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Cortical sources of resting state electroencephalographic rhythms in Parkinson's disease related dementia and Alzheimer's disease

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HIGHLIGHTS

- Diverse neurodegenerative disorders induce cognitive impairment such as PDD and AD.
- Cortical source mapping of resting EEG could characterize these disorders.
- Topography and frequency of resting EEG rhythms distinguished PDD and AD groups.

ABSTRACT

Objective: Here we test the hypothesis that cortical source mapping of resting state electroencephalographic (EEG) rhythms could characterize neurodegenerative disorders inducing cognitive impairment such as Parkinson's disease related dementia (PDD) and Alzheimer's disease (AD).
Methods: To address this issue, eyes-closed resting state EEG rhythms were recorded in 13 PDD, 20 AD, and 20 normal elderly (Nold) subjects. Age, gender, and education were carefully matched across the three groups. Mini Mental State Evaluation (MMSE) score probed subjects' global cognitive status, and was matched between the PDD and AD groups. EEG rhythms of interest were delta (2–4 Hz), theta (4–8 Hz), alpha1 (8–10.5 Hz), alpha2 (10.5–13 Hz), beta1 (13–20 Hz), and beta2 (20–30 Hz). EEG cortical sources were estimated by low resolution brain electromagnetic source tomography (LORETA).
Results: With respect to the Nold and AD groups, the PPD group was characterized by peculiar abnormalities of central delta sources and posterior cortical sources of theta and beta1 rhythms. With respect to the Nold group, the PDD and AD groups mainly pointed to lower posterior cortical sources of alpha1 rhythms, which were positively correlated to MMSE score across all PDD and AD subjects as a whole (the lower the alpha sources, the lower the MMSE score). This alpha decrease was greater in the AD than PPD patients.
Conclusions: The results suggest that topography and frequency of eyes-closed resting state cortical EEG rhythms distinguished PDD and AD groups.
Significance: We report the existence of different effects of neurodegeneration on the cortical neural synchronization mechanisms generating resting state EEG rhythms in PDD and AD patients.

1. Introduction

Neurodegenerative disorders inducing cognitive impairment include Parkinson disease (PD) and Alzheimer' disease (AD). Even in the early stages of PD, cognitive deficits are found in the majority of patients even if with no impact on their global abilities within the cognitive spectrum (Muslimovic et al., 2005). In up to 60% of PD patients, cognitive deficits progress to dementia, defined as a cognitive dysfunction in multiple domains that interferes with activities of daily living and contributes significantly to the impairment of the patients' quality of life (Aarsland et al., 2003; Hughes et al., 2000; Levy et al., 2000; Buter et al., 2008). Main cognitive deficits of Parkinson related dementia (PDD) include executive dysfunction, memory complaints, attentional deficits and fluctuating cognition (Dubois and Pillon, 1997), whereas apraxia, aphasia

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and agnosia are not very common (Dubois and Pillon, 1997; Huber et al., 1989). In PDD subjects, cognitive symptoms are often accompanied by psychotic symptoms including visual hallucinations (Wolters, 2001; Emre et al., 2007).

Distinction between PDD and AD patients poses no major challenge to the clinician's diagnostic ability. Indeed, parkinsonism always precedes the onset of dementia in PPD patients, whereas extrapyramidal signs are variable and, if present, clearly follow the onset of cognitive deterioration in AD patients. Neurobiological and neurophysiological mechanisms underlying PDD and AD are still insufficiently understood, limiting the power of prognosis and drug discovery. In PDD patients, development of cognitive dysfunction and dementia would be due to the loss of nigrostriatal and corticopetal dopaminergic (and serotonergic/noradrenergic) systems (Lewis et al., 2005; Mattay et al., 2002; Owen et al., 1998; Paulus and Jellinger, 1991; Rinne et al., 1989). In addition, it has been invoked a neurodegeneration of cholinergic cortical projections and/or cortical Lewy body- and tau-pathology (Bosboom et al., 2004). On the other hand, development of cognitive dysfunction and dementia in AD patients would be due to neurodegenerative processes selectively involving specific neuronal tracks including hippocampal, amygdaloid , anterior cingulate, and parieto-temporal regions (Braak and Braak, 1996; Etiene et al., 1998), with a special involvement of cholinergic projections to cerebral cortex (Chen et al., 2009; Nyakas et al., 2010). Putative markers of these neurodegenerative processes are abnormal levels of A-beta amyloid 42 and phospo tau proteins in cerebrospinal fluid, atrophy of hippocampus and selected areas of cerebral cortex, reduced regional cerebral blood flow in temporo-parietal regions, and neuroimages of the deposition of A beta amyloid at cortical level (Dubois et al., 2007). Furthermore, we have proposed that eyes-closed resting state cortical electroencephalographic (EEG) rhythms are promising instrumental markers of AD neurodegenerative processes, as a reflection of the effects of ascending neuromodulation systems on synchronization of cortical neurons and on functional brain connectivity (Rossini et al., 2007; Babiloni et al., 2009).

Several studies have investigated eyes-closed resting state EEG rhythms in PD patients (Neufeld et al., 1994; Pezard et al., 2001; Primavera and Novello, 1992; Soikkeli et al., 1991; Tanaka et al., 2000). With reference to age-matched normal elderly controls (Nold), PD subjects showed a topographically widespread slowing of EEG rhythms, including higher amplitude of delta (<4 Hz) and/or theta (4–7 Hz) rhythms (Neufeld et al., 1988, 1994; Bonanni et al., 2008; Serizawa et al., 2008; Pugnetti et al., 2010). Such an EEG slowing increased with the progression of the disease (Morita et al., 2009), and was associated with a decrease of frontal alpha rhythms (8–12 Hz) in those PD subjects with executive dysfunctions (Kamei et al., 2010). In PDD patients, dopaminergic therapy was able to reduce slowing of EEG rhythms at theta band and to enhance alpha rhythms (Fünfgeld, 1995). There was also difference in the amplitude of eyes-closed resting state EEG rhythms between non-demented PD and PDD patients. Amplitude of alpha rhythms was lower in PDD than non-demented PD patients (regardless the level of motor disability), whereas there were prominent motor deficits and greater amplitude of diffuse delta and theta rhythms in non-demented PD compared with PDD patients (Soikkeli et al., 1991; Neufeld et al., 1994).

