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RESEARCH ARTICLE

Resting-State Functional Connectivity in Frontostriatal and Posterior Cortical Subtypes in Parkinson's Disease-Mild Cognitive Impairment

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ABSTRACT: Background: The "dual syndrome hypothesis" distinguished two subtypes in mild cognitive impairment (MCI) in Parkinson's disease: frontostriatal, characterized by attentional and executive deficits; and posterior cortical, characterized by visuospatial, memory, and language deficits.

Objective: The aim was to identify resting-state functional modifications associated with these subtypes.

Methods: Ninety-five nondemented patients categorized as having normal cognition (n = 31), frontostriatal (n = 14), posterior cortical (n = 20), or mixed (n = 30) cognitive subtype had a 3 T resting-state functional magnetic resonance imaging scan. Twenty-four age-matched healthy controls (HCs) were also included. A group-level independent component analysis was performed to identify resting-state networks, and the selected components were subdivided into 564 cortical regions in addition to 26 basal ganglia regions. Global intra- and inter-network connectivity along with global and local efficiencies was compared between groups. The network-based statistics approach was used to identify connections significantly different between groups.

Results: Patients with posterior cortical deficits had increased intra-network functional connectivity (FC) within the basal ganglia network compared with patients with frontostriatal deficits. Patients with frontostriatal deficits had reduced inter-network FC between several networks, including the visual, default-mode, sensorimotor, salience, dorsal attentional, basal ganglia, and frontoparietal networks, compared with HCs, patients with normal cognition, and patients with a posterior cortical subtype. Similar results were also found between patients with a mixed subtype and HCs.

Conclusion: MCI subtypes are associated with specific changes in resting-state FC. Longitudinal studies are needed to determine the predictive potential of these markers regarding the risk of developing dementia. © 2021 International Parkinson and Movement Disorder Society

Key Words: cognition; independent component analysis; cognitive subtypes; dual syndrome hypothesis

Abbreviations

AUC	area under the curve	MCI	mild cognitive impairment
FC	functional connectivity	PD	Parkinson's disease
FDR	false discovery rate	PDD	Parkinson's disease dementia
FWE	family-wise error	PD-FS	Parkinson's disease—frontostriatal subtype
HC	healthy controls	PD-MS	Parkinson's disease—mixed subtype

PD-NC Parkinson's disease—normal cognition
PD-PC Parkinson's disease—posterior cortical subtype

Mild cognitive impairment (MCI) is common and heterogeneous in Parkinson's disease (PD).[1,2] Using a data-driven approach, Williams-Gray and colleagues[3] reported two distinct cognitive syndromes in PD: (1) frontostriatal, characterized by deficits in attentional and executive functions and related to the dopaminergic dysfunction due, in part, to the loss of *substantia nigra* neurons; and (2) posterior cortical, characterized by deficits in visuospatial, memory, and language functions and related to nondopaminergic dysfunction and cortical Lewy bodies. This study generated the formulation of the "dual syndrome hypothesis" in PD.[4] Interestingly, the posterior cortical subtype (PD-PC) was associated with a higher risk of developing early Parkinson's disease dementia (PDD), whereas the frontostriatal was not.[3,5] It suggests a critical role of subtyping MCI in PD to detect at-risk patients and personalize support. Up to now, no study has explored functional markers associated with each subtype.

Resting-state functional connectivity (FC) can be used to analyze intra- and inter-network connectivity. A meta-analysis reported that PD-MCI and PDD patients had reduced FC in cerebral regions associated with the default-mode, the frontoparietal, the auditory, and the sensorimotor networks compared to PD patients with normal cognition (PD-NC) and/or healthy controls (HCs).[6] However, only two resting-state FC studies have considered the heterogeneity of PD-MCI and found FC alterations in the default-mode, frontoparietal, dorsal attentional, and visual networks, in amnestic and nonamnestic subtypes.[7,8] Regarding the dual syndrome hypothesis, Lang and colleagues[9] reported decreased FC in the sensorimotor network associated with a dysexecutive factor, whereas a posterior cortical factor was associated with reduced FC in the frontoparietal network and increased FC in the temporo-limbic network. However, in this study, although PD patients had lower cognitive performance than HCs, it was not specified whether they met the criteria for PD-MCI. Besides, only intra-network connectivity was studied, whereas inter-network connectivity dysfunction has been found in PD and PD-MCI.[10-12] Therefore, the aim of the present study was to identify intra- and inter-network connectivity changes associated with each cognitive subtype defined in the dual syndrome hypothesis in a PD-MCI population. Our hypothesis was that, compared to HCs and PD-NC, PD-MCI patients would display intra-network and inter-network FC changes in distinct resting-state networks specific to their cognitive subtype. More specifically, we expected FC changes in networks, including frontal and striatal regions in patients with a frontostriatal subtype, whereas patients with a PD-PC would have FC changes in networks, including posterior regions.

