present study on source connectivity adopted a similar design of statistical analysis. Specifically, ANOVAs tested differences in delta and alpha source connectivity between pairs of groups (i.e., Nold, ADMCI, and DLBMCI). Furthermore, correlation and classification (i.e., AUROC curve analysis) procedures tested if the delta and alpha source connectivity showing differences between the groups conveyed information contents at the individual level. We expected that markers of functional cortical connectivity may enrich our view of prodromal AD and DLB in relation to the insight provided by previous evidence at the dementia stage (Babiloni et al., 2018a).

2. Materials and methods

Details on the subjects, diagnostic criteria, rsEEG recording, and preliminary data analysis can be found in the previous reference article (Babiloni et al., 2017). A short description of those aspects is given in the next sections for readers' convenience.

2.1. Subjects and diagnostic criteria

This study reused rsEEG data of our International Consortium, composed by clinical, neuroimaging, electrophysiological, and neuropsychological data in 30 Nold, 23 DLBMCI, and 30 ADMCI individual data sets (Babiloni et al., 2017). 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), University "G. d'Annunzio" of Chieti-Pescara (Italy), General Hospital of Linz (Austria), Dokuz Eylul University (Turkey), Istanbul Medipol University (Turkey), and University of Basel (Switzerland). These groups were selected to be matched for the gender, age, and education. The MCI groups were matched for the score of mini-mental state evaluation, MMSE (Folstein et al., 1975). Table 1 provides 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 (Fisher-Freeman-Halton test), education (ANOVA), and MMSE score (Kruskal-Wallis test). As expected, a statistically significant difference was found among the Nold and the other 2 groups for the MMSE score ($p < 0.00001$). 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 3 groups ($p > 0.05$). All individuals signed the written informed consensus allowing the use of all neuropsychological, clinical, and other data in an anonymous form for scientific purposes.

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 AD status. The patients with ADMCI received different neuroimaging diagnostic procedures and laboratory analyses to confirm the AD diagnosis. In particular, the AD diagnosis implied "positivity" to the next biomarkers (one or more): (1) fluorodeoxyglucose positron emission tomography of parietal, posterior cingulate, temporal, and hippocampal regions; (2) Aβ1-42/phospho-tau measured in cerebrospinal fluid; and/or (3) T1-weighted MRI of parietal, posterior cingulate, temporal, and hippocampal regions (Albert et al., 2011). The "positivity" of the marker(s) was evaluated by medical staff in charge of the assessment and care of patients, in line with local good clinical practice and routine. The judgment of that marker was done blinded to the present rsEEG markers. The inclusion criteria for the selection of the patients with ADMCI were as follows: (1) age of 55–90 years; (2) reported memory complaints confirmed by a relative; (3) MMSE score of 24 or higher; (4) Clinical Dementia Rating score of 0.5 (Morris, 1993); (5) logical memory test (Wechsler, 1987) score of 1.5

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 (ADMCI) and Lewy body (DLBMCI) diseases

	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	Fisher-Freeman-Halton: 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)

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

standard deviation lower than the mean adjusted as age; the cognitive deficits were not so strong to interfere significantly with the functional independence in the activities of the daily living; (6) Geriatric Depression Scale (15-item GDS; Brown and Schinka, 2005) score of 5 or lower; (7) modified Hachinski ischemia (Rosen et al., 1980) score of 4 or lower and education of 5 years or higher; and (8) single- or multi-domain MCI status. The exclusion criteria for the selection of the patients with ADMCI were as follows: (1) other significant systemic, psychiatric neurological illness; (2) mixed dementia; (3) actual participation to a clinical trial using disease-modifying drugs; (4) systematic use of antidepressant drugs with anticholinergic side effects; (5) chronic use of neuroleptics, narcotics, analgesics, sedatives, or hypnotics; and (6) medications to treat parkinsonians (cholinesterase inhibitors and Memantine allowed); and (7) major depression disorders described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).

All patients with ADMCI 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 (Osterrieth, 1944) and the delayed recall of a story (Spinnler and Tognoni, 1987). The tests assessing language included the 1-minute verbal fluency for letters, fruits, animals, or car trades (Novelli et al., 1986) and/or the Token test (De Renzi and Faglioni, 1978). The tests assessing executive function and attention included the trail making test part A and B (Reitan, 1958). Finally, the tests assessing visuoconstruction included the copy of Rey figures.

Probable DLB (at the stage of MCI) was diagnosed based on international consensus guidelines reported by McKeith et al., 2005, 2017). All patients with DLBMCI except one received DaTscan to confirm the DLB diagnosis. Concerning the evaluation of suggestive/indicative and core DLB features, (1) Neuropsychiatric Inventory (NPI item-2) probed frequency and severity of hallucinations when present (Cummings et al., 1994), (2) Clinician Assessment of Fluctuations (Walker et al., 2000a, b) and Frontal Assessment Battery (FAB; Dubois et al., 2000) investigated frontal dysfunctions and cognitive fluctuations, respectively; (3) Unified Parkinson Disease Rating Scale-III (UPDRS-III) evaluated extrapyramidal symptoms (Fahn and Elton, 1987); (4) rapid eye movement sleep behavior disorders were tested based on minimal International Classification of Sleep Disorders criteria (1992). The inclusion criteria for the selection of the patients with DLBMCI were as follows: (1) age of 55–90 years; (2) a gradual decline, in the context of an established DLB, in the cognitive status reported by either the patient or informant, or observed by the clinicians; (3) cognitive deficits not so strong to interfere significantly with the functional independence in the activities of the daily living, although slight difficulties on complex functional tasks may be present; (4) MMSE score of 24 or higher; (5) Clinical Dementia Rating score of 0.5; and (6) GDS score of 5 or lower. On the basis of clinical features and neuroradiological findings, the exclusion criteria for the patients with DLBMCI included the following forms of parkinsonism: (1) Parkinson's disease (PD; Gelb et al., 1999); (2) secondary parkinsonism, including drug-induced parkinsonism; (3) cerebrovascular parkinsonism; (4) atypical parkinsonism with absent or minimal responses to antiparkinsonian drugs; and (5) mixed dementia. As this retrospective study was based on data of several clinical units that did not follow a harmonized protocol, the patients with DLBMCI underwent a different battery of clinical scales including the Neuropsychiatric Inventory (NPI; Cummings et al., 1994), the scale for the assessment of behavioral and psychological symptoms of dementia, the MMSE score, the Dementia Rating Scale-2 (Jurica et al., 2001), the Epworth Sleepiness Scale for estimating subjective sleep disturbances, and the Alzheimer's Disease Cooperative Study for the Activities of Daily Living. Furthermore, the present patients with DLBMCI underwent a different battery of neuropsychological tests to evaluate the status of MCI (Donaghy et al., 2017). 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).

In all ADMCI and DLBMCI patients, drugs were suspended for about 24–48 hours before EEG recordings. This did not ensure a complete washout of the drug for obvious ethical reasons. Rather, this procedure made it comparable EEG data in relation to the drug condition in the ADMCI and DLBMCI patients.

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 to suffer from a subjective cognitive impairment. The Nold subjects affected by any chronic systemic illnesses (e.g., diabetes mellitus) were excluded, as were the Nold subjects receiving chronic psychoactive drugs. The Nold 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 at the time of the enrollment.

2.2. rsEEG recordings and preliminary data analysis

The rsEEG activity was collected for about 5 minutes while subjects were relaxed with eyes closed on a comfortable reclined chair (128 Hz or higher sampling rate, with related antialiasing bandpass between 0.01 Hz and 100 Hz). Electrode montage included 19 scalp leads placed following 10–20 system (i.e., O1, O2, P3, Pz, P4, T3, T5, T4, T6, C3, Cz, C4, F7, F3, Fz, F4, F8, Fp1, and Fp2). A frontal ground electrode was used. Electrodes impedances were kept below 5 kΩ. Vertical and horizontal electro-oculographic potentials (0.3–70 Hz bandpass) were recorded to control eye movements and blinking. Linked earlobe electrodes were used as an electrode reference when available (Recording units followed their methodological facilities and standard internal protocols).

