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Electrocortical networks in Parkinson's disease patients with Mild Cognitive Impairment. The PaCoS study

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ABSTRACT

Introduction: Parkinson's Disease (PD) is frequently associated with cognitive dysfunction ranging from Mild Cognitive Impairment (PD-MCI) to dementia. Few electrophysiological studies are available evaluating potential pathogenetic mechanisms linked to cognitive impairment in PD since its initial phases. The objective of the study is to analyze electrocortical networks related with cognitive decline in PD-MCI for identifying possible early electrophysiological markers of cognitive impairment in PD.

Methods: From the PaCoS (Parkinson's disease Cognitive impairment Study) cohort, a sample of 102 subjects including 46 PD-MCI and 56 PD with normal cognition (PD-NC) was selected based on the presence of a neuropsychological assessment and at least one EEG recording. EEG signal epochs were analysed using Independent Component Analysis LORETA and spectral analysis by computing the Power Spectral Density (PSD) of site-specific signal epochs.

Results: LORETA analysis revealed significant differences in PD-MCI patients compared to PD-NC, with a decreased network involving alpha activity over the occipital lobe, an increased network involving beta activity over the frontal lobe associated with a reduction over the parietal lobe, an increased network involving theta and delta activity over the frontal lobe and a reduction of networks involving theta and delta activity in the parietal lobe. Quantitative EEG analysis showed a significant decrease of alpha PSD over the occipital regions and an increase of delta PSD over the left temporal region in PD-MCI as compared to PD-NC.

Conclusion: Electrocortical abnormalities detected in PD-MCI patients may represent the instrumental counterpart of early cognitive decline in PD.

1. Introduction

Parkinson's Disease (PD) is frequently associated with cognitive dysfunction ranging from Mild Cognitive Impairment (PD-MCI) to Dementia (PDD) [1]. Mechanisms underlying progressive cognitive decline in PD are not yet completely understood. The main pathological marker associated with PDD is the presence of Lewy bodies inclusions in the cortex and specifically in the limbic system, as suggested by Braak [2]. Other mechanisms, however, may also contribute, including deposition of amyloid plaques, tau protein aggregates as well as vascular alterations, involving not only the dopaminergic system, but also the cholinergic (basal Meynert nucleus), noradrenergic (locus coeruleus) and serotoninergic (dorsal nucleus of rafe) circuits; these multiple neural involvements may justify the heterogeneous pattern of cognitive alterations observed in PD [3]. In particular, the early dysfunction of the nigrostriatal dopaminergic system, affecting frontostriatal and parallel mesocorticolimbic circuits could be responsible for the impairment of executive functioning including impaired working memory often observed in PD [3]. On the other hand, the involvement of other neurotransmitters and brain sites, including the temporal lobe, would instead be responsible for the impairment of visuospatial and semantic abilities [4].

MCI affects up to 50% of non-demented parkinsonian patients [5,6] and about 30% of newly diagnosed patients [7] representing an

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important risk factor for the subsequent development of dementia. The most common subtype in PD is the non-amnesic single and multiple-domain MCI in which memory is spared, but executive functions are involved [8]. Although the clinical phenotype of PD-MCI is widely known, there is a growing interest in the research of early instrumental markers which can be used to support the diagnosis.

Imaging studies may provide information on the anatomical and functional alterations of brain structures involved in cognitive degeneration. Magnetic resonance imaging (MRI) studies demonstrated a reduction of cortical and subcortical volumes and white matter alterations of the parietal, frontal and hippocampal lobes in PD-MCI [9]. Positron Emission Tomography (PET) studies, on the other hand, showed a glucose metabolism reduction in the parietal, temporal, frontal and cingulate cortex [10].

Electrophysiological studies may also provide additional information concerning cortical physiopathology involved in PD with cognitive decline. Quantitative EEG (qEEG) analysis of electrocortical activity demonstrated that a decrement of the background rhythm frequency (alpha rhythm) together with an increase of the slow-frequency activity (delta and theta) [3] can be associated with the degree of cognitive decline in PD [11].

Functional studies of brain connectivity can be helpful for identifying significant alterations in PD with cognitive dysfunction. Variations in the quantity and quality of the connections between brain regions appear in fact to be related to neuropsychological performances [12]. In PD patients with normal cognition (PD-NC), there is an increase in the local integration of information and connections that are created between brain areas, which is however associated with a reduction in their efficiency [13]. The cause is still unclear, but probably lies in the degeneration of subcortical structures that influence the formation of these networks. In people with cognitive deficit, there is instead evidence of a significant reduction in these connections, especially within the alpha band [12].

Most of available studies focused on patients with clinically-established PDD, failing to identify a potential early marker of cognitive impairment in PD since its initial phases, which would be the most important goal to achieve in order to investigate its pathophysiological mechanisms and to search for new therapeutic strategies.

This study is part of The Parkinson's disease Cognitive impairment Study (PaCoS), a multicenter study involving two centers located in south Italy (Sicily) aimed to evaluate frequency, clinical features and biomarkers associated with MCI in a large hospital-based cohort of PD patients [7].

The main objective of the present study was to analyze, by means of low-resolution electromagnetic tomography (LORETA) and qEEG analysis, the electrocortical networks possibly related with cognitive dysfunctions in PD-MCI.