Patients and Methods

Participants

One hundred and fifty-six consecutive PD patients were recruited among outpatients of two independent European movement disorder centers, in Lille, France (n = 82), and Maastricht, the Netherlands (n = 76), between March 2013 and August 2014.[13] Patients who met the United Kingdom Brain Bank criteria for idiopathic PD[14] and did not suffer from other neurological disorder were included. For the present study, patients with moderate to severe dementia (score > 1 on the Clinical Dementia Rating Scale[15]) and meeting the Movement Disorders criteria for PDD[16] were excluded. All participants provided informed consent. The study was approved by the local institutional review boards (CPP Nord-Ouest IV [2012-A01317-36] for Lille [France] and METC azM/UM [NL42701.068.12] for Maastricht [the Netherlands]; ClinicalTrials.gov identifier: NCT01792843).

For neuroimaging analysis, data of HCs, acquired in Lille (France) in the context of a different study (n = 27), were also used. Inclusion criteria for HCs were as follows: (1) no severe neurological or psychiatric disorders, (2) no contraindications for magnetic resonance imaging (MRI), and (3) no cognitive impairment defined as a total score ≥ 28 on the Mini-Mental State Examination.[17] To improve age matching, HC participants below 41 years were not included. HCs provided permission to use their data in this study. The study from which HC data were obtained had been approved by the local institutional review board (CPP Nord-Ouest IV [2013-A01758-37]).

Demographic and Clinical Variables

Age, sex, and duration of formal education were recorded for all participants. Clinical data collected for PD were disease duration, age at onset, and side of onset. Moreover, the Movement Disorders Society-Unified Parkinson Disease Rating Scale[18] was used to assess the severity of motor symptoms (part III), the disease severity (Hoehn & Yahr stage), and the presence of hallucinations (part I, item 2). Depression, anxiety, and apathy were also assessed using the Hamilton Depression Scale,[19] the Parkinson Anxiety Scale,[20] and the Lille Apathy Rating Scale,[21] respectively. All antiparkinsonian medications were registered, and doses were converted to levodopa equivalent daily dose.[22] Frequencies of treatment with acetylcholinesterase inhibitors, antipsychotics, antidepressants, or benzodiazepines were also recorded.

Neuropsychological Assessment and Cognitive Categorization

A full description of the comprehensive neuropsychological evaluation and the cognitive categorization procedure can be found in Devignes et al.[23] Briefly, as recommended by international diagnostic criteria,[24] a battery of tests were used to assess global cognition and five specific cognitive domains: (1) attention and working memory, (2) executive functions, (3) verbal episodic memory, (4) visuospatial functions, and (5) language. Patients received their usual antiparkinsonian medication. A cognitive domain was considered impaired when performance on at least two tests (or one test if only one was used to assess the domain) was ≤5th percentile or ≤−1.645 standard deviations compared to normative data.[1] Patients were then assigned to a subtype: (1) normal cognition (PD-NC), that is, no cognitive domain impaired; (2) frontostriatal subtype (PD-FS), that is, deficits in attention/working memory and/or executive functions without deficits in visuospatial functions, episodic memory, and language; (3) PD-PC, that is, deficits in visuospatial functions and/or episodic memory and/or language without deficits in attention/working memory and executive functions; and (4) mixed subtype (PD-MS), that is, deficits in attention/working memory and/or executive functions with deficits in visuospatial functions, episodic memory, and/or language.

MRI Analysis

A group-level independent component analysis with all subjects was performed using the methodology described by Varoquaux et al,[25] resulting in eight resting-state networks (Appendix S1, Fig. S1) that were subdivided into functional regions based on an atlas.[26] Furthermore, we added a basal-ganglia network, including caudate nuclei, putamen, pallidum, and thalami from the atlas[26] because they are involved in the pathophysiology of cognitive disorders in PD.[27] Our analyses were therefore performed on 590 regions (Appendix S1, Table S1). Finally, the time course of the blood–oxygen level-dependent signal was averaged among voxels within each area, and a Pearson correlation coefficient was calculated between each pair of regions, resulting in a 590×590 connectivity matrix for each participant. Details regarding MRI acquisition, preprocessing, and determination of regions of interest are provided in Appendix S2.

Statistical Analyses

All the analyses were performed with the R software version 4.0.3[28] and were corrected for multiple comparisons using a false discovery rate (FDR) fixed at 0.05,[29] except the network-based statistics[30] that were performed using Matlab version R2020a (MathWorks, Natick, MA, USA), and used a family-wise error (FEW) correction. Corrected P-values <0.05 were considered significant.

For demographic and clinical numerical variables, group comparisons were performed using the Kruskal–Wallis test and post hoc comparisons using the Wilcoxon-Mann-Whitney test, whereas categorical variables were compared using Fisher's exact test. For neuropsychological variables, comparisons were performed using ANCOVA (analysis of covariance) combined to a permutation test (number of permutations = 10,000), with age, sex, and educational level as covariates.

