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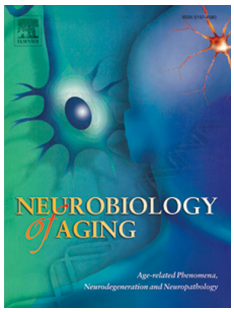

Levodopa May Affect Cortical Excitability In Parkinson's Disease Patients With Cognitive Deficits As Revealed By Reduced Activity Of Cortical Sources Of Resting State Electroencephalographic Rhythms

Claudio Babiloni, Claudio Del Percio, Roberta Lizio, Giuseppe Noce, Susanna Lopez, Andrea Soricelli, Raffaele Ferri, Maria Teresa Pascarelli, Valentina Catania, Flavio Nobili, Dario Arnaldi, Francesco Famà, Francesco Orzi, Carla Buttinelli, Franco Giubilei, Laura Bonanni, Raffaella Franciotti, Marco Onofrj, Paola Stirpe, Peter Fuhr, Ute Gschwandtner, Gerhard Ransmayr, Lucia Fraioli, Lucilla Parnetti, Lucia Farotti, Michela Pievani, Fabrizia D'Antonio, Carlo De Lena, Bahar Güntekin, Lutfu Hanoğlu, Görsev Yener, Derya Durusu Emek-Savaş, Antonio Ivano Triggiani, John Paul Taylor, Ian McKeith, Fabrizio Stocchi, Laura Vacca, Giovanni B. Frisoni, Maria Francesca De Pandis

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LEVODOPA MAY AFFECT CORTICAL EXCITABILITY IN PARKINSON'S DISEASE PATIENTS WITH COGNITIVE DEFICITS AS REVEALED BY REDUCED ACTIVITY OF CORTICAL SOURCES OF RESTING STATE ELECTROENCEPHALOGRAPHIC RHYTHMS

Claudio Babiloni[1,2], Claudio Del Percio[3], Roberta Lizio[1,2], Giuseppe Noce[3], Susanna Lopez[1], Andrea Soricelli[3,4], Raffaele Ferri[5], Maria Teresa Pascarelli[5], Valentina Catania[5], Flavio Nobili[6], Dario Arnaldi[6], Francesco Famà[6], Francesco Orzi[7], Carla Buttinelli[7], Franco Giubilei[7], Laura Bonanni[8], Raffaella Franciotti[8], Marco Onofrj[8], Paola Stirpe[2], Peter Fuhr[9], Ute Gschwandtner[9], Gerhard Ransmayr[10], Lucia Fraioli[2], Lucilla Parnetti[11], Lucia Farotti[11], Michela Pievani[12], Fabrizia D'Antonio[13], Carlo De Lena[13], Bahar Güntekin[14], Lutfu Hanoğlu[15], Görsev Yener[16], Derya Durusu Emek-Savaş[17], Antonio Ivano Triggiani[18], John Paul Taylor[19], Ian McKeith[19], Fabrizio Stocchi[2], Laura Vacca[20], Giovanni B. Frisoni[12,21], and Maria Francesca De Pandis[2]

[1] Department of Physiology and Pharmacology "Vittorio Erspamer", University of Rome "La Sapienza", Rome, Italy;
[2] Institute for Research and Medical Care, IRCCS San Raffaele Pisana, Rome, Italy, and Hospital San Raffaele of Cassino, Italy;
[3] IRCCS SDN, Napoli, Italy;
[4] Department of Motor Sciences and Healthiness, University of Naples Parthenope, Naples, Italy;
[5] Oasi Research Institute - IRCCS, Troina, Italy;
[6] IRCCS Ospedale Policlinico San Martino, Genova, Italy - Dipartimento di Neuroscienze,Oftalmologia, Genetica, Riabilitazione e Scienze Materno-infantili (DiNOGMI), Università di Genova, Italy;
[7] Department of Neuroscience, Mental Health and Sensory Organs, University of Rome "La Sapienza", Rome, Italy;
[8] Department of Neuroscience Imaging and Clinical Sciences and CESI, University G d'Annunzio of Chieti-Pescara, Chieti, Italy;
[9] Universitätsspital Basel, Abteilung Neurophysiologie, Petersgraben 4, 4031 Basel, Switzerland;
[10] Department of Neurology 2, Med Campus III, Faculty of Medicine, Johannes Kepler University, Kepler University Hospital, Krankenhausstr. 9, A-4020 Linz., Austria;
[11] Centre for Memory Disturbances, Lab of Clinical Neurochemistry, Section of Neurology, University of Perugia, Italy;
[12] Laboratory of Alzheimer's Neuroimaging and Epidemiology, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy;
[13] Department of Neurology and Psychiatry, Sapienza, University of Rome, Italy;
[14] Department of Biophysic, Istanbul Medipol University, Istanbul, Turkey;
[15] Department of Neurology, University of Istanbul-Medipol, Istanbul, Turkey;
[16] Department of Neurosciences and Department of Neurology, Dokuz Eylül University Medical School, Izmir, Turkey;
[17] Department of Psychology and Department of Neurosciences, Dokuz Eylül University, Izmir, Turkey;
[18] Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy.
[19] Institute of Neuroscience, Newcastle University, Newcastle, UK.
[20] Casa di Cura Privata del Policlinico (CCPP) Milano SpA, Milan, Italy.
[21] Memory Clinic and LANVIE - Laboratory of Neuroimaging of Aging, University Hospitals and University of Geneva, Geneva, Switzerland;

Corresponding author: Prof. Claudio Babiloni, Ph.D.
Department of Physiology and Pharmacology "V. Erspamer"
University of Rome "La Sapienza"
P. le A. Moro 5, 00185, Rome, Italy
Phone: +39 0649910989
E-mail: claudio.babiloni@uniroma1.it

Running title: Functional brain connectivity in mild cognitive impairment.

Abstract

We hypothesized that dopamine neuromodulation might affect cortical excitability in Parkinson's disease (PD) patients set in quiet wakefulness, as revealed by resting state electroencephalographic (rsEEG) rhythms at alpha frequencies (8-12 Hz). Clinical and rsEEG rhythms in PD with dementia (PDD, N=35), PD with mild cognitive impairment (PDMCI, N=50), PD with normal cognition (PDNC, N=35), and normal (Nold, N=50) older adults were available from an international archive. Cortical rsEEG sources were estimated by eLORETA. Compared with the Nold group, the PD groups showed reduced occipital alpha sources and increased widespread delta (<4 Hz) sources. Widespread frontal and temporal alpha sources exhibited an increase in PDD compared with PDMCI and PDNC groups, as function of dopamine depletion severity, typically greater in the former than the latter groups. A daily dose of levodopa induced a widespread reduction in cortical delta and alpha sources in a sub-group of 13 PD patients under standard chronic dopaminergic regimen. In PD patients in quiet wakefulness, alpha cortical source activations may reflect an excitatory effect of dopamine neuromodulation.

Keywords: Functional brain connectivity; Resting state EEG rhythms; Mild cognitive impairment due to Alzheimer's disease (ADMCI); Mild cognitive impairment due to Parkinson's disease (PDMCI).

Introduction

Parkinson's disease (PD) is characterized by motor symptoms but often goes hand in hand with subtle mild cognitive impairment at the disease onset. This cognitive dysfunction is progressive in most of patients (Muslimovic et al., 2005). Indeed, the percentage of PD patients progressing to dementia in 20 years is ~~included~~ between 60% (Aarsland et al., 2003; Buter et al., 2008; Hughes et al., 2000; Levy et al., 2000) and more than 80% (Hely et al., 2008).

The patho-aetiology of the cognitive deficits in PD is heterogeneous and thus patients may need personalized treatments to mitigate the cognitive decline. Ideally, this ~~monitoring~~ should be done with biomarkers reflecting those neuropathological processes or the effects of those processes on brain functions. Among various candidates, resting state eyes-closed electroencephalographic (rsEEG) rhythms are cost-effective, non-invasive, and can be repeated several times. For this reason, they have extensively been studied as biomarkers to evaluate the neurophysiological mechanisms of dementing disorders (Breslau et al., 1989; Briel et al., 1999).