2. Materials and methods

2.1. Study population

Patients affected by PD diagnosed according to the Brain Bank criteria [14] attending the Movement Disorder Center and the Neurologic Clinic of the "*Policlinico Vittorio Emanuele*" in Catania and the Memory and Parkinson's disease Center of the "*Policlinico Paolo Giaccone*" in Palermo, over a four-year period (2013–2016) were retrospectively selected as part of the PaCoS cohort. From the original cohort of non-demented 659 patients, a sample of 102 patients (46 PD-MCI and 56 PD-NC) was included in the present study based on the following criteria: a comprehensive neuropsychological assessment and at least one artefact-free EEG recording. We excluded all the patients who had a different diagnosis during follow-up and those who satisfied the diagnostic criteria for PDD [15]. A group of PD patients with a disease duration of one year or less ("early" PD patients) has been also identified.

The clinical-instrumental assessment was part of the routinely diagnostic work-up of PD patients.

All participants provided their written informed consent prior to entering the study, which was approved by the local medical Ethics Committees and it was in accordance with the Declaration of Helsinki.

2.2. Clinical and neuropsychological assessment

All patients underwent a comprehensive neurological examination performed by movement disorder specialists. Demographic, clinical and pharmacological data were recorded. PD severity was evaluated in accordance with the Unified Parkinson Disease Rating Scale - Motor Examination (UPDRS-ME) [16] and the Hoehn and Yahr (HY) [17] scales. Cumulative daily dosage of dopaminergic drugs was converted using the Levodopa Equivalent Dosage (LED) [18]. Patients were evaluated in practical "off" motor state after an overnight fast. All PD subjects underwent a comprehensive neuropsychological and behavioural assessment when in "on" state, considered as the condition of pharmacological response to dopaminergic drugs. The following five cognitive domains were evaluated: episodic memory, attention, executive function, visuospatial function, and language. MCI subtypes were defined as follows: Amnestic MCI Single Domain (aMCIsd), Non Amnestic MCI Single Domain (naMCIsd), Amnestic MCI Multi Domain (aMCImd), Non Amnestic MCI Multiple Domain (naMCImd). Diagnosis of PD-MCI was made according to the Movement Disorder Society Taske Force Level II criteria [6].

Details about the neuropsychological assessment used in the PaCoS sample have been extensively explained elsewhere [7].

2.3. EEG recordings

In all subjects participating in the study a resting (eye-closed task) EEG recording was performed in "on" state using 19 electrodes placed according to the international 10–20 International System (Fp2, F4, C4, P4, O2, F8, T4, T6, Fz, Cz, Pz, Fp1, F3, C3, P3, O1, F7, T3, T5), with unipolar derivation and common reference (G2) located between Fz and Cz (acquisition system: SystemPLUS ver.1.02.1109 for BRAINQUICK BQ132 S, Micromed). The impedance of the EEG signal was kept between 2 and 10 kΩ at the homologous sites. The signal underwent NOTCH and bandwidth filtering (1.6 and 30 Hz) being digitized using the default sampling rate. Five visually selected epochs of 4-s artefacts-free EEG signal of clear-cut wakefulness, excluding the EEG activity of drowsiness, for each patient were randomly selected by an expert electroencephalographist (LG) to ensure quality of samples and data generalizability.

2.4. LORETA analysis

LORETA (Low Resolution Brain Electromagnetic Tomography) is a method by which the non-invasive measurement of electrical potentials carried out by EEG can be used to estimate the distribution of neuronal electrical activity. Signal epochs were analysed to evaluate the presence of networks between brain regions with similar electrical activity. In this study, we focused on the Independent Components Analysis (ICA), which is a technique to separate linearly mixed sources. The implementation of ICA in the LORETA software allows for decomposition of cortical electrical activity which is non-Gaussian into independent components in different frequency bands. It assumes that brain activity is organized and structured to create network connections between functionally connected brain regions. Within the same network, different brain regions activate together and at the same frequencies [19]. The networks processed using the standardized LORETA method were represented by images (one for each frequency band). In this study the following frequency bands were considered: delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz) and beta (13–30 Hz). Within each image, algebraic and statistical differences between the groups were shown

through a colour scale, and localization was expressed in anatomical terms, specifying the lobe, the gyrus and the Brodmann area of the abnormality. A maximum number of seven networks was tested.

2.5. qEEG analysis

To perform spectral analysis, A Welch's periodogram (50% overlap between 1-s Hamming windowed segments) was applied to the 4-s artefacts-free electroencephalographic signal epochs recorded from specific homologous pairs of electrodes over each hemisphere (F3/4, F7/8, T3/4, P3/4, O1/2) based on a standardized protocol [20]. Welch's method is an improvement of the standard periodogram spectrum to reduce noise caused by imperfect and finite data. The method consists of dividing the time series data into overlapping segments, computing a modified periodogram of each segment, and then averaging the PSD estimates. The averaging of modified periodograms tends to decrease the variance of the estimate relative to a single periodogram estimate of the entire data record [21]. Power Spectral Density (PSD) of sampled signals epochs over each homologous site was computed for each selected frequency band (delta, theta, alpha and beta). Signal analysis was performed for all selected epochs of the EEG recordings through an ad hoc created script [20]. Test-retest reliability analysis of resting-EEG PSD values per frequency band and site of recording over the five recorded EEG samples was tested before performing any statistical inference to ensure data reproducibility. The computed Intraclass Correlation Coefficients showed high test-retest reliability among PSD values obtained from the five selected samples for each frequency band and site of recording (please see Supplementary Material). Frequency band-specific PSD values obtained for each coordinate from the five selected epochs of EEG signal for each patient were averaged to be used for the statistical inference.

2.6. Statistical analysis

Data have been analysed using STATA 12.1 software packages. Data cleaning has been performed before the data analysis considering both range and consistence checks. Quantitative variables are described using mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate, categorical variables as frequency and percent. Data have been tested for normality using Shapiro-Wilk test. Parametric independent-samples *t*-test for parametric data or Mann-Whitney test for non-parametric data were used for comparisons between means and medians respectively while chi-square test has been used for used to study categorical variables. For LORETA analysis, student *t*-test for independent groups has been carried out to compare PD-MCI versus PD-NC datasets. A $p < 0.05$ was set as level of significance.

Finally, a stratified analysis was carried out for PD patients with a disease duration of one year or less ("early" PD patients).

3. Results

102 patients were selected from the PaCoS Cohort and enrolled in the present study. Of these 46 (45.1%) PD patients fulfilled the Level II MDS diagnostic criteria for PD-MCI. Baseline characteristics of the selected study population are shown in Table 1A. Baseline characteristics (sex, age, disease duration, education, age of onset, UPDRS-ME, Hoehn and Yahr stage, LED) of the sampled population were not significantly different with respect to the original cohort of the PaCoS study [7] that consisted of 659 PD patients.

In the investigated population, PD-MCI patients had a significantly longer duration of the disease (2 ± 7 vs 1 ± 2; p = 0.02) and fewer years of education (5 ± 6.5 vs 8 ± 8; p = 0.01) as compared to PD-NC. The PD-MCI group presented more patients with naMCImd, followed by aMCImd, whereas PD-MCI single domain (both amnestic and non amnestic) accounted for only 15.2% of patients (Table 1A).

Table 1
Clinical characteristics of study patients.

(A)	All patients	PD-NC	PD-MCI
	N = 102	N = 56	N = 46
Sex (males)	54 (52.9%)	29 (52%)	25 (54.4%)
Age (years)	65.7 ± 8.4	65.4 ± 8.7	66.13 ± 8.1
Disease duration (years)[a]	1 ± 4[b]	1 ± 2[b]	2 ± 7[b]
Education (years)[a]	8 ± 8[b]	8 ± 8[b]	5 ± 6.5[b]
Age of onset (years)	62.3 ± 9.3	62.7 ± 9.3	61.9 ± 9.5
UPDRS-ME score	29 ± 10.9	27.7 ± 11.6	30.5 ± 9.8
Hoehn & Yahr stage	2 ± 0.5[b]	2 ± 0.5[b]	2 ± 0.5[b]
LED (mg/die)	270.8 ± 404.7	274.2 ± 568.4	335.6 ± 423.4
MCI subtypes			
aMCIsd (n,%)	–	–	3 (6.5)
aMCImd (n,%)	–	–	12 (26.1)
naMCIsd (n,%)	–	–	4 (8.7)
naMCImd (n,%)	–	–	27 (58.7)

(B)	All patients N = 55	PD-NC N = 36	PD-MCI N = 19
Sex (males)	31 (56.4%)	17 (47.2%)	14 (73.7%)
Age (years)	65 ± 9.1	64.5 ± 9.3	66.1 ± 8.8
Disease duration (years)	1 ± 0[b]	1 ± 0[b]	1 ± 0[b]
Education (years)	8 ± 8[b]	8 ± 8[b]	8 ± 8[b]
Age of onset (years)	64.3 ± 9.2	63.7 ± 9.5	65.4 ± 8.8
UPDRS-ME score	26.6 ± 10.3	25.2 ± 10.1	20 ± 10.4
Hoehn & Yahr stage	2 ± 0[b]	2 ± 0[b]	2 ± 0[b]
LED (mg/die)	80.7 ± 218	86.8 ± 255.4	69.2 ± 124.4
MCI subtypes			
aMCIsd (n,%)	–	–	1 (5.3)
aMCImd (n,%)	–	–	6 (31.6)
naMCIsd (n,%)	–	–	2 (10.5)
naMCmd (n,%)	–	–	10 (52.6)

Data are frequency (percent) and mean ± standard deviation. (A) Study population. (B) "*early*" PD.
Abbreviation: PD-NC, Parkinson disease with normal cognition; PD-MCI, Parkinson disease with Mild Cognitive Impairment; LED, Levodopa Equivalent Dosage; aMCIsd, amnestic Mild Cognitive Impairment single domain; aMCImd, amnestic Mild Cognitive Impairment multiple domain; naMCIsd, non-amnestic Mild Cognitive Impairment single domain; naMCImd, non-amnestic Mild Cognitive Impairment multiple domain.
[a] Statistically significant differences between PD-NC and PD-MCI ($p < 0.05$).
[b] Described as median ± interquartile range.

For sub-groups analysis, the sample was further divided into two groups according to disease duration: patients with a disease length of one year or less ("early" PD = 55) and patients with a disease length of more than one year (PD = 47). The clinical characteristics of the subgroup of *early* PD are shown in Table 1B. No significant differences were evident for the examined clinical variables between PD-NC and PD-MCI.

3.1. LORETA analysis

LORETA analysis revealed significant differences in the PD-MCI group compared to PD-NC, with a decreased alpha activity over the occipital lobe (lingual gyrus, Brodmann area 17) (Fig. 1A), an increased beta activity over the frontal lobe associated with a reduction over the parietal lobe (precuneus, Brodmann area 7) (Fig. 1B), an increased theta and delta activity over the frontal lobe (superior and middle frontal gyrus respectively, Broadmann area 11) (Fig. 1C and E) and delta activity over the frontal lobe (middle frontal gyrus, Brodmann area 11), and a reduction of theta and delta activity in the parietal lobe (postcentral gyrus Brodmann area 7) (Fig. 1D and F).