Regarding MRI data, based on individual connectivity matrices, we computed the area under the curve (AUC) representing the cumulative distribution of connections as a function of correlation coefficients for the entire connectivity matrix (global connectivity), between regions within a network (intra-connectivity), or between regions of a given network versus all the other regions (inter-network connectivity). Higher AUC represents lower region-to-region correlation coefficients (ie, lower FC) and vice versa. It is noteworthy that the AUC is dependent on the number of regions (ie, the higher the number of regions, the higher the AUC values). Moreover, to study functional integration differences between groups, we analyzed global network metrics based on graph theory approach using the Brain Connectivity Toolbox[31]: (1) the global efficiency and (2) the local efficiency. The efficiency of a graph is inversely proportional to the shortest distance. Therefore, the global efficiency of a network represents the average inverse shortest path length when considering all regions, whereas the local efficiency represents the average inverse shortest path length among the first neighbors of an area when it is removed. Pairwise comparisons between the five groups were performed on the AUC and global/local efficiency values using ANCOVA and a permutation test (number of permutations = 10,000). Finally, we used the network-based statistics approach[30] to identify functional connections showing differences between groups. Pairwise comparisons between the five groups were performed using the t test and permutation test (number of permutations = 10,000). For each significant comparison, the mean effect size was computed from the effect sizes (Cohen's d) of significant connections. The MRI analyses were controlled for age, sex, educational level, and center of recruitment.

For visualization, we used the BrainNet toolbox[32] to project peak coordinates (in the Montreal Neurological Institute space) of major brain regions involved in significant between-group comparisons.

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[1]This value for standard deviations corresponds to the fifth percentile.

Results

Population

The flowchart of the study is shown in Appendix S1, Figure S2. Twelve patients meeting criteria for PDD as well as 30 patients whose MRI scan was nonexploitable were excluded. Moreover, 9 participants had pronounced motion displacement. Finally, 13 participants were excluded for poor-quality preprocessed data. Analyses were thus performed on 119 participants.

Comparisons between HC and PD patients on major variables and MRI quality criteria are presented in Table S2. The only significant result was lower Mini-Mental State Examination[17] total score in PD patients compared to HCs ($p_{FDR} = 0.022$).

PD-MCI Subtype Categorization

In total, 31 (32.63%) PD patients were PD-NC, whereas 64 (67.37%) had a PD-MCI. Within the PD-MCI group, 14 (21.87%) had a PD-FS subtype, 20 (31.25%) a PD-PC subtype, and 30 (46.88%) a PD-MS subtype. PD-FS patients were mainly characterized by executive deficits (92.86%), PD-PC by visuospatial deficits (60.00%), and PD-MS by executive (93.33%) and visuospatial (86.67%) deficits. Frequencies of impaired cognitive domains are provided in Table 1.

Demographic and Clinical Characterization of PD-MCI Subtypes

Results on demographic and clinical variables are presented in Table 2. Sex ratio was lower in PD-MS compared to PD-NC and PD-FS, with more men in these last two groups. Formal education was shorter in PD-MS compared to the other three groups and in PD-PC compared to PD-FS. The total score on the Parkinson Anxiety Scale[20] was higher in the three PD-MCI subgroups compared to PD-NC. Finally, the Lille/Maastricht ratio was lower in PD-NC compared to PD-PC and PD-MS and lower in PD-FS compared to PD-MS (**Table S3** for demographic and clinical data according to the recruitment center).

Regarding cognitive variables (Table 1), PD-MS had lower global cognitive efficiency than PD-NC and PD-PC. As expected, PD-FS had lower performance in attention/working memory and executive functions than PD-NC and, to a lesser extent, PD-PC. PD-PC had lower performance in visuospatial functions, episodic memory, and language than PD-NC. Finally, PD-MS had lower performance in all cognitive domains compared with PD-NC, in frontostriatal domains compared with PD-PC, and for visuospatial functions compared with PD-FS.

FC Analyses

Global Connectivity and Global and Local Efficiencies

There were no significant between-group differences for global connectivity (Appendix S1, Fig. S3 and Table S4), global efficiency (Appendix S1, Fig. S4), and local efficiency.

Intra- and Inter-Network Connectivity

Results for intra-network connectivity are shown in Figure 1 (Appendix S1, Table S4 for details). PD-PC patients had a smaller AUC compared with PD-FS ($p_{FDR} = 0.028$) within the basal ganglia network (Fig. 1, top left). To better characterize this difference, we computed the AUC between the regions composing the basal ganglia network and compared the AUC between PD-PC and PD-FS. This analysis showed smaller AUC in PD-PC compared to PD-FS in 16 of 26 basal ganglia regions: the anterior and ventral parts of the left caudate; the ventral part of the right caudate; the bilateral pallidum; the anterior part of the left putamen; the dorsolateral, ventromedial, and anterior parts of the right putamen; and almost all regions composing the bilateral thalami (Table S5). Finally, PD-PC patients tended to have smaller AUC compared with PD-NC within the basal ganglia network ($p_{FDR} = 0.066$) (Fig. 1). For inter-network connectivity, there was no significant comparison (Appendix S1, Fig. S5 and Table S4).