The rsEEG data were centrally analyzed in blind about the subjects' diagnosis at the Sapienza University of Rome. The rsEEG data were divided into segments of 2 seconds and analyzed offline. The

epochs affected by any physiological (ocular/blinking, muscular, and head movements) or nonphysiological (bad contact electrode scalp) artifacts were preliminarily identified by an automatic computerized procedure (Moretti et al., 2003). EEG epochs with sporadic and well-shaped blinking artifacts (less than 10% of the total) were, then, corrected by an autoregressive method on the basis of the electrooculographic activity (Moretti et al., 2003). Furthermore, 2 independent experimenters manually checked and confirmed the artifact-free rsEEG epochs, before successive analyses. Specifically, they controlled for the presence of ocular and blinking artifacts based on electro-oculographic signals, whereas muscular and head artifacts were recognized by analyzing EEG signals. Particular attention was dedicated to the identification of extracerebral contamination of ocular activity (i.e., blinking) in frontal (i.e., F7, F3, Fz, F4, and F8) and prefrontal (Fp1 and Fp2) electrodes, comparing electrooculographic and EEG traces. Moreover, head artifacts were detected by a sudden and great increase in amplitude of slow EEG waves in all scalp electrodes. Finally, muscle artifacts were recognized by observing the effects of several frequency bandpass filters in different ranges and by the inspection of EEG power density spectra. Muscle tension is related to unusually high and stable values of EEG power density from 30 to 100 Hz, which contrast with the typical declining trend of EEG power density from 25 Hz onward. The 2 independent experimenters also detected EEG epochs with signs of sleep such as K complexes, sleep spindles, and slow waves. As a result, the artifact-free epochs showed the same proportion of the total amount of rsEEG recorded in all groups (>80%). In particular, the 2 experimenters selected 129 (±10 SE) artifact-free EEG epochs in the Nold group, 121 (±7 SE) in ADMCI group, and 123 (±6 SE) in DLBMCI group. A statistical procedure showed no statistically significant difference of the amount of artifact-free EEG epochs among the 3 groups (ANOVA, $p > 0.05$).

The frequency bands of interest were determined subject by subject based on transition frequency (TF) and the IAF. In brief, TF marks the transition frequency between alpha and theta bands. It is defined as the minimum rsEEG power density between 3 and 8 Hz (i.e., between delta and alpha power peaks). Instead, IAF marks the peak of power density between 14 and 6 Hz. TF and IAF were proposed by the group of Dr Wolfgang Klimesch 2 decades ago and repeatedly used in EEG research (Klimesch, 1999; Klimesch et al., 1996, 1998). Based on TF and IAF, individual delta, theta, and alpha bands were defined as follows: (1) high-frequency alpha (or alpha 3) from IAF to IAF+2 Hz; (2) low-frequency alpha (alpha 1 and alpha 2) from TF to IAF; (3) theta from TF −2 Hz to TF; and (4) delta from TF −4 Hz to TF −2 Hz (details in the study by Babiloni et al., 2018a, b). 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.

2.3. Estimation of functional connectivity of rsEEG cortical sources

"Functional cortical connectivity" was computed by the toolbox of exact LORETA (eLORETA) freeware (Pascual-Marqui, 2007a) called lagged linear connectivity (LLC; Pascual-Marqui et al., 2011). This toolbox gives linear measurements (LLC solutions) of statistical interdependence of pairs of (eLORETA) cortical source currents estimated from scalp-recorded rsEEG rhythms frequency bin-by-frequency bin. Specifically, LLC solutions were produced for all combinations of voxels in the eLORETA source space (Pascual-Marqui et al., 2011). LLC solutions were averaged for couples of regions of interest (ROIs) to account for their intrinsic low spatial resolution.

LLC estimates functional cortical source connectivity removing zero-lag instantaneous phase coupling between cortical sources of rsEEG rhythms assessed by eLORETA. Indeed, zero-lag phase interactions might be due at least in part by (instantaneous) physical spread of ionic currents from a given neural source to the others as a result of effects of the head as a volume conductor (Pascual-Marqui, 2007a). However, the LLC solutions may not be totally immune by the effect of "common drive/source" of a "third" source on LLC solutions estimated between 2 cortical sources of interest.

For each frequency band (i.e., from delta to gamma) and subject, LLC solutions were computed for 5 ROIs, namely frontal, central, parietal, occipital, and temporal lobes in the eLORETA cortical source space (Pascual-Marqui, 2007b).

Interhemispheric LLC solutions were estimated between all voxels of a given ROI of one hemisphere with all voxels of the homologous one of the opposite hemisphere. All LLC solutions between the 2 ROIs were averaged. For the mentioned frequency bands, 5 interhemispheric LLC solutions were computed such as temporal (i.e., temporal right − temporal left LLC), occipital (i.e., occipital right - occipital left LLC), parietal (i.e., parietal right - parietal left LLC), central (i.e., central right - central left LLC), and frontal (i.e., frontal right - frontal left LLC).

Intrahemispheric LLC solutions were estimated between all voxels of a given ROI of one hemisphere with all voxels of each ROI of the same hemisphere. All LLC solutions between the paired ROIs were averaged. For the mentioned frequency bands, 5 interhemispheric LLC solutions were computed such as temporal (i.e., mean among left temporal - frontal, left temporal - central, left temporal - parietal, and left temporal - occipital LLC), occipital (i.e., mean among left occipital - frontal, left occipital - central, left occipital - parietal, and left occipital - temporal LLC), parietal (i.e., mean among left parietal - frontal, left parietal - central, left parietal - temporal, and left parietal - occipital LLC), central (i.e., mean among left central - frontal, left central - parietal, left central - temporal, and left central - occipital LLC), and frontal (i.e., mean among left frontal - central, left frontal - parietal, left frontal - temporal, and left frontal - occipital LLC). The same procedure was repeated for the right hemisphere.

2.4. Statistical analysis of the LLC of rsEEG cortical sources

STATISTICA 10 software (StatSoft Inc, www.statsoft.com) was used to evaluate the hypothesis that eLORETA LLC solutions between paired rsEEG sources may be altered in the DLBMCI and ADMCI groups compared with the control Nold group. Furthermore, it tested possible differences between the 2 pathological groups. Two ANOVAs were used with eLORETA LLC solutions as dependent variables ($p < 0.05$). LLC solutions were preliminarily transformed by square root function to produce Gaussian distributions of the variables. Mauchly's test assessed sphericity assumption while Greenhouse-Geisser procedure corrected degrees of freedom when appropriate ($p < 0.05$). Specifically, 2 ANOVAs were implemented.

The first ANOVA assessed differences in interhemispheric LLC solutions (1) between Nold and MCI groups (i.e., Nold ≠ both ADMCI and DLBMCI) and (2) between DLBMCI and ADMCI groups (i.e., DLBMCI ≠ ADMCI). The ANOVA used the following factors: group (Nold, DLBMCI, and ADMCI), band (from delta to gamma), and ROI (occipital, temporal, parietal, central, and frontal).

The second ANOVA assessed differences in intrahemispheric LLC solutions (1) between Nold and MCI groups (i.e., Nold ≠ both ADMCI and DLBMCI) and (2) between DLBMCI and ADMCI groups (i.e., DLBMCI ≠ ADMCI). The ANOVA used the following factors: group (Nold, DLBMCI, and ADMCI), hemisphere (right and left), band (from delta to gamma), and ROI (occipital, temporal, parietal, central, and frontal).

In this statistical session, the hypothesis confirmation required (1) an effect with group ($p < 0.05$) and (2) a post hoc (Duncan) test showing LLC solutions with statistically significant differences ($p < 0.05$, one-tailed) between Nold versus MCI groups (i.e., Nold < ADMCI and DLBMCI as delta sources; DLBMCI and ADMCI < Nold as alpha sources; $p < 0.05$, one-tailed). Furthermore, a post hoc Duncan test differences in LLC solutions between DLBMCI and ADMCI groups ($p > 0.05$, two-tailed).

Grubbs' test ($p < 0.0001$) controlled for outliers in LLC solutions.

Concerning the statistical analysis at individual level, Spearman test assessed the correlation between relevant LLC solutions and MMSE score in all Nold, ADMCI, and DLBMCI individuals as a whole (Bonferroni corrected $p < 0.05$). The hypothesis is that those LLC solutions are related to the global cognitive status in general. Furthermore, MMSE scores have too low scatter within a single group level. Statistical threshold was based on Bonferroni correction ($p < 0.05$ corrected).

2.5. Accuracy of the discrimination between the Nold, ADMCI, and DLBMCI individuals

Relevant eLORETA LLC solutions were used to classify Nold versus MCI individuals (i.e., Nold vs. ADMCI and Nold vs. DLBMCI) by the computation of ROC curves (DeLong et al., 1988) using the GraphPad Prism software (Inc, California, USA). Standard indexes of the ROC curves were used (i.e., sensitivity, specificity, accuracy, and area under the ROC curve, AUROC; details in Babiloni et al. (2018a).

3. Results

3.1. eLORETA interhemispheric LLC solutions in Nold, ADMCI, and DLBMCI groups

Fig. 1 plots means (±standard error mean, SE) of interhemispheric LLC solutions for 3 groups (Nold, ADMCI, and DLBMCI), 5 ROIs (frontal, central, parietal, occipital, and temporal), and 8 bands (from delta to gamma). It is noted that magnitude and profile of interhemispheric LLC solutions were different among Nold, ADMCI, and DLBMCI groups. In the Nold group, interhemispheric LLC solutions were maximum in temporal (here they showed highest values), parietal, and occipital alpha 2 and alpha 3 sources. Other LLC solutions were low (widespread delta, theta, and alpha 1 sources) or very low (beta 1, beta 2, and gamma sources). Compared with that group, the ADMCI and DLBMCI groups showed interhemispheric LLC solutions with similar frequency and spatial profile but characterized by a lower magnitude. Both MCI groups presented lower values in interhemispheric LLC solutions in temporal, frontal, occipital, parietal, and central alpha 2 and 3 sources. Of note, the 2 MCI groups exhibited no remarkable differences in LLC solutions.