Regarding the subgroup of *early* PD patients when compared with PD-NC, we found an increased beta activity over the frontal lobe with a reduction over the parietal lobe (precuneus, Brodmann area 7) (Fig. 2A)

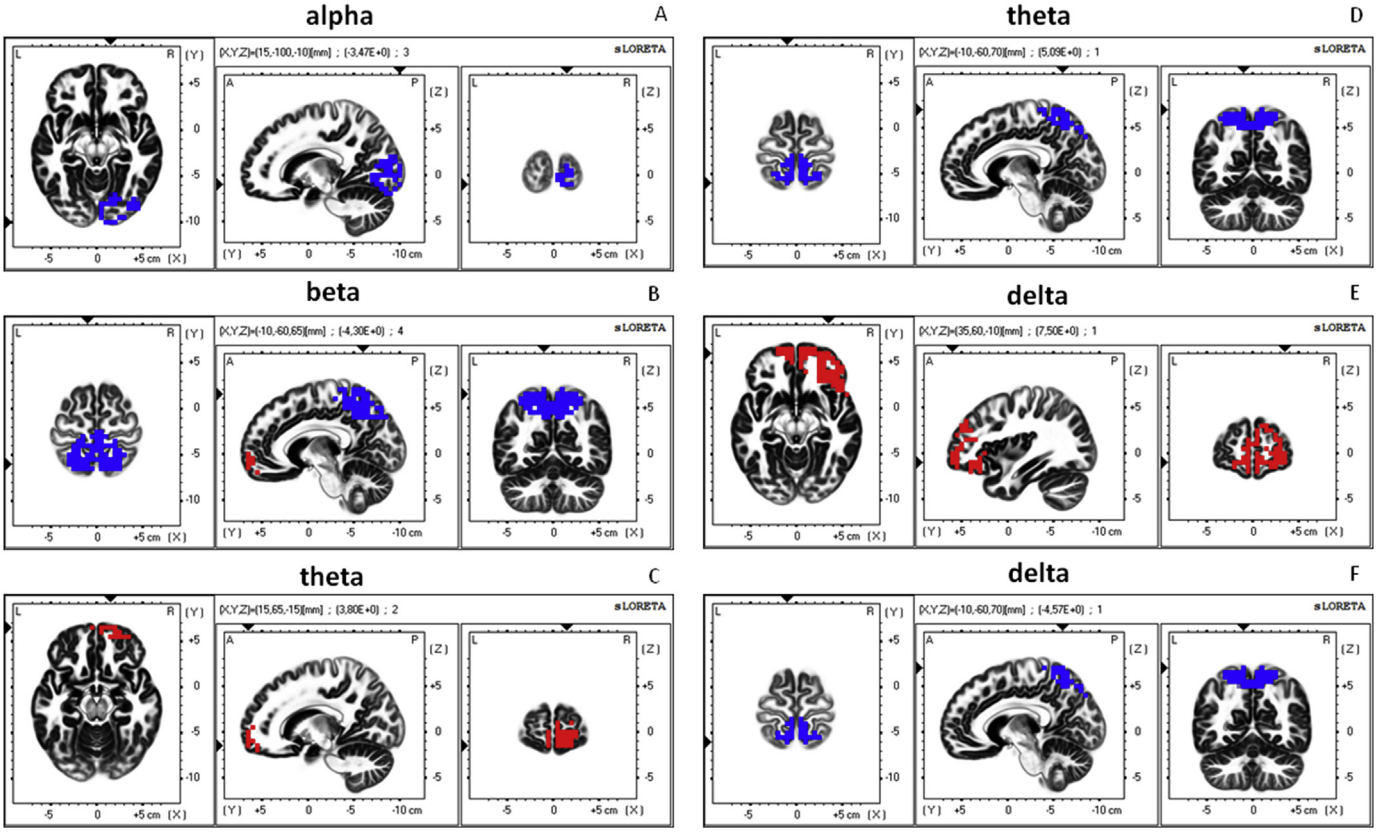

Fig. 1. LORETA ICA showing increased (red) and decreased (blue) regional electrocortical activity based on specified frequency bands for six identified functional networks. Presented data have a statistical significance of $p < 0.05$ using a z-score threshold of 3.0. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and an increased delta activity over the frontal lobe (superiorfrontal gyrus, Brodmann area 11) (Fig. 2B) with a significant reduction of delta activity in the parietal lobe (postcentral gyrus, Brodmann area 7) (Fig. 2C).

For all comparisons no differences between left and right hemisphere have been found.

3.2. qEEG analysis

The comparison of the PSD values for each frequency band over all the recorded electrodes showed significant differences between PD-MCI and PD-NC, specifically PD-MCI group exhibited a significant decrease of alpha PSD average values over the occipital region O1 ($p = 0.02$) and O2 ($p = 0.01$), and a borderline significant increase of delta PSD over the left temporal region (T3; $p = 0.05$), as shown in Fig. 3.

4. Discussion

PD is the most common neurodegenerative disease after Alzheimer's disease, accounting for 0.3% of the total population in western countries [22]. It is mainly a movement disorder, however various and disabling non-motor symptoms are associated with the disease [23]. Among these, cognitive impairment greatly contributes to the disability and reduction of quality of life of these subjects. Many studies are focusing their attention on this condition [24], recently defined as a specific diagnostic entity by a Task Force of the Movement Disorders Society [6]. The objective is to identify patients with cognitive impairment early enough to provide adequate treatments. Moreover, the study of the initial phases of cognitive impairment can allow obtaining insights on the pathophysiological mechanisms of these deficits with the aim of searching for new therapeutic strategies.