The aforementioned EEG results have been confirmed and extended by studies using magnetoencephalographic (MEG) techniques (for a review see Berendse and Stam, 2007; Stam, 2010). With reference to Nold subjects, PD patients showed abnormal delta and theta rhythms (Kotini et al., 2005), which were normalized together with motor symptoms by a treatment with transcranial magnetic stimulation (Anninos et al., 2007). Furthermore, PD subjects were characterized by an abnormal coupling of theta, alpha and beta rhythms (>13 Hz) over cortical motor areas as a function of the severity of parkinsonian symptoms (Silberstein et al., 2005; Stoffers et al., 2008). In this framework, non-demented PD patients pointed to a diffuse increase in amplitude of frequencies at the border of theta and low-frequency alpha rhythms, together with an amplitude decrease of beta rhythms (Stoffers et al., 2007). Furthermore, there was a correlation between alpha rhythms and cognitive deficits, namely the lower the alpha rhythms, the lower the global cognitive status (Stoffers et al., 2007). Noteworthy, amplitude of the mentioned eyes-closed resting state MEG rhythms was abnormal at the early stages of the disease and was not strongly affected by disease progression and 'ON'/'OFF' response to L-Dopa treatment, possibly reflecting non-dopaminergic (e.g. cholinergic?) and non-motor correlates of parkinsonism (Stoffers et al., 2007). With reference to non-demented PD patients, PDD patients showed an amplitude increase of delta rhythms and an amplitude decrease of alpha and beta rhythms, which could benefit by the administration of acetylcholinesterase inhibitors (Bosboom et al., 2006). Furthermore, there was a loss of functional coupling of frontal and temporal alpha rhythms, namely a pattern different from that observed in non-demented PD patients (Bosboom et al., 2009) and similar to that observed in AD patients (Stam et al., 2006). On the other hand, several EEG and MEG studies have shown that posterior alpha rhythms are markedly reduced in amplitude in AD patients when compared to Nold and/or amnesic mild cognitive impairment (MCI) subjects, whereas the opposite was true for slow EEG frequencies including delta and theta rhythms (Dierks et al., 1993, 2000; Huang et al. 2000; Jelic et al., 2000; Ponomareva et al., 2003; Jeong, 2004; Babiloni et al., 2006a).

Summarizing, EEG and MEG studies have shown that PDD patients are characterized by a pattern of eyes-closed resting state cortical rhythms similar to that of AD patients, namely a diffuse amplitude increase of delta and theta rhythms and an amplitude reduction of alpha rhythms (Soikkeli et al., 1991; Neufeld et al., 1994; Bosboom et al., 2006; Berendse and Stam, 2007; Rossini et al., 2007; Stam, 2010). These observations suggest that parallel pathophysiological mechanisms must come into play in the development of dementia in PDD patients, and raise the issue of the neurophysiological differences and similarities between PDD and AD patients. This issue has been, at least in part, addressed to by a recent EEG study reporting abnormally higher amplitude of delta and theta rhythms in patients suffering from dementia with Lewy body (DLB) and PDD, when compared to AD subjects (Bonanni et al., 2008). It has been also shown a higher amplitude of extended alpha rhythms (8–12 Hz) in the AD patients than in PDD subjects having fluctuations of cognitive symptoms, the most relevant group differences being observed at posterior scalp electrodes (Bonanni et al., 2008). These findings strongly motivate further investigations aimed at exploring fine-grain differences in frequency and spatial detail of eyes-closed resting state EEG rhythms in AD and PPD subjects to better define similarities and differences, especially at alpha sub-bands. To this aim, we have recently proposed a methodological approach for a detailed mapping of cortical sources of eyes-closed resting state EEG rhythms at different stages of AD. The methodological approach is based on a regional source analysis of EEG rhythms by popular software called low resolution brain electromagnetic source tomography (LORETA) as well as on the use of narrow low- (8–10.5 Hz) and high-frequency (10.5–13 Hz) alpha sub-bands. With this methodological approach, we have demonstrated a positive correlation between posterior cortical sources of low-frequency alpha power (8–10.5 Hz) and global cognitive status across the continuum among Nold, amnesic MCI, and mild AD subjects, whereas the correlation was negative for occipital cortical sources of delta power (Babiloni et al., 2006b,c,d, 2007, 2008; Rossini et al., 2006).

Keeping in mind the above data and considerations, here we tested the hypothesis that the source mapping of eyes-closed resting state EEG rhythms characterizes groups of PDD and AD patients, as a reflection of the underlying neurodegenerative processes and of their effects on the cortical neural synchronization mechanisms at the basis of EEG rhythmic oscillations. To test this hypothesis, eyes-closed resting state EEG rhythms were recorded in carefully matched PDD, AD, and Nold subjects, while EEG cortical sources were estimated by LORETA and compared across the three groups.

2. Methods

2.1. Subjects

This study evaluated 13 PDD patients recruited from Parkinson Rehabilitation Unit of San Raffaele Cassino Hospital. Furthermore, two age-matched control groups of 20 cognitively normal elderly (Nold) subjects and 20 AD patients (age- and MMSE-matched with PDD) were formed by selecting individuals from whom we recorded eyes-closed resting state EEG data in previous multicentric studies (for example see Babiloni et al., 2004, 2006a,b,c,d,e). The selection was performed to obtain the best matching of age, gender, and education among the groups of PDD, AD, and Nold subjects as well as the best matching of mini mental state evaluation (MMSE) score between the groups of PDD and AD subjects. Demographic and clinical data of the PDD, AD, and Nold subjects are summarized in Table 1. With respect to the previous EEG studies of this Consortium (see Rossini et al., 2007 for a review), the novel and original scientific actions were (i) the recruitment and data collection/analysis in the aforementioned 13 PDD subjects, (ii) the selection of the proper archive EEG data sets in the Nold and AD subjects, and (iii) the comparison of the cortical sources of eyes-closed resting state EEG rhythms in the three groups (i.e. PDD, AD, Nold).

