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

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Running title: EEG alterations specific to PD-MCI subtypes

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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 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.

Keywords: PD-MCI, dual syndrome hypothesis; spectral decomposition; functional connectivity; cognition.

1. Introduction

According to a recent meta-analysis, the pooled prevalence of mild cognitive impairment (MCI) in Parkinson's disease (PD) is about 40% [1]. 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 [2]. This subtyping system emerged from the follow-up of the CamPaIGN cohort [3] and both subtypes were shown to differ in terms of their prognosis. PD-PC patients developed PD dementia (PDD) earlier than PD-FS patients [4], 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 [5] and functional [6] 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. [7] 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. [8] 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 [9] 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 [10]. 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 [11]. Patients met the United Kingdom Brain Bank criteria [12] 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 [13] and meeting the Movement Disorders Society criteria for PD dementia [14] 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 [15] was used to assess the severity of motor and non-motor symptoms. Disease severity was evaluated by Hoehn and Yahr stage [16]. The levodopa equivalent daily dose were calculated according to the method of Tomlinson et al. [17]. Anxiety was assessed using the Parkinson Anxiety Scale [18] , depression by the Hamilton Depression Rating Scale [19], and apathy by the Lille Apathy Rating Scale [20].

The patients underwent a comprehensive neuropsychological assessment including the Mattis Dementia Rating Scale [21] 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 antiparkinsonian medication. Complete details of the assessment procedure can be found in Dujardin et al. [11].

A detailed description of the cognitive categorization can be found in Devignes et al. [5]. 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.

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	0.004[1]*	PD-FS ≠ PD-NC PD-FS ≠ PD-PC
Age (year)		63.97±7.42	64.27±10.02	65.77±8.26	0.74[2]	-
Age of onset (year)		55.19±10.72	58.45±9.91	57.63±9.45	0.31[2]	-
Education (year)		13.51±3.97	14.27±3.52	12.03±3.01	0.17[2]	-
Disease duration (year)		8.67±7.31	5.90±5.06	8.25±5.64	0.35[2]	-
MDS-UPDRS 3 (/132)		27.70±12.52	27.36±11.2	29.07±11.51	0.77[2]	-
Hoehn & Yahr stage		2.01±0.43	2.09±0.30	2.03±0.51	0.80[2]	-
LEDD (mg/day)		749.79±514.76	591.60±512.64	696.50±547.03	0.31[2]	-
HAMD (/54)		5.14 (4.76)	4.82(2.52)	6.52 (5.21)	0.34[2]	-
LARS (/36)		-27.22 (6.55)	-25.27 (5.76)	-25.19 (6.62)	0.17[2]	-
PAS (/48)		4.70 (5.98)	7.36 (5.03)	7.67 (6.55)	0.048[2]*	Not significant
MDRS (/144)		140.32 (3.25	137.82 (5.15)	139.63 (3.15)	0.54[2]*	-
MEAN COGNITIVE Z-SCORES AND FREQUENCIES OF DEFICIT PER COGNITIVE DOMAIN						
Attention/working memory	Mean z-score	-0.17 (0.69)	-1.10 (0.71)	-0.33 (0.71)	0.005[2]*	PD-NC > PD-FS PD-PC > PD-FS
	Impaired, frequency (%)	0 (0.00)	3 (27.27)	0 (0.00)	-	-
Executive functions	Mean z-score	0.06 (1.13)	-0.84 (0.52)	-0.13 (0.45)	<0.001[2]*	PD-NC > PD-FS