Functional Connections

The analysis with the network-based statistics approach[30] revealed significant functional connection differences for HC > PD-FS ($p_{FWE} = 0.012$; mean effect size = 1.19), PD-NC > PD-FS ($p_{FWE} = 0.010$; mean effect size = 1.13), PD-PC > PD-FS ($p_{FWE} = 0.010$; mean effect size = 1.14), and HC > PD-MS ($p_{FWE} = 0.047$; mean effect size = 0.95) comparisons. Connectograms are presented in Figure 2 (see Appendix S1, Fig. S6 for details). For the HC > PD-FS comparison, 92.28% were inter-network connections. These connections involved 440 of 590 selected regions and were mainly part of the five following networks: visual network (51.6%), default-mode network (34.4%), salience network (23.0%), sensorimotor network (21.6%), and frontoparietal network (19.1%). For the PD-NC > PD-FS comparison, 91.31% were inter-network connections. These connections involved 453 regions and were mainly part of the five following networks: visual network (43.5%), sensorimotor network (33.9%), dorsal attentional network (30.4%), salience network (28.0%), and default-mode network (21.3%). For the PD-PC > PD-FS comparison, 90.22% were inter-network connections. These connections involved 474 regions and were mainly part of the five following

TABLE 1 *Cognitive test performance from study groups*

	PD-NC (n = 31)	PD-FS (n = 14)	PD-PC (n = 20)	PD-MS (n = 30)	p_{FDR}-value	Post hoc test
Overall efficiency						
Mattis Dementia Rating Scale (/144)	140.16 (3.49)	137.36 (5.61)	139.85 (3.20)	131.80 (8.29)	<0.001*	PD-NC > PD-MS; PD-PC > PD-MS
Attention/working memory						
Impaired, frequency (%)	0 (0.00)	3 (21.43)	0 (0.00)	16 (53.33)		
WAIS-R forward digit span (/14)	8.55 (1.65)	7.57 (2.03)	8.05 (2.35)	6.50 (2.32)	0.020*	PD-NC > PD-MS
WAIS-R backward digit span (/14)	6.61 (1.75)	5.36 (1.69)	6.25 (1.37)	4.53 (1.89)	0.020*	PD-NC > PD-MS; PD-PC > PD-MS
SDMT: correct substitutions in 90 s	51.00 (7.84)	37.93 (12.39)	47.05 (8.73)	30.60 (8.14)	<0.001*	PD-NC > PD-FS; PD-NC > PD-MS; PD-PC > PD-MS
Executive functions						
Impaired, frequency (%)	0 (0.00)	13 (92.86)	0 (0.00)	28 (93.33)		
Trail making test (time B)	77.74 (27.60)	134.71 (61.44)	90.94 (33.39)	194.83 (57.09)	<0.001*	PD-NC > PD-FS; PD-NC > PD-MS; PD-PC > PD-FS; PD-PC > PD-MS
Stroop: interference time	52.05 (10.50)	84.05 (33.40)	59.70 (18.21)	89.35 (33.56)	<0.001*	PD-NC > PD-FS; PD-NC > PD-MS; PD-PC > PD-MS
Stroop: errors	1.58 (6.80)	2.71 (3.34)	1.10 (1.52)	7.20 (9.97)	0.28	NA
Phonemic fluency: naming in 60 s	15.68 (5.23)	11.43 (4.01)	13.80 (3.05)	10.10 (3.78)	0.002*	PD-NC > PD-FS; PD-NC > PD-MS; PD-PC > PD-MS
Alternating fluency: naming in 60 s	15.48 (3.94)	8.93 (3.34)	12.25 (3.01)	7.87 (3.73)	<0.001*	PD-NC > PD-FS; PD-NC > PD-PC; PD-NC > PD-MS; PD-PC > PD-FS; PD-PC > PD-MS
HVLT—frequency of retrieval deficit (%)	1 (3.23)	1 (7.14)	0 (0.00)	4 (13.33)	0.28	NA
Episodic memory						
Impaired, frequency (%)	0 (0.00)	0 (0.00)	6 (30.00)	9 (30.00)		
HVLT—frequency of encoding/storage deficit (%)	0 (0.00)	0 (0.00)	6 (30.00)	9 (30.00)	<0.001*	PD-NC > PD-PC; PD-NC > PD-MS
Visuospatial functions						
Impaired, frequency (%)	0 (0.00)	0 (0.00)	12 (60.00)	26 (86.67)		
Judgment of line orientation (/15)	13.35 (1.28)	13.79 (1.25)	10.95 (2.67)	8.93 (2.50)	<0.001*	PD-NC > PD-PC; PD-NC > PD-MS; PD-FS > PD-MS
Language						
Impaired, frequency (%)	0 (0.00)	0 (0.00)	4 (20.00)	14 (46.67)		
Boston Naming Test (/15)	14.10 (1.04)	13.71 (1.20)	12.55 (2.01)	11.20 (1.97)	<0.001*	PD-NC > PD-PC; PD-NC > PD-MS

Means (standard deviations) are presented for each cognitive parameter (except frequencies [%] of deficit for the HVLT) along with frequencies (%) of impairment for each cognitive function. *p_{FDR} values were considered significant when < 0.05.