The aforementioned LLC solutions were square root transformed to became Gaussian (confirmed by Kolmogorov–Smirnov, $p > 0.05$). The transformed LLC solutions presented an interaction group X band ($F = 4.9$, $p = 0.00001$). Duncan test showed that discriminant LLC pattern ADMCI and DLBMCI < Nold was confirmed by global alpha 2 ($p < 0.00001$) and alpha 3 ($p < 0.0005$) sources. This effect distinguished ADMCI/DLBMCI versus Nold subjects at the group level. No difference was found between the ADMCI and the DLBMCI group ($p > 0.05$).

3.2. eLORETA intrahemispheric LLC solutions in Nold, ADMCI, and DLBMCI groups

Fig. 2 shows means (±SE) of intrahemispheric LLC solutions for 3 groups (Nold, ADMCI, and DLBMCI), 5 ROIs (frontal, central, parietal, occipital, and temporal), and 8 bands (from delta to gamma). It is noted that magnitude and profile of intrahemispheric LLC solutions were different among Nold, ADMCI, and DLBMCI groups. In the Nold group, intrahemispheric LLC solutions were maximum in parietal (highest values), temporal, and occipital alpha 2 and 3 sources.

Other LLC solutions were low (widespread delta, theta, and alpha 1 sources) or very low (beta 1, beta 2, and gamma sources). Compared with that group, the ADMCI and DLBMCI groups showed

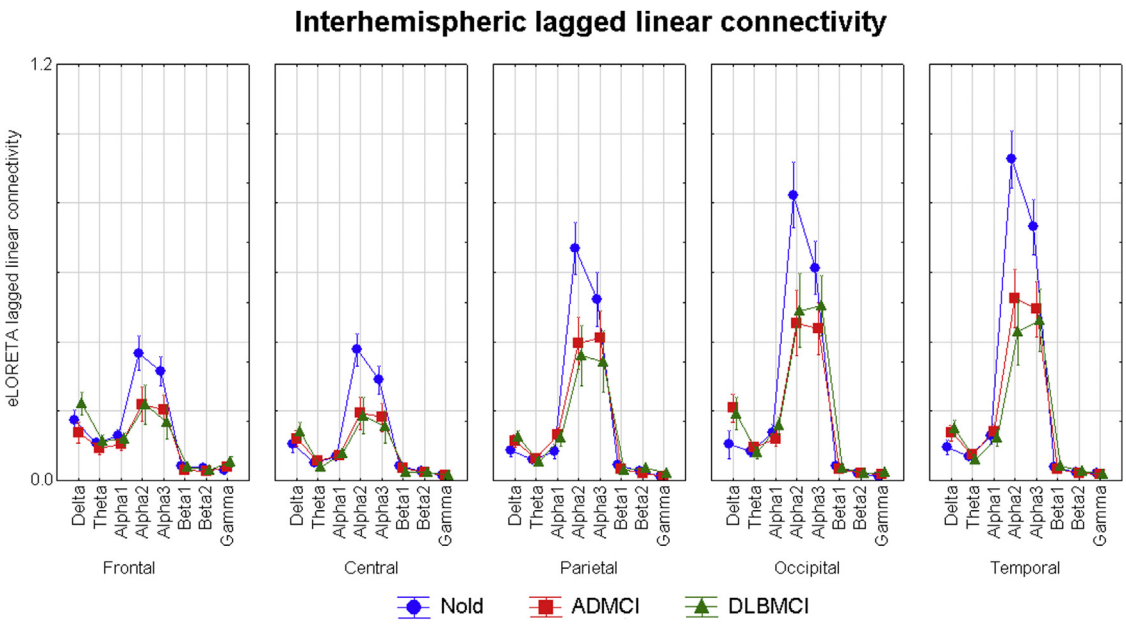

Fig. 1. Mean values (±SE) of the interhemispheric lagged linear connectivity (LLC) of eLORETA resting-state eyes-closed electroencephalographic (rsEEG) cortical sources in the groups of normal elderly (Nold) subjects and patients with mild cognitive impairment due to Alzheimer's (ADMCI) and Lewy body (DLBMCI) diseases. These values refer to the 3 groups (Nold, ADMCI, and DLBMCI), 8 bands (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and 5 regions of interest (ROIs) (frontal, central, parietal, occipital, and temporal).

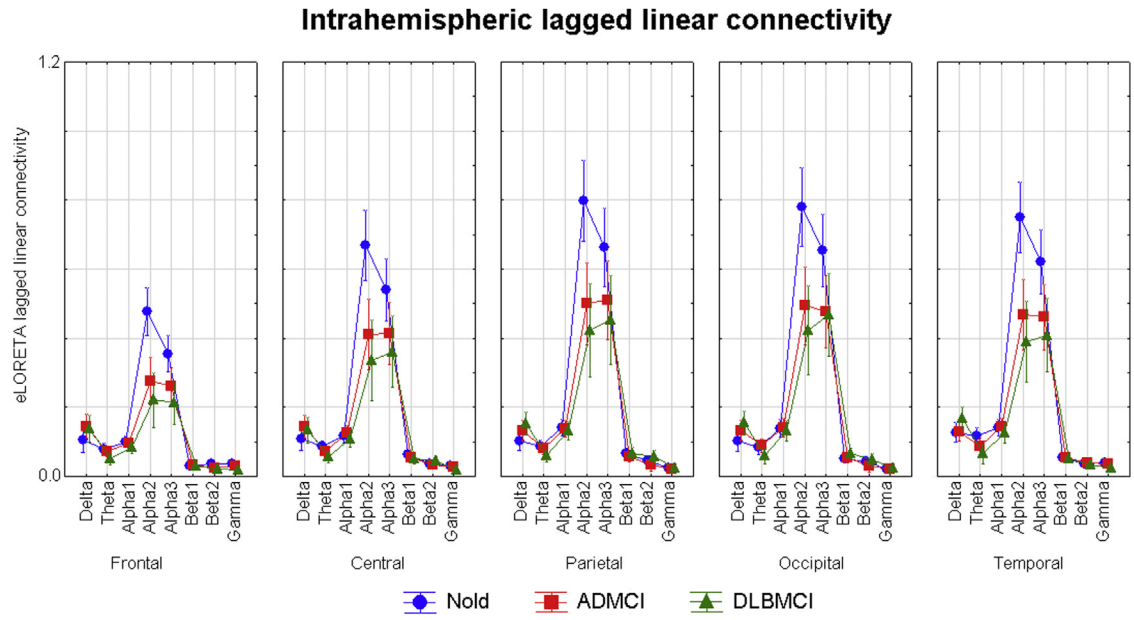

Fig. 2. Mean values (±SE) of the intrahemispheric lagged linear connectivity (LLC) of eLORETA rsEEG cortical sources for 3 groups (Nold, ADMCI, and DLBMCI), 8 bands (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and 5 ROIs (frontal, central, parietal, occipital, and temporal). Abbreviations: ADMCI, mild cognitive impairment due to Alzheimer's disease; DLBMCI, mild cognitive impairment due to Lewy body disease; Nold, normal elderly; rsEEG, resting-state eyes-closed electroencephalographic; ROI, region of interest.

intrahemispheric LLC solutions with similar frequency and spatial profile but characterized by a lower magnitude. Both MCI groups presented lower values in intrahemispheric LLC solutions in temporal, frontal, occipital, parietal, and central alpha 2 and 3 sources. Of note, the 2 MCI groups exhibited no remarkable differences in LLC solutions.

As for interhemispheric LLC solutions, the intrahemispheric LLC solutions were square root transformed to became Gaussian (confirmed by Kolmogorov–Smirnov, $p > 0.05$). The transformed LLC solutions presented an interaction group X band ($F = 3.2$, $p = 0.0005$), indicating a substantial symmetry between right and left hemispheres. Duncan test showed that discriminant LLC pattern ADMCI and DLBMCI < Nold was confirmed by global ($p < 0.0001$) and alpha 3 ($p < 0.01$) sources averaged. This effect distinguished ADMCI/DLBMCI versus Nold subjects at the group level. No difference was found between the ADMCI and the DLBMCI group ($p > 0.05$).

Grubbs' test ($p < 0.0001$) tested outliers in the relevant interhemispheric and intrahemispheric LLC solutions in alpha 2 and alpha 3 sources in the Nold, ADMCI, and DLBMCI groups. No outlier was found (see Fig. 3), thus confirming the results of the main statistical analysis.