The study was approved by the local Institutional ethics committee, and follows prescriptions of the Good Clinical Practice (GCP); informed and overt consent of subjects or subjects' legal representatives, in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the Author's Institutional Review Board.

2.2. Diagnostic criteria

In the present study, the diagnosis of PD was based on a standard clinical assessment of tremor, rigidity and akinesia. As measures of severity of motor disability, the Hoehn and Yahr stage (Hoehn and Yahr, 1967) and the Unified Parkinson Disease Rating Scale-III (UPDRS-III; Fahn and Elton, 1987) for extrapyramidal symptoms were used. All PDD patients followed a continuous antiparkinsonian medication at optimal individual dosage.

A diagnosis of PDD was given to the patients with a history of dementia preceded by PD for at least 24 months. On the basis of clinical features and neuroradiological findings, exclusion criteria for PPD included the following forms of parkinsonism: (1) dementia with Lewy bodies (Geser et al., 2005; McKeith et al., 1996), (2) drug induced parkinsonism, (3) vascular parkinsonism, and (4) atypical parkinsonism with absent or minimal responses to antiparkinsonian drugs. All PDD subjects underwent a battery of neuropsychological tests including the Neuropsychiatric Inventory (NPI; Cummings et al., 1994) scale for the assessment of Behavioral and Psychological Symptoms of Dementia (BPSD), the Mini-Mental State Examination (MMSE) and the Dementia Rating Scale-2 (DRS-2; Jurica et al., 2001) for cognitive function, the Ten Clock Point-drawing Test (TCPT) to assess visuo-construction functions (Manos and Wu, 1994), 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). Table 2 reports the mean score to the neuropsychological battery in our PDD subjects.

AD was diagnosed according to NINCDS–ADRDA (McKhann et al., 1984) and DSM IV criteria. AD patients underwent general medical, neurological, and psychiatric assessments. They were also rated with a number of standardized diagnostic and severity instruments that included the MMSE (Folstein et al., 1975), Clinical Dementia Rating Scale (CDR; Hughes et al., 1982), Geriatric Depression Scale (GDS, Yesavage et al., 1983), Hachinski Ischemic Scale (Rosen et al., 1980), and Instrumental Activities of Daily Living (IADL, Lawton and Brodie, 1969). In addition, they underwent neuroimaging diagnostic procedures (CT or MRI) and complete laboratory analysis.

The Nold subjects were recruited mostly among non-consanguineous patients' relatives. All Nold subjects underwent physical and neurological examinations as well as cognitive screening. Subjects affected by chronic systemic illnesses, those receiving psychoactive drugs, or with a history of neurological or psychiatric disease were excluded. All Nold subjects had a GDS score lower than 14 (no depression).

2.3. EEG recordings

Eyes-closed resting state EEG data were recorded with the following features: 0.3–70 Hz bandpass; cephalic reference; and spatial sampling from 19 electrodes positioned according to the International 10–20 System (i.e. Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2). To monitor eye movements, the horizontal and vertical electrooculogram (EOG, 0.3–70 Hz bandpass) was also collected. All data were digitized in continuous recording mode (5 min of EEG; 256 Hz sampling rate). Recordings were performed in the late morning in all subjects. In order to keep constant the level of vigilance, an experimenter controlled on-line the subject and EEG–EOG traces. He verbally alerted the subject any time there were signs of behavioral and/or EEG drowsiness.

Of note, the duration of the EEG recording (5 min) allowed the comparison of the present results with several previous AD studies using either EEG recording periods shorter than 5 min (Babiloni et al., 2004, 2006a,b,c,d; Buchan et al., 1997; Pucci et al., 1999; Rodriguez et al., 2002; Szelies et al., 1999) or about 1 min (Dierks et al., 1993, 2000); longer epochs would have reduced data variability but increased risks for dropping vigilance and arousal. The recorded EEG data were analyzed and fragmented off-line in

Table 1
Demographic data of healthy elderly (Nold), Parkinson's disease related dementia (PDD), and Alzheimer's disease (AD) subjects.

	Total	Gender	Age (years ± SEM)	MMSE (± SEM)	Education (± SEM)
Nold	20	14F/6 M	71.2 ± 1.1	27.82 ± 0.3	7.3 ± 0.9
PDD	13	9F/4 M	72 ± 1.9	17.15 ± 0.8	7.15 ± 0.8
AD	20	14F/6 M	72.4 ± 2.2	17.3 ± 0.9	7.2 ± 0.9

Abbreviations: M, male; F, female; MMSE, Mini Mental State Examination.

Table 2
Neuropsychological data of the PDD subjects.

	Hoehn and Yahr (±SEM)	UPDRS-III (±SEM)	MMSE (±SEM)	DRS-2 (±SEM)	TPCT (±SEM)	ESS (±SEM)	NPI (±SEM)	ADCS-ADL (±SEM)
PDD	3.30 ± 0.1	43.77 ± 2.7	17.15 ± 0.8	91.08 ± 5.2	3.31 ± 0.9	7.33 ± 0.6	25 ± 4.8	27.33 ± 4.0

Abbreviations: UPDRS-III, Unified Parkinson Disease Rating Scale-III; MMSE, Mini Mental State Examination; DRS-2, Dementia Rating Scale-2; TPCT, Ten Clock Point Test; ESS, Epworth Sleepiness Scale; NPI, Neuropsychiatric Inventory; ADCS-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory.

consecutive epochs of 2 s. The EEG epochs with ocular, muscular, and other types of artifact were preliminarily identified and excluded by a computerized automatic procedure. EEG epochs with sporadic blinking artifacts (less than 10% of the total) were corrected by an autoregressive method (Moretti et al., 2003). Two independent experimenters, blind to the diagnosis, manually confirmed the EEG segments accepted for further analysis. Such analysis was performed on the artifact free EEG segments. On average, we obtained 145 (±23.4 SEM) EEG segments for the Nold, 124 EEG segments (±7.3 SEM) for the PDD, and 174 (±20.5 SEM) EEG segments for the AD patients. Each subject was associated to more than 30 EEG segments in line with previous EEG studies of this Consortium (Babiloni et al., 2006a,b,c,d).

2.4. Spectral analysis of the EEG data

A digital FFT-based power spectrum analysis (Welch technique, Hanning windowing function, no phase shift) computed power density of EEG rhythms with 0.5 Hz frequency resolution. The following standard frequency bands of interest were delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–10.5 Hz), alpha 2 (10.5–13 Hz), beta 1 (13–20 Hz), and beta 2 (20–30 Hz), in continuity with a bulk of previous studies on the cortical sources of resting EEG rhythms in pathological aging (Babiloni et al., 2004, 2006a,b,c,d,e) and with other previous EEG studies on dementia (Holschneider et al., 1999; Besthorn et al., 1997; Cook and Leuchter, 1996; Jelic et al., 1996; Kolev et al., 2002; Leuchter et al., 1993; Pucci et al., 1998).

Choice of the fixed EEG bands did not account for individual alpha frequency (IAF) peak, defined as the frequency associated to the strongest EEG power at the extended alpha range (Klimesch, 1999). However, this should not affect the results, since more than 90% of the subjects had the IAF peaks within the alpha 1 band (8–10.5 Hz) and the IAF was used (together with age, education, MMSE, gender and medications) as a covariate in the statistics on cortical sources of EEG rhythms. We performed a control analysis to evaluate if the present results depend on the slowing in frequency of the EEG power peak. Values of IAF and transition frequency (TF; defined as the frequency showing the power minimum between the power peaks of delta and alpha) were compared between PDD and AD patients. The statistical analyses showed no statistically significant difference between the two groups ($p > 0.05$), suggesting that the LORETA differences between PDD and AD depended on changes in power of delta, theta, and alpha 1 rhythms rather than in frequency. However, the IAF and TF values were used as covariates in further statistical analyses to account even for non significant differences of these parameters in the two groups (indeed, the relatively small groups of patients could not unveil some differences in frequencies).

2.5. Cortical source of EEG rhythms as computed by LORETA

LORETA software as provided at http://www.unizh.ch/keyinst/NewLORETA/LORETA01.htm was used for the estimation of cortical sources of EEG rhythms (Pascual-Marqui and Michel, 1994; Pascual-Marqui et al., 1999, 2002). LORETA is a functional imaging technique belonging to a family of linear inverse solution procedures (Valdès et al., 1998) modeling 3D distributions of EEG sources (Pascual-Marqui et al., 2002). With respect to the dipole modeling of cortical sources, no a priori decision of the dipole position is required by LORETA procedure. LORETA belongs to the family of linear inverse algorithms like minimum norm solution, weighted minimum norm solution or weighted resolution optimization (Pascual-Marqui et al., 1999; Phillips et al., 2002; Yao and He, 2001), and has been successfully used in recent EEG studies on pathological brain aging using the same experimental set up of the present study, including frequency sampling and 19-electrodes 10–20 system montage (Dierks et al., 2000; Babiloni et al., 2004, 2006a,b,c,d,e). Noteworthy, this electrode montage is considered as an adequate EEG spatial sampling for the estimation of cortical sources of eyes closed resting state EEG rhythms, since these rhythms are widely represented across all human cerebral cortex, in contrast to the circumscribed functional topography of event-related EEG changes (especially at high frequencies) in response to specific sensory or motor events. Therefore, eyes closed resting state EEG rhythms can be properly sampled with a relatively low spatial sampling (i.e. 19 electrodes), as opposed to the higher spatial sampling required to take into account to the detailed functional topography of event-related EEG activity. Furthermore, it should be remarked that LORETA solutions are intrinsically maximally smoothed at source space, due to its regularization procedure (Pascual-Marqui and Michel, 1994).

LORETA computes 3D linear solutions (LORETA solutions) for the EEG inverse problem within a 3-shell spherical head model including scalp, skull, and brain compartments. The brain compartment is restricted to the cortical gray matter/hippocampus of a head model (co-registered to the Talairach probability brain atlas) that was digitized at the Brain Imaging Center of the Montreal Neurological Institute (Talairach and Tournoux, 1988). This compartment includes 2394 voxels (7 mm resolution), each voxel containing an equivalent current dipole. Regularization procedure of LORETA software is described in detail at the official WEB site of LORETA software (http://www.uzh.ch/keyinst/NewLORETA/SomePapers/LORETAcve/01-Reply.htm).

LORETA solutions consisted of voxel *z*-current density values able to predict EEG spectral power density at scalp electrodes, being a reference-free method of EEG analysis, in that one obtains the same LORETA source distribution for EEG data referenced to any reference electrode including common average. A normalization of the data was obtained by normalizing the LORETA current density at each voxel with the power density averaged across all frequencies (0.5–45 Hz) and across all 2394 voxels of the brain volume. The normalization was made on the range of EEG frequencies that can be typically investigated on the basis of scalp EEG recordings (Babiloni et al., 2004, 2006a,b,c,d,e). After the normalization, the solutions lost the original physical dimension and were represented by an arbitrary unit scale. This procedure reduced inter-subjects variability and was used in previous EEG studies (Babiloni et al., 2004, 2006a,b,c,d,e). The general procedure fitted the LORETA solutions in a Gaussian distribution and reduced inter-subject variability (Leuchter et al., 1993; Nuwer, 1988).

Solutions of the EEG inverse problem are under-determined and ill conditioned when the number of spatial samples (electrodes) is lower than that of the unknown samples (current density at each voxel). In order to properly address this problem, the cortical

Table 3
Brodmann areas included in the cortical regions of interest (ROIs) of the present study. LORETA solutions were collapsed in frontal, central, parietal, occipital, and temporal ROIs.

Loreta 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

LORETA solutions predicting scalp EEG spectral power density were regularized to estimate distributed rather than punctual EEG source patterns (Pascual-Marqui and Michel, 1994; Pascual-Marqui et al., 1999, 2002). In line with the low spatial resolution of the adopted technique, we used our MATLAB software to collapse the voxels of LORETA solutions at frontal, central, parietal, occipital, and temporal regions of the brain model coded into Talairach space. The Brodmann areas listed in Table 3 formed each of these regions of interest (ROIs).

Finally, the main advantage of the regional analysis of LORETA solutions – using an explicit source model coregistered into Talairach space – was that our modeling could disentangle rhythms of contiguous cortical areas (namely those from the occipital source were disentangled with respect to those of the contiguous parietal and temporal sources, etc.).

2.6. Statistical analysis of the LORETA solutions

Statistical analysis was performed by ANOVA using normalized regional LORETA solutions as a dependent variable, while the subjects' age, education, gender, IAF, medications, and MMSE served as covariates ($p < 0.05$). ANOVA factors were Group (Nold, PDD and AD; independent variable), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (frontal, central, parietal, occipital, temporal). Mauchly's test evaluated the sphericity assumption. Correction of the degrees of freedom was made with the Greenhouse–Geisser procedure. Duncan test was used for the post hoc testing ($p < 0.05$). The planned post hoc testing evaluated the prediction of differences in amplitude of the LORETA solutions following the two patterns (i) PDD ≠ Nold and AD (where Nold = AD) for probing the peculiar EEG abnormalities in the PPD patients; and (ii) PDD and AD ≠ Nold as well as a linear correlation with MMSE score (Pearson test, Bonferroni correction based on the number of test repetition, $p < 0.05$) for probing EEG abnormalities possibly related to dementia.

3. Results

3.1. Topography of the EEG cortical sources as estimated by LORETA

For illustrative purposes, Fig. 1 maps the grand average of the LORETA solutions (i.e. relative power current density at cortical voxels) modeling the distributed EEG cortical sources for delta, theta, alpha 1, alpha 2, beta 1, and beta 2 bands in the Nold, PDD, and AD groups. A qualitative description of the maps indicates that posterior alpha 1 sources dominated in the Nold group, whereas the AD and PDD groups were characterized by some power changes in these sources and slower frequencies.

3.2. Statistical comparisons of LORETA EEG sources

Fig. 2 shows mean regional normalized LORETA solutions (distributed EEG sources) relative to a statistical ANOVA interaction

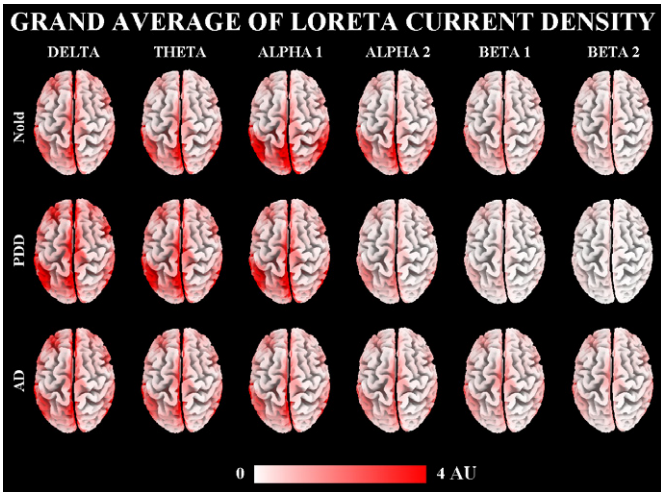

Fig. 1. Grand average of low resolution brain electromagnetic tomography (LORETA) solutions (i.e. normalized relative current density at the cortical voxels, represented by an arbitrary unit scale (AU)) modeling the distributed electroencephalographic (EEG) cortical sources for delta, theta, alpha 1, alpha 2, beta 1, beta 2, bands in normal elderly (Nold), Parkinson's disease related dementia (PDD), and Alzheimer's disease (AD). The left side of the maps (top view) corresponds to the left hemisphere. Legend: LORETA, low resolution brain electromagnetic tomography. Color scale: all power density estimates were scaled based on the averaged maximum value (i.e. alpha 1 power value of occipital region in Nold).

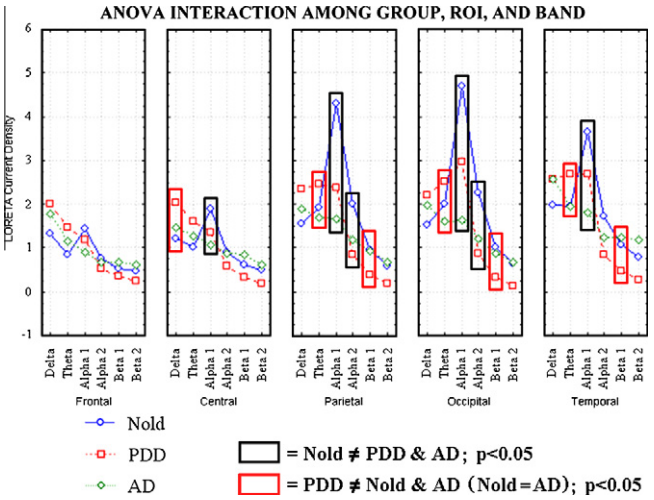

Fig. 2. Regional normalized LORETA solutions (mean across subjects) relative to a statistical ANOVA interaction ($F(40, 1000) = 2.57$; $p < 0.00001$) among the factors Group (Nold, PDD, AD), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (frontal, central, parietal, occipital, temporal). This ANOVA design used the regional normalized LORETA solutions as a dependent variable. Subjects' age, education, MMSE, education, gender and medications were used as covariates. Regional normalized LORETA solutions modeled the EEG relative power spectra as revealed by a sort of "virtual" intracranial macro-electrodes located on the macrocortical regions of interest. Legend: the black rectangles refer to the cortical regions and frequency bands in which LORETA solutions presented statistically significant LORETA patterns Nold ≠ PDD and AD ($p < 0.001$). The red rectangles refer to the cortical regions and frequency bands in which LORETA solutions presented statistically significant LORETA patterns PDD ≠ Nold and AD (Nold = AD) ($p < 0.05$).

($F(40,1000) = 2.57$, $p < 0.00001$) among the factors Group (Nold, PDD and AD, independent variable), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (frontal, central, parietal, occipital, temporal). Age, education, MMSE, IAF, gender and medications were used as covariates. In this figure, the LORETA solutions have the shape of EEG relative power spectra. Notably, profile and magnitude of these spectra in the Nold, PDD, and AD groups differed across various cortical macro-regions, thus supporting the idea

that scalp EEG rhythms are generated by a distributed pattern of cortical sources. The planned post hoc testing tested the pattern PDD ≠ Nold and AD (Nold = AD). It was shown that with respect to both Nold and AD groups, the PDD group presented higher values of central delta ($p < 0.05$) and parietal, occipital and temporal theta sources ($p < 0.05$), as well as lower values of parietal, occipital, and temporal beta 1 sources ($p < 0.05$).

The planned post hoc testing also evaluated the pattern PDD and AD ≠ Nold. It was shown that with respect to the Nold group, the AD and PDD groups presented lower values of central, parietal, occipital, and temporal alpha 1 sources ($p < 0.05$) as well as of parietal and occipital alpha 2 sources ($p < 0.05$). Linear correlation between the amplitude of these 5 alpha sources and MMSE score in all subjects as a single group was performed (Pearson test, Bonferroni correction for 5 repetitions of the test gave the threshold $p < 0.01$ to obtain the Bonferroni corrected $p < 0.05$). The MMSE score positively correlated to parietal ($r = 0.34$, $p = 0.01$) and occipital ($r = 0.41$, $p = 0.002$) alpha 1 sources. To test the control hypothesis that these sources were not specifically related to global cognition, we performed a correlation analysis (Spearman test, $p < 0.05$) even with motor deficits as indexed by Hoehn and Yahr stage (Hoehn and Yahr, 1967) and UPDRS-III (Fahn and Elton, 1987). No statistically significant correlation was found ($p > 0.01$). Table 4 summarizes the post hoc results allowing the differentiation between the two groups of patients on the basis of the LORETA solutions. The pattern PDD > AD was found ($p < 0.05$) in central delta, as well as in parietal, occipital and temporal for both theta and alpha 1 sources. The opposite trend was found in temporal beta 1 and beta 2 sources.

As a further control, we focused on alpha 1 normalized regional LORETA solutions with an ANOVA including the factors Group (Nold, PDD and AD; independent variable) and ROI (frontal, central, parietal, occipital, temporal). There was a statistically significant ANOVA interaction ($F(8200) = 4.27$; $p < 0.0001$) between the two factors. The planned post hoc testing showed a source pattern Nold > PDD > AD for occipital and temporal alpha 1 sources ($p < 0.05$; Fig. 3), confirming that the maximum amplitude reduction of alpha 1 sources was observed in the AD group.

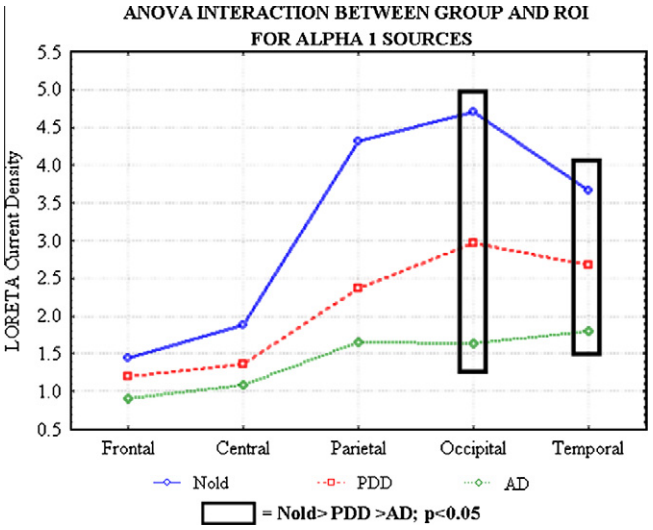

Fig. 3. Regional normalized LORETA solutions (mean across subjects) relative to a statistical ANOVA interaction ($F(8200) = 4.27$; $p < 0.0001$) between the factors Group (Nold, PDD, AD), and ROI (frontal, central, parietal, occipital, temporal) for the alpha 1 band. This ANOVA design used the regional normalized LORETA solutions as a dependent variable. Legend: the black rectangles refer to the cortical regions and frequency bands in which LORETA solutions presented statistically significant LORETA patterns Nold > PDD > AD ($p < 0.05$).

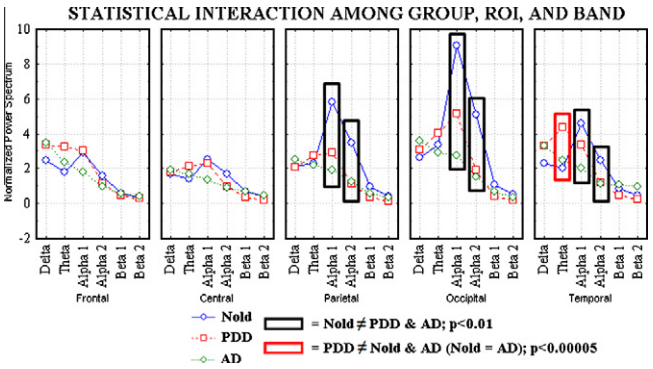

Fig. 4. Normalized electroencephalographic (EEG) spectral power density relative to a statistical ANOVA interaction ($F(40, 1000) = 3.20$; $p < 0.00001$) among the factors Group (Nold, PDD, AD), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (frontal, central, parietal, occipital, temporal). Legend: the black rectangles refer to the cortical regions and frequency bands in which normalized power spectrum presented statistically significant patterns Nold ≠ PDD and AD ($p < 0.01$). The red rectangles refer to the cortical regions and frequency bands in which normalized power spectrum presented statistically significant patterns PDD ≠ Nold and AD (Nold = AD) ($p < 0.00005$). (For interpretation of the references in colour in this figure legend, the reader is referred to the web version of this article.)

3.3. Control analysis

We performed a control data analysis to cross-validate the present LORETA results. Specifically, we repeated the analysis of EEG spectral power density computed at the scalp electrodes, strictly following the general methodological approach used for the analysis of the LORETA solutions. The EEG spectral power density at each electrode was normalized to the EEG spectral power density averaged across all frequencies (0.5–45 Hz) and the electrodes, which were representative of the following scalp zones: (i) F7, F3, Fz, F4 and F8 electrodes for the frontal zone; (ii) C3, Cz and C4 electrodes for the central zone; (iii) P3, Pz and P4 electrodes for the parietal zone; (iv) O1 and O2 electrodes for the occipital zone; and (v) T3 and T4 for the temporal zone. Normalized EEG spectral power density was used as an input for an ANOVA using the factors Group (Nold, PDD, AD; independent variable), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2), and ROI (frontal, central, parietal, occipital, temporal). This ANOVA design showed a statistical interaction among all factors ($F(40, 1000) = 3.20$; $p < 0.00001$). Fig. 4 shows the profile and magnitude of the EEG spectral power density relative to this interaction. This profile confirmed the results of the regional LORETA solutions. The planned post hoc testing evaluated the

Table 4
Planned post hoc comparison between Parkinson (PDD) and Alzheimer (AD) patients. Gray and black characters mean PDD > AD and PDD < AD, respectively.

	Delta	Theta	Alpha 1	Alpha 2	Beta 1	Beta 2
Frontal	–	–	–	–	–	–
Central	$p < 0.05$	–	–	–	–	–
Parietal	–	$p < 0.005$	$p < 0.01$	–		–
Occipital	–	$p < 0.005$	$p < 0.000001$	–	–	–
Temporal	–	$p < 0.01$	$p < 0.001$	–	$p < 0.005$	$p < 0.001$

pattern PDD and AD ≠ Nold. It was shown that with respect to the Nold group, the AD and PDD groups presented lower values of parietal, occipital, and temporal alpha 1 sources ($p < 0.01$) as well as of parietal and occipital alpha 2 sources ($p < 0.01$). These results globally confirmed the abnormal amplitude in the PDD subjects, in line with the LORETA solutions. The planned post hoc testing also evaluated the pattern PDD ≠ Nold and AD (Nold = AD). It was shown that with respect to both Nold and AD groups, the PDD group presented higher values of temporal theta sources ($p < 0.00005$). Of note, the added value of the LORETA solutions is the topographic specification of the differences between the groups of subjects in terms of cortical lobes coded into the Talairach space. As an advantage, the LORETA solutions can be potentially integrated and combined to results of structural (MRI) and functional (fMRI, PET) neuroimaging coded into the same space. This is not true for EEG rhythms relative to given scalp electrodes, which are typically generated not only from underlying cortical sources but also from remote generators.

4. Discussion

Does source mapping of eyes-closed resting state EEG rhythms characterize PDD and AD patients? To address this issue, cortical sources of these rhythms were compared in PDD and AD patients carefully matched for age, gender, education, and MMSE score, while Nold subjects served as a control group. The present results extend as spatial and/or frequency detail previous EEG and MEG evidence on eyes-closed resting state cortical rhythms in PD patients (Neufeld et al., 1994; Pezard et al., 2001; Primavera and Novello, 1992; Soikkeli et al., 1991; Tanaka et al., 2000; Berendse and Stam, 2007; Stam, 2010). The present results complement previous evidence showing that compared to normal subjects, PD patients with no evidence of dementia were characterized by fronto-insulo-temporal LORETA sources (absolute values) higher in amplitude at theta and beta frequencies, as well by frontal and cingulate LORETA sources (absolute values) higher in amplitude at gamma frequencies (30–45 Hz; Moazami-Goudarzi et al., 2008). As a novelty, the present results showed that with respect to the Nold and AD groups, the PPD group was characterized by peculiar amplitude increase of central (i.e. motor cortex) and posterior (parietal, occipital and temporal) theta sources. Furthermore, there was an amplitude decrease of posterior (parietal, occipital and temporal) low-frequency beta sources. A limit of our study was that the low size of the present PPD group did not allow understanding the relationships between the mapped EEG sources and the progression of the disease, the incidence of the cognitive fluctuation, the amount of motor deficits or the effects of the dopaminergic therapy (Morita et al., 2009; Kamei et al., 2010; Fünfgeld, 1995). Furthermore, the lack of a control group of non-demented PD patients prevented a better understanding of the relationships between resting state EEG rhythms, motor, and cognitive functions in PD. This should be considered as a preliminary study whose results motivate the allocation of resources for the recruitment and EEG recordings in PDD and non demented PD patients with paired personal (i.e. age, gender, education) and pharmacological (i.e. therapeutic regimens) features.

The present results also extend as spatial and/or frequency detail a recent important EEG study characterizing PDD with respect to DLB and AD patients, which has shown diffuse inter-groups differences within an extended alpha range spanning 8–12 Hz (Bonanni et al., 2008). In that study, the Authors have reported the slowing of posterior EEG rhythms in PDD subjects when compared to AD subjects, as revealed by higher amplitude of diffuse delta and theta rhythms and of reduced amplitude within the extended alpha range (Bonanni et al., 2008). As a step forward, the present results showed that the amplitude of parietal, occipital, and temporal low-frequency (8–10.5 Hz) alpha sources was high in Nold subjects, intermediate in PDD patients and quite low in AD patients, whereas similar contrasts at high-frequency alpha frequencies (10.5–13 Hz) were observed in occipital and temporal sources. In these localized low frequency alpha sources, there was a positive linear correlation with MMSE score across all Nold, PDD, and AD subjects as a whole group (the lower the alpha sources, the lower the MMSE score), suggesting a strict relationship with subjects' cognitive picture regardless the therapeutic regimens (i.e. cholinergic in the AD patients and dopaminergic in the PDD patients). Furthermore, these sources were not correlated with motor deficits in the PDD patients. This spatial and frequency specification extends previous EEG and MEG evidence showing higher amplitude of delta/theta rhythms and lower amplitude of alpha and beta rhythms in PDD than non-demented PD patients (Soikkeli et al., 1991; Neufeld et al., 1994; Bosboom et al. 2006; Stoffers et al., 2007), as well as a positive correlation between alpha rhythms and cognitive status in PPD patients; namely, the lower the alpha rhythms, the lower the cognitive performance (Stoffers et al., 2007).