Abbreviations: PD-NC, Parkinson's disease—normal cognition; PD-FS, Parkinson's disease—frontostriatal subtype; PD-PC, Parkinson's disease—posterior cortical subtype; PD-MS, Parkinson's disease—mixed subtype; FDR, false discovery rate; WAIS-R, Wechsler for Adults Intelligence Scale-Revised; SDMT, Symbol Digit Modalities Test; HVLT, Hopkins Verbal Learning Test-Revised; NA, not applicable.

TABLE 2 *Sociodemographic and clinical features from study groups*

	PD-NC (n = 31)	PD-FS (n=14)	PD-PC (n = 20)	PD-MS (n = 30)	p_{FDR}-Value	Post hoc test
Demographics						
Age (y)	63.32 (8.66)	67.26 (7.61)	63.30 (7.83)	67.24 (7.35)	0.41	NA
Sex (men/women ratio)	5.20	13.00	1.50	1.00	0.026*	PD-NC ≠ PD-MS; PD-FS ≠ PD-MS
Educational level (years of full-time education)	13.58 (4.19)	14.79 (2.97)	11.85 (2.66)	10.20 (2.54)	0.002*	PD-NC > PD-MS; PD-FS > PD-PC; PD-FS > PD-MS; PD-PC > PD-MS
Clinical characteristics						
Disease duration (y)	9.52 (7.93)	8.93 (7.41)	6.80 (3.55)	8.20 (4.40)	0.89	NA
Age at onset (y)	53.77 (11.67)	58.43 (6.41)	56.65 (8.58)	59.07 (7.19)	0.56	NA
Side of onset (left/right/bilateral/undefined)	9/14/7/1	6/6/1/1	8/10/1/1	16/13/1/0	0.57	NA
MDS-UPDRS III score	28.84 (12.55)	34.21 (15.01)	27.50 (10.61)	29.13 (14.01)	1.00	NA
Hoehn & Yahr stage	2.02 (0.38)	2.32 (0.82)	2.00 (0.32)	2.26 (0.68)	0.14	NA
MDS-UPDRS 1.2 (%)	2 (6.45)	2 (14.29)	3 (15.00)	3 (10.00)	0.98	NA
Center (Lille/Maastricht ratio)	0.19	0.40	1.86	2.33	<0.001*	PD-NC ≠ PD-PC; PD-NC ≠ PD-MS; PD-FS ≠ PD-MS
Medication						
LEDD (mg/d)	727.97 (673.69)	781.99 (561.61)	731.19 (603.74)	815.26 (490.82)	0.92	NA
Acetylcholinesterase inhibitors (%)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	NA	NA
Antipsychotic (%)	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.33)	NA	NA
Antidepressant (%)	4 (12.90)	3 (21.43)	2 (10.00)	4 (13.33)	0.87	NA
Benzodiazepine (%)	2 (6.45)	0 (0.00)	1 (5.00)	8 (26.67)	0.12	NA
Neuropsychiatry						
Hamilton Depression Rating Scale (/52)	4.81 (4.16)	4.79 (3.02)	6.95 (5.38)	5.83 (4.33)	0.69	NA
Lille Apathy Rating Scale (/36)	−27.29 (5.05)	−26.57 (5.43)	−26.90 (5.75)	−23.00 (6.87)	0.14	NA
Parkinson Anxiety Scale (/48)	3.39 (4.15)	7.71 (5.25)	8.95 (6.00)	8.07 (7.11)	0.013*	PD-NC > PD-FS; PD-NC > PD-PC; PD-NC > PD-MS