						PD-NC > PD-PC PD-PC > PD-FS
	Impaired, frequency (%)	0 (0.00)	10 (90.91)	0 (0.00)	-	-
Visuospatial functions	Mean z-score	0.88 (0.62)	1.10 (0.60)	-0.47 (1.42)	<0.001[2]*	PD-NC > PD-PC PD-FS > PD-PC
	Impaired, frequency (%)	0 (0.00)	0 (0.00)	17 (62.96)	-	-
Episodic memory	Mean z-score	-0.10 (0.92)	-0.26 (0.67)	-0.85 (1.65)	0.28[2]	-
	Impaired, frequency (%)	0 (0.00)	0 (0.00)	9 (33.33)	-	-
Language	Mean z-score	0.60 (0.61)	0.52 (0.80)	-0.14 (1.42)	0.12[2]	-
	Impaired, frequency (%)	0 (0.00)	0 (0.00)	7 (25.93)	-	-

* = significant p-value ≤0.05; [1]Fisher's exact test; [2]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.

2.2 Electroencephalography acquisition and processing

Patients were assessed when they were in the ON state. EEG data were acquired during 10 minutes, 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 µV threshold and 4-second length epoching.

Spectral parameters were estimated using signal frequency decomposition by Fast Fourier Transformation with a 2-second duration and 50% overlap (EEGLAB toolbox [22]) 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 [23] (**Figure 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 [24] for the inverse problem resolution and source localization and the Phase Locking Value (PLV) method [25] for connectivity quantification was used as it was estimated as the most appropriate for a group comparison study ([26;27]). 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 [28].

Therefore, the source signals were estimated from the scalp using the wMNE method and by using an average template (Brainstorm toolbox [29]). The obtained cortical source signals were projected on the 68 regions of interest (ROI) of the Desikan-Killiany (DK) atlas [30] and the 68x68 connectivity matrices were calculated by the PLV method using the EEGNET toolbox [31]. 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 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.