Why did enhanced delta/theta rhythms and reduced low-frequency beta rhythms characterize PDD compared with AD patients? There is consensus that such pattern of EEG rhythms is linked to abnormal interactions between thalamic and cortical neural populations, associated to a loss of functional connectivity and to a sort of functional isolation of cortical modules (Klimesch, 1999; Pfurtscheller and Lopez da Silva, 1999; Steriade and Llinas, 1988). Such pattern of EEG rhythms might be related to cortical hypoperfusion (Brenner et al., 1986; Dossi et al., 1992; Kwa et al., 1993; Niedermeyer et al., 1997; Passero et al., 1995; Rae-Grant et al., 1987; Stigsby et al., 1981; Steriade, 1994; Rodriguez et al., 1999) and to an early degeneration of mesial temporal cortex (Killiany et al., 1993; Fernandez et al., 2003). In the present study, the enhancement of delta/theta sources was stronger in PDD than AD patients, in line with previous seminal evidence (Timmermann et al., 2003). Keeping in mind these data, it can be speculated that EEG cortical sources characterizing PDD compared with AD subjects are related to a pathological synchronization of the brain motor systems to slow frequencies maybe related to tremor or sensorimotor integration (Rossini et al., 1991).

Why were reduced alpha rhythms related to global cognition in PDD and AD patients showing an overt dementia? From a physiological point of view, alpha rhythms are mainly modulated by thalamo-cortical and cortico-cortical interactions (Pfurtscheller and Lopez da Silva, 1999; Steriade and Llinas, 1988), whereas, it is an open issue the role of cholinergic tracts from basal forebrain to cerebral cortex, including a gross branch connecting visual cortex typically targeted by neurodegenerative processes (Helkala et al., 1996; Holschneider et al., 1999; Mesulam et al., 2004; Ricceri et al., 2004; Teipel et al., 2005). A relationship between cholinergic neuromodulation and alpha rhythms has been hinted by the evidence that scopolamine – a cholinergic antagonist – reproduced in healthy subjects the typical abnormal pattern of alpha and theta rhythms observed in AD patients (Osipova et al., 2003). Finally, loss of cholinergic connections to cerebral cortex has reduced the power of resting state posterior alpha sources in amnesic MCI subjects, who are considered at high risk to progress to AD (Babiloni et al., 2008). Keeping in mind these data, it can be speculated that in both PDD and AD subjects, magnitude decrease of posterior low-frequency alpha sources reflects the loss of thalamic and cortical neurons/synapses as well as an unselective desynchronizing activity of cholinergic pathways from basal forebrain and thalamus to cerebral cortex (Kobayashi and Isa, 2002; Sarter and Bruno, 1997, 1998). As a consequence, cortical excitability would be unselectively enhanced in these patients, in agreement with previous

neurophysiological evidence observed in AD subjects (Alagona et al., 2001; Babiloni et al., 2000; Bachman et al., 1993; Ferreri et al., 2003; Pennisi et al., 2002). In the present study, the alpha sources were stronger in AD than PDD patients even if their MMSE score was carefully matched, thus suggesting more advanced brain neurodegeneration and adaptive plastic changes in AD than PDD patients. Noteworthy, previous studies have shown that a long-term therapy with acetylcholinesterase inhibitor has been found to improve, at least for a period, cognitive status in responders of both AD and PD patients (Areosa and Sherriff, 2003; Farlow et al., 2000; Litvinenko et al., 2008; Moretti et al., 2007). Furthermore, posterior cortical sources of resting state (EEG) alpha rhythms have been relatively preserved in AD subjects responding to 1-year therapy with acetylcholinesterase inhibitors (Babiloni et al., 2006f). Moreover, diffuse enhancement of resting (MEG) delta/theta rhythms has been reversed by this therapy even in PDD patients (Bosboom et al., 2006). Finally, a previous study using source localization has shown a power enhancement of theta rhythms in temporo-parietal and subcortical areas in a sub-group of 5 Nold subjects who converted to AD after a lot of months when compared to a sub-group of 5 "cognitively stable" Nold subjects (Prichep, 2007).

5. Conclusions

The present study tested the hypothesis that source mapping of resting state EEG rhythms characterize PDD and AD patients. To address this issue, eyes-closed resting state EEG rhythms were recorded in PDD, AD, and Nold subjects carefully matched as age, gender, and education. MMSE score was carefully matched between the PDD and AD groups. With respect to the Nold and AD groups, the PPD group was characterized by peculiar abnormalities of central (i.e. over motor cortex) delta sources and posterior cortical sources of theta and beta 1 rhythms. With respect to the Nold group, the PDD and AD groups mainly pointed to lower posterior cortical sources of alpha 1 rhythms, which were positively correlated to MMSE score across all subjects as a whole group (the lower the alpha sources, the lower the MMSE score and cognitive status). This alpha decrease was greater in the AD than PPD patients despite the similar cognitive status, pointing to deeper neurodegenerative processes and adaptive brain plasticity in the former than in the latter group. The present results suggest that topography and frequency of eyes-closed resting state cortical EEG rhythms distinguished the groups of PDD and AD patients, leading support to the hypothesis of different topographic tracks of neurodegeneration and diverse effects on the cortical neural synchronization mechanisms generating EEG rhythms in PDD and AD patients. These results motivate future studies comparing resting state EEG rhythms in PDD and non-demented PD subjects with paired personal and pharmacological features, towards the evaluation of clinical hypotheses.

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