Means (standard deviations) are presented for numerical variables and frequencies (%) for categorical variables. *p_{FDR} values were considered significant when < 0.05.
Abbreviations: PD-NC, Parkinson's disease—normal cognition; PD-FS, Parkinson's disease—frontostriatal subtype; PD-PC, Parkinson's disease—posterior cortical subtype; PD-MS, Parkinson's disease—mixed subtype; FDR, false discovery rate; NA, not applicable; MDS-UPDRS 3, Movement Disorders Society sponsored revision of the Unified Parkinson's Disease Rating Scale-Part III (severity of motor symptoms); MDS-UPDRS 1.2, Movement Disorders Society sponsored revision of the Unified Parkinson's Disease Rating Scale-Part I item 2 (presence of hallucinations); LEDD, levodopa equivalent daily dose.
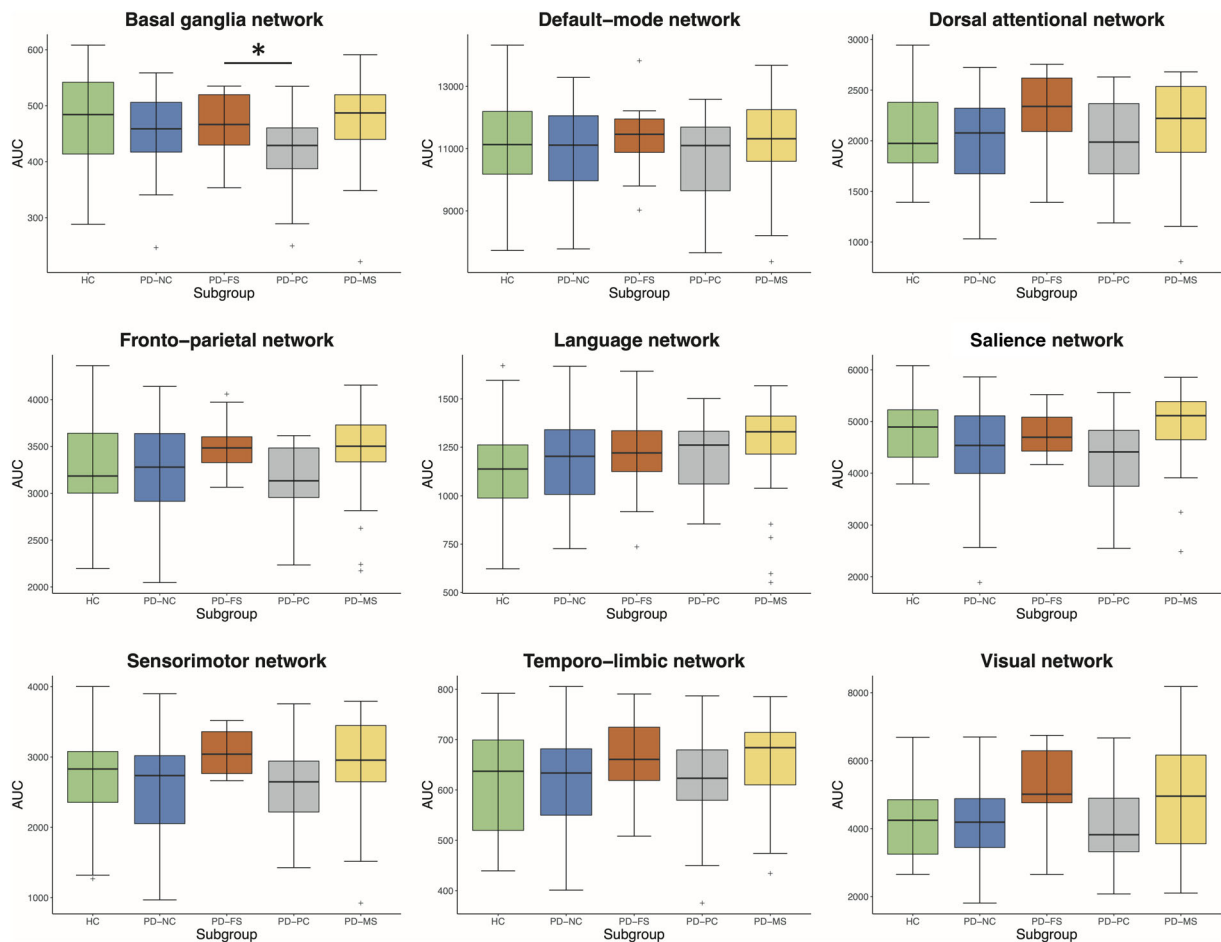
FIG. 1. Representation of intra-network connectivity for each network according to the subgroup. The boxplots represent the distribution of the average area under the curve values. The thick bars represent the medians and the crosses the outliers. $*p_{FDR} < 0.05$; AUC, area under the curve; FDR, false discovery rate; HC, healthy control; PD-FS, Parkinson's disease—frontostriatal subtype; PD-MS, Parkinson's disease—mixed subtype; PD-NC, Parkinson's disease—normal cognition; PD-PC, Parkinson's disease—posterior cortical subtype. [Color figure can be viewed at wileyonlinelibrary.com]

networks: salience network (36.0%), visual network (31.1%), default-mode network (29.3%), sensorimotor network (24.8%), and basal ganglia network (24.7%). Finally, for the HC > PD-MS comparison, 96.44% were inter-network connections. These connections involved 308 regions and were mainly part of the five following networks: visual network (62.7%), default-mode network (29.0%), sensorimotor network (27.1%), language network (26.0%), and frontoparietal network (16.1%). Regarding the spatial location of the involved regions (Fig. 3), significant differences between PD-FS and HC/PD-NC as well as between HC and PD-MS concerned mainly posterior cortical regions, whereas significant differences between PD-FS and PD-PC concerned mainly striatal and frontal regions (see Appendix S1, Table S6 and Fig. S7 for more details).