In our study, the EEG recordings of 102 patients with PD were analysed with the aim of identifying distinctive features in their cortical electrical activity that would differentiate PD-NC from PD-MCI. We used a bimodal approach by exploring topographical localization of potentially involved electrocortical networks using LORETA, as well as by computing quantitative parameters using qEEG analysis in order to detect potential biomarkers of cognitive impairment in PD, even at an early stage of the disease.

We found a significant reduction in the alpha band over the occipital lobes bilaterally in PD-MCI patients, a finding widely known in the literature. In fact, various studies have already demonstrated a slowdown in the background activity in PD patients with cognitive impairment [11,25]. Furthermore, the reduction of alpha activity especially in the posterior regions has been identified as one of the parameters that can discriminate between PD-NC and PD-MCI [11].

In our study, to differentiate PD patients with normal cognition from those with MCI based on their cortical electrical activity, the brain networks of the two groups of subjects analysed by means of ICA were compared. In PD-MCI patients we found a reduction of the alpha (8–12 Hz) component at the level of the lingual gyrus in the occipital lobe. Significant alterations of the alpha band have been already showed by numerous studies investigating cortical connections [11]. In particular, a study comparing the cerebral networks of PD patients with cognitive impairment of different severity through the “EEG source connectivity method” revealed a reduction in connectivity within both alpha 1 (8–10 Hz) and alpha 2 (10–13 Hz) bands even when cognitive deficits are still mild [26]. The alpha rhythm is the dominant rhythm during relaxed wakefulness and reflects the attentional ability of the subject and the integration of sensory-motor information mediating the activation of cortico-thalamic and cortico-cortical connections. Therefore, its alteration in patients with cognitive impairment is not

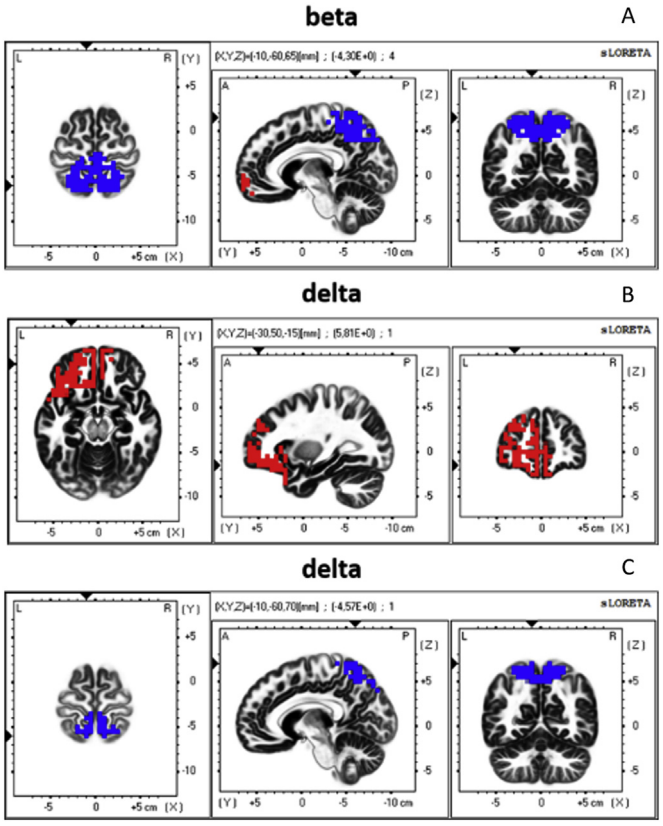

Fig. 2. LORETA ICA showing increased (red) and decreased (blue) regional electrocortical activity based on specified frequency bands for three identified functional networks (A: alpha, B and C: delta) in the subgroup of *early* PD patients. Presented data have a statistical significance of $p < 0.05$ using a z-score threshold of 3.0. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

surprising.

Concerning the beta band, we found an increase of its frontal representation in patients with MCI and a reduction in the region of precuneus. In our precedent work, using quantitative indices, we detected a greater lateralization in beta band frontal electrocortical activity of *de novo* PD subjects as compared to controls, suggesting that this behaviour could be the results of disease-related oscillatory networks between the cortex and specific subcortical regions [21]. Connections between brain regions within the beta band appear to be altered in PD patients; in fact, an increase in cortico-cortical connectivity was found especially in the range of 10–35 Hz in PD patients, which was related with the worsening of the disease [27]. In another study, a similar alteration involving the fronto-occipital network was found in PDD compared to subjects with PD-NC [28]. It can be hypothesized that this "hyper-synchronization" would be expression of a pathophysiological mechanism of PD and that cognitive decline is also a manifestation of this mechanism [27]. On the other hand, the precuneus is an associative area involved in episodic memory, visuospatial processing and aspects of consciousness [29]. This area has been found to be compromised in PD-NC and PD-MCI patients by functional-MRI studies [30]. In particular, PD patients may present an inverse activation/deactivation pattern of the precuneus, expression of the reduction of attention and visuospatial abilities, typical of PD patients [31].

As complementary result, the slower frequency components of EEG were found to be increased over the frontal regions in PD-MCI patients both within the delta and theta bands. Until now, there are no similar findings in the literature comparing PD-MCI to PD-NC, but significant differences have already been demonstrated comparing PD-NC patients with PDD subjects [32].

A subgroup of patients with a disease duration of less than one year ("*early PD*") was also analysed from the whole sample, in order to highlight the alterations which occur early in patients with MCI. The majority of the data found in the entire sample have been confirmed in this group, highlighting the hypothesis that the found abnormalities can be an early marker of cognitive decline in PD patients. However, new evidences are needed to better understand our findings, trying to discover new parameters that can be used as early markers of cognitive decline in PD patients.

Certainly, it would have been of interest to evaluate if the differences found in our study are specific of the different subgroups, amnestic or non amnestic, depending on the functional brain areas involved. However, we were not able to compare subjects with different subtypes of MCI because the sample sizes of the single groups were too small to allow comparisons. Moreover, we did not adjust for the effect of age on EEG activities, usually slower in older subjects. Despite of this, we did not find significant differences among PD patients with normal cognition and PD patients with MCI regarding age, excluding a possible confounding effect of age on the PSD values differences that we found between the two groups.

We are aware of the intrinsic limitations of the LORETA ICA method, due to its poor resolution in terms of anatomical definition.

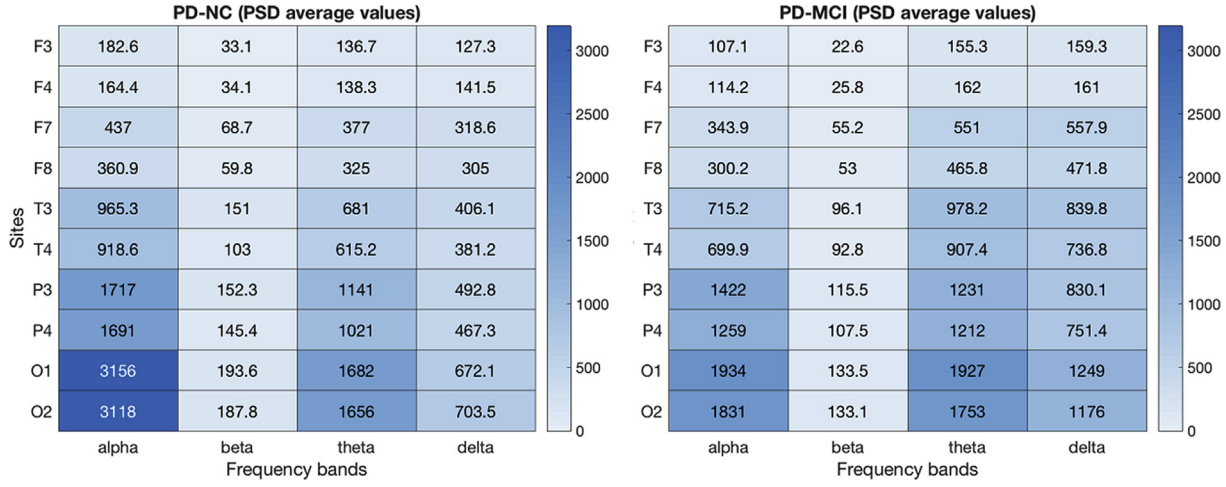

Fig. 3. Heatmaps showing mean Power Spectral Density (PSD) values ($\mu V^2/Hz$) of selected site-specific frequency bands in PD-NC and PD-MCI. Heatmap visually represents by a chromatic scale the individual values of PSD contained in the constructed sites-by-frequency band matrixes for both PD-NC and PD-MCI groups, giving a representation of the frequency bands distribution over the different sites of recording.

However, the particular form of used standardization allows for exact localization albeit with low spatial resolution. It should be also noted that all the presented data of LORETA analysis are those who reached the level of statistical significance of $p < 0.05$, among all the different outputs. In our opinion, this could increase the validity of the results, despite the limitation implicit in the used method.

In conclusions, in this study we aimed to analyze, by LORETA and qEEG analysis, the electrocortical networks possibly related with cognitive functioning in patients with PD-MCI. We found reduced occipital resting-state alpha rhythms and enhanced frontal low-frequency electrocortical networks in PD-MCI as compared to PD-NC, confirming similar findings obtained with different techniques such as magnetoencephalography [33]. Our findings on electrocortical alterations in PD-MCI patients, obtained through the use of different methodologies, were in overlap, confirming their validity and giving more strength to the obtained results.

The results of our study may be useful for better understanding pathogenetic mechanisms underlying cognitive impairment in PD-MCI as well as for proposing possible instrumental biomarker related to cognitive dysfunction in such patients. They could in fact be integrated in recently developed predictive algorithms which seem to provide a reliable score for the prediction of future cognitive impairment in patients with PD [34].

Declarations of interest

None.

Author roles

(1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.): Giovanni Mostile: 1A, 1B, 1C, 2A, 2B, 3A; Loretta Giuliano: 1A, 1B, 1C, 2A, 2B, 3A; Roberto Monastero: 1A, 1B, 1C, 3B; Antonina Luca: 1B, 1C, 3B; Calogero Edoardo Cicero: 1B, 1C, 3B; Giulia Donzuso: 1B, 1C, 3B; Valeria Dibilio:1B, 1C, 3B; Roberta Baschi: 1B, 1C, 3B; Roberta Terranova: 1B, 1C, 3B; Vincenzo Restivo: 1B, 1C, 3B; Vito Sofia: 1B, 1C, 3B; Mario Zappia: 1B, 3A, 3B; Alessandra Nicoletti: 1A, 1B, 1C, 2A, 2C, 3B.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.03.027.

References

[1] P. Svenningsson, E. Westman, C. Ballard, D. Aarsland, Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment, Lancet Neurol. 11 (2012) 697–707, https://doi.org/10.1016/S1474-4422(12)70152-7.
[2] H. Braak, J.R. Bohl, C.M. Müller, U. Rüb, R.A. de Vos, K. Del Tredici Stanley, Fahn Lecture 2005: the staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered, Mov. Disord. 21 (2006) 2042–2051.
[3] D. Aarsland, B. Creese, M. Politis, K.R. Chaudhuri, D.H. Ffytche, D. Weintraub, C. Ballard, Cognitive decline in Parkinson disease, Nat. Rev. Neurol. 13 (2017) 217–231, https://doi.org/10.1038/nrneurol.2017.27.
[4] A.A. Kehagia, R.A. Barker, T.W. Robbins, Cognitive impairment in Parkinson's disease: the dual syndrome hypothesis, Neurodegener. Dis. 11 (2013) 79–92, https://doi.org/10.1159/000341998.
[5] J.C. Goldman, N.T. Aggarwal, C.D. Schroeder, Mild cognitive impairment: an update in Parkinson's disease and lessons learned from Alzheimer's disease, Neurodegener. Dis. Manag. 5 (2015) 425–443, https://doi.org/10.2217/nmt.15.34.
[6] I. Litvan, J.c. Goldman, A.I. Tröster, B.A. Schmand, D. Weintraub, R.C. Petersen, B. Mollenhauer, C.H. Adler, K. Marder, C.H. Williams-Gray, D. Aarsland, J. Kulisevsky, M.C. Rodriguez-Oroz, D.J. Burn, R.A. Barker, M. Emre, Diagnostic criteria for mild cognitive impairment in Parkinson's disease: movement Disorder Society Task Force guidelines, Mov. Disord. 27 (2012) 349–356, https://doi.org/10.1002/mds.24893.
[7] R. Monastero, C.E. Cicero, R. Baschi, M. Davì, A. Luca, V. Restivo, C. Zangara, B. Fierro, M. Zappia, A. Nicoletti, Mild cognitive impairment in Parkinson's disease: the Parkinson's disease cognitive study (PACOS), J. Neurol. 265 (2018) 1050–1058, https://doi.org/10.1007/s00415-018-8800-4.
[8] J.C. Goldman, H. Weis, G. Stebbins, B. Bernard, C.G. Goetz, Clinical differences among mild cognitive impairment subtypes in Parkinson's disease, Mov. Disord. 27 (2012) 1129–1136, https://doi.org/10.1002/mds.25062.
[9] e. Mak, L. Su, G.B. Williams, M.J. Firbank, R.A. Lawson, A.J. Yarnall, G.W. Duncan, A.M. Owen, T.K. Khoo, D.J. Brooks, J.B. Rowe, R.A. Barker, D.J. Burn, J.T. O'Brien, Baseline and longitudinal grey matter changes in newly diagnosed Parkinson's disease: ICICLE-PD study, Brain 138 (2015) 2974–2986, https://doi.org/10.1093/brain/awv211.
[10] L. Wu, F.T. Liu, j.j. Ge, j. Zhao, Y.L. Tang, W.B. Yu, H. Yu, T. Anderson, C.T. Zuo, L. Chen, J. Wang, Clinical characteristics of cognitive impairment in patients with Parkinson's disease and its related pattern in (18) F-FDG PET imaging, Hum. Brain Mapp. 39 (2018) 4652–4662, https://doi.org/10.1002/hbm.24311.
[11] V.V. Cozac, U. Gschwandtner, F. Hatz, M. Hardmeier, S. Rüegg, P. Fuhr, Quantitative EEG and cognitive decline in Parkinson's disease, Parkinson's Dis. (2016), https://doi.org/10.1155/2016/9060649.
[12] R.L. Utianski, J.N. Caviness, E.C. van Straaten, T.G. Beach, B.N. Dugger, H.A. Shill, E.D. Driver-Dunckley, M.N. Sabbagh, S. Mehta, C.H. Adler, J.C. Hentz, Graph theory network function in Parkinson's disease assessed with electroencephalography, Clin. Neurophysiol. 127 (2016) 2228–2236, https://doi.org/10.1016/j.clinph.2016.02.017.
[13] D. Zhang, X. Liu, J. Chen, B. Liu, J. Wang, Widespread increase of functional connectivity in Parkinson's disease with tremor: a resting-state FMRI study, Front. Aging Neurosci. 6 (2015) 6, https://doi.org/10.3389/fnagi.2015.00006.
[14] C.E. Clarke, S. Patel, N. Ives, C.E. Rick, R. Woolley, K. Wheatley, et al., on behalf of the PD REHAB Collaborative Group, UK Parkinson's Disease Society Brain Bank Diagnostic Criteria, [Internet] NIHR Journals Library, 2016.
[15] M. Emre, P.J. Ford, B. Bilgiç, E.Y. Uç, Cognitive impairment and dementia in Parkinson's disease: practical issues and management, Mov. Disord. 29 (2014) 663–672, https://doi.org/10.1002/mds.25870.
[16] S. Fahn, R.L. EltonThe members of the UPDRS development committee, Unified Parkinson's disease rating scale, in: S. Fahn, C.D. Marsden, D.B. Calne (Eds.), Recent Developments in Parkinson's Disease, MacMillan, London, 1987, pp. 153–163.
[17] M.M. Hoehn, M.D. Yahr, Parkinsonism: onset, progression and mortality, Neurology 17 (1967) 427–442.
[18] C.L. Tomlinson, R. Stowe, S. Patel, C. Rick, R. Gray, C.E. Clarke, Systematic review of levodopa dose equivalency reporting in Parkinson's disease, Mov. Disord. 25 (2010) 2649–2653, https://doi.org/10.1002/mds.23429.
[19] R.D. Pascual-Marqui, R.J. Biscay-Lirio, Interaction patterns of brain activity across space, time and frequency. Part I: methods, ArXiv11032852 Math Q-Bio Stat., 2011 accessed http://arxiv.org/abs/1103.2852 , Accessed date: 9 October 2018.
[20] G. Mostile, A. Nicoletti, V. Dibilio, A. Luca, I. Pappalardo, L. Giuliano, C.E. Cicero, G. Sciacca, L. Raciti, D. Contrafatto, E. Bruno, V. Sofia, M. Zappia, Electroencephalographic lateralization, clinical correlates and pharmacological response in untreated Parkinson's disease, Park. Relat. Disord. 21 (2015) 948–953, https://doi.org/10.1016/j.parkreldis.2015.06.006.
[21] P. Welch, The use of fast Fourier transform for the estimation of power spectra: a method based on time averaging over short, modified periodograms, IEEE Trans. Audio Electroacoust. 15 (1967) 70–73.
[22] D.J. Gelb, E. Oliver, S. Gilman, Diagnostic criteria for Parkinson disease, Arch. Neurol. 56 (1999) 33–39.
[23] D. Berg, R.B. Postuma, C.H. Adler, B.R. Bloem, P. Chan, B. Dubois, T. Gasser, C.G. Goetz, G. Halliday, L. Joseph, A.E. Lang, I. Liepelt-Scarfone, I. Litvan, K. Marek, J. Obeso, W. Oertel, C.W. Olanow, W. Poewe, M. Stern, G. Deuschl, MDS research criteria for prodromal Parkinson's disease, Mov. Disord. 30 (2015) 1600–1611, https://doi.org/10.1002/mds.26431.
[24] M. Delgado-Alvarado, B. Gago, I. Navalpotro-Gomez, H. Jiménez-Urbieta, M.C. Rodriguez-Oroz, Biomarkers for dementia and mild cognitive impairment in Parkinson's disease, Mov. Disord. 31 (2016) 861–881, https://doi.org/10.1002/mds.26662.
[25] K.T. Olde Dubbelink, D. Stoffers, J.B. Deijen, J.W. Twisk, J.C. Stam, H.W. Berendse, Cognitive decline in Parkinson's disease is associated with slowing of resting-state brain activity: a longitudinal study, Neurobiol. Aging 34 (2013) 408–418, https://doi.org/10.1016/j.neurobiolaging.2012.02.029.
[26] M. Hassan, L. Chaton, P. Benquet, A. Delval, C. Leroy, L. Plomhause, A.J. Moonen, A.A. Duits, A.F. Leentjens, V. van Kranen-Mastenbroek, L. Defebvre, P. Derambure, F. Wendling, K. Dujardin, Functional connectivity disruptions correlate with cognitive phenotypes in Parkinson's disease, Neuroimage Clin 14 (2017) 591–601, https://doi.org/10.1016/j.nicl.2017.03.002.
[27] P. Silberstein, A. Pogosyan, A.A. Kühn, G. Hotton, S. Tisch, A. Kupsch, P. Dowsey-Limousin, M.I. Hariz, P. Brown, Cortico-cortical coupling in Parkinson's disease and its modulation by therapy, Brain 128 (2005) 1277–1291.
[28] L.C. Fonseca, G.M. Tedrus, P.N. Carvas, E.C. Machado, Comparison of quantitative EEG between patients with Alzheimer's disease and those with Parkinson's disease dementia, Clin. Neurophysiol. 124 (2013) 1970–1974, https://doi.org/10.1016/j.clinph.2013.05.001.

[29] A.E. Cavanna, M.R. Trimble, The precuneus: a review of its functional anatomy and behavioural correlates, Brain 129 (2006) 564–583.
[30] G.W. Duncan, M.J. Firbank, J.T. O'Brien, D.J. Burn, Magnetic resonance imaging: a biomarker for cognitive impairment in Parkinson's disease? Mov. Disord. 28 (2013) 425–438, https://doi.org/10.1002/mds.25352.
[31] T. van Eimeren, O. Monchi, B. Ballanger, A.P. Strafella, Dysfunction of the default mode network in Parkinson disease: a functional magnetic resonance imaging study, Arch. Neurol. 66 (2009) 877–883, https://doi.org/10.1001/archneurol.2009.97.
[32] L. Pugnetti, F. Baglio, E. Farina, M. Alberoni, E. Calabrese, A. Gambini, E. Di Bella, M. Garegnani, L. Deleonardis, R. Nemni, EEG evidence of posterior cortical disconnection in PD and related dementias, Int. J. Neurosci. 128 (2010) 88–98, https://doi.org/10.3109/00207450903436346.
[33] L.I. Boon, A. Hillebrand, K.T.E. Olde Dubbelink, C.J. Stam, H.W. Berendse, Changes in resting-state directed connectivity in cortico-subcortical networks correlate with cognitive function in Parkinson's disease, Clin. Neurophysiol. 128 (2017) 1319–1326, https://doi.org/10.1016/j.clinph.2017.04.024.
[34] G. Liu, J.J. Locascio, J.C. Corvol, B. Boot, Z. Liao, K. Page, D. Franco, K. Burke, I.E. Jansen, A. Trisini-Lipsanopoulos, S. Winder-Rhodes, C.M. Tanner, A.E. Lang, S. Eberly, A. Elbaz, A. Brice, G. Mangone, B. Ravina, I. Shoulson, F. Cormier-Dequaire, P. Heutink, J.J. van Hilten, R.A. Barker, C.H. Williams-Gray, J. Marinus, C.R. Scherzer, Prediction of cognition in Parkinson's disease with a clinical-genetic score: a longitudinal analysis of nine cohorts, Lancet Neurol. 16 (2017) 620–629, https://doi.org/10.1016/S1474-4422(17)30122-9.