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, Percalcarine

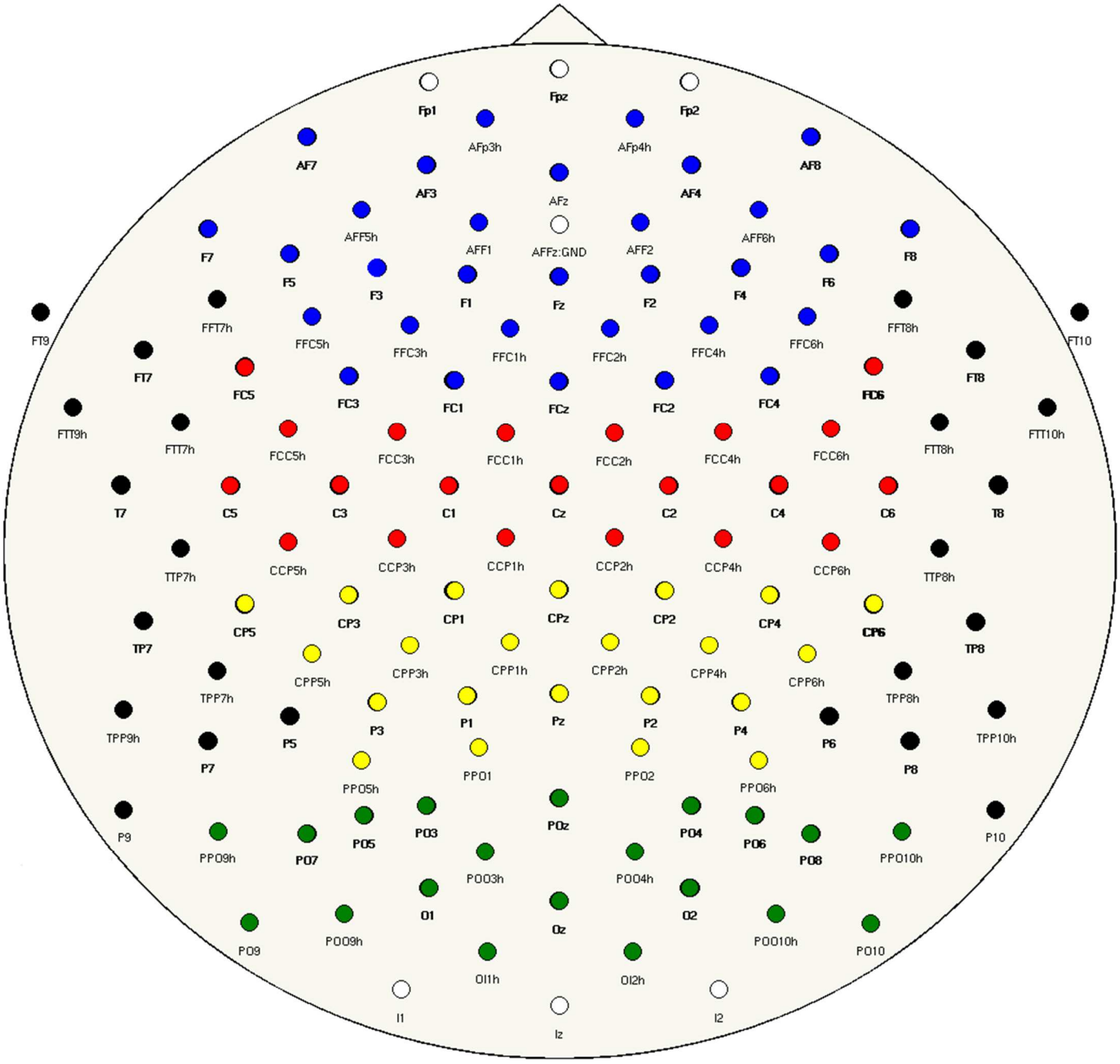

Figure 1 – Electrodes grouping into regions of interest: Blue: frontal region. Red: central region. Black: temporal region. Yellow: parietal region and Green: occipital region.

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 ≤ 0.5 and multiple comparisons corrections were applied using the approach proposed by Benjamini and Hochberg [32] 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 **Figure 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=0.035) with post-hoc analyses revealing a significantly higher power in PD-FS than PD-NC (p=0.013), in the theta band (ANCOVA, p=0.03) with post-hoc analyses revealing a significantly higher power in PD-FS than in PD-NC (p=0.02) and PD-PC (p=0.01) and lastly, in the beta2 band (ANCOVA, p=0.008) with post-hoc analyses revealing a significantly lower power in PD-FS than PD-NC (p=0.004) and PD-PC (p=0.005).

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=0.03, post-hoc tests PD-NC < PD-FS, p=0.01), in the theta band (p=0.025, post-hoc tests PD-NC < PD-FS, p=0.02, PC-PC < PD-FS, p=0.01) and in the beta2 band (p=0.002, post-hoc tests PD-NC > PD-FS, p=0.001, PD-PC > PD-FS, p=0.002). Differences were also found in the central region in the delta band (p=0.02, post-hoc tests PD-NC < PD-FS, p=0.008), in the theta band (p=0.01, post-hoc tests PD-NC < PD-FS, p=0.01, PD-PC < PD-FS, p=0.007) and in the beta2 band (p=0.01, post-hoc tests PD-NC > PD-FS, p=0.007, PD-PC > PD-FS, p=0.005). Lastly, differences were found in the parietal region in the theta band

(p=0.01, post-hoc tests PD-NC < PD-FS, p=0.01, PC-PC < PD-FS, p=0.008) and in the beta2 band (p=0.006, post-hoc tests PD-NC > PD-FS, p=0.004, PD-PC > PD-FS, p=0.002).

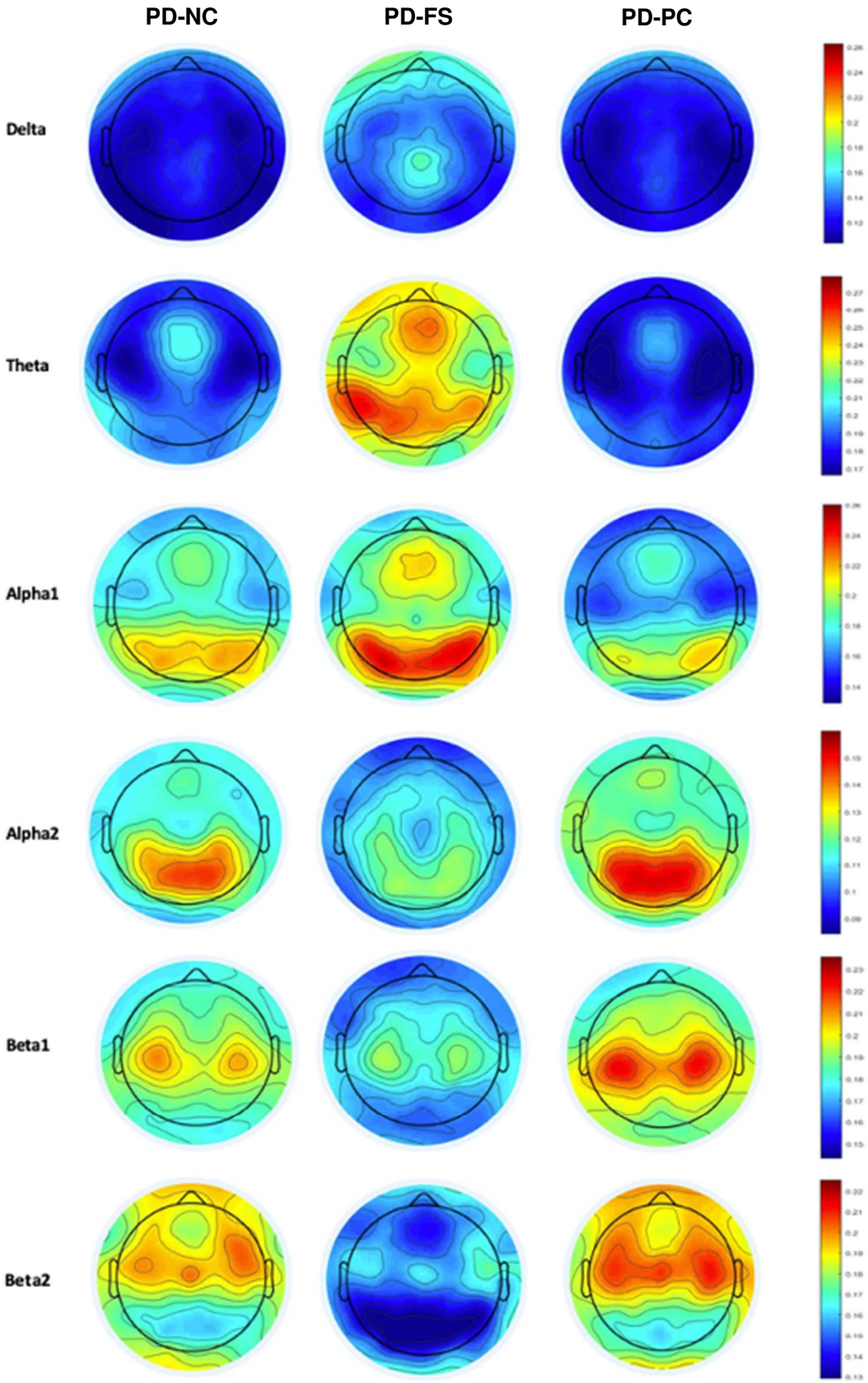

Figure 2 – Topography of the spatial distribution of the relative spectral powers in the 6 bands for the three groups. Cold colors indicate lowest values while hot colors the highest.
PD = Parkinson's disease; PD-FS = PD patients with frontostriatal subtype; PD-NC = PD patients with normal cognition;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

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=0.02). 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=0.006) and the PD-NC group (p=0.04), respectively. Detailed results for all the frequency bands are summarized in **Table 3**.

Table 3 – Mean (± 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	*p*	*Post-hoc*
Delta	1010.63±200.67	995.96±155.33	1050.61±144.86	0.07	-
Theta	1150.46±230.88	1082.90±131.08	1190.61±144.86	0.08	-
Alpha1	106.04±22.05	101.52±27.07	110.06±29.92	0.44	-
Alpha2	87.35±17.30	80.0±15.11	90.50±17.03	0.06	-
Beta1	74.88±13.12	68.74±8.41	74.76±12.12	0.24	-
Beta2	915.30±213.41	798.64±67.16	957.75±239.13	**0.02***	PD-NC > PD-FS PD-PC > PD-FS

* = significant p-value ≤0.05; 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.

Figure 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 [33]. 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.

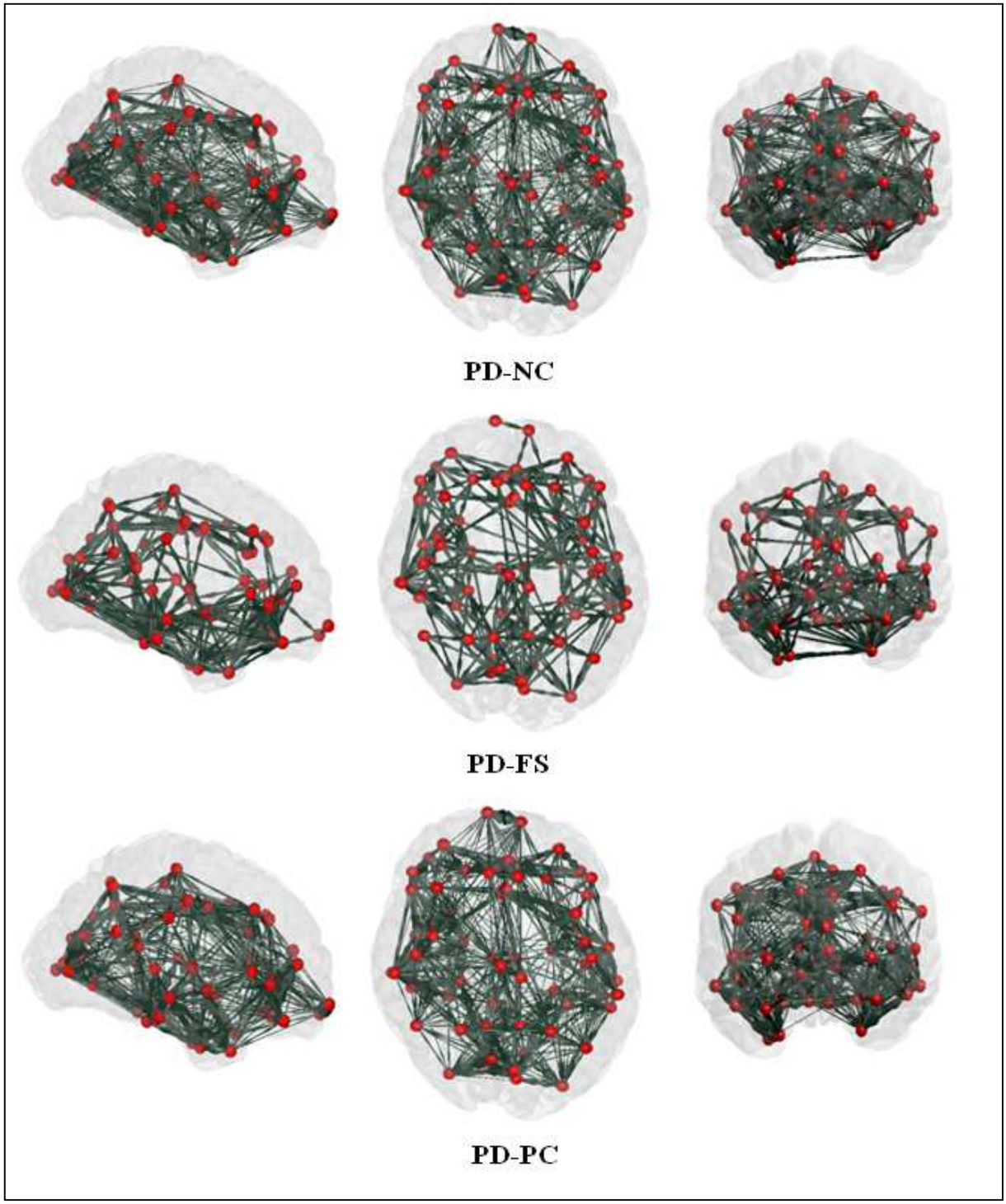

Figure 3 – Graphs of the average functional connectivity matrices computed in each patient group in the beta2 band.

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.

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

Connections	*p*	*Post hoc*
Fronto-occipital	0.08	-
Fronto-parietal	0.001*	PD-FS < PD-NC, *p*=0.004 PD-FS < PD-PC, *p*=0.0001
Fronto-temporal	0.053	-
Fronto-limbic	0.001*	PD-FS < PD-NC, *p*=0.004 PD-FS < PD-PC, *p*=0.0001
Temporo-parietal	0.003*	PD-FS < PD-NC, *p*=0.009 PD-FS < PD-PC, *p*=0.002
Temporo-limbic	0.003*	PD-FS < PD-NC, *p*=0.01 PD-FS < PD-PC, *p*=0.001
Temporo-occipital	0.02	-
Parieto-limbic	0.007*	PD-FS < PD-NC, *p*=0.009 PD-FS < PD-PC, *p*=0.002
Parieto-occipital	0.02	-
Occipito-limbic	0.007*	PD-FS < PD-NC, *p*=0.009 PD-FS < PD-PC, *p*=0.002

* = significant p-value after false discovery rate correction for multiple comparisons; 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.

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 [2]. 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.

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 ([34], [35], [36], [37], [38], [39]) or the connectivity approach ([34], [40], [41], [42], [43], [44]). 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. [45] 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 ([36], [38]). Results from connectivity analyses can be summarized by a higher functional connectivity in the theta band ([40], [41]) and lower functional connectivity in the alpha band ([42], [43]) in PD-MCI compared to PD-NC. Results are more inconsistent for the delta band [44] and the beta band [34]. Interestingly, Mostile et al. [34] 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 ([43], [44]) and higher integration in the delta and theta bands [43]. 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.

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 (**Figure 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 ([36], [40], [39], [39]). In summary, these studies reported (a) negative correlations between spectral EEG parameters in the delta band and executive and visuospatial scores [36], (b) negative correlations between spectral and/or functional EEG parameters in the theta band and executive, attentional, memory and/or visuospatial scores ([36], [40]), (c) positive correlations between spectral and/or functional EEG parameters in

the alpha band and memory and/or visuospatial scores ([40], [39]) and (d) positive correlation between functional EEG parameters in the beta band and attentional, working memory and executive scores ([40], [43]). However, it is noteworthy that only one study [40] used the international consensus criteria [10] to identify PD-MCI. Besides, He et al. [46] reported a "visuospatial/executive" cognitive score without distinction between these two different cognitive domains. Finally, Kamei et al. [9] 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 ([47], [48]). This finding is thus consistent with the cognitive profile of the PD-FS subtype.

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 [6]. In the present study, we report for the first time that the two subtypes described in the dual syndrome hypothesis [2] 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 ([49], [36], [44]). 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 ([4;50]), 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 (**Figure 2**) as well as the graphs of the functional connectivity matrices (**Figure 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 **Figure 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 [2]. Indeed, this model suggests that 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.

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 [10] 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 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 [6]. 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.

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.

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.

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.

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