A prominent application of quantitative rsEEG techniques in PD patients was the computation of power (density) of rsEEG rhythms in standard frequency bands from delta (< 4 Hz) to gamma (> 30 Hz) at scalp electrodes placed over the whole scalp, as a neurophysiological biomarker of thalamocortical and corticothalamic neural synchronization of oscillatory cycles of cellular excitation and inhibition. Results have shown that when compared to normal healthy elderly (Nold) individuals, PD patients with cognitive deficits (PDCD) were characterized by widespread higher power in delta and theta (4-7 Hz) rhythms and some reduction of alpha power (Bonanni et al., 2008; Bosboom et al., 2009,2006; Caviness et al., 2016; Fünfgeld, 1995; Kamei et al., 2010; Melgari et al., 2014; Pugnetti et al., 2010; Serizawa et al., 2008). PDCD patients also showed lower frequency of the alpha (8-12 Hz) power peak, greater global theta and delta power, and lower power in the alpha and beta (13-30 Hz) frequency bands even compared with a PD group with normal cognitive status (Caviness et al., 2007).

The above rsEEG techniques have received some validation for clinical applications in individual patients. A step-wise method using an input of 20 discriminant rsEEG power and coherence for a statistical pattern recognition procedure exhibited an accuracy of classification (area under the receiving operator characteristic curve) of 0.90 between participants with dementia due to AD (ADD) and PD (PDD; Engedal et al., 2015). Another study using a multi-modal combination of rsEEG variables with clinical, cerebrospinal fluid, neuroimaging, neuropsychological, and visual EEG data reached a

classification accuracy of 0.87 in the discrimination between ADD, PDD, and dementia with Lewy bodies (DLB) individuals (Dauwan et al., 2016b). Finally, a rsEEG study in a small database obtained a 100% classification accuracy of individuals with PDD/DLB, ADD, and frontotemporal dementia (FTD) using 25 discriminant variables based on scalp rsEEG power and interrelatedness (i.e. Granger causality) as an input to a support vector machine (Garn et al., 2017).

In summary, compared with Nold individuals, PD patients with cognitive deficits show a reduced activation of posterior cortical sources of alpha rhythms in quiet wakefulness, which is associated with increased widespread delta rhythms. It is well known that such reduced alpha rhythms reflect cortical over-excitability in quiet wakefulness (Babiloni et al., 2015a) but the relationship of this effect with dopamine neuromodulation is poorly known. This is particularly pertinent given PD patients with cognitive deficits are affected by neurodegenerative neuropathology of subcortical projection to cerebral cortex lobe including deposition of α-synuclein in Lewy bodies and neurites, loss of tegmental dopamine cell populations, loss of basal forebrain cholinergic projection to the cortex, and a variable degree of coexisting AD neuropathology (Barker and Williams-Gray, 2016; Irwin et al., 2017).

The present exploratory and observational study tested the hypothesis that the dopamine neuromodulation may affect cortical excitability in PD patients set in quiet wakefulness, as assessed by the examination of resting state cortical alpha rhythms. Our aim therefore was to make use of clinical and rsEEG rhythms in PDD, PDMCI, PD with normal cognition (PDNC), and Nold subjects from an available international our archive including all data coming from the PDWAVE Consortium. An assumption of this study was that compared to PD patients without cognitive deficits, those with MCI and dementia have had a longer disease with a consequent progression in the depletion of dopaminergic brain neurons, although the relationship betwwen duration and severity of the disease is not linear. For some of these patients under a standard chronic dopaminergic regimen, clinical and rsEEG rhythms were available before (OFF) and after (ON) about 60 minutes from the administration of one daily dose of Levodopa. From a methodological point of view, we used exact low-resolution brain electromagnetic tomography (eLORETA) freeware to estimate rsEEG cortical sources at individual frequency bands (Pascual-Marqui, 2007) to improve the topographic analysis of alpha rhythms. In previous studies of our group, this methodology unveiled different characteristics of abnormal cortical delta and alpha source activity in PD patients with cognitive deficits in relation not

only to Nold subjects but also to patients with cognitive deficits due to AD and DLB (Babiloni et al., 2018a,b, 2017a,b). Compared with Nold subjects, PD patients with cognitive deficits showed a reduced activation in posterior cortical sources of alpha rhythms, associated with increased widespread delta source activation. Furthermore, such increment in delta source activation was greater than that observed in AD and DLB patients. In contrast, PDCD patients exhibited less reduction in alpha source activation than that observed in AD and DLB patients. Keeping in mind, these previous data, the present methodology may provide quite sensitive markers of cortical neural synchronization and excitability in PD patients as a function of cognitive deficits, which are a rough but useful index of PD progression and dopamine depletion severity over time.

Materials and Methods

Subjects and diagnostic criteria

In the present exploratory and observational study, clinical and rsEEG data in age-, sex-, and education-matched groups of PD patients and Nold subjects were taken from an international archive formed by the Clinical Units of our Consortium. Specifically, the groups were formed by 35 PDD, 50 PDMCI, 35 PD with normal cognition, and 35 Nold individuals. Table 1 summarizes the most relevant demographic features (i.e., age, gender, education) and global cognitive status (i.e., mini mental state evaluation, MMSE, score) of those groups. Further the table reports the results of the presence or absence of statistically significant differences ($p < 0.05$) between the groups as age (t-test), gender (Mann-Whitney U Test), education (t-test), and MMSE score (Mann-Whitney U Test). No statistically significant differences were found between the Nold and the PD groups in those variables ($p > 0.05$) with the obvious exception of MMSE score.

In a sub-group of PD patients, eyes-closed (3-5 minutes) rsEEG data were recorded in the late morning before (OFF) and after (ON) about 60 minutes from the acute administration of one daily dose of levodopa. In the ON condition, it is expected a peak of levodopa in the blood flow (Adamiak et al., 2010; Simon et al., 2016). Specifically, this sub-group was formed by 7 PD, 4 PDMCI, and 2 PDD patients. Table 2 reports relevant demographic features (i.e., age, gender, education) and, in ON and OFF conditions, the global cognitive status (i.e., mini mental state evaluation, MMSE, score).

Insert here Tables 1 and 2

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

In this study, the diagnosis of PD was based on a standard clinical assessment of tremor, rigidity, and bradykinesia (Gelb et al., 1999). 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; Martínez-Martín et al., 2015) for extrapyramidal symptoms were used. The mean UPDRS score was 15.1 (± 1.2 standard error of the mean, SE) in the PD group, 21.0 (± 2.4 SE) in the PDMCI group, and 39.8 (± 3.5 SE) in the PDD group. The ANOVA showed a significant effect ($p < 0.0001$) of the factor Group (PD, PDMCI, and PDD) with the mean UPDRS score higher in the PDD than the PDMCI and the PD group ($p< 0.05$).

The status of PDMCI was based on the Diagnostic Criteria for Mild Cognitive Impairment in PD (Litvan et al., 2011). Specifically, the inclusion criteria comprised: (1) a diagnosis of PD as specified above; (2) a gradual decline, in the context of an established PD, in the cognitive status reported by either the patient or a reliable informant, or observed by the clinicians; (3) an abnormally low score to at least one of the neuropsychological tests mentioned in a following section, as defined by performances 1.5 standard deviations (SDs) from the mean value for age- and education-matched controls or equivalent scores for abnormality according relative manuals of the tests used; (4) at least a partial functional independence in instrumental activities of the daily living under the effect of dopamine treatment (ON condition), although slight difficulties on complex functional tasks may be present. Clinical dementia rating score of 0.0 or 0.5; and (5) daily chronic levodopa regimen for more than 6 months to ensure that the daily administration of the dose of levodopa (875 mg/die ± 121 SE) in the present experimental day did not induce any placebo effect. This regimen included levodopa, or melevodopa with other dopamine agonists such as rotigotine, ropinirole, pramipexole, amantadine and monoamine oxidase inhibitor (selegiline). COMT inhibitor (i.e., entacapone) or DOPA decarboxylase inhibitor (i.e., carbidopa or benserazide) were also given in some patients.

The exclusion criteria for PDMCI included the following forms of parkinsonism: (1) dementia of any kind, including DLB (Geser et al., 2005; McKeith et al., 1996, 2017); (2) drug-induced or cerebrovascular parkinsonism; (3) atypical parkinsonism with absent or minimal responses to antiparkinsonian drugs; and (4) mixed neurodegenerative diseases as revealed by cerebrospinal fluid or neuroimaging (i.e., structural magnetic resonance imaging, positron emission tomography or single photon computerized emission tomography).

A diagnosis of PDD was given to the patients with a history of dementia (inclusion criteria as for ADD) preceded by a diagnosis of PD for at least 12 months. On the basis of the clinical features and neuroradiological findings, the inclusion criteria included: (1) a diagnosis of PD as specified above; (2) a gradual decline, in the context of an established PD, in the cognitive status reported by either the patient or a reliable informant, or observed by the clinicians; (3) an abnormally low score to at least one of the neuropsychological tests mentioned in a following section, as defined by performances 1.5 standard deviations (SDs) from the mean value for age- and education-matched controls or equivalent scores for abnormality according relative manuals of the tests used; (4) moderate to severe impairment in the functional independence in instrumental activities of the daily living under the effect of dopamine treatment (ON condition). Clinical dementia rating score greater than 0.05; and (5) daily chronic levodopa regimen (see above the list of the drugs) for more than 6 months to ensure that the daily administration of the dose of levodopa in the present experimental day did not induce any placebo effect. The exclusion criteria for PDD included the following forms of parkinsonism: (1) DLB (McKeith et al., 1996), (2) drug-induced parkinsonism, (3) cerebrovascular parkinsonism, and (4) atypical parkinsonism with absent or minimal responses to antiparkinsonian drugs.

All PD patients underwent a battery of clinical scales including Neuropsychiatry inventory (NPI; Cummings et al. (1994), Epworth Sleepiness Scale (ESS; Johns, 1991), Geriatric depression scale (GDS; Yesavage et al., 1983), Activities of Daily Living (ADL), and the Barthel index for the evaluation of independence in the daily activities. Cognitive functions were tested by neuropsychological tests including Montreal Cognitive Assessment (MOCA; Nasreddine et al., 2005), MMSE (Folstein et al., 1975), and Frontal Assessment Battery (FAB; Dubois et al., 2000).

Concerning psychoactive medications add-on to levodopa, some PD patients used anti-depressant (i.e., selective serotonin reuptake inhibitor: sertraline, citalopram, paroxetine,

escitalopram or Acetylcholine inhibitors, AChEIs (i.e., rivastigmine). Less than 10% of the PD patients took anti-psychotic medications (i.e., clozapine, quetiapine).

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 or psychiatric disorder. 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. Subjects affected by chronic systemic illnesses (diabetes mellitus, as an example) were excluded, as well as subjects receiving chronic psychoactive drugs. Subjects with a history of previous or present neurological or psychiatric disease were also excluded.

rsEEG recordings and preliminary data analysis

Before the EEG recording, instructions encouraged the Nold and PDCD individuals to experience a quiet wakefulness with muscle relaxation, no voluntary movements, no talking or developing a systematic goal-oriented mentalization. A quiet wondering mode of mentalization was kindly required.

The rsEEG data were recorded with a sampling frequency of 256-1,024 Hz and related antialiasing bandpass between 0.01 Hz and 100 Hz. Nineteen scalp electrodes positioned according to the 10–20 System (i.e. Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2) were used with respect to a cephalic ground (i.e., frontal) and an extracephalic electrode reference (i.e., linked auricular or mastoid). Electrodes impedances were kept below 5 KOhm. Bipolar vertical and horizontal electrooculographic (EOG), and one-channel electrocardiographic signals were also acquired (256-1,024 Hz) for artifact detection and off-line correction (when possible).

The recorded rsEEG data were divided into epochs of 2 seconds and analyzed off-line. The epochs affected by any physiological (ocular/blinking, muscular, head movements) or non-physiological (bad contact electrode-scalp) artifacts were preliminarily identified by an automatic computerized procedure (Moretti et al., 2003). Furthermore, two independent experimenters manually checked and (dis)confirmed the artifact-free rsEEG epochs, before successive analyses. Specifically, they controlled for the presence of ocular and blinking artifacts based on EOG signals, while muscular and head artifacts were recognized by analyzing EEG signals. 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 observing the effects of several frequency bandpass filters in different ranges and by the inspection of EEG power density spectra. Indeed, muscle tension is related to unusually high and stable values of EEG power density from 30 to 100-150 Hz, which contrast with the typical declining trend of EEG power density from 25 Hz onward.

Spectral analysis of the rsEEG epochs

A standard digital FFT-based power spectrum analysis (Welch technique, Hanning windowing function, no phase shift) computed the power density of scalp rsEEG rhythms with 0.5 Hz of frequency resolution.

According to a previous study of our group (Moretti et al., 2004), the frequency bands of interest were individually identified based on the following frequency landmarks: the transition frequency (TF) and the individual alpha frequency peak (IAF). In the EEG power density spectrum, the TF marks the transition frequency between the theta and alpha bands, defined as the minimum of the rsEEG power density between 3 and 8 Hz (between the delta and the alpha power peak). IAF is defined as the maximum power density peak between 6 and 14 Hz. These frequency landmarks were previously well described by Dr. Wolfgang Klimesch (Klimesch, 1999, 1996, Klimesch et al., 1998).

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

Cortical sources of rsEEG epochs as computed by eLORETA

We used the freeware tool called exact LORETA (eLORETA) for the linear estimation of the cortical source activity generating scalp-recorded rsEEG rhythms (Pascual-Marqui, 2007a). The

present implementation of eLORETA uses a head volume conductor model composed of the scalp, skull, and brain. In the scalp compartment, exploring electrodes can be virtually positioned to give EEG data as an input to the source estimation (Pascual-Marqui, 2007a). The brain model is based on a realistic cerebral shape taken from a template typically used in the neuroimaging studies, namely that of the Montreal Neurological Institute (MNI152 template). The eLORETA freeware solves the so-called EEG inverse problem estimating "neural" current density values at any cortical voxel of the mentioned head volume conductor model. The solutions are computed rsEEG frequency bin-by-frequency bin.

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

In line with the general low spatial resolution of the present EEG methodological approach (i.e. 19 scalp electrodes), we performed a regional analysis of the eLORETA solutions. For this purpose, we collapsed the eLORETA solutions within frontal, central, temporal, parietal, occipital, and limbic macroregions (ROIs) considered separately. Table 3 reports the list of the BAs used for the ROIs considered in the present study. Of note, the main advantage of the regional analysis of eLORETA solutions was that we could disentangle the rsEEG source activity in contiguous cortical areas. For example, the rsEEG source activity in the occipital ROI was disentangled from that estimated in the parietal and temporal ROIs, etc. This was made possible by the fact that eLORETA solves the linear inverse problem by taking into account (at least in part) the effects of the head as a volume conductor. In contrast, the solutions of rsEEG power density computed at a parietal scalp electrode reflect the contribution of source activities not only of the underlying parietal cortex but also of sorrounding occipital and temporal cortices.

For the present eLORETA cortical source estimation, a frequency resolution of 0.5 Hz was used, namely, the maximum frequency resolution allowed by the use of 2-s artifact free EEG epochs.

Insert here Table 3

Statistical analysis of the rsEEG eLORETA source activity

All the statistical sessions were performed by the commercial tool STATISTICA 10 (StatSoft Inc., www.statsoft.com) to test two main hypotheses. Firstly, alpha source activities might differ in PD groups (i.e., PD, PDMCI, PDD) as a function of the severity of the cognitive deficits (i.e., as a probe of dopamine depletion severity). Secondly, rsEEG source activities showing that effect in PD patients with different cognitive deficits might show a modulation between the ON and OFF conditions in those patients, thus confirming its dependency by brain dopamine levels. In all the ANOVAs, Mauchly's test evaluated the sphericity assumption and degrees of freedom were corrected by the Greenhouse-Geisser procedure when appropriate ($p < 0.05$). Duncan test was used for post-hoc comparisons ($p < 0.05$). The results of the following statistical analyses were controlled by the Grubbs test ($p < 0.01$) for the presence of outliers in the distribution of the eLORETA source solutions.

A first ANOVA was computed using the regional normalized eLORETA solutions (normalized current density at all voxels of a given ROI) as a dependent variable ($p < 0.05$). The ANOVA factors were Group (Nold, PD, PDMCI, PDD), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). Individual TF and the IAF were used as covariates. The sphericity assumption was evaluated with the Mauchly's test. The degrees of freedom were corrected by the means of Greenhouse-Geisser procedure when appropriate. The Duncan test was used for post-hoc comparisons ($p < 0.05$). The planned post-hoc testing evaluated the prediction of the differences in rsEEG source solutions related to cognitive deficits between the PDMCI and and PDD groups using the Nold and PD groups as control references. Specifically, we expected: (1) a statistical 3-way interaction effect including the factors Group, ROI, and Band ($p < 0.05$); (2) a post-hoc test indicating statistically significant differences of the regional normalized eLORETA solutions with the pattern Nold and PD ≠ PDMCI and PDD (Duncan test, $p < 0.05$).

A second ANOVA was computed using the regional normalized eLORETA solutions as a dependent variable ($p < 0.05$). The ANOVA factors were Condition (ON, OFF), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The planned post-hoc testing evaluated the prediction of the differences in rsEEG source solutions between the ON and OFF conditions. Specifically, we expected: (1) a statistical interaction effect including the factor Condition and Band ($p < 0.05$); (2) a post-hoc test indicating statistically

significant differences of the regional normalized eLORETA solutions in the alpha frequency band with the pattern ON ≠ OFF (Duncan test, $p < 0.05$).

Correlation between the clinical scale and the eLORETA solutions in the ON condition

Spearman test ($p < 0.05$) was used to evaluate the correlation between the MMSE score and rsEEG source activities showing statistically significant differences ($p < 0.05$) between the PD groups (i.e., PD, PDMCI, and PDD). Indeed, a reduction in widespread rsEEG cortical source activation in the alpha range as a function of cognitive deficits may be interpreted as a clinically-relevant increase in the resting state cortical excitability, possibly related to the dopamine depletion. In the same line, Spearman test ($p < 0.05$) was also used to evaluate the correlation between the MMSE score and rsEEG source activities showing statistically significant differences ($p < 0.05$) between the ON and OFF conditions in the sub-group of PD patients examined.

Accuracy of the rsEEG source activity in the discrimination between Nold, ADD, PDD, and DLB individuals

rsEEG sources showing the highest statistically significant differences between the four groups were used as discriminant variables for the classification of Nold and PD individuals of a given group and between the individuals of two groups of PD patients. The correct blind classifications of these rsEEG source activities were performed by Matlab 2010b software (Mathworks Inc., Natick, MA, USA) for the production of the receiver operating characteristic (ROC) curves (DeLong et al., 1988). The following indexes measured the performance of the above binary classification: (1) Sensitivity: the rate of positives who were correctly classified as positives (i.e. “true positive rate” in the signal detection theory); (2) Specificity: the rate of negatives (control) who were correctly classified as negatives (i.e. “true negative rate” in the signal detection theory); (3) Accuracy:–the mean of the sensitivity and specificity (the amount of subjects in the groups was the same); and (4) Area under the ROC (AUROC) curve. The AUROC curve was a major reference index of the global classification accuracy.

Results

Statistical comparison of the EEG cortical sources in the Nold, PD, PDMCI, and PDD groups

Table 4 reports the mean values of TF and IAF for the four groups (i.e. Nold, PD, PDMCI, and PDD), together with the results of the statistical comparisons between the groups (ANOVA, $p < 0.05$). The mean TF was 6.2 Hz (± 0.1 SE) in the Nold group, 5.8 Hz (± 0.2 SE) in the PD group, 5.5 Hz (± 0.2 SE) in the PDMCI group, and 4.7 Hz (± 0.2 SE) in the PDD group. Furthermore, the mean IAF was 9.5 Hz (± 0.1 SE) in the Nold group, 8.6 Hz (± 0.2 SE) in the PD group, 8.5 Hz (± 0.2 SE) in the PDMCI group, and 7.3 Hz (± 0.2 SE) in the PDD group. The ANOVAs using these values as an input showed the following statistically significant findings: (1) a significant effect ($F = 12.3$, $p < 0.00001$) of the factor Group (Nold, PD, PDMCI, and PDD) with the mean TF lower in the PDD than PDMCI, PD, and Nold ($p< 0.05$). The mean TF was also lower in the PDMCI than the Nold group ($p< 0.05$); (2) a significant effect ($F = 24.6$, $p < 0.0001$) of the factor Group (Nold, PD, PDMCI, and PDD) with the mean IAF lower in the PDD than the PDMCI and the PD group ($p< 0.05$). The mean IAF was also lower in the PDMCI and PD groups than the Nold group ($p< 0.05$).

These findings stress the importance of individual differences in the TF and IAF in the determination of the delta to alpha frequency bands in PD patients.

Insert Table 4 here

Figure 1 shows the grand average of regional rsEEG source activities (i.e., eLORETA solutions) relative to a statistically significant ANOVA interaction effect ($F = 5.3$; $p < 0.00001$) among the factors Group (Nold, PD, PDMCI, and PDD), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, gamma), and ROI (frontal, central, parietal, occipital, temporal, limbic). In the figure, rsEEG source activities have the shape of typical rsEEG relative power spectra. Notably, the profile and magnitude of the spectra of the rsEEG source activity in the Nold, PD, PDMCI, and PDD groups are different across the ROIs, thus suggesting the concept that scalp-recorded rsEEG rhythms are produced by a distinct pattern of cortical source activity in these groups.

Concerning the most relevant effects, the discriminant pattern Nold and PD < PDMCI and PDD was fitted by the frontal, central, parietal, temporal, occipital, and limbic delta source activities ($p < 0.05$ to $p < 0.000001$). Furthermore, the discriminant pattern Nold and PD > PDMCI and PDD was

fitted by occipital alpha 2 source activities ($p < 0.05$ to $p < 0.000001$). As additional findings of interest, alpha 3 sources showed a paradoxical greater magnitude as a function of the global cognitive deficits. Specifically, a pattern "PD < PDMCI < PDD" was fitted by temporal alpha 3 source activities ($p < 0.05$ to $p < 0.000001$). Furthermore, a pattern "PD and PDMCI < PDD" was fitted by frontal, central, and temporal alpha 3 source activities ($p < 0.05$ to $p < 0.000001$). Of note, these findings were not due to outliers from those individual eLORETA solutions, as shown by Grubbs' test with an arbitrary threshold of $p < 0.0001$ (Figure 2).

Insert Figures 1 and 2 here

The above effects in the delta sources were clinically relevant as shown by results of a correlation analysis between those source activities and the MMSE score in the Nold, PD, PDMCI, and PDD subjects as a whole group (Spearman test, $p < 0.05$). Specifically, a statistically significant negative correlation was found between widespread delta source activities and the MMSE score ($r = -0.32$ to -0.48, $p < 0.0001$ to 0.000001; Table 5). The higher delta source activities, the lower the MMSE score (the worsen the global cognition). These effects were also confirmed when all PD, PDMCI, and PDD patients were considered as a whole group (Spearman test, $p < 0.05$). Indeed, a statistically significant negative correlation was found between widespread delta source activities and the MMSE score ($r = -0.24$ to -0.42, $p < 0.005$ to 0.00005; Table 5). Of note, alpha 3 sources showing a paradoxical greater magnitude as a function of the global cognitive deficits showed no statistically significant correlation with the MMSE score in the Nold, PD, PDMCI, and PDD subjects as a whole group (Spearman test, $p > 0.05$).

Insert Table 5 here

Classification among Nold, PD, PDMCI, and PDD individuals based on delta and alpha source activities

The above significant delta and alpha source activities served as discriminant input variables for the computation of the AUROC curves. These AUROC curves aimed at indexing the classification accuracy in the discrimination between Nold, PD, PDMCI, and PDD individuals. The results of this analysis are reported in detail in Table 6. In general, the best classification accuracies between Nold

vs. PD patients with cognitive deficits (PDMCI, PDD) were obtained using widespread delta source activities. AUROC values were of 0.73-0.81 for the Nold vs. PDMCI individuals and 0.90-0.95 for Nold vs. PDD individuals. In the same line, the best classification accuracies between PD vs. PDMCI and PDD subjects were still obtained using widespread delta source activities. Specifically, AUROC values were of 0.70-0.73 for the PD vs. PDMCI individuals and 0.76-0.94 for PD vs. PDD individuals. Finally, significant classification accuracies using "paradoxical" alpha sources (i.e. those showing greater magnitude as a function of the global cognitive deficits) were as follows. AUROC values were of 0.74 for the Nold vs. PD individuals and 0.76 for PD vs. PDD individuals.

Insert Table 6 here

Effect on delta and alpha sources of the administration of a daily dose of levodopa in PD patients under chronic dopamine treatment

Figure 3 shows the grand average of regional rsEEG source activities (i.e., eLORETA solutions) relative to a statistically significant ANOVA interaction effect ($F = 1.5$; $p < 0.05$) among the factors Condition (ON, OFF), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, gamma), and ROI (frontal, central, parietal, occipital, temporal, limbic) in the small sub-group of 13 PD patients under chronic dopamine treatment (e.g., 7 PD, 4 PDMCI, and 2 PDD individuals) whose rsEEG sources were compared before vs. after a daily dose of levodopa. In the figure, rsEEG source activities have the general shape of those of Figure 1, based on the eLORETA solutions of the extended groups of PD, PDMCI, and PDD patients. When compared to the OFF condition, the ON condition induced a marked reduction in parietal, temporal, and occipital alpha 2 and alpha 3 source activities ($p < 0.05$ to $p < 0.00001$). Furthermore, the ON condition also induced a reduction in parietal and occipital delta source activities ($p < 0.05$ to $p < 0.00001$). As the only exception, frontal delta source activities were higher in the ON than the OFF condition ($p < 0.00001$). Of note, these findings were not due to outliers from those individual eLORETA solutions, as shown by Grubbs' test with an arbitrary threshold of $p < 0.0001$ (Figure 4).

Insert Figures 3 and 4 here

Table 7 reports results of the correlation analysis (Spearman test, $p < 0.05$) performed between clinical and neuropsychological scales and rsEEG cortical sources at delta and alpha sources in the small sub-group of 13 PD patients (e.g., 7 PD, 4 PDMCI, and 2 PDD individuals) in the ON condition (about 60 minutes after the administration of a daily dose of levodopa). A statistically significant positive correlation was found between parietal alpha 2 source activities and the NPI score ($r = 0.56$, $p < 0.05$) and between parietal alpha 3 source activities and GDS ($r = 0.61$, $p < 0.05$). The higher alpha source activities, the higher the NPI (the worsen the psychiatric symptoms) and GDS (the worsen the depression) scores. Furthermore, a statistically significant positive correlation was also found between temporal alpha 2 ($r = -0.70$, $p < 0.005$) and alpha 3 ($r = -0.57$, $p < 0.05$) source activities and the FAB score ($r = 0.56$, $p < 0.05$). The higher alpha source activities, the lower the FAB score (the worsen the frontal executive dysfunctions). These results unveiled the paradox that in those PD patients in the ON condition, the higher alpha 2 and alpha 3 source activities in some posterior areas, the greater the abnormalities in clinical and neuropsychological tests ($p < 0.05$).

Insert Table 7 here

Discussion

In the present exploratory and observational study, we assessed whether dopamine modulation may reflect cortical excitability in PD patients. When compared to the Nold group, the PD groups without and with cognitive deficits (i.e., PDMCI and PDD) showed reduced activity in posterior alpha sources, which was associated with increased activity in widespread delta (< 4 Hz) sources. In relation to the PD group, the PDMCI and PDD groups showed a greater reduction in occipital low-frequency alpha source activity, associated with greater increase in widespread delta (< 4 Hz) source activities. However, interestingly, widespread frontal, central, and temporal high-frequency alpha sources exhibited a paradoxical increase in activity in the PDD group compared with the PDMCI and PD groups. At the individual level, all delta sources exhibited clinically relevant correlations with global cognitive status (i.e., MMSE score) in all Nold and PD subjects considered as a whole group, while some delta and alpha sources showed moderate (> 0.7) to good (> 0.9) classification accuracies in the discrimination between Nold and PD individuals with cognitive deficits.

Two main assumptions underpin the ~~our~~ interpretation of the present findings. Firstly, compared with PD, PDD is supposed to be characterized by a longer neurodegenerative disease duration and consequently a greater loss of brain dopaminergic neurons, although the relationship between duration and severity of the disease is not linear. Secondly, the resting state eyes-closed alpha power in posterior scalp regions is typically lower in amplitude when underlying cortical neurons are excited. Keeping in mind these assumptions, the results of the present study lends support to the working hypothesis that dopamine neuromodulation in the cerebral cortex may increase local neural pathological excitation in quiet wakefulness. In line with this tentative explanation, the other main results of this study showed that a daily dose of levodopa induced a widespread reduction in cortical delta and alpha source activations in a sub-group of PD patients taking a standard chronic dopaminergic regimen.

The present results in the cortical rsEEG source space extend previous evidence based on rsEEG and its magnetoencephalographic (rsMEG) counterpart in PD patients compared with Nold subjects, namely a reduction in alpha and a decrease in delta power at the scalp electrode level (Bonanni et al., 2008; Bosboom et al., 2006, 2009; Caviness et al., 2007, 2016; Fünfgeld, 1995; Kamei et al., 2010; Melgari et al., 2014; Pugnetti et al., 2010; Serizawa et al., 2008). In this framework, rsMEG investigations showed a diffuse increase in delta power in PDD patients in comparison with non-demented ones (Bosboom et al., 2006). Furthermore, those investigations showed parieto-occipital and temporal alpha power increased and fronto-central and parieto-occipital delta power decreased after an add-on regimen with Acetylcholine inhibitors (Bosboom et al., 2009). Finally, previous rsMEG evidence showed a widespread progressive slowing of brain rhythms in initially non-demented PD patients, with decreasing cognitive performance associated with increased delta and theta power, as well as decreases in alpha and gamma power (Olde Dubbelink et al., 2013). In that study, motor impairment was associated with a theta power increase only (Olde Dubbelink et al., 2013).

The neurophysiological model

At the present stage of the research, we cannot provide a conclusive explanation about the neurophysiologic underpinning of the reported findings. Rather, we can speculate based on known

fundamentals concerning the basal ganglia circuits and mechanisms generating alpha rhythms. According to those fundamentals, a daily dose of levodopa in a chronic regimen may induce an increase in cortical excitation in PD patients with cognitive deficits during a quiet wakefulness, as revealed by a reduction in widespread cortical alpha source activity. This effect may depend on a complex modulation between thalamocortical and basal ganglia circuits that generate multiple brain rhythms from delta to gamma frequencies; in this regard previous studies have shown an interrelatedness of posterior alpha and frontal beta rhythms between cerebral cortex and subthalamic nucleus In PD patients (Hirschmann et al., 2011, 2013; Litvak et al., 2011) and relatedly frontal motor areas was shown to trigger the suppression of interfering beta rhythms in the subthalamic nucleus (Gaynor et al., 2008).

In previous investigations, there were contrasting effects of levodopa administration on cortical rsEEG rhythms in PD patients (Priori et al., 2004; Stoffers et al., 2007). In those patients, a daily dose of levodopa inhibited alpha rhythms in the cerebral cortex (including hemispherical asymmetry in occipital regions) in relation to clinical responses (Mostile et al., 2015). Furthermore, the dopaminergic therapy strongly promoted the interrelatedness of alpha rhythms between the cerebral cortex and pedunculopontine nucleus (Androulidakis et al., 2008). Moreover, the levodopa dose also decreased exaggerated beta rhythms in the cerebral cortex (Mostile et al., 2015) and subthalamic nucleus (Priori et al., 2004; Wang et al., 2016). Among these effects, those on beta rhythms were related to an improvement of motor symptoms and can represent an important candidate biomarker of PD (Wang et al., 2016). In those previous investigations, the levodopa dose also partially recovered some rsEEG rhythms such as suppressed theta and exaggerated high-frequency gamma (110-170 Hz) recorded in the thalamus (Kane et al., 2009) and subthalamic nucleus in relation to normative data (Priori et al., 2004; Wang et al., 2016). Compared with the levodopa dose, deep brain high-frequency stimulation (i.e. 130 Hz/2V) in the subthalamic nucleus decreased both alpha and beta rhythms and increased delta-theta rhythms recorded from that nucleus (Blumenfeld et al., 2015; Giannicola et al., 2012). Noteworthy, those exaggerated subthalamic beta rhythms were found to be triggered by primary and supplementary motor areas (Gaynor et al., 2008).

Previous findings in PD patients are globally corroborated by previous animal models of the disease. It was shown that the hyperdirect pathway of basal ganglia may propagate exaggerated cortical beta rhythms to the subthalamic nucleus under dopamine depletion as “anti-movement”

consequences (Magill et al., 2001). Furthermore, the severity of experimental parkinsonism correlates with increases in theta and alpha power recorded in frontal motor areas and internal global pallidus, in association with decreased cortical beta power (Devergnas et al., 2014). In those animal studies, a dose of levodopa reversed the exaggerated amplitude in alpha rhythms recorded in cerebral cortex and internal global pallidus (Costa et al., 2006). This effect was paralleled by a decrease in the exaggerated amplitude of (1) beta rhythms detected in the cerebral cortex, thalamus, and pedunculopontine nucleus (Devergnas et al., 2014; Geng et., 2016) and (2) the abnormal coherence of these beta rhythms between cerebral cortex and subthalamic nucleus (Sharott et al., 2005) or pedunculopontine nucleus (Geng et., 2016).

Keeping in mind the present and previous findings, it can be speculated that the multiple oscillatory activities (e.g., from delta to high-frequency gamma) recordable in cerebral cortex, basal ganglia, and pedunculopontine loops may regulate thalamocortical re-entrant signals to cerebral cortex and modulate the efficiency of neural signal transfer underpinning different aspects of postural control and motor performance (e.g. postural adaptations and gait, oculomotor control, sensorimotor integration, and voluntary movements). In this physiological framework, the PD-related dopaminergic depletion in the substantia nigra might be associated with a pathological enhancement in slow-frequency (i.e. delta-theta) and beta rhythms in the functional connectivity between cerebral cortex and subthalamus. This pathological enhancement in the cortical-basal ganglia-pedunculopontine system may be partially recovered by daily doses of levodopa. In this regard, the present results suggest that the partial normalization of low-frequency rhythms in the PD cerebral cortex can be non-invasively observed at delta band in quiet wakefulness. Moreover, a brain dopaminergic modulation might also induce an increase of cerebral arousal in the quiet wakefulness as revealed by the reduction of alpha rhythms. This effect may facilitate higher sensorimotor information processes and transfer of motor commands. Future studies should clarify if these effects of the brain dopaminergic modulation are mainly mediated by direct, indirect or hyperdirect pathways of basal ganglia (Alexander et al, 1986; Albin et al., 1989; Wichmann et al., 2011).

Methodological remarks

There are a number of methodological limitations to our study

Firstly, the relatively small number of the patients in the PD, PDMCI, and PDD groups (N = 35-50) did not allow to adequately covary or contrast for a number of potential factors which are known to affect the EEG such pharmacological intervention (e.g. cholinergic, dopaminergic, serotoninergic), the severity of dementia and motor symptoms, and/or the disease duration.

In this retrospective study, data were collected without a single experimental protocol in the clinical units. For this reason, some biomarkers, clinical indexes, and neuropsychological scores were not available in all subjects, e.g. APOE genotyping, DAT scan, and ADAS-Cog as a measurement of the global cognitive status. Indeed, the only common measurement was the MMSE score (typically used for the assessment of the global cognitive functions in elderly subjects, with special attention to the area of memory). However, it may be not equally sensitive to global cognitive deficits in all neurodegenerative dementing disorders.

The subjects of this study did not receive identical instructions in all clinical units, and the experimenters did not receive the same qualification training to set the environmental conditions for the rsEEG recording. However, these aspects might not have a major impact on the final results as the experimental procedures of this study are very standard in the practice of the expert clinical units of the E-DLB and PDWAIVE Consortia.

In the clinical units, rsEEG activity was recorded using different hardware systems and various recording parameters (i.e. antialiasing passband, frequency sampling, and reference electrode). To reduce potential sources of variability, data analysis was centralized: a common antialiasing bandpass filtering and down-sampling to 128 Hz; a re-referencing of all rsEEG data to the common average reference; and a normalization of the eLORETA rsEEG sources to remove the effects of the local amplifier gain and electrode resistance.

Finally, the lack of serial rsEEG recordings within a day for a large cohort of PD patients and follow-ups did not allow the evaluation of the rsEEG fluctuation as motor, cognitive, and behavioral symptoms.

Conclusions

In this observational and retrospective study, we hypothesized that dopamine neuromodulation may affect cortical excitability in PD patients with cognitive deficits set in quiet wakefulness, as

revealed by rsEEG rhythms at alpha frequencies. Our results showed that widespread frontal and temporal alpha source activities exhibited an increase in magnitude in the PDD compared with the PDMCI and PD groups, as a possible function of dopamine depletion severity, which is typically greater in the former than the latter groups. In this line, a daily dose of levodopa (i.e., ON condition) induced a widespread reduction in cortical delta and alpha source activations in a sub-group of 13 PD patients under standard chronic dopaminergic regimen. Interestingly, this effect was related to relevant clinical and neuropsychological scores. On the whole, these findings suggest that in PD patients set in quiet wakefulness, alpha cortical source activations may reflect an excitatory effect of dopamine neuromodulation. Long-term impact of daily dopamine supplementation on cortical excitability in PD patients should be tested in future studies.

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Table legends

Table 1. Mean values (± standard error of the mean, SE) of the demographic and clinical data and results of their statistical comparisons ($p < 0.05$) in the present groups of healthy normal seniors (Nold), Parkinson's disease subjects with normal cognition (PD), with mild cognitive impairment (PDMCI), and dementia (PDD). Legend: MMSE = Mini Mental State Evaluation; M/F = males/females; n.s. = not significant ($p > 0.05$).

Table 2. Mean values (± SE) of the demographic and clinical data as well as the results of their statistical comparisons ($p < 0.05$) in a small sub-group of 13 PD patients (e.g., 7 PD, 4 PDMCI, and 2 PDD individuals). Legend: MMSE = Mini Mental State Evaluation; M/F = males/females; n.s. = not significant ($p > 0.05$).

Table 3. Broadman areas (BAs) corresponding to the regions of interest (ROIs) in solutions of the exact low-resolution brain electromagnetic tomography (eLORETA) freeware to estimate rsEEG cortical sources.

Table 4. Mean values (± SE) of transition frequency (TF) and individual alpha frequency peak (IAF) computed from resting state eyes-closed electroencephalographic (rsEEG) power density spectra in the groups of Nold, PD, PDMCI, and PDD subjects. The table also reports the p values of the statistical comparisons of these values between the groups ($p < 0.05$).

Table 5. Results of the correlation analysis (Spearman test, $p < 0.05$) performed between clinical scales and rsEEG cortical sources at delta and alpha sources in all Nold, PD, PDMCI, and PDD subjects considered as a whole group as well as all PD, PDMCI, and PDD subjects considered as a whole group. In particular, these results include Pearson's correlation coefficient (r) and the associated level of significance (p). The statistically significant results ($p < 0.05$) are highlighted in red.

Table 6. Results of the classification among Nold, PD, PDMCI, and PDD individuals based on delta and alpha source activities. These source activities were those showing statistically significant differences between the groups in the main statistical analysis (i.e. Nold, PD, PDMCI, and PDD). The classification rate is computed by the analysis of the area under the receiver operating characteristic (AUROC) curve. The table reports the classification accuracy for all the rsEEG source activities having a value higher than 0.70 in the AUROC curves.

Table 7. Results of the correlation analysis (Spearman test, $p < 0.05$) performed between clinical and neuropsychological scales and rsEEG cortical sources at delta and alpha sources in the small sub-group of 13 PD patients (e.g., 7 PD, 4 PDMCI, and 2 PDD individuals) in the ON condition (about 60 minutes after the administration of a daily dose of levodopa). In particular, these results include Spearman correlation coefficient (r) and the associated level of significance (p). The statistically significant results ($p < 0.05$) are highlighted in red. The pathological cut-off of the clinical and neuropsychological scales are the following. Hoehn and Yahr stage (H&Y): Cut-off ≥ 4 (range 0-5; 1-3 moderate); Unified Parkinson Disease Rating Scale (UPDRS-III Motor Part): Cut-off ≥ 59 (range 0-80; 0-32 mild; 33-58

moderate); Neuropsychiatory inventory (NPI): Cut-off > 50 (range 0-144; ≤ 20 mild; 21-50 moderate); Montreal Cognitive Assessment (MOCA): Cut-off ≤ 23 (range 0-30; 24-26 mild); Mini-Mental State Examination (MMSE): Cut-off ≤ 20 (range 0-30; 21-24 mild); Frontal Assessment Battery (FAB): Cut-off ≤ 14 (range 0-18); Epworth Sleepiness Scale (ESS): Cut-off ≥ 16 (10-15 moderate); Geriatric depression scale (GDS): Cut-off ≥ 17 (0-10 depression absent; 11-16 moderate).

Figure legends

Figure 1. Regional normalized exact low-resolution brain electromagnetic tomography (eLORETA) solutions (mean across subjects) of the rsEEG rhythms relative to a statistical ANOVA interaction among the factors Group (healthy normal seniors, Nold; Parkinson's disease subjects with normal cognition, PD; PD subjects with mild cognitive impairment, PDMCI; PD subjects with dementia, PDD), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2 and gamma), and Region of interest, ROI (central, frontal, parietal, occipital, temporal, limbic). This ANOVA design used the regional normalized eLORETA solutions as a dependent variable. Regional normalized eLORETA solutions modeled the rsEEG relative power spectra as revealed by a sort of "virtual" intracranial macro-electrodes located on the macro-cortical regions of interest. Legend: the rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions statistically presented a significant eLORETA patterns "PD ≠ PDMCI ≠ PDD" ($p < 0.05$).

Figure 2. Individual values of the normalized eLORETA solutions from delta to gamma in Nold, PD, PDMCI, and PDD individuals. Grubbs' test showed no outlier at the arbitrary threshold of $p < 0.0001$.

Figure 3. Regional normalized eLORETA solutions (mean across subjects) of the rsEEG rhythms before (OFF) and after (ON) about 60 minutes from the administration of one daily dose of Levodopa in a small sub-group of 13 PD patients (e.g., 7 PD, 4 PDMCI, and 2 PDD individuals). These solutions are relative to a statistical ANOVA interaction ($p < 0.05$) among the factors Condition (OFF, ON), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2 and gamma), and ROI (central, frontal, parietal, occipital, temporal, limbic). Legend: the rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions statistically presented a significant eLORETA pattern "OFF ≠ ON" ($p < 0.05$).

Figure 4. Individual values of the normalized eLORETA solutions from delta to gamma in the small sub-group of 13 PD patients (e.g., 7 PD, 4 PDMCI, and 2 PDD individuals) for the OFF and ON conditions. Grubbs' test showed no outlier at the arbitrary threshold of $p < 0.0001$.

Table 1

DEMOGRAPHIC CHARACTERISTICS AND GLOBAL COGNITIVE STATUS					
	Nold	**PD**	**PDMCI**	**PDD**	**Statistical analysis**
N	50	35	50	35	-
Age (years)	70.8 (± 0.7 SE)	71.3 (± 1.2 SE)	71.5 (± 1.0 SE)	73.8 (± 1.2 SE)	ANOVA: n.s.
Gender (F/M)	26/24	18/17	29/21	21/14	Freeman-Halton: n.s.
Education (years)	9.2 (± 0.4 SE)	8.9 (± 0.7 SE)	8.8 (± 0.6 SE)	7.9 (± 0.6 SE)	ANOVA: n.s.
MMSE score	28.4 (± 0.1 SE)	28.2 (± 0.3 SE)	25.6 (± 0.4 SE)	19.0 (± 0.8 SE)	Kruskal-Wallis: $H = 94.1$ $p < 0.00001$ (PDD < PDMCI < PD, Nold)

Table 2

DEMOGRAPHIC CHARACTERISTICS AND GLOBAL COGNITIVE STATUS	
N	13
Cognitive status	7 PD, 4 PDMCI, 2PDD
Age (years)	67.1 (± 2.1 SE)
Gender (F/M)	4/7
Education (years)	8.0 (± 0.9 SE)
MMSE score (OFF)	26.8 (± 1.1 SE)
MMSE score (ON)	26.6 (± 1.0 SE)

Table 3

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

Table 4

MEAN VALUES (± SE) OF TRANSITION FREQUENCY (TF) AND INDIVIDUAL ALPHA FREQUENCY PEAK (IAF)					
	Nold	**PD**	**PDMCI**	**PDD**	**Statistical analysis**
TF	6.2 (± 0.1 SE)	5.8 (± 0.2 SE)	5.5 (± 0.2 SE)	4.7 (± 0.2 SE)	ANOVA: F = 12.3 p < 0.00001 (PDD < PDMCI, PD, Nold; PDMCI < Nold)
IAF	9.5 (± 0.1 SE)	8.6 (± 0.2 SE)	8.5 (± 0.2 SE)	7.3 (± 0.2 SE)	ANOVA: F = 24.6 p < 0.0001 (PDD < PDMCI, PD < Nold)

Table 5

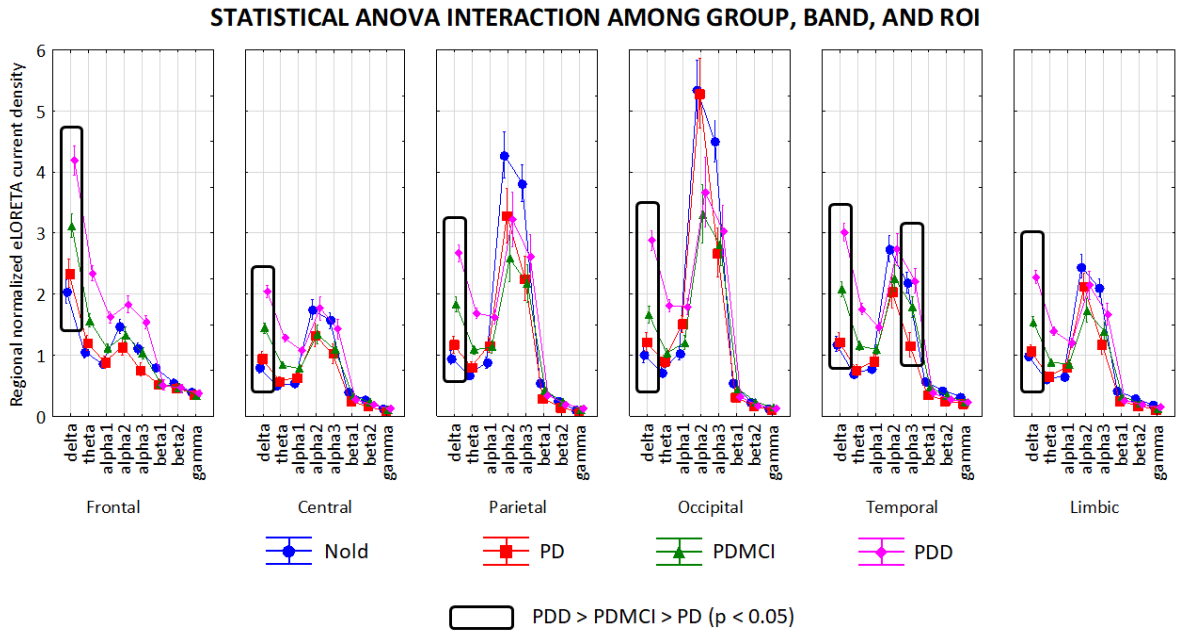
CORRELATION BETWEEN THE eLORETA SOURCE ACTIVITY OF THE RSEEG RHYTHMS AND THE MMSE SCORE			
		Spearman R	**p**
Nold, PD, PDMCI and PDD subjects as a whole group	Frontal delta vs. MMSE	-0.32	0.001
	Central delta vs. MMSE	-0.46	0.000001
	Parietal delta vs. MMSE	-0.48	0.000001
	Occipital delta vs. MMSE	-0.44	0.000001
	Temporal delta vs. MMSE	-0.44	0.000001
	Limbic delta vs. MMSE	-0.41	0.000001
	Temporal alpha 3 vs. MMSE	n.s.	n.s.
PD, PDMCI and PDD subjects as a whole group	Frontal delta vs. MMSE	-0.24	0.008
	Central delta vs. MMSE	-0.42	0.000003
	Parietal delta vs. MMSE	-0.42	0.000002
	Occipital delta vs. MMSE	-0.40	0.000009
	Temporal delta vs. MMSE	-0.38	0.00004
	Limbic delta vs. MMSE	-0.35	0.0001
	Temporal alpha 3 vs. MMSE	n.s.	n.s.

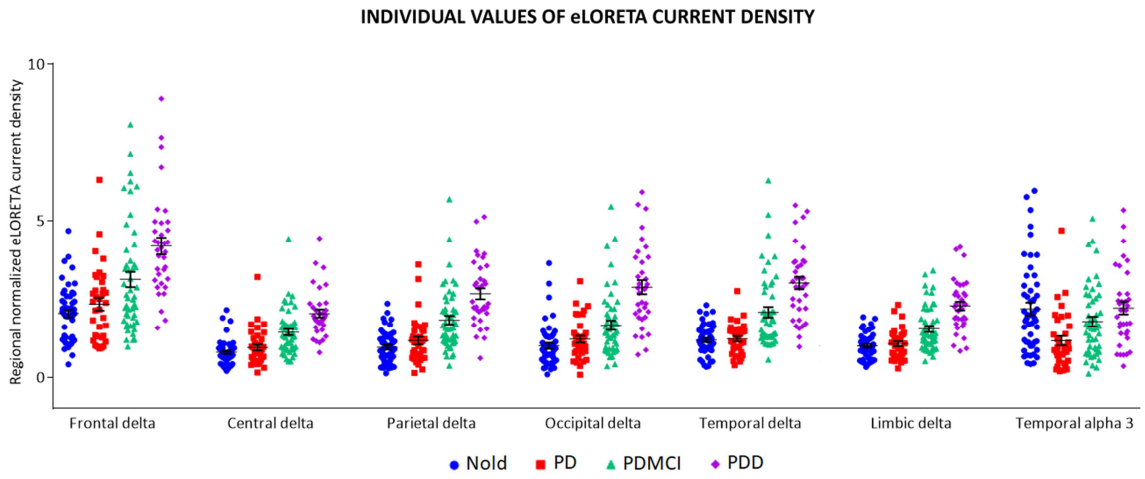
Table 6

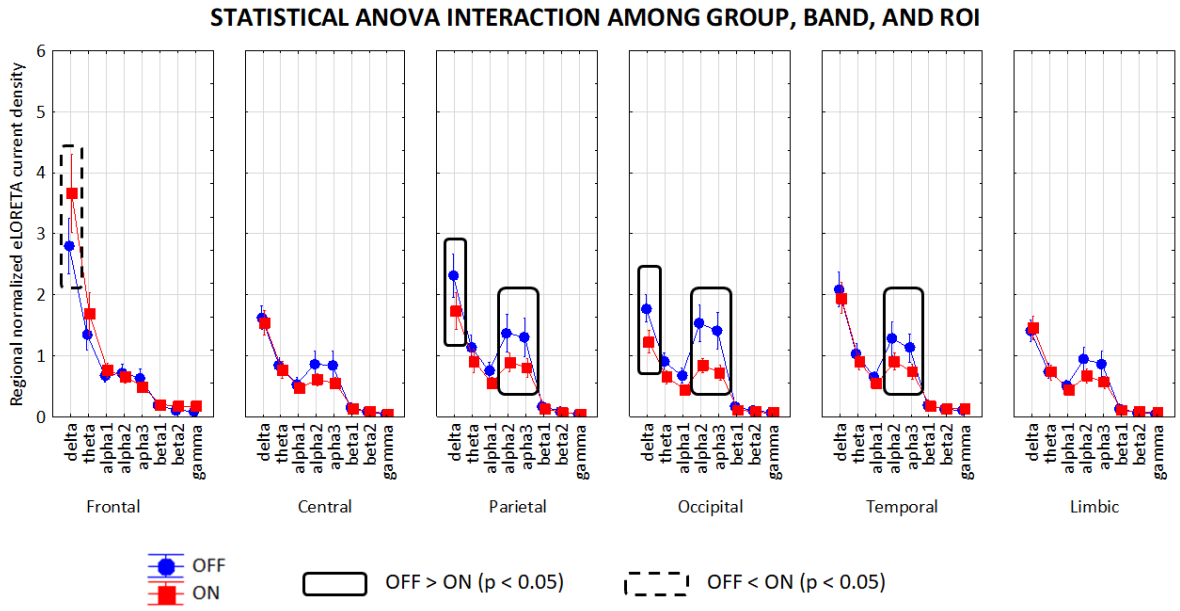
CLASSIFICATION OF NOLD, PD, PDMCI, AND PDD INDIVIDUALS BASED ON rsEEG SOURCE ACTIVITIES (AUROC > 0.7)						
	Nold vs. PD	**Nold vs. PDMCI**	**Nold vs. PDD**	**PD vs. PDMCI**	**PD vs. PDD**	**PDMCI vs. PDD**
Frontal delta			0.903		0.851	0.715
Central delta		0.814	0.953	0.732	0.908	0.755
Parietal delta		0.800	0.945	0.723	0.898	0.753
Occipital delta		0.726	0.915		0.884	0.787
Temporal delta		0.770	0.941	0.731	0.941	0.742
Limbic delta		0.745	0.929	0.702	0.901	0.762
Temporal alpha 3	0.741				0.767	

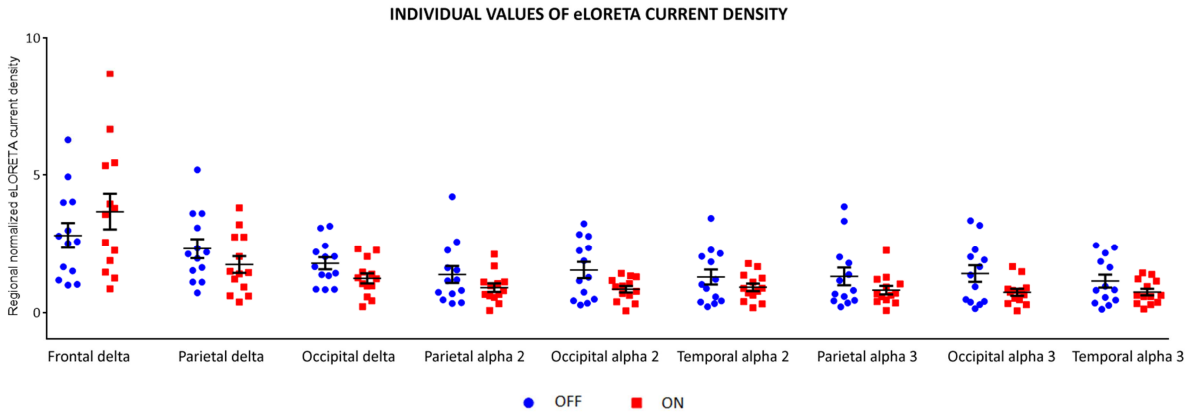
Table 7

CORRELATION BETWEEN RSEEG SOURCES VS. CLINICAL AND NEUROPSYCHOLOGICAL SCORES IN PD PATIENTS IN THE ON CONDITION								
	Parietal delta	**Occipital delta**	**Parietal alpha 2**	**Occipital alpha 2**	**Temporal alpha 2**	**Parietal alpha 3**	**Occipital alpha 3**	**Temporal alpha 3**
H&Y on	-.2304	-.3054	.3872	.4342	.5362	.2427	.2064	.4534
	p=.449	p=.310	p=.191	p=.138	p=.059	p=.424	p=.499	p=.120
UPDRS on	-.1097	-.0294	-.0196	-.1528	.0658	-.0075	-.1376	-.0286
	p=.721	p=.924	p=.949	p=.618	p=.831	p=.981	p=.654	p=.926
NPI on	-.1963	-.0669	.5401	.3850	.2639	.5579	.2960	.2772
	p=.520	p=.828	p=.057	p=.194	p=.384	p=.048	p=.326	p=.359
MOCA on	.0352	-.2118	-.1699	-.3421	-.4854	-.1168	-.2985	-.4225
	p=.909	p=.487	p=.579	p=.253	p=.093	p=.704	p=.322	p=.150
MMSE on	-.0499	-.2652	-.3288	-.4426	-.4523	-.2170	-.3997	-.4122
	p=.871	p=.381	p=.273	p=.130	p=.121	p=.476	p=.176	p=.162
FAB on	.0710	-.1425	-.2473	-.3386	-.6984	-.0754	-.1474	-.5693
	p=.818	p=.642	p=.415	p=.258	p=.008	p=.807	p=.631	p=.042
ESS on	-.2884	-.1509	.4387	.2889	.3943	.4553	.3755	.4342
	p=.339	p=.623	p=.134	p=.338	p=.182	p=.118	p=.206	p=.138
GDS on	.0304	.0788	.6122	.3814	.2742	.5031	.2145	.2733
	p=.921	p=.798	p=.026	p=.198	p=.365	p=.080	p=.482	p=.366









HIGHLIGHTS:

- EEG rhythms differed in Parkinson's disease (PD) patients and in Nold (group level);
- EEG rhythms differed in PD with dementia (PDD), PD with mild cognitive impairment (PDMCI), and PD with normal cognition (PCNC);
- Levodopa modulated cortical delta and alpha rhythms in a sub-group of PD patients under standard chronic dopaminergic regimen.