Discussion

The aim of the present study was to determine whether subtypes in PD-MCI, as determined by the

dual syndrome hypothesis, were associated with specific FC modifications. We showed for the first time that (1) PD-PC patients had higher FC within the basal ganglia network compared with PD-FS patients and (2) PD-FS and PD-MS patients had reduced FC in several resting-state networks compared with HC, PD-NC, or PD-PC. These changes were independent of age, sex, and education as well as disease duration and severity of motor symptoms. As global connectivity did not significantly differ between groups, our functional results were also independent of this variable. ■

FC Modifications Are Associated with MCI and Not PD Itself

No significant between-group differences were found between HCs and PD-NC, whereas there were significant differences between HC/PD-NC and PD-MCI subtypes. Overall, these results suggest that our results are related to the presence of cognitive impairment and not to the mere presence of PD itself. Although previous studies reported significant FC differences between HCs
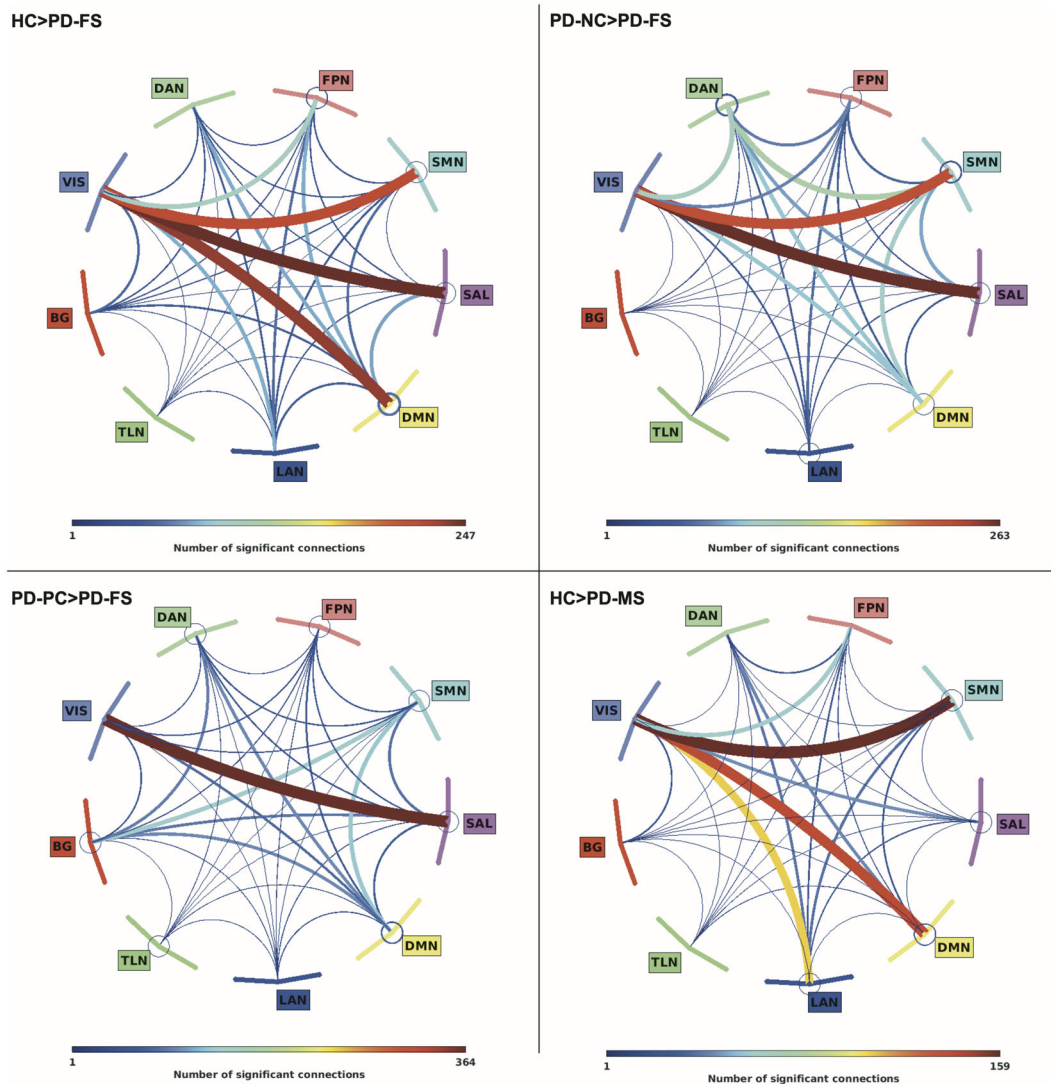
FIG. 2. Connectograms of significant intra- and inter-network connections for each significant between-group comparison. The thickness and color of the links represent the number of significant connections. The spherical links indicate the presence of significant intra-network connections. BG, basal ganglia network; DAN, dorsal attentional network; DMN, default mode network; FPN, frontoparietal network; HC, healthy control; LAN, language network; PD-FS, Parkinson's disease—frontostriatal subtype; PD-MS, Parkinson's disease—mixed subtype; PD-NC, Parkinson's disease—normal cognition; PD-PC, Parkinson's disease—posterior cortical subtype; SAL, salience network; SMN, sensorimotor network; TLN, temporo-limbic network; VIS, visual network. [Color figure can be viewed at wileyonlinelibrary.com]

and PD patients, there were inconsistencies.[33] Moreover, if most of the studies excluded PDD patients, often based on a screening score, they did not check for MCI in their study population, making it difficult to know if these changes were due to the potential presence of MCI.

Besides, resting-state FC alterations in PD-MCI have been more consistently reported.[6,34] Regarding cognitive subtyping, only two studies have considered the cognitive heterogeneity of PD-MCI when analyzing FC.[7,8] Their results showed decreased FC in various networks, including the default-mode, frontoparietal, dorsal attentional, and visual networks, in PD patients with amnestic or nonamnestic MCI compared with HC and/or PD-NC. However, in these studies, most PD-MCI patients had

deficits in several cognitive domains, including memory, attentional, executive, and visuospatial functions. According to the dual syndrome hypothesis, these subtypes could therefore be considered as mixed given the presence of frontostriatal and posterior cortical deficits. Finally, as no previous study used the dual syndrome hypothesis to determine PD-MCI subtypes, our results are difficult to compare with the literature.

Posterior Cortical Deficits Are Associated with Higher FC within the Basal Ganglia Network

Intra-network FC within the basal ganglia network was increased in PD-PC compared to PD-FS patients. This increased FC concerned most basal ganglia
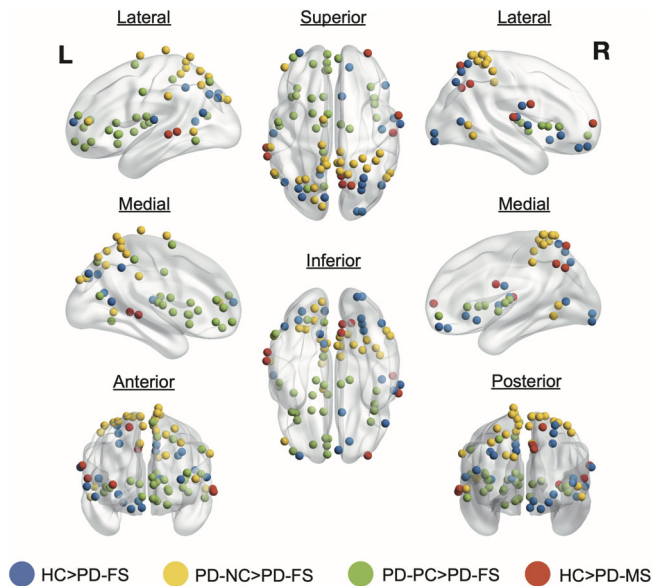
FIG. 3. Spatial location of brain regions for each significant comparison. The MNI coordinates of the barycenter of the region were projected on a smoothed MNI template, with colors representing between-group comparisons. Only regions with at least 25 significant connections are reported. HC, healthy control; L, left; MNI, Montreal Neurological Institute; PD-FS, Parkinson's disease—frontostriatal subtype; PD-MS, Parkinson's disease—mixed subtype; PD-NC, Parkinson's disease—normal cognition; PD-PC, Parkinson's disease—posterior cortical subtype; R, right. [Color figure can be viewed at wileyonlinelibrary.com]

regions, suggesting that all basal ganglia structures play a role in the manifestation or presentation of cognitive symptoms. There was also a trend toward increased intra-network FC within the basal ganglia network in PD-PC patients compared to PD-NC. Overall, these results suggest that patients with isolated posterior cortical deficits have hyperconnectivity within the basal ganglia network. Besides, there was no significant difference between HC/PD-NC and PD-PC. This result was unexpected, especially as we showed recently that PD patients with posterior cortical deficits, isolated or not, exhibited more frequent and more abundant structural alterations compared with PD-NC and, to a lesser extent, PD-FS patients, notably in the caudate nuclei, the right thalamus, and several white matter tracts.[23] Moreover, Lang and colleagues[9] reported a significant association between a posterior cortical factor and decreased FC within the frontoparietal network in PD patients. Therefore, our assumption was that PD-PC patients would have reduced FC compared to HCs and PD-NC patients, especially in networks including posterior cortical regions, but such alterations were not found. Nevertheless, the structural alterations found in PD-PC in our previous study were subtle and referred to local modifications observed with accurate neuroimaging methods.[23] There was no advanced gray matter atrophy nor loss of white matter integrity as observed in PDD, which is typically associated with FC alterations.[35-37] Furthermore, the differences between our

results and those of Lang and colleagues[9] can be explained by methodological discrepancies. Indeed, Lang and colleagues[9] used a data-driven approach to determine their cognitive factors. Moreover, meeting PD-MCI criteria[24] was not an inclusion criteria in their study, whereas it was in ours. Finally, we assigned the language domain to the PD-PC subtype, whereas this domain was associated with the dysexecutive factor in Lang and colleagues.[9]

Regarding the increased FC in our PD-PC subtype, previous studies showed increased FC in PD-MCI.[10,38,39] Baggio and colleagues[10] found increased FC between the default-mode network and parieto-occipital regions in PD-MCI compared to HC and PD-NC, which was associated with poor visuospatial performance. Interestingly, these regions presented a cortical thinning especially in PD-MCI, suggesting a potential relation between structural alterations and increased FC. Zhan and colleagues[38] reