

The frontostriatal subtype of mild cognitive impairment in Parkinson's disease, but not the posterior cortical one, is associated with specific EEG alterations

Citation for published version (APA):

Betrouni, N., Devignes, Q., Bayot, M., Derambure, P., Defebvre, L., Leentjens, A. F., Delval, A., & Dujardin, K. (2022). The frontostriatal subtype of mild cognitive impairment in Parkinson's disease, but not the posterior cortical one, is associated with specific EEG alterations. *Cortex*, 153, 166-177. <https://doi.org/10.1016/j.cortex.2022.04.015>

Document status and date:

Published: 01/08/2022

DOI:

[10.1016/j.cortex.2022.04.015](https://doi.org/10.1016/j.cortex.2022.04.015)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

Taverne

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Download date: 25 Apr. 2024



Research Report

The frontostriatal subtype of mild cognitive impairment in Parkinson's disease, but not the posterior cortical one, is associated with specific EEG alterations



Nacim Betrouni ^{a,b,*}, Quentin Devignes ^{a,b}, Madli Bayot ^{a,b,c},
Philippe Derambure ^{a,b,c}, Luc Defebvre ^{a,b,d}, Albert FG. Leentjens ^e,
Arnaud Delval ^{a,b,c} and Kathy Dujardin ^{a,b,d}

^a Univ. Lille, U1172 – LilnCog – Lille Neuroscience & Cognition, F-59000, Lille, France

^b Inserm, U1172, F-59000, Lille, France

^c CHU Lille, Clinical Neurophysiology Department, F-59000, Lille, France

^d CHU Lille, Neurology and Movement Disorders Department, F-59000, Lille, France

^e Maastricht University Medical Center, Maastricht, the Netherlands

ARTICLE INFO

Article history:

Received 21 October 2021

Reviewed 06 Jan 2022

Revised 27 January 2022

Accepted 7 April 2022

Action editor Michael Swartze

Published online 11 May 2022

Keywords:

PD-MCI

Dual syndrome hypothesis

Spectral decomposition

Functional connectivity

Cognition

ABSTRACT

Background: The 'dual syndrome' hypothesis states that two cognitive subtypes can be distinguished in mild cognitive impairment in Parkinson's disease (PD-MCI): a frontostriatal one, characterized by attentional and/or executive deficits, and a posterior cortical one, characterized by visuospatial, memory and/or language deficits. The latter type has been associated with a higher risk of earlier development of PD dementia. The functional bases of these subtypes remain partly unknown.

Objective: To identify EEG modifications associated with PD-MCI subtypes.

Methods: 75 non-demented PD patients underwent a comprehensive neuropsychological assessment and a high-density EEG. They were classified as having normal cognition (PD-NC; $n = 37$), PD-MCI with a frontostriatal subtype (PD-FS; $n = 11$) or PD-MCI with a posterior cortical subtype (PD-PC; $n = 27$). Two EEG analyses were performed: (a) spectral powers quantification and (b) functional connectivity analysis.

Results: PD-FS patients displayed spectral and functional EEG alterations, namely (a) higher powers in the theta and delta bands, (b) lower powers in the beta2 band and (c) lower functional connectivity in the beta2 band compared to PD-NC and PD-PC patients. These alterations were mainly located in the frontal, limbic and parietal regions. There were no significant differences between PD-NC and PD-PC.

Conclusion: EEG alterations previously reported in PD-MCI may only concern the frontostriatal subtype, and not the posterior-cortical subtype. This provides evidence for the dual

* Corresponding author. INSERM U1172 – Lille Neuroscience & Cognition Laboratoire de Pharmacologie Faculté de Médecine 1, Place de Verdun, 59000, Lille, France.

E-mail address: nacim.betrouni@inserm.fr (N. Betrouni).

<https://doi.org/10.1016/j.cortex.2022.04.015>

0010-9452/© 2022 Elsevier Ltd. All rights reserved.

syndrome hypothesis and emphasizes the importance of identifying PD-MCI subtypes. It also shows the promising potential of EEG to discriminate between PD-MCI subtypes.

© 2022 Elsevier Ltd. All rights reserved.

1. Introduction

According to a recent meta-analysis, the pooled prevalence of mild cognitive impairment (MCI) in Parkinson's disease (PD) is about 40% (Baiano et al., 2020). Among patients with PD-related MCI (PD-MCI), the majority (31%) had multidomain MCI. However, the single/multidomain distinction does not completely consider the heterogeneity of the cognitive profiles in PD. The dual syndrome hypothesis of cognitive decline allows subtyping PD-MCI. According to this hypothesis, there are two main cognitive subtypes: (a) a frontostriatal (PD-FS) one, which is characterized by deficits in attention and/or executive functions, seems to be related to dopaminergic dysfunction; (b) and a posterior-cortical (PD-PC) one, which is characterized by deficits in visuospatial functions, episodic memory, and/or language, seems to have a non-dopaminergic origin and to be influenced by microtubule-associated protein tau genotype (Kehagia et al., 2012). This subtyping system emerged from the follow-up of the CamPaIGN cohort (Foltyniec et al., 2004) and both subtypes were shown to differ in terms of their prognosis. PD-PC patients developed PD dementia (PDD) earlier than PD-FS patients (Williams-Gray et al., 2013), demonstrating the critical interest of considering cognitive subtypes in PD-MCI. Besides, the anatomo-functional bases of each subtype remain partly unknown.

Up to now, few studies investigated this classification to identify imaging markers associated with each subtype. Devignes et al. used the dual syndrome hypothesis to classify PD-MCI patients according to their cognitive subtype and explored the related structural (Devignes et al., 2021) and functional (Devignes et al., 2022) brain changes using magnetic resonance imaging (MRI). Using structural sequences, they showed that patients with posterior cortical deficits have more abundant and more extensive gray and white matter alterations than PD-FS patients while using resting state functional MRI, they found that PD-PC patients have increased intra-network functional connectivity within the basal ganglia network compared with PD-FS patients. Furthermore, these latter have reduced inter-network connectivity between several networks, including the visual, default-mode, sensorimotor, salience, dorsal attentional, basal ganglia, and frontoparietal networks, compared with, patients with normal cognition, and patients with a posterior cortical subtype. In another study using a data-driven approach on cognitive and resting-state functional MRI data from PD patients, Lang et al., 2019 reported that an executive factor was associated with a decrease in functional connectivity within the sensorimotor network, while a posterior cortical factor was associated with an increase in functional connectivity within the temporo-limbic network and a decrease in functional connectivity within the central executive network. Taken together, these MRI studies suggest that cognitive

subtypes as defined by the dual syndrome hypothesis display specific structural and functional brain changes.

About electroencephalography (EEG), the literature is lacking studies using the dual syndrome classification. In a systematic review of clinical correlates of quantitative EEG in PD, Geraedts et al. (2018) reported that most studies described an increased EEG slowing correlated with severity of cognitive impairment. EEG slowing was reflected by either higher power in the delta and theta frequency bands or lower power in the alpha and beta frequency bands. In terms of functional connectivity, they described a reduced synchronization and network integration in cognitively impaired patients. To date, only one EEG study (Kamei, Morita, Serizawa, Mizutani, & Hirayanagi, 2010) identified a PD-MCI subtype and showed that the spectral ratio (i.e., sum of the absolute power values for alpha and beta bands divided by the sum of the absolute power values for delta and theta bands) in the frontal pole and frontal cortex was a significant predictor of executive impairment. However, in this study, only the executive functions were assessed, which is insufficient to identify PD-MCI according to the international consensus criteria (Litvan et al., 2012). The question regarding the presence of EEG alterations specific to PD-MCI cognitive subtypes remains thus unanswered. Besides, EEG is an accessible and inexpensive method which can be easily used in clinical practice, emphasizing the interest of identifying EEG markers.

Therefore, the aim of the present study was to identify EEG markers of PD-MCI subtypes defined according to the dual syndrome hypothesis. Two analysis methods were used: spectral signal decomposition and functional connectivity analysis. We assumed that, compared to patients with normal cognition (PD-NC), patients with PD-MCI would have alterations of the spectral EEG parameters and changes in connectivity patterns and topographies. We also expected that these alterations would differ according to the PD-MCI subtypes (PD-FS vs PD-PC).

2. Material and methods

2.1. Study population and data

The data came from a previous study including patients with PD in two movements disorders centers in Lille, France and Maastricht, The Netherlands (Dujardin et al., 2015). Patients met the United Kingdom Brain Bank criteria (Gibb & Lees, 1988) for idiopathic PD and did not suffer from a neurological disease other than PD. Patients with moderate to severe dementia defined as a score above 1 on the Clinical Dementia Rating scale (Morris, 1993) and meeting the Movement Disorders Society criteria for PD dementia (Emre et al., 2007) were excluded.

Age, sex, duration of formal education, age of onset and disease duration were recorded. The Movement Disorders Society Unified Parkinson Disease Rating Scale (Goetz et al., 2008) was used to assess the severity of motor and non-motor symptoms. Disease severity was evaluated by Hoehn and Yahr stage (Hoehn & Yahr, 1967). The levodopa equivalent daily dose were calculated according to the method of Tomlinson et al. (Tomlinson et al. 2010). Anxiety was assessed using the Parkinson Anxiety Scale (Leentjens et al., 2014), depression by the Hamilton Depression Rating Scale (Hamilton, 1960), and apathy by the Lille Apathy Rating Scale (Soczek et al., 2006).

The patients underwent a comprehensive neuropsychological assessment including the Mattis Dementia Rating Scale (Mattis, 1976) for global cognition and standardized tests evaluating five cognitive domains, namely attention/working memory, executive functions, verbal episodic memory, visuospatial functions and language. Patients were assessed in the ON state, after having received their usual anti-parkinsonian medication. Complete details of the assessment procedure can be found in Dujardin et al. (2015).

A detailed description of the cognitive categorization can be found in Devignes et al. (2021). Briefly, based on their performance at the comprehensive battery of neuropsychological tests, patients were classified as having normal cognition (PD-NC) or PD-MCI using the recommended cut-offs. In addition, within the PD-MCI group, we distinguished PD-MCI patients with a frontostriatal subtype (PD-FS), that is patients having attention/working memory and/or executive deficits without visuospatial, memory and language deficits and PD-MCI patients with a posterior-cortical subtype (PD-PC), that is patients having visuospatial, memory and/or language deficits without attention/working memory and executive deficits.

All participants gave their informed consent to participate in the study. Approval was obtained from the local institutional review boards (Lille: CPP Nord-Ouest IV, 2012-A 01317-36; Maastricht: METC azM/UM, NL42701.068.12). There were no deviations from the preregistered study procedures in <https://www.clinicaltrials.gov/ct2/show/NCT01792843?id=NCT01792843>.

The study population consisted of 156 patients. EEG data were available for 118 patients. Among these 37 (31.36%) belonged to the PD-NC group, 11 (9.32%) to the PD-FS group and 27 (22.88%) to the PD-PC group. The remaining 43 patients had multiple domain deficits and their data were not considered in the present study. Table 1 summarizes their main demographic, clinical and cognitive characteristics.

2.2. Electroencephalography acquisition and processing

Patients were assessed when they were in the ON state. EEG data were acquired during 10 min, with a closed eyes resting-state protocol. A high-resolution system with 128 electrodes (ANT Software BV, Enschede, The Netherlands) was used with a sampling rate of 512 Hz. All the recordings were carried out at the end of the morning to limit sleepiness. An investigator monitored the subject and EEG and verbally alerted the

subject every time there were EEG or behavioral signs of sleepiness. Samples of EEG with signs of sleepiness (slowing of background) were excluded off-line from the analyses.

Preprocessing steps were performed using the BrainVision Analyzer software (BrainProducts GMBH, Gilching, Germany). They included averaging of each electrode's signal to the signal of the reference electrode, checking and removing of periods of drowsiness, muscle activity removing by applying a 90 μ V threshold and 4-s length epoching.

Spectral parameters were estimated using signal frequency decomposition by Fast Fourier Transformation with a 2-s duration and 50% overlap (EEGLAB toolbox (Delorme & Makeig, 2004)) of the scalp signals. Powers were then measured in the six frequency bands: delta (1–4 Hz), theta (4–7 Hz), alpha1 (8–10.5 Hz), alpha2 (10.5–13 Hz), beta1 (13–20 Hz) and beta2 (20–30 Hz) and relative powers were estimated by normalizing each value by the sum of the powers in all the considered frequency bands, on each EEG channel. The obtained values were averaged on scalp to obtain global values and by region by grouping the electrodes into regions of interest (ROI). The electrodes were separated into five ROIs: frontal, central, parietal, occipital and temporal following the anatomical correlations made on MRI of cortical projections (Koessler et al., 2009) (Fig. 1). Each region was divided into right and left sides. Six electrodes (Fpz, Fp1, Fp2, Iz, I1, I2), located at the margin of the anatomical brain regions, were not considered for the analysis.

Functional connectivity was measured at the sources' level. The combination of the weighted Minimum Norm Estimate (wMNE) method (Lin et al., 2004) for the inverse problem resolution and source localization and the Phase Locking Value (PLV) method (Lachaux et al., 1991) for connectivity quantification was used as it was estimated as the most appropriate for a group comparison study ((Hassan et al., 2014; Hassan et al., 2015)). Furthermore, the PLV is said to be sensitive to volume conduction because it does not remove zero-lag connectivity. Moreover, it has recently been reported that PLV-based functional networks are significantly correlated with fMRI networks during resting state, while it was not the case with other methods such as Phase Locking Index (PLI) method (Rizkallah et al., 2020).

Therefore, the source signals were estimated from the scalp using the wMNE method and by using an average template (Brainstorm toolbox (Tadel et al., 2011)). The obtained cortical source signals were projected on the 68 regions of interest (ROI) of the Desikan-Killiany (DK) atlas (Desikan et al., 2006) and the 68×68 connectivity matrices were calculated by the PLV method using the EEGNET toolbox (Hassan, et al., 2015). A connectivity matrix was estimated for each of the above defined spectral bands.

Lastly, global connectivity strength was estimated by summing PLV values of all the connections and regional strengths were measured by considering lobes pair-wise connections. The cortical parcellation of the DK atlas was used to rearrange the ROIs on the basis of lobes (frontal, limbic, temporal, parietal and temporal). Thus, we define the connectivity strength between two lobes by summing the PLV

Table 1 – Demographic, clinical and cognitive characteristics according to cognitive status.

	PD-NC (n = 37)	PD-FS (n = 11)	PD-PC (n = 27)	p	Post hoc	
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS						
Sex (F/M)	7/30	0/11	11/16	.004 ^{a,c}	PD-FS ≠ PD-NC PD-FS ≠ PD-PC	
Age (year)	63.97 ± 7.42	64.27 ± 10.02	65.77 ± 8.26	.74 ^b	–	
Age of onset (year)	55.19 ± 10.72	58.45 ± 9.91	57.63 ± 9.45	.31 ^b	–	
Education (year)	13.51 ± 3.97	14.27 ± 3.52	12.03 ± 3.01	.17 ^b	–	
Disease duration (year)	8.67 ± 7.31	5.90 ± 5.06	8.25 ± 5.64	.35 ^b	–	
MDS-UPDRS 3 (/132)	27.70 ± 12.52	27.36 ± 11.2	29.07 ± 11.51	.77 ^b	–	
Hoehn & Yahr stage	2.01 ± .43	2.09 ± .30	2.03 ± .51	.80 ^b	–	
LEDD (mg/day)	749.79 ± 514.76	591.60 ± 512.64	696.50 ± 547.03	.31 ^b	–	
HAMD (/54)	5.14 (4.76)	4.82 (2.52)	6.52 (5.21)	.34 ^b	–	
LARS (/36)	–27.22 (6.55)	–25.27 (5.76)	–25.19 (6.62)	.17 ^b	–	
PAS (/48)	4.70 (5.98)	7.36 (5.03)	7.67 (6.55)	.048 ^{b,c}	Not significant	
MDRS (/144)	140.32 (3.25)	137.82 (5.15)	139.63 (3.15)	.54 ^{b,c}	–	
MEAN COGNITIVE Z-SCORES AND FREQUENCIES OF DEFICIT PER COGNITIVE DOMAIN						
Attention/working memory	Mean z-score	–.17 (.69)	–1.10 (.71)	–.33 (.71)	.005 ^{b,c}	PD-NC > PD-FS PD-PC > PD-FS
Executive functions	Impaired, frequency (%)	0 (.00)	3 (27.27)	0 (.00)	–	–
	Mean z-score	.06 (1.13)	–.84 (.52)	–.13 (.45)	<.001 ^{b,c}	PD-NC > PD-FS PD-NC > PD-PC PD-PC > PD-FS
Visuospatial functions	Impaired, frequency (%)	0 (.00)	10 (90.91)	0 (.00)	–	–
	Mean z-score	.88 (.62)	1.10 (.60)	–.47 (1.42)	<.001 ^{b,c}	PD-NC > PD-PC PD-FS > PD-PC
Episodic memory	Impaired, frequency (%)	0 (.00)	0 (.00)	17 (62.96)	–	–
	Mean z-score	–.10 (.92)	–.26 (.67)	–.85 (1.65)	.28 ^b	–
Language	Impaired, frequency (%)	0 (.00)	0 (.00)	9 (33.33)	–	–
	Mean z-score	.60 (.61)	.52 (.80)	–.14 (1.42)	.12 ^b	–
	Impaired, frequency (%)	0 (.00)	0 (.00)	7 (25.93)	–	–

^a Fisher's exact test.
^b Kruskal-Wallis test; HAMD = Hamilton Depression Rating Scale; LARS = Lille Apathy Rating Scale; LEDD = levodopa equivalent daily dose; MDRS = Mattis Dementia Rating Scale; MDS-UPDRS = Movement Disorders Society-Unified Parkinson's Disease Rating Scale; PAS = Parkinson Anxiety Scale; PD = Parkinson's disease; PD-FS = PD patients with frontostriatal subtype; PD-NC = PD patients with normal cognition; PD-PC = PD patients with posterior cortical subtype.
^c Significant P-value ≤.05.

values of all connections linking a region of the former to a region of the latter. Table 2 presents the correspondence between the ROIs and the lobes.

2.3. Statistical analyses

According to Table 1, sex was considered as a confounding factor in all the analyses. Spectral powers in each frequency band as well as the connectivity strengths were compared between the groups using analysis of covariance (ANCOVA). In case of significance, post-hoc pair-wise analyses using Mann–Whitney tests were run for pair-wise comparisons. Significance was fixed at P-value ≤ .5 and multiple comparisons corrections were applied using the approach proposed by Benjamini and Hochberg (Benjamini & Hochberg, 1995) to control the false discovery rate between the values (spectral parameters and connectivity strengths) of the six frequency bands.

All the analyses were performed with the XLStat software (Addinsoft. XLSTAT 2019: Data Analysis and Statistical Solution for Microsoft Excel. Paris, France).

3. Results

3.1. Spectral relative powers

3.1.1. Global

The topography of the spatial distribution of the average relative powers in the six frequency bands is shown in Fig. 2. Visual examination reveals that the PD-FS subtype differed from the PD-PC and PD-NC groups by a power increase in the low frequency bands and a decrease in the high frequency bands. After correction for multiple comparisons, significant between-group differences were found in the delta band (ANCOVA, P = .035) with post-hoc analyses revealing a significantly higher power in PD-FS than PD-NC (P = .013), in the theta band (ANCOVA, P = .03) with post-hoc analyses revealing a significantly higher power in PD-FS than in PD-NC (P = .02) and PD-PC (P = .01) and lastly, in the beta2 band (ANCOVA, P = .008) with post-hoc analyses revealing a significantly lower power in PD-FS than PD-NC (P = .004) and PD-PC (P = .005).

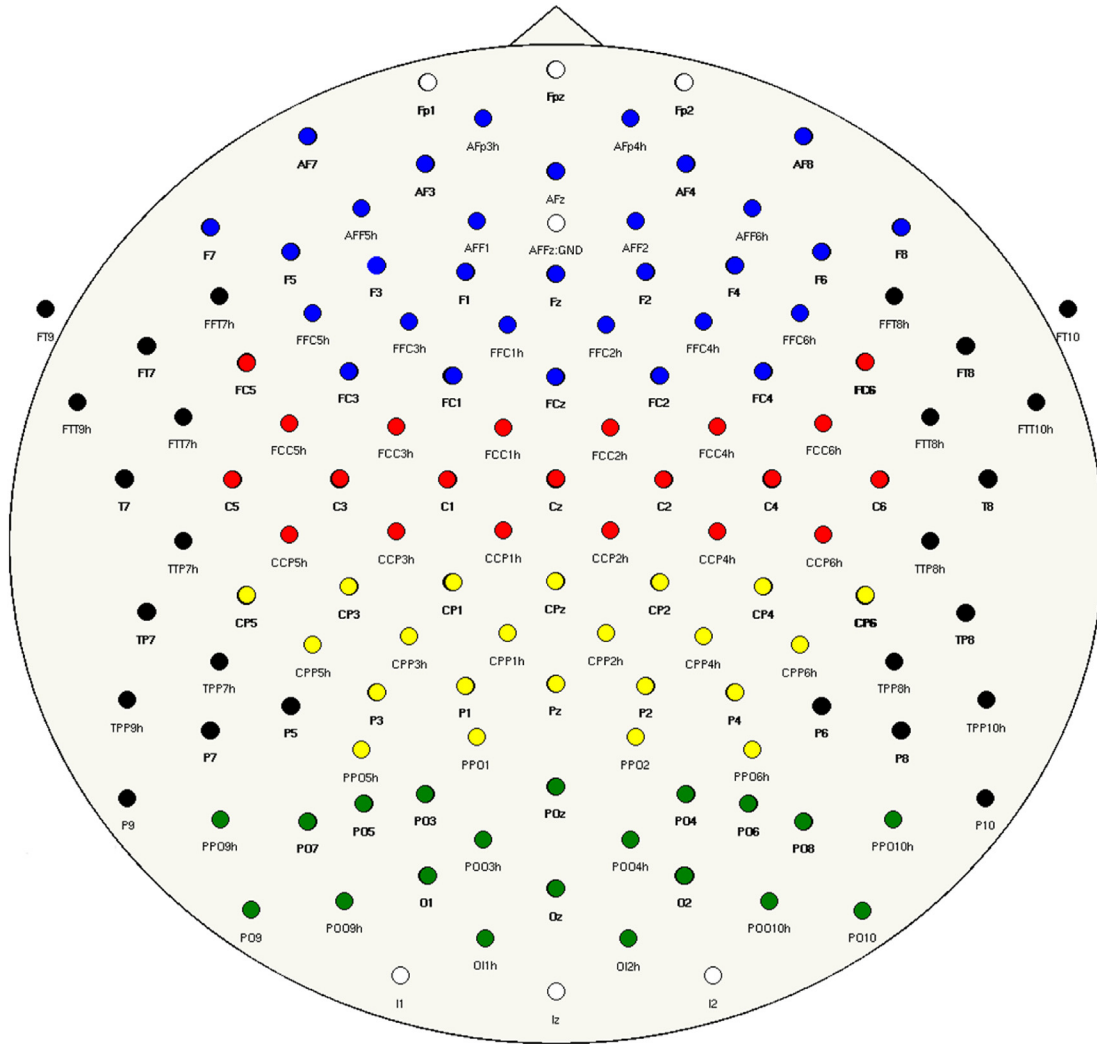


Fig. 1 – Electrodes grouping into regions of interest: Blue: frontal region. Red: central region. Black: temporal region. Yellow: parietal region and Green: occipital region.

Table 2 – Lobes organization of the regions of interest of the Deikan-Killiany atlas.

Lobes	Regions of interest
Frontal	Caudal middle frontal, Frontal pole, Lateral orbitrofrontal, Pars opercularis, Pars orbitalis, Pars triangularis, Rostral middle frontal, Superior frontal, Precentral gyrus
Limbic	Caudate anterior cingulate, Rostral anterior cingulate, Isthmus cingulate, Posterior cingulate
Temporal	Bankssts, Entorhinal, fusiform, Inferior temporal, Middle temporal, Temporal lobe, Transverse pole
Parietal	Inferior parietal, Postcentral, Precuneus, Superior parietal lobule, Supramarginal gyrus
Occipital	Cuneus, Lateral occipital gyrus, Lingual, Pericalcarine

3.1.2. Regional

Analyses of the regional relative spectral powers reinforce the results of the global powers since the ANCOVA revealed significant group differences in the frontal region in the delta band ($P = .03$, post-hoc tests PD-NC < PD-FS, $P = .01$), in the theta band ($P = .025$, post-hoc tests PD-NC < PD-FS, $P = .02$, PC-PC < PD-FS, $P = .01$) and in the beta2 band ($P = .002$, post-hoc tests PD-NC > PD-FS, $P = .001$, PD-PC > PD-FS, $P = .002$). Differences were also found in the central region in the delta band ($p = .02$, post-hoc tests PD-NC < PD-FS, $P = .008$), in the theta band ($P = .01$, post-hoc tests PD-NC < PD-FS, $P = .01$, PD-PC < PD-FS, $P = .007$) and in the beta2 band ($P = .01$, post-hoc tests PD-NC > PD-FS, $P = .007$, PD-PC > PD-FS, $P = .005$). Lastly, differences were found in the parietal region in the theta band ($p = .01$, post-hoc tests PD-NC < PD-FS, $P = .01$, PC-PC < PD-FS, $P = .008$) and in the beta2 band ($P = .006$, post-hoc tests PD-NC > PD-FS, $P = .004$, PD-PC > PD-FS, $P = .002$).

3.2. Functional connectivity

The ANCOVA analyses on the connectivity strengths values in the different frequency bands, showed significant between-group differences in the beta2 band ($P = .02$). Post-hoc analyses showed that the global connectivity strength in the PD-FS group was significantly lower than that in the PD-PC group ($P = .006$) and the PD-NC group ($P = .04$), respectively. Detailed results for all the frequency bands are summarized in Table 3.

Fig. 3 depicts the average network maps computed in each patient group from the connectivity matrices in the beta2 frequency band. For display purposes, the matrices were first thresholded using the efficiency cost optimization (ECO) criterion (De Vico Fallani et al., 2017). This method avoids choosing an arbitrary threshold and selects it based on the optimization of the tradeoff between the efficiency of a network and its wiring cost.

As for the spectral analysis, visual examination reveals that the PD-NC and PD-PC groups had quite similar patterns of connectivity while the PD-FS showed a global connectivity loss, characterized by reduced PLV values (indicating a less dense network), compared with the two other groups.

Pair-wise lobes connections strengths analyses are presented in Table 4. Significant between-group differences concerned the fronto-parietal, fronto-limbic, temporo-parietal, temporo-limbic, parieto-limbic, occipito-limbic connections. Systematically, connectivity strength was lower in PD-FS compared with PD-NC and PD-PC. There was no significant difference between PD-NC and PD-PC.

4. Discussion

This cross-sectional study aimed at studying the EEG patterns associated with the frontostriatal and posterior cortical PD-MCI subtypes as defined by the dual syndrome hypothesis (Kehagia et al., 2012). Two approaches were used: spectral powers quantification and functional connectivity analysis. We found that only the PD-FS subtype of MCI, but not the PD-PC subtype, was characterized by specific spectral and functional alterations on EEG when compared to cognitively healthy PD patients.

4.1. A specific PD-MCI subtype is associated with EEG alterations

Previous studies reported EEG alterations in PD-MCI compared to healthy controls and/or PD-NC patients using either the spectral approach ((Mostile et al., 2019), (Caviness et al., 2015), (Caviness et al., 2007), (Babiloni et al., 2017), (Bousleiman et al., 2014), (Yilmaz et al., 2020)) or the connectivity approach ((Mostile et al., 2019), (Chaturvedi et al., 2019), (Cai et al., 2021), (Babiloni et al., 2018), (Peláez Suárez et al., 2021), (Utianski et al., 2016)). The results of spectral analysis approaches can be summarized by the presence of an EEG slowing, that is higher delta and/or theta powers and lower alpha and/or beta powers, in PD-MCI compared to healthy controls and/or PD-NC. However, the bands displaying significant results varied across studies, with more consistent results for the theta band

and more inconsistent results for the delta, alpha and beta bands. In a review including 23 studies, Cozac et al. (2016) reported that the spectral parameters with the largest effect sizes to distinguish PD-NC and PD-MCI were the global alpha power (decreased in PD-MCI), the peak background frequency (decreased in PD-MCI) and the global theta power (increased in PD-MCI). However, these results must be considered with caution given that they were based only on two studies that compared PD-NC and PD-MCI ((Caviness et al., 2007), (Bousleiman et al., 2014)). Results from connectivity analyses can be summarized by a higher functional connectivity in the theta band ((Chaturvedi et al., 2019), (Cai et al., 2021)) and lower functional connectivity in the alpha band ((Babiloni et al., 2018), (Peláez Suárez et al., 2021)) in PD-MCI compared to PD-NC. Results are more inconsistent for the delta band (Utianski et al., 2016) and the beta band (Mostile et al., 2019). Interestingly, Mostile et al., 2019 showed that functional connectivity can be both higher and lower in PD-MCI compared to PD-NC depending on cortical locations. In the alpha band, they identified lower connectivity in the occipital lobe and higher connectivity in the frontal lobe, and in the delta, theta and beta bands they reported lower connectivity in the parietal in PD-MCI compared to PD-NC. Moreover, two studies used graph theory metrics and reported lower segregation, global efficiency and connectivity between hubs in the alpha band ((Peláez Suárez et al., 2021), (Utianski et al., 2016)) and higher integration in the delta and theta bands (Peláez Suárez et al., 2021). Inter-study discrepancies for both the spectral and functional analyses can be partly explained by methodological differences, especially regarding the criteria used to identify PD-MCI or the analysis used to compare PD-MCI to PD-NC. The results of our study are partly in line with the current literature as spectral and functional EEG alterations have been found in the delta, theta and beta bands in PD-MCI patients compared to PD-NC patients. However, our results weight the previous ones as we demonstrated for the first time that these EEG modifications are associated only with one specific PD-MCI subtype, namely the frontostriatal subtype.

4.2. Slowing of cortical rhythms and loss of connectivity characterize the frontostriatal subtype

We found (a) significant EEG slowing concerning the delta, theta and beta2 bands and (b) lower functional connectivity concerning both the number of connections and the number of hubs (Fig. 3) in the beta2 band in PD-FS patients compared with PD-NC and PD-PC. Although previous studies showed EEG modifications in PD-MCI compared to PD-NC, their relationship with specific cognitive deficits remains partly unknown. Indeed, few studies comparing PD-NC and PD-MCI, performed correlation analysis between EEG parameters and cognitive performance ((Caviness et al., 2007), (Chaturvedi et al., 2019), (Yilmaz et al., 2020), (Yilmaz et al., 2020)). In summary, these studies reported (a) negative correlations between spectral EEG parameters in the delta band and executive and visuospatial scores (Caviness et al., 2007), (b) negative correlations between spectral and/or functional EEG parameters in the theta band and executive, attentional, memory and/or visuospatial scores ((Caviness et al., 2007),

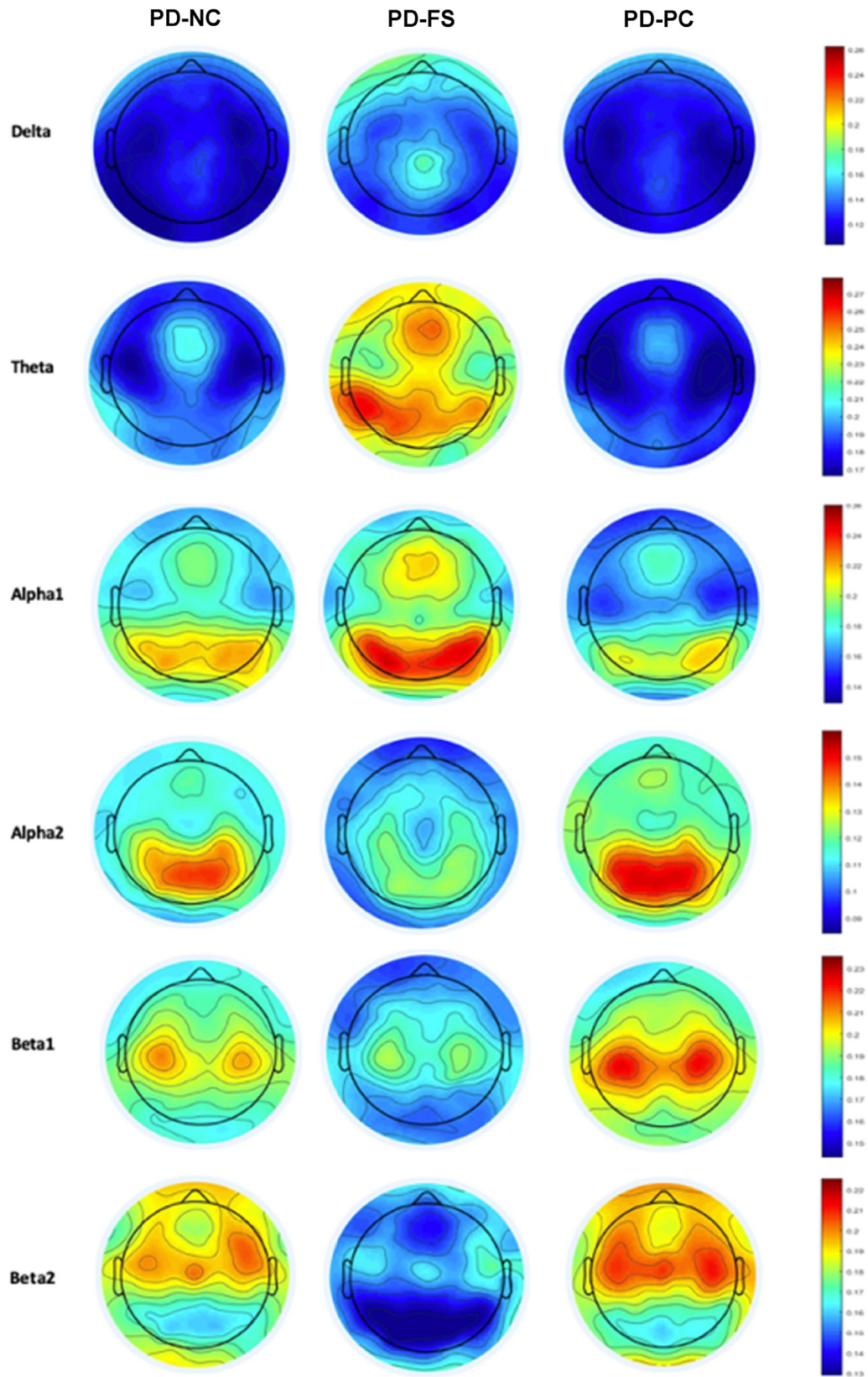


Fig. 2 – Topography of the spatial distribution of the relative spectral powers in the 6 bands for the three groups. Gold colors indicate lowest values while hot colors the highest. PD = Parkinson's disease; PD-FS = PD patients with frontostriatal subtype; PD-NC = PD patients with normal cognition; PD-PC = PD patients with posterior cortical subtype.

Table 3 – Mean (\pm standard deviation) connectivity strength values (measured as the sum of the phase locking values of the different connections) in each group.

Band	PD-NC	PD-FS	PD-PC	<i>p</i>	Post-hoc
Delta	1010.63 \pm 200.67	995.96 \pm 155.33	1050.61 \pm 144.86	.07	–
Theta	1150.46 \pm 230.88	1082.90 \pm 131.08	1190.61 \pm 144.86	.08	–
Alpha1	106.04 \pm 22.05	101.52 \pm 27.07	110.06 \pm 29.92	.44	–
Alpha2	87.35 \pm 17.30	80.0 \pm 15.11	90.50 \pm 17.03	.06	–
Beta1	74.88 \pm 13.12	68.74 \pm 8.41	74.76 \pm 12.12	.24	–
Beta2	915.30 \pm 213.41	798.64 \pm 67.16	957.75 \pm 239.13	.02 ^a	PD-NC > PD-FS PD-PC > PD-FS

PD = Parkinson's disease; PD-FS = PD patients with frontostriatal subtype; PD-NC = PD patients with normal cognition; PD-PC = PD patients with posterior cortical subtype.

^a Significant P-value $\leq .05$.

(Chaturvedi et al., 2019)), (c) positive correlations between spectral and/or functional EEG parameters in the alpha band and memory and/or visuospatial scores ((Chaturvedi et al., 2019), (Yilmaz et al., 2020)) and (d) positive correlation between functional EEG parameters in the beta band and attentional, working memory and executive scores ((Chaturvedi et al., 2019), (Peláez Suárez et al., 2021)). However, it is noteworthy that only one study (Chaturvedi et al., 2019) used the international consensus criteria (Litvan et al., 2012) to identify PD-MCI. Besides, He et al. (2017) reported a “visuospatial/executive” cognitive score without distinction between these two different cognitive domains. Finally, Kamei, Morita, Serizawa, Mizutani, & Hirayanagi, 2010 identified a group of PD patients with executive deficits and showed that the spectral ratio in the frontal cortex and pole was significantly associated with executive impairment. However, in this study, cognitive domains other than the executive functions were not assessed. Taken together, in all these studies EEG alterations, especially in the delta, theta and beta bands, were associated with attentional, working memory and executive functions in PD-MCI. Although these results must be considered with caution given that they are mainly based on correlation analyses (only one study identified a PD-MCI subtype) and present several methodological limitations, it is not surprising that we found EEG alterations in our PD-FS subtype compared to PD-NC.

For the cortical locations of the EEG changes in PD-FS, both spectral and connectivity analyses showed significant results mainly in the frontal, parietal and central regions. These regions are involved in attentional and executive networks ((Yeo et al., 2011), (Fan et al., 2007)). This finding is thus consistent with the cognitive profile of the PD-FS subtype.

4.3. The EEG as a promising tool to discriminate PD-MCI subtypes

Interestingly, we found significant EEG alterations in PD-FS compared to PD-PC with both spectral and functional connectivity approaches. In a previous study based on the same cohort, we reported significant structural alterations in PD patients with posterior cortical deficits and, to a lesser extent, in PD-FS patients, but no significant differences in cortical volume or thickness between the two subtypes (Devignes et al., 2022). In the present study, we report for the first time

that the two subtypes described in the dual syndrome hypothesis (Kehagia et al., 2012) can be distinguished using the EEG. Moreover, these two groups were homogenous in terms of demographic and clinical characteristics. The EEG differences are therefore independent of variables such as the age, the disease severity and duration and the overall cognitive efficiency. It is of critical interest because it shows that this model is relevant to identify PD-MCI subtypes which are different not only with the nature of their cognitive deficits but also with regard to cortical activity.

At first glance, it may seem surprising that EEG alterations were only found in PD-FS patients since EEG alterations are usually more abundant and more extensive with cognitive decline. Indeed, several studies assessed EEG patterns in PD-NC, PD-MCI and PDD patients and reported a more pronounced slowing and functional connectivity loss in demented patients than in PD-MCI compared to PD-NC ((Fonseca et al., 2009), (Caviness et al., 2007), (Utianski et al., 2016)). Hence, EEG alterations were expected in both PD-MCI subtypes with differences between them, especially regarding the cortical locations. Moreover, as the PD-PC subtype was shown to develop PDD earlier than the PD-FS subtype ((Williams-Gray et al., 2013; Williams-Gray et al., 2009)), larger alterations could have been expected in PD-PC patients. However, neither the spectral nor the functional approaches revealed significant EEG alterations in the PD-PC subtype compared to PD-NC. The topographies of the distributions of the relative spectral powers (Fig. 2) as well as the graphs of the functional connectivity matrices (Fig. 3) were even very close between these two groups. As no previous study used a cognitive categorization based on the dual syndrome hypothesis, it is difficult to compare our results with the current literature. We can assume a compensatory mechanism in PD-PC patients which may potentially allow this subtype to be at the same functional level as patients with normal cognition. A careful analysis of the results of the functional connectivity analysis in Fig. 3 reveals that the density of the connections, especially involving the frontal region, in PD-PC is very close, even higher than that of PD-NC. This observation is confirmed quantitatively as the mean connectivity powers in PD-PC were higher than those in PD-NC. However, as significance was not reached, we cannot refer to hyper-connectivity in this subtype. This hypothesis is not in contradiction with the dual syndrome hypothesis (Kehagia et al., 2012). Indeed, this model suggests that

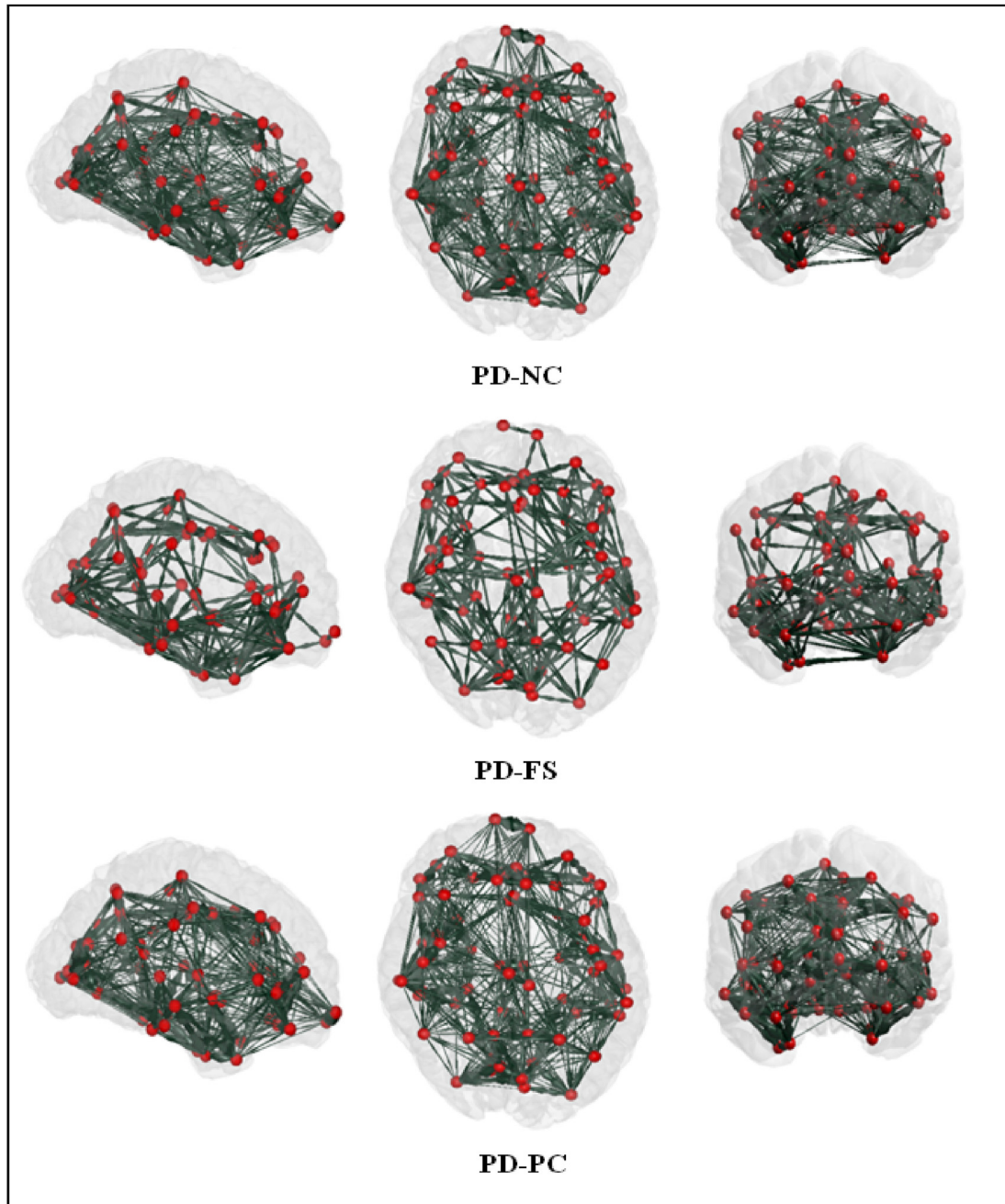


Fig. 3 – Graphs of the average functional connectivity matrices computed in each patient group in the beta2 band. PD = Parkinson's disease; PD-FS = PD patients with frontostriatal subtype; PD-NC = PD patients with normal cognition; PD-PC = PD patients with posterior cortical subtype.

posterior cortical deficits are associated with a higher risk of developing earlier PDD. It does not suggest that patients with frontostriatal deficits would not develop PDD during the course of the disease. A compensatory mechanism could allow PD-PC patients to be at the same functional level as PD-NC, but a faster cognitive deterioration may appear as the disease progresses, while PD-FS patients would present a slower cognitive deterioration. Further studies investigating dynamic functional connectivity derived from task-based EEG exploring specifically posterior cortical cognitive functions are needed to better understand this potential compensatory mechanism.

4.4. Study strengths and limits

The main strength of our study was the use of data from a previous study which was specifically set up to identify cognitive subtypes in PD. Therefore, cognitive performance was available for the main cognitive functions, allowing us to identify PD-MCI patients according to the international guidelines (Litvan et al., 2012) and to determine cognitive subtypes as described in the dual syndrome hypothesis. Furthermore, as the three PD groups did not differ in terms of demographic and clinical characteristics, the effect of the

Table 4 – Comparisons of regional pair-wise connectivity strengths between the three patient groups in the beta2 band.

Connections	<i>p</i>	Post hoc
Fronto-occipital	.08	–
Fronto-parietal	.001*	PD-FS < PD-NC, <i>P</i> = .004 PD-FS < PD-PC, <i>P</i> = .0001
Fronto-temporal	.053	–
Fronto-limbic	.001*	PD-FS < PD-NC, <i>P</i> = .004 PD-FS < PD-PC, <i>P</i> = .0001
Temporo-parietal	.003*	PD-FS < PD-NC, <i>P</i> = .009 PD-FS < PD-PC, <i>P</i> = .002
Temporo-limbic	.003*	PD-FS < PD-NC, <i>P</i> = .01 PD-FS < PD-PC, <i>P</i> = .001
Temporo-occipital	.02	–
Parieto-limbic	.007*	PD-FS < PD-NC, <i>P</i> = .009 PD-FS < PD-PC, <i>P</i> = .002
Parieto-occipital	.02	–
Occipito-limbic	.007*	PD-FS < PD-NC, <i>P</i> = .009 PD-FS < PD-PC, <i>P</i> = .002

PD = Parkinson's disease; PD-FS = PD patients with frontostriatal subtype; PD-NC = PD patients with normal cognition; PD-PC = PD patients with posterior cortical subtype.
* = Significant *P*-value after false discovery rate correction for multiple comparisons.

cognitive status could be assessed independently of confounding variables. There was only an unbalanced sex distribution, which was controlled for in our statistical analysis.

The main limitation of our study was the small sample size in the PD-FS subtype ($n = 11$). This did not prevent us from finding significant results in this subtype that are in line with those recently reported with resting-state fMRI connectivity (Devignes et al., 2022). Nevertheless, our results need to be confirmed in further studies with a higher number of subjects. Besides, another limit was the lack of follow-up data to observe how patients in each PD-MCI subtype progress as well as their EEG pattern.

5. Conclusion

We show that in PD, patients with frontostriatal deficits display EEG alterations classically associated with cognitive decline in PD, while those with posterior cortical deficits exhibit an EEG pattern similar as patients with normal cognition. These results weight previous studies showing EEG alterations in PD-MCI and emphasize the interest of considering cognitive heterogeneity in PD-MCI. Besides, these EEG alterations were also found between the frontostriatal and posterior cortical subtypes, demonstrating that the dual syndrome hypothesis is a relevant model to determine PD-MCI subtypes and that EEG is a promising approach to identify markers associated with each subtype.

Data availability statement

Legal copyright restrictions of the Lille University Hospital do not permit us to publicly archive the full set of data (EEG and

neuropsychological tests scores) in this study. Readers seeking access to the data are advised to contact the lead author Professor Dujardin (kathy.dujardin@univ-lille.fr) who will share them unconditionally.

Sample size and data exclusion statement

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, all manipulations, and all measures in the study. All inclusion/exclusion criteria were established prior to data analysis.

CRediT author statement

N. Betrouni: Conceptualization, Methodology, Software, Formal analysis, Writing - Original Draft.

Q. Devignes: Investigation, Visualization, data curation, Writing - Review & Editing.

M. Bayot: Software.

P. Derambure: Resources, Writing - Review & Editing.

L. Defebvre: Resources, Writing - Review & Editing.

A. Leentjens: Funding acquisition, Writing - Review & Editing.

A. Delval: Methodology, Writing - Review & Editing.

K. Dujardin: Conceptualization, Funding acquisition, Investigation, Writing -Original Draft. Project administration.

Financial disclosures

None.

Funding agencies

Michael J Fox Foundation for Parkinson's disease research.

Declaration of competing interest

The authors declare no competing financial interests. No part of the study analyses was pre-registered prior to the research being conducted.

Open practices section

The study in this article earned a Preregistered badge for transparent practices. Materials and data for the study are available at The raw data (EEG and neuropsychological tests scores) supporting the conclusions of this study can be made available by identified requests, sent to the principal investigator of the study Pr Dujardin (kathy.dujardin@univ-lille.fr).

These data are still being used in different projects. They can be made available for two purposes. Askers should indicate their case and commit to:

1 Reproducing the results, without publication.

OR

2 Conducting a new investigation, collaborations should be discussed with Pr Dujardin.

Acknowledgments

The authors thank all patients of the study for their patience and cooperation, and Marie Dellioux, Lucie Plomhause, Annelien Duits and Anja Moonen for their help with the organization and data collection, including neuropsychological assessment, of the study.

REFERENCES

- Babiloni, C., Del Percio, C., Lizio, R., Noce, G., Cordone, S., Lopez, S., Soricelli, A., Ferri, R., Pascarelli, M. T., Nobili, F., Arnaldi, D., Famà, F., Aarsland, D., Orzi, F., Buttinelli, C., Giubilei, F., Onofri, M., Stocchi, F., Gschwandtner, U., et al. (2017). Abnormalities of cortical neural synchronization mechanisms in subjects with mild cognitive impairment due to Alzheimer's and Parkinson's diseases: An EEG study. *Journal of Alzheimers Disease*, 59(1), 339–358.
- Babiloni, C., Del Persio, C., Lizio, R., Noce, G., Lopez, S., Soricelli, A., Ferri, R., Pascarelli, M. T., Catania, V., Nobili, F., Arnaldi, D., Famà, F., Orzi, F., Buttinelli, C., Giubilei, F., Bonanni, L., Franciotti, R., Onofri, M., Gschwandtner, U., et al. (2018). Functional cortical source connectivity of resting state electroencephalographic alpha rhythms shows similar abnormalities in patients with mild cognitive impairment due to Alzheimer's and Parkinson's diseases. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, 129(4), 766–782.
- Baiano, C., Barone, P., Trojano, L., & Santangelo, G. (2020). Prevalance and clinical aspects of mild cognitive impairment in Parkinsons disease: A meta analysis. *Movement Disord*, 35(45), 54.
- Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of Reasearch Station Society Ser B Methodology*, 57(289), 300.
- Bousleiman, H., Zimmermann, R., Ahmed, S., Hardmeier, M., Hatz, F., Schindler, C., Roth, V., Gschwandtner, U., & Fuhr, P. (2014). Power spectra for screening parkinsonian patients for mild cognitive impairment. *Annales Clinical Translational Neurology*, 1(11), 884–890.
- Cai, M., Dang, G., Su, X., Zhu, L., Shi, X., Che, S., Lan, X., Luo, X., & Guo, Y. (2021). Identifying mild cognitive impairment in Parkinson's disease with electroencephalogram functional connectivity. *Frontiers Aging Neuroscience*, 13, 701499.
- Caviness, J. N., Hentz, J. G., Belden, C. M., Shill, H. A., Driver-Dunckley, E. D., Sabbagh, M. N., Powell, J. J., & Adler, C. H. (2015). Longitudinal EEG changes correlate with cognitive measure deterioration in Parkinson's disease. *Journal of Parkinson's Disease*, 5(1), 117–124.
- Caviness, J. N., Hentz, J. G., Evidente, V. G., Driver-Dunckley, E., Samanta, J., Mahant, P., Connor, D. J., Sabbagh, M. N., Shill, H. A., & Adler, C. H. (2007). Both early and late cognitive dysfunction affects the electroencephalogram in Parkinson's disease. *Parkinsonism & Related Disorders*, 13(6), 348–354.
- Chaturvedi, M., Bogaarts, J. G., Kozak Cozac, V. V., Hatz, F., Gschwandtner, U., Meyer, A., Fuhr, P., & Roth, V. (2019). Phase lag index and spectral power as QEEG features for identification of patients with mild cognitive impairment in Parkinson's disease. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, 130(10), 1937–1944.
- Cozac, V. V., Gschwandtner, U., Hatz, F., Hardmeier, M., Rüegg, S., & Fuhr, P. (2016). Quantitative EEG and cognitive decline in Parkinson's disease. *Parkinsons Disease*, 9060649.
- De Vico Fallani, F., Latora, V., & Chavez, M. (2017). A topological criterion for filtering information in complex brain networks. *Plos Computational Biology*, 13(1), Article e1005305.
- Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, 134, 9–21, 134 :9-21 2004.
- Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., & Hyman, B. T. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, 31, 968–980, 31 :968-980.
- Devignes, Q., Bordier, C., Viard, R., Defebvre, L., Kuchcinski, G., Leentjens, A. F. G., ... Dujardin, K. (2022). Resting-state functional connectivity in frontostriatal and posterior cortical subtypes in Parkinson's disease-mild cognitive impairment. *Movement Disorders: Official Journal of the Movement Disorder Society*, 37(3), 502–512.
- Devignes, Q., Viard, R., Betrouni, N., Carey, G., Kuchcinski, G., Defebvre, L., Leentjens, A. F. G., Lopes, R., & Dujardin, K. (2021). Posterior cortical cognitive deficits are Associated With structural brain alterations in mild cognitive impairment in Parkinson's Disease. *Frontier Aging Neuroscience*.
- Dujardin, K., Moonen, A., Behal, H., Defebvre, L., Duhamel, A., Duits, A. A., Plomhause, L., Tard, C., & Leentjens, A. F. G. (2015). Cognitive disorders in Parkinson's disease: Confirmation of a spectrum of severity. *Parkinsonism & Related Disorders*, 21, 1299–1305.
- Emre, M., Aarsland, D., Brown, R., Burn, D. J., Duyckaerts, C., Mizuno, Y., Broe, G. A., Cummings, J., Dickson, D. W., Gauthier, S., Goldman, J., Goetz, C., Korczyn, A., Lees, A., Levy, R., Litvan, I., McKeith, I., Olanow, W., Poewe, W., ... Dubois, B. (2007). Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*, 22, 1689–1707.
- Fan, J., Byrne, J., Worden, M. S., Guise, K. G., McCandliss, B. D., Fossella, J., & Posner, M. I. (2007). The relation of brain oscillations to attentional networks. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*, 27, 6197–6206, 27 :6197-6206.
- Foltynie, T., Brayne, C. E. G., Robbins, T. W., & Barker, R. A. (2004). The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. *Brain: a Journal of Neurology*, 127, 550–560.
- Fonseca, L. C., Tedrus, G. M., Letro, G. H., & Bossoni, A. S. (2009). Dementia, mild cognitive impairment and quantitative EEG in patients with Parkinson's disease. *Clinical EEG and Neuroscience*, 40(3), 168–172.
- Geraedts, V. J., Marinus, J., Gouw, A. A., Mosch, A., Stam, C. J., van Hilten, J. J., Contarino, M. F., & Tannemaat, M. R. (2018). Quantitative EEG reflects non-dopaminergic disease severity in Parkinson's disease. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, 129(8), 1748–1755.
- Gibb, W. R., & Lees, A. J. (1988). A comparison of clinical and pathological features of young- and old-onset Parkinson's disease. *Neurology*, 38(9), 1402–1406.

- Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M. B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P. A., Rascol, O., et al. (2008). Movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders*, 23(15), 2129–2170.
- Hamilton, M. (1960). A rating scale for depression. *Neurologia I Neurochirurgia Polska*, 23, 56–62, 23 :56-62 1960.
- Hassan, M., Benquet, P., Biraben, A., Berrou, C., Dufor, O., & Wendling, F. (2015). Dynamic reorganization of functional brain networks during picture naming. *Cortex; a Journal Devoted To the Study of the Nervous System and Behavior*, 73, 276–288.
- Hassan, M., Dufor, O., Merlet, I., Berrou, C., & Wendling, F. (2014). EEG source connectivity analysis: From dense array recordings to brain networks. *Plos One*, 9(8), Article e105041.
- Hassan, M., Shamas, M., Khalil, M., El Falou, W., & Wendling, F. (2015). EEGNET: An open source tool for analyzing and visualizing M/EEG connectome. *Plos One*, 10, Article e0138297.
- He, X., Zhang, Y., Chen, J., Xie, C., Gan, R., Wang, L., & Wang, L. (2017). Changes in theta activities in the left posterior temporal region, left occipital region and right frontal region related to mild cognitive impairment in Parkinson's disease patients. *International Journal of Neuroscience*, 127(1), 66–72.
- Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: Onset, progression and mortality. *Neurology*, 17, 427–442, 17 :427-442 1967.
- Kamei, S., Morita, A., Serizawa, K., Mizutani, T., & Hirayanagi, K. (2010). Quantitative EEG analysis of executive dysfunction in Parkinson disease. *Journal of Clinical Neurophysiology*, 27(3), 193–197, 27 (3):193-197.
- Kehagia, A. A., Barker, R. A., & Robbins, T. W. (2012). Cognitive impairment in Parkinson's disease: The dual syndrome hypothesis. *Neuro-degenerative Diseases*, 11(2), 79–92.
- Koessler, L., Maillard, L., Benhadid, A., Vignal, J. P., Felblinger, J., Vespignani, H., & Braun, M. (2009). Automated cortical projection of EEG sensors: Anatomical correlation via the international 10-10 system. *NeuroImage*, 46(1), 64–72.
- Lachaux, J.-P., Rodriguez, E., Martinerie, J., & Varela, F. J. (1991). Measuring phase synchrony in brain signals. *Human Brain Mapping*, 8, 194–208.
- Lang, S., Hanganu, A., Gan, L. S., Kibreab, M., Auclair Ouellet, N., Alrazi, T., Ramezani, M., Cheetham, J., Hammer, T., Kathol, I., Sarna, J., & Monchi, O. (2019). Network basis of the dysexecutive and posterior cortical cognitive profiles in Parkinson's disease. *Movement Disorders*, 34, 893–902.
- Leentjens, A. F., Dujardin, K., Pontone, G. M., Starkstein, S. E., Weintraub, D., & Martinez-Martin, P. (2014). The Parkinson anxiety scale (PAS): Development and validation of a new anxiety scale. *Movement Disorders: Official Journal of the Movement Disorder Society*, 29(8), 1035–1043.
- Lin, F.-H., Witzel, T., Hamalainen, M. S., Dale, A. M., Belliveau, J. W., & Stufflebeam, S. M. (2004). Spectral spatiotemporal imaging of cortical oscillations and interactions in the human brain. *NeuroImage*, 23, 582–595.
- Litvan, I., Goldman, J. G., Tröster, A. I., Schmand, B. A., Weintraub, D., Petersen, R. C., Mollenhauer, B., Adler, C. H., Marder, K., Williams-Gray, C. H., Aarsland, D., Kulisevsky, J., Rodriguez-Oroz, M. C., Burn, D. J., Barker, R. A., & Emre, M. (2012). Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Movement Disorders: Official Journal of the Movement Disorder Society*, 27(3), 349–356.
- Mattis, S. (1976). In L. Bellak, & T. Karasu (Eds.), *Mental status examination for organic mental syndrome in the elderly patients* (pp. 77–121).
- Morris, J. C. (1993). The clinical dementia rating (CDR): Current version and scoring rules. *Neurology*, 43(11), 2411–2414.
- Mostile, G., Giuliano, L., Monastero, R., Luca, A., Cicero, C. E., Donzuso, G., Dibilio, V., Baschi, R., Terranova, R., Restivo, V., Sofia, V., Zappia, M., & Nicoletti, A. (2019). Electro cortical networks in Parkinson's disease patients with Mild Cognitive Impairment. The PaCoS study. *Parkinsonism & Related Disorders*, 64, 156–162.
- Peláez Suárez, A. A., Berrillo Batista, S., Pedroso Ibáñez, I., Casabona Fernández, E., Fuentes Campos, M., & Chacón, L. M. (2021). EEG-derived functional connectivity patterns associated with mild cognitive impairment in Parkinson's disease. *Behaviour Science*, 11(3), 40.
- Rizkallah, J., Amoud, H., Fraschini, M., Wendling, F., & Hassan, M. (2020). Exploring the correlation between M/EEG source-space and fMRI networks at rest. *Brain Topography*, 33(2), 151–160.
- Sockeel, P., Dujardin, K., Devos, D., Denève, C., Destée, A., & Defebvre, L. (2006). The lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: Validation in Parkinson's disease. *Neurologia I Neurochirurgia Polska*, 77(5), 579–584.
- Tadel, F., Baillet, S., Mosher, J. C., Pantazis, D., & Leahy, R. M. (2011). Brainstorm: A user-friendly application for MEG/EEG analysis. *Computational Intelligence and Neuroscience*, 8, 8 2011.
- Tomlinson, C. L., Stowe, R., Patel, S., Rick, C., Gray, R., & Clarke, C. E. (2010). Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*, 25(15), 2649–2653 2010.
- Utianski, R. L., Caviness, J. N., van Straaten, E. C., Beach, T. G., Dugger, B. N., Shill, H. A., Driver-Dunckley, E. D., Sabbagh, M. N., Mehta, S., Adler, C. H., & Hentz, J. G. (2016). Graph theory network function in Parkinson's disease assessed with electroencephalography. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, 127(5), 2228–2236.
- Williams-Gray, C. H., Evans, J. R., Goris, A., Foltynie, T., Ban, M., Robbins, T. W., Brayne, C., Kolachana, B. S., Weinberger, D. R., Sawcer, S. J., & Barker, R. A. (2009). The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. *Brain: a Journal of Neurology*, 132(11), 2958–2969.
- Williams-Gray, C. H., Mason, S. L., Evans, J. R., Foltynie, T., Brayne, C., Robbins, T. W., & Barker, R. A. (2013). The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. *Journal of Neurology, Neurosurgery, and Psychiatry*, 84, 1258–1264.
- Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zöllei, L., Polimeni, J. R., Fischl, B., Liu, H., & Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, 106(3), 1125–1165.
- Yılmaz, N. H., Çalybođlu, P., Güntekin, B., & Hanođlu, L. (2020). Correlation between alpha activity and neuropsychometric tests in Parkinson's disease. *Neuroscience Letters*, 738, 135346.