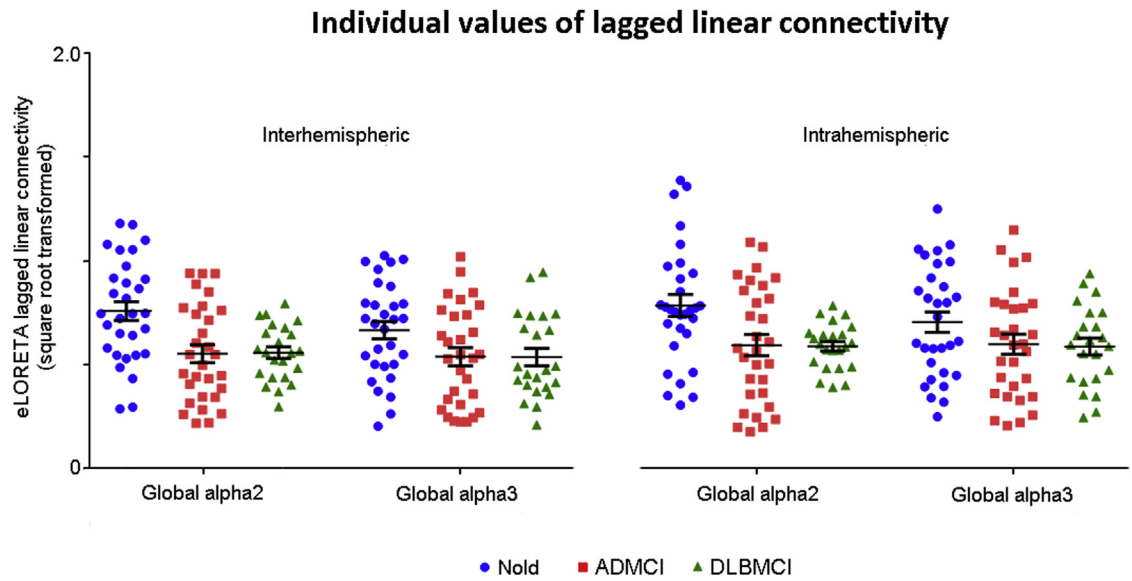

Fig. 3. Individual values of the interhemispheric and intrahemispheric LLC (square root transformed) of eLORETA rsEEG cortical sources showing statistically significant ($p < 0.05$) differences among the Nold, ADMCI, and DLBMCI groups (i.e., interhemispheric global alpha 2, interhemispheric global alpha 3, intrahemispheric global alpha 2; and intrahemispheric global alpha 3). Noteworthy, Grubbs' test showed no outliers from those individual values of the LLC of eLORETA rsEEG cortical sources (arbitrary threshold of $p < 0.0001$). Abbreviations: ADMCI, mild cognitive impairment due to Alzheimer's disease; DLBMCI, mild cognitive impairment due to Lewy body disease; LLC, lagged linear connectivity; Nold, normal elderly; rsEEG, resting-state eyes-closed electroencephalographic.

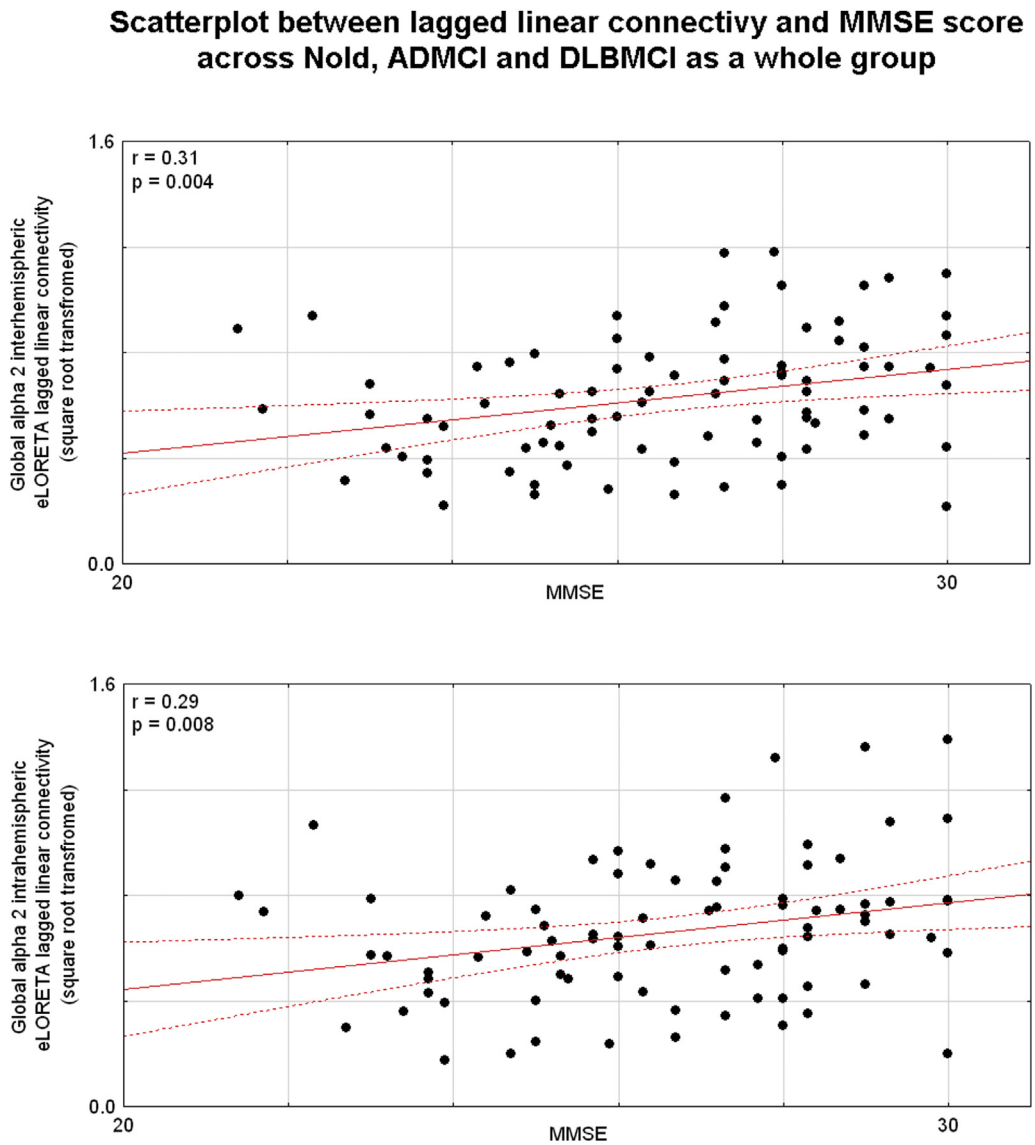

Fig. 4. Scatterplots showing the correlation between the interhemispheric and intrahemispheric LLC (square transformed) of global alpha 2 rsEEG cortical sources and the Mini-Mental State Evaluation (MMSE) score in the Nold, ADMCI, and DLBMCI subjects as a whole group. The Spearman test evaluated the hypothesis of a correlation these LLC and MMSE variables (Bonferroni corrected $p < 0.05$). The r and p values are reported within the diagrams. Abbreviations: ADMCI, mild cognitive impairment due to Alzheimer's disease; DLBMCI, mild cognitive impairment due to Lewy body disease; LLC, lagged linear connectivity; Nold, normal elderly; rsEEG, resting-state eyes-closed electroencephalographic.

3.3. Correlation between LLC solutions and MMSE score in ADMCI, DLBMCI, and Nold subjects

Spearman test assessed the correlation between the MMSE score and the square root transformed 4 LLC solutions (intrahemispheric and interhemispheric LLC solutions in alpha 2 and 3 sources) that differed between the MCI and the Nold group ($p < 0.05$).

A statistically significant ($p < 0.0125$ to give $p < 0.05$ corrected) positive correlation was computed between (1) the interhemispheric LLC solutions in global alpha 2 sources averaged across the ROIs and the MMSE score ($r = 0.31$, $p < 0.004$); (2) the intrahemispheric LLC solutions in global alpha 3 sources averaged across the ROIs and the MMSE score ($r = 0.29$, $p < 0.008$). The higher the LLC solutions, the higher the MMSE score. Fig. 4 shows the scatterplots of those LLC solutions exhibiting significant correlations ($p < 0.05$ corrected). It can be noted the variability in alpha source connectivity even in the Nold group and the basically low correlation values.

As a control analysis, the correlation test was computed for any group separately. No statistically significant effect ($p > 0.05$) was revealed, probably due to small scatter of MMSE scores within any group.

3.4. ROC curves for Nold, ADMCI, and DLBMCI individuals

Only interhemispheric LLC solutions in global alpha 2 sources overcome the statistical threshold of AUROC curve = 0.7 (i.e., "moderate" classification rate) in the discrimination between the Nold and ADMCI individuals. Specifically, they reached (Fig. 5 top) 70.7% of sensitivity, 66.7% of specificity, 68.7% of accuracy, and 0.72 of AUROC curve.

Concerning the discrimination between Nold and DLBMCI individuals, only the intrahemispheric LLC solutions in global alpha 2 sources overcome the statistical threshold of AUROC curve = 0.7. Specifically, they reached (Fig. 5 bottom) 87.0% of sensitivity, 66.7% of specificity, 75.5% of accuracy, and 0.75 of AUROC curve.

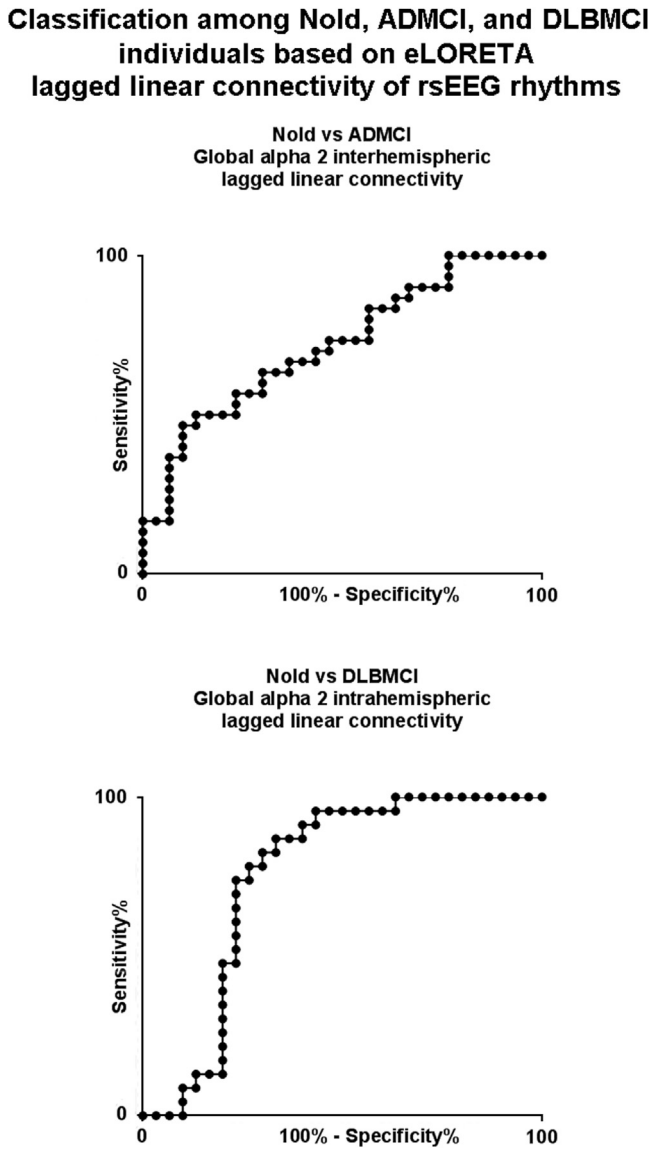

Fig. 5. Top: Receiver operating characteristic (ROC) curve illustrating the classification of the ADMCI and Nold individuals based on interhemispheric LLC in global alpha 2 rsEEG cortical sources. The area under the receiving operator characteristic (AUROC) curve was 0.72 indicating a moderate classification accuracy of the ADMCI and Nold individuals. Bottom: ROC curve illustrating the classification of the DLBMCI and Nold individuals based on the intrahemispheric LLC in global alpha 2 cortical sources. The AUROC was 0.75 indicating a moderate classification accuracy of the DLBMCI and Nold individuals. Abbreviations: ADMCI, mild cognitive impairment due to Alzheimer's disease; DLBMCI, mild cognitive impairment due to Lewy body disease; LLC, lagged linear connectivity; Nold, normal elderly; rsEEG, resting-state eyes-closed electroencephalographic.

Classification between the ADMCI and DLBMCI individuals had AUROC curve values lower than 0.7 and was not considered.

3.5. Control analyses

Previous studies have shown that the brain of healthy seniors with 75–84 years of age and the oldest-old ones (≥85 year old) may show AD-DLB neuropathology (i.e., the deposition of hyperphosphorylated-τ, amyloid-β, and α-synuclein) even in the absence of clinical manifestations of the disease (Tyas et al., 2007), and this deposition increases with the age (Elobeid et al., 2016). Specifically, about 40% of octogenarians exhibited abnormalities in AD neuropathology (Elobeid et al., 2016). Therefore, one may argue that the present main results showing differences in the alpha LLC solutions between the MCI and Nold groups (i.e., ADMCI and DLBMCI ≠ Nold) may be affected by the presence of Nold subjects with age >75 y and AD-DLB neuropathology (i.e., oldest-old Nod subjects). To address this confounding factor, we performed the following control analysis. We selected 3 subgroups of Nold (N = 12), ADMCI (N = 14), and DLBMCI (N = 8) subjects younger than 75 years (Cohen-Mansfield et al., 2013; Martin et al., 2015; Park et al., 2014; Zizza et al., 2009). These subgroups were matched for gender, age, and education (see the new Table 2). The MCI young-old subgroups were also matched for the MMSE score (Folstein et al., 1975). The eLORETA LLC solutions (square root transformed) of these groups were compared by 2 ANOVAs ($p < 0.05$). The first ANOVA assessed differences in interhemispheric LLC solutions between the Nold and MCI young-old subgroups (i.e., Nold ≠ both ADMCI and DLBMCI) with the following factors: group (Nold, DLBMCI, and ADMCI), band (from delta to gamma), and ROI (occipital, temporal, parietal, central, and frontal). The second ANOVA assessed differences in intrahemispheric LLC solutions between the Nold and MCI young-old subgroups (i.e., Nold ≠ both ADMCI and DLBMCI with the following factors: group (Nold, DLBMCI, and ADMCI), hemisphere (right and left), band (from delta to gamma), and ROI (occipital, temporal, parietal, central, and frontal). The confirmation of the hypothesis may require: (1) an effect with the group factor ($p < 0.05$) and (2) a post hoc (Duncan) test showing LLC solutions with statistically significant differences ($p < 0.05$, one-tailed) between the Nold versus MCI young-old groups ($p < 0.05$, one-tailed). Grubbs' test ($p < 0.0001$) controlled for outliers in LLC solutions.

Fig. 6 and Fig. 7 report the mean values (±SE) of the interhemispheric and intrahemispheric LLC solutions for the 3 young-old subgroups (Nold, ADMCI, and DLBMCI), 5 ROIs (frontal, central, parietal, occipital, and temporal), and 8 bands (from delta to gamma). The results of the first ANOVA showed a significant interaction group X ROI ($F = 4.1$, $p = 0.00001$). The Duncan test showed that the discriminant LLC pattern ADMCI and DLBMCI < Nold was confirmed by global alpha 2 ($p < 0.00001$) and alpha 3 ($p < 0.0005$) sources. This interhemispheric effect distinguished ADMCI/DLBMCI versus Nold young-old subjects at the group level. No difference in the interhemispheric LLC solutions was found between the ADMCI and the DLBMCI young-old groups ($p > 0.05$). Similarly, the results of the second ANOVA showed a significant interaction group X ROI ($F = 5.4$, $p = 0.00001$). The Duncan test showed that the discriminant LLC pattern ADMCI and DLBMCI < Nold was confirmed by global alpha 2 ($p < 0.00001$) and alpha 3 ($p < 0.00001$) sources. This intrahemispheric effect distinguished ADMCI/DLBMCI versus Nold young-old subjects at the group level (Grubbs' test showed no outlier in the lagged non-linear connectivity (LNLC) solutions, $p > 0.0001$). Furthermore, no difference in the intrahemispheric LLC solutions was found between the ADMCI and the DLBMCI young-old groups ($p > 0.05$). In conclusion, the results of the control analysis in the young-old Nold, ADMCI, and DLBMCI subgroups were similar to those obtained in the full ADMCI and DLBMCI groups, thus indicating that the differences of LLC solutions in the alpha band among the 3 groups (i.e., ADMCI and DLBMCI ≠ Nold) were not affected by the presence of oldest-old subjects with AD-DLB neuropathology.

Another control analysis evaluated whether the differences in the alpha source connectivity between the MCI and Nold groups (i.e., ADMCI and DLBMCI ≠ Nold) estimated by (eLORETA) LLC solutions may be cross-validated by the (eLORETA) LNLC solutions (Pascual-Marqui et al., 2011). The procedure of the control analysis was as follows. First, the LNLC toolbox of the eLORETA freeware was used to calculate the LNLC solutions from scalp-recorded rsEEG rhythms, frequency bin by frequency bin between all voxels of the source space. Second, for each frequency band (i.e., from delta to

Table 2
Mean values (±SE) of the demographic and clinical data and results of their statistical comparisons ($p < 0.05$) in the subgroups of Nold, ADMCI, and DLBMCI subjects with age <75 y (young-old subgroups)

	Nold	ADMCI	DLBMCI	Statistical analysis
N	12	14	8	-
Age	70.7 (±0.9)	70.9 (±0.7)	69.8 (±1.0)	ANOVA: n.s.
Gender (M/F)	9/3	8/6	6/2	Fisher-Freeman-Halton: n.s.
Education	8.6 (±1.1)	9.2 (±0.9)	8.5 (±1.9)	ANOVA: n.s.
MMSE	28.5 (±0.3)	25.6 (±0.6)	25.5 (±0.5)	Kruskal-Wallis: $p < 0.001$

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

gamma) and subject, the interhemispheric and intrahemispheric LNLC solutions were estimated between ROIs following the same methodology of the analysis performed by the LLC toolbox. Third, 2 ANOVAs used the eLORETA LNLC solutions (square root transformed) as dependent variables. The first ANOVA assessed differences in interhemispheric LNLC solutions between the Nold and MCI groups (i.e., Nold ≠ both ADMCI and DLBMCI) with the following factors: group (Nold, DLBMCI, and ADMCI), band (from delta to gamma), and ROI (occipital, temporal, parietal, central, and frontal). The second ANOVA assessed differences in the intrahemispheric LNLC solutions between the Nold and MCI groups (i.e., Nold ≠ both ADMCI and DLBMCI) with the following factors: group (Nold, DLBMCI, and ADMCI), hemisphere (right and left), band (from delta to gamma), and ROI (occipital, temporal, parietal, central, and frontal). The confirmation of the hypothesis required (1) an effect with the group factor ($p < 0.05$) and (2) a post hoc (Duncan) test showing LNLC solutions with statistically significant differences ($p < 0.05$, one-tailed) between the Nold and MCI groups ($p < 0.05$, one-tailed). Grubbs' test controlled for outliers in the LNLC solutions ($p < 0.0001$).

Figs. 8 and 9 report the mean values (±SE) of the interhemispheric and intrahemispheric LNLC solutions for 3 groups (Nold, ADMCI, and DLBMCI), 5 ROIs (frontal, central, parietal, occipital, and temporal), and 8 bands (from delta to gamma). The results of the first ANOVA showed no statistically significant effect with the group factor ($p > 0.05$), so no difference in the interhemispheric LNLC solutions was found between the ADMCI/DLBMCI and Nold groups. By contrast, the results of the second ANOVA exhibited a significant interaction group X ROI ($F = 2.3$, $p = 0.00001$). Duncan test indicated that the intrahemispheric alpha 2 LNLC pattern ADMCI and DLBMCI < Nold was the only statistically significant effect ($p < 0.01$). Grubbs' test showed no outlier in the LNLC solutions ($p > 0.0001$). In conclusion, only intrahemispheric alpha source connectivity pointed to similar differences ADMCI/DLBMCI versus Nold groups as revealed by both LLC and NLLC solutions ($p > 0.05$).

4. Discussion

This study assessed the hypothesis of an abnormal rsEEG cortical source connectivity (i.e., as revealed by eLORETA LLC solutions) in ADMCI and DLBMCI patients compared with Nold subjects, as a possible neural correlate of cognitive deficits. An important aspect of this study was to ascertain whether such source connectivity may be nonredundant when compared with the typical topography of source activation used in the investigation of prodromal stages of ADMCI and DLBMCI (see results reported in Babiloni et al., 2018a, b). Main issues of the present study were whether delta and theta (i.e., one or both) source connectivity may pathologically increase or decrease in DLBMCI compared with ADMCI subjects, and if intrahemispheric and interhemispheric functional connectivity values (i.e., one or both) may be altered or not.

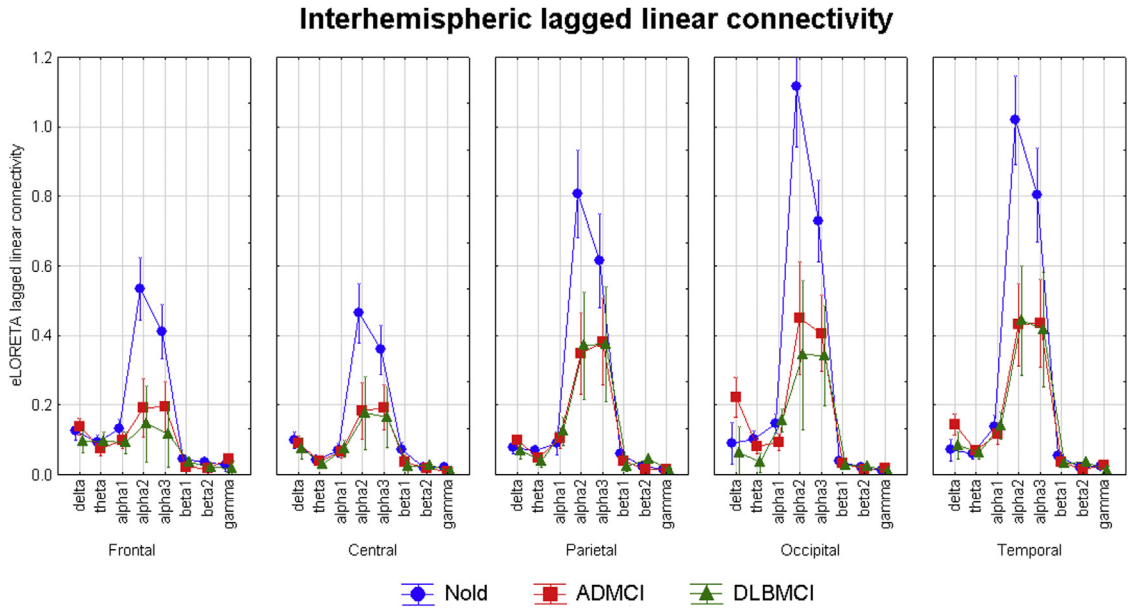

Fig. 6. Mean values (±SE) of the interhemispheric lagged linear connectivity (LLC) of eLORETA rsEEG cortical sources for 3 young-old subgroups with age <75 years (Nold, ADMCI, and DLBMCI), 8 bands (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and 5 ROIs (frontal, central, parietal, occipital, and temporal). Abbreviations: ADMCI, mild cognitive impairment due to Alzheimer's disease; DLBMCI, mild cognitive impairment due to Lewy body disease; Nold, normal elderly; rsEEG, resting-state eyes-closed electroencephalographic; ROI, region of interest.

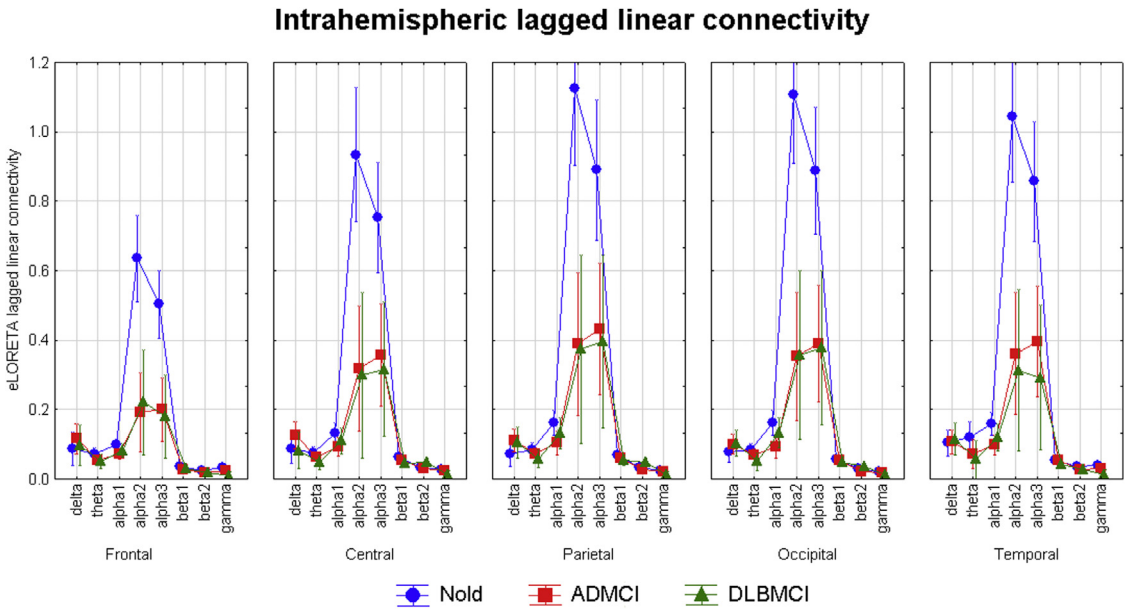

Fig. 7. Mean values (±SE) of the intrahemispheric lagged linear connectivity (LLC) of eLORETA rsEEG cortical sources for 3 young-old subgroups with age <75 years (Nold, ADMCI, and DLBMCI), 8 bands (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and 5 ROIs (frontal, central, parietal, occipital, and temporal). Abbreviations: ADMCI, mild cognitive impairment due to Alzheimer's disease; DLBMCI, mild cognitive impairment due to Lewy body disease; Nold, normal elderly; rsEEG, resting-state eyes-closed electroencephalographic; ROI, region of interest.

4.1. Abnormal alpha source connectivity in ADMCI and DLBMCI groups

Here we report that widespread interhemispheric and intrahemispheric alpha (but not delta) linear source connectivity was lower in both ADMCI and DLBMCI groups as compared with the group of Nold subjects, whereas only nonlinear intrahemispheric alpha source connectivity was lower in 2 pathological groups over the control group. Furthermore, such alpha source connectivity did not differ between the ADMCI and DLBMCI groups. This finding was confirmed even discarding the data in Nold, ADMCI, and DLBMCI subjects older than 75 years (young-old subgroups) to control for the possible confounding effects of AD-DLB neuropathologies in the oldest Nold subjects (Elobeid et al., 2016; Tyas et al., 2007). These findings enrich previous evidence demonstrating differences in the inter-relatedness of rsEEG rhythms at electrode pairs in ADD and DLB (dementia status) groups compared with groups of Nold individuals (Adler et al., 2003; Anghinah et al., 2000; Besthorn et al., 1994a; Dunkin et al., 1994; Dauwan et al., 2016b; Fonseca et al., 2013, 2011; Jelic et al., 2000; Knott et al., 2000; Locatelli et al., 1998; Pogarell et al., 2005; Sloan et al., 1994; van Dellen et al., 2015). In the previous studies using fixed rsEEG frequency bands,

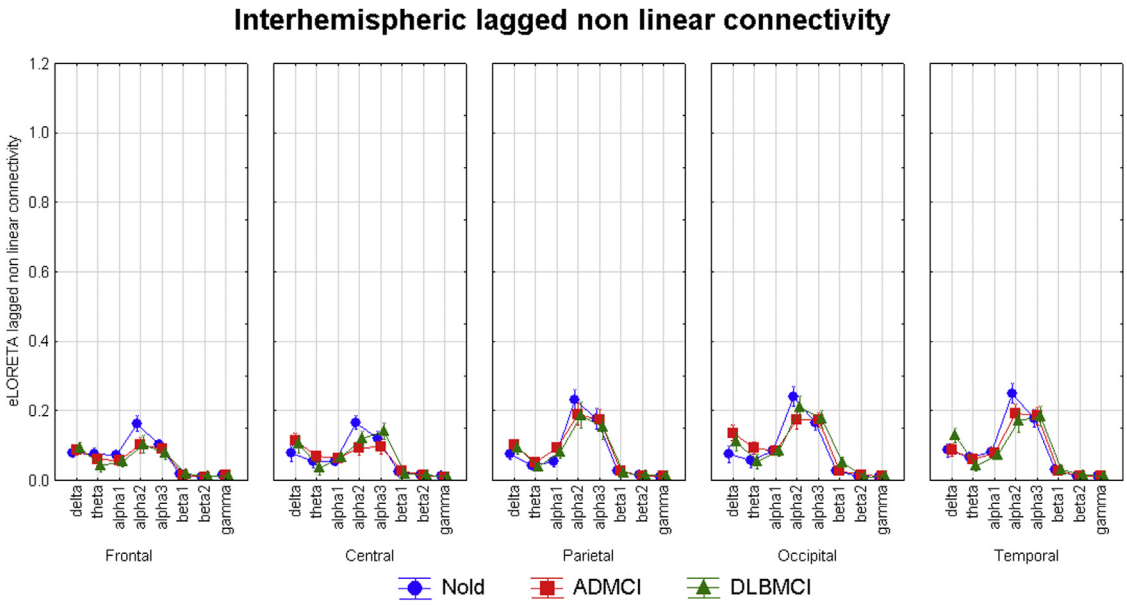

Fig. 8. Mean values (±SE) of the interhemispheric lagged nonlinear connectivity (LNLC) of eLORETA rsEEG cortical sources for the 3 groups (Nold, ADMCI, and DLBMCI), 8 bands (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and 5 ROIs (frontal, central, parietal, occipital, and temporal). Abbreviations: ADMCI, mild cognitive impairment due to Alzheimer's disease; DLBMCI, mild cognitive impairment due to Lewy body disease; Nold, normal elderly; rsEEG, resting-state eyes-closed electroencephalographic; ROI, region of interest.

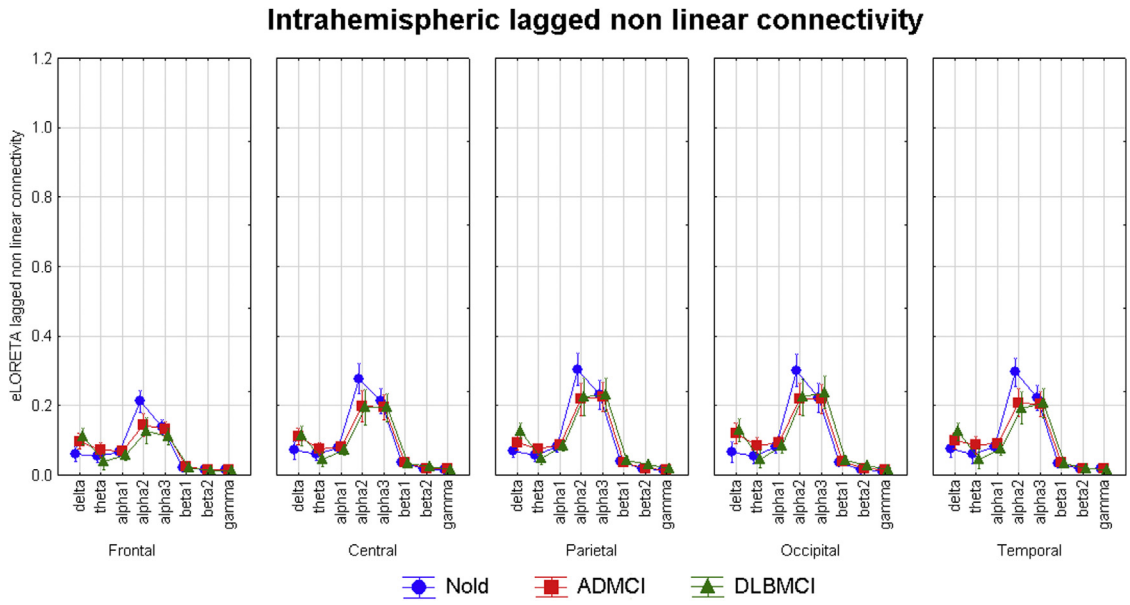

Fig. 9. Mean values (±SE) of the intrahemispheric lagged nonlinear connectivity (LNLC) of eLORETA rsEEG cortical sources for the 3 groups (Nold, ADMCI, and DLBMCI), 8 bands (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and 5 ROIs (frontal, central, parietal, occipital, and temporal). Abbreviations: ADMCI, mild cognitive impairment due to Alzheimer's disease; DLBMCI, mild cognitive impairment due to Lewy body disease; Nold, normal elderly; rsEEG, resting-state eyes-closed electroencephalographic; ROI, region of interest.

ADD groups showed lower inter-relatedness of alpha rhythms at electrode pairs, especially within the anterior-posterior axis (Adler et al., 2003; Anghinah et al., 2000; Babiloni et al., 2004, 2006b, 2016a; Besthorn et al., 1994b; Blinowska et al., 2017; Dunkin et al., 1994; Fonseca et al., 2013, 2011; Jelic et al., 1997, 2000; Knott et al., 2000; Leuchter et al., 1987, 1992; Locatelli et al., 1998; Pogarell et al., 2005; Sloan et al., 1994). In the same vein, previous reports using that methodology showed altered values of spectral coherence between anterior and posterior electrode pairs in patients with DLB (Dauwan et al., 2016a). For the first time, the results of the present study showed an abnormality in the alpha source connectivity even at the stage of MCI in both AD and DLB patients. As the present methodology previously unveiled lower alpha source connectivity in ADD than DLB at the dementia stage (Babiloni et al., 2018a), the current lack of differences in alpha source connectivity between ADMCI and DLBMCI groups may hint a relevant role of cholinergic rather than dopaminergic neuromodulation in the functional cortical connectivity in patients suffering from prodromal stages of AD and DLB before a substantial dopaminergic derangement in DLB. Indeed, there is consensus that motor deficits and related dopaminergic symptoms appear after cognitive deficits in the DLB natural history of the disease (McKeith et al., 2005, 2017).

4.2. Abnormal alpha source connectivity in ADMCI and DLBMCI individuals

An interesting result of the present study is a positive correlation between MMSE score (as a marker of global cognitive status) and intrahemispheric and interhemispheric alpha source connectivity across all Nold, DLBMCI, and ADMCI subjects as a whole population. Even if the correlation coefficient showed relatively low values and explained variance (i.e., r = 0.29–0.31), it was significant from a statistical point of view ($p < 0.01$). These findings hint that alpha source connectivity in the resting-state condition explains just a minor part of the neural correlates of global cognitive functions in ADMCI and DLBMCI patients. Therefore, future studies should use experimental tasks to complement the actual picture in the resting-state condition. Alpha source connectivity should be investigated during tasks involving selective attention, short- and long-term memory, frontal executive and control, language, and other functions. It can be speculated that rsEEG source connectivity in those conditions may be able to explain a greater variance of MMSE score in Nold and MCI subjects.

Another interesting result of the present study is a moderate accuracy in the classification between ADMCI and Nold individuals based on interhemispheric alpha source connectivity (i.e., 0.72 of AUROC curve). Of note, the discriminant alpha source connectivity between DLBMCI and Nold subjects was found in the intrahemispheric (i.e., 0.75 of AUROC curve) but not intrahemispheric analysis. However, those LLC solutions were not able to discriminate ADMCI versus DLBMCI individuals.

The current results extend previous findings reporting a classification accuracy of 1.0–0.45 between Nold and ADD subjects (e.g., 1 = 100%), 0.92–0.78 between MCI and ADD subjects, and 0.87–0.60 in the progression from MCI to ADD diagnosis (Adler et al., 2003; Babiloni et al., 2016a; Bennys et al., 2001; Blinowska et al., 2017; Brassen et al., 2004; Buscema et al., 2007; Claus et al., 1999; Engedal et al., 2015; Garn et al., 2017; Huang et al., 2000; Jelic et al., 2000; Knyazev et al., 2011; Lizio et al., 2015; Missonnier et al., 2006). These results also extend preceding findings reporting a classification accuracy of 0.75–0.80 between Nold and DLB subjects with dementia (Andersson et al., 2008) and 0.80–1.0 when DLB and PD subjects with dementia were considered in a single group (Engedal et al., 2015; Garn et al., 2017; Snaedal et al., 2012). To the best of our knowledge, no other cross-validated classification studies unveiled a discriminative ability of markers of inter-relatedness of EEG rhythms at electrode pairs in the classification between ADMCI and DLBMCI individuals.

4.3. Normality of delta source connectivity in ADMCI and DLBMCI groups

As mentioned previously, widespread interhemispheric and intrahemispheric delta source connectivity did not differ in ADMCI and DLBMCI groups over the group of Nold subjects. Furthermore,

this connectivity did not differ between the ADMCI and DLBMCI groups. Of note, the same methodology documented that delta source connectivity was higher in ADD and DLB than Nold subjects during the resting-state condition (Babiloni et al., 2016b). Furthermore, other approaches disclosed differences in the inter-relatedness of resting-state delta rhythms between Nold and ADD individuals at scalp sensors (Adler et al., 2003; Blinowska et al., 2017; Knott et al., 2000; Locatelli et al., 1998; Sankari et al., 2011). Unfortunately, we cannot explain these discrepancies based on the present knowledge platform. It can be just speculated that abnormalities in the inter-relatedness of delta and theta rhythms at electrode (source) pairs might depend on the progression of the neurodegenerative diseases belonging to dementia in AD and DLB patients. Furthermore, a certain insensitivity of the present methodology might depend on the gray zone of diagnostic criteria in the discrimination of patients with MCI due to AD and DLB, even with the advancement of the available clinical and biomarker diagnostic criteria (Albert et al., 2011; Dubois et al., 2014; McKeith et al., 2017). Future investigations should mitigate these possible causes of variance in the data and clarify this matter.

4.4. A neurophysiological model of functional cortical connectivity in ADMCI and DLBMCI

The present results enrich with the insight of alpha source connectivity the current concept that AD and DLB are due at least in part to a cortical disconnection syndrome (Bokde et al., 2009; Teipel et al., 2016). In a previous reference study, we provided this enrichment at the dementia stage, while we did so at the prodromal stage of ADD and DLB in the present investigation.

As mentioned previously, alpha source connectivity did not differ between DLBMCI and ADMCI patients, thus suggesting that cholinergic ascending systems, which are affected in those diseases (Bohnen et al., 2015), might modulate functional cortical connectivity at their prodromal stage. This hypothesis is grounded on a bulk of previous findings. In healthy adults, a single dose of scopolamine (i.e., muscarinic cholinergic antagonist) over placebo increased delta and theta power density in the resting state condition, whereas it reduced alpha and beta power density (Ebert and Kirch, 1998; Liem-Moolenaar et al., 2011). Similar findings were reported in Nold and ADD patients (Neufeld et al., 1994). Moreover, a single administration of scopolamine in patients with ADD deranged delta to gamma not only as power density but also as coherence (Johannsson et al., 2015; Snaedal et al., 2010).

In the evaluation of this “cholinergic” hypothesis, one should take into account the contrasting findings about the administration of acetylcholinesterase inhibitor agents in patients with ADD. On one hand, some investigations in patients with ADD disclosed their beneficial specific effects on alpha or theta/alpha rhythms (Agnoli et al., 1983; Babiloni et al., 2006a; Balkan et al., 2003). On the other hand, those agents also reduced theta (Adler et al., 2004; Brassen and Adler, 2003; Gianotti et al., 2008) and delta (Adler and Brassen, 2001; Balkan et al., 2003; Gianotti et al., 2008; Reeves et al., 2002) rhythms in those patients.

4.5. Methodological limitations

In the present study, the ADMCI (N = 30) and DLBMCI (N = 23) patients formed relatively small groups not allowing a stratification based on the disease severity and other relevant clinical features (i.e., trajectories of the diseases over time). Furthermore, the nature of this study is retrospective, lacking harmonized protocols in relevant methodological aspects from patients' enrollment to biomarker assessment. Future prospective longitudinal multicentric studies should cross-validate the present results in larger groups of ADMCI and DLBMCI patients receiving harmonized clinical and biomarker protocols across all clinical units.

Here we used 128 Hz sampling rate for the EEG data analysis, as it maximized the inclusion of a relatively large number of individual EEG data sets in Nold and MCI subjects to test the working hypothesis of this study. Such hypothesis did focus on delta (<4 Hz) and alpha (about 8–12 Hz) source connectivity, based on previous findings of our consortium (Babiloni et al., 2017, 2018a, b). However, the use of 128 Hz sampling rate for the present EEG data analysis prevented the analysis of rsEEG source connectivity at frequencies >40 Hz due to the aliasing effect. Future studies may use EEG data sets recorded with 256 Hz or higher frequency sampling to test additional hypotheses for gamma bands >40 Hz. In this regard, it should be noted that Figs. 2 and 3 unveiled that the magnitude of the LLC solutions at the beta 2 and gamma (i.e., 20–40 Hz) bands was negligible in the present experimental conditions (i.e., eyes closed resting state and use of standard fixed frequency bands for beta 1, beta 2, and gamma). Therefore, it is not probable that relevant effects among the Nold and MCI groups may be observed at frequencies >40 Hz in the present experimental conditions.

5. Conclusions

A previous study of our group showed robust abnormalities in cortical alpha source connectivity in ADD and DLB groups at the dementia stage set in resting-state condition, relative to a group of Nold subjects (Babiloni et al., 2018a). Furthermore, another study of our group unveiled different abnormalities in delta and source activation in ADMCI and DLBMCI groups (Babiloni et al., 2018b). Keeping in mind those findings, here we reanalyzed original rsEEG rhythms in the ADMCI and DLBMCI groups to estimate delta and alpha source connectivity as revealed by eLORETA LLC solutions. The study hypothesis was that delta and alpha source connectivity may be abnormal even in the groups of ADMCI and DLBMCI patients and may provide nonredundant insights on neurophysiological mechanisms underpinning brain arousal and vigilance in prodromal AD and DLB when compared with the reference publications (Babiloni et al., 2018a, 2018b).

Results of the present study disclosed that intrahemispheric and interhemispheric alpha source (but not delta) connectivity decreased in both ADMCI and DLBMCI groups relative to the Nold group with no differences between the 2 MCI populations. Furthermore, this alpha (but not delta) source connectivity allowed a moderate classification between Nold and MCI subjects (0.72–0.75) with no differences between ADMCI and DLBMCI individuals.

These results hint similar abnormalities in alpha source connectivity in ADMCI and DLBMCI patients, possibly reflecting a common cholinergic impairment, before a substantial dopaminergic derangement, in the activating ascending systems underpinning cerebral arousal and low vigilance. It is concluded that alpha source connectivity provides nonredundant information when compared with source activation maps in the investigation of prodromal stages of ADMCI and DLBMCI (results reported in Babiloni et al., 2018b). Furthermore, the present findings hint that delta source connectivity in the resting-state condition may become pathological in AD at the stage of dementia (results reported in Babiloni et al., 2018a).

Disclosure

The authors have no actual or potential conflicts of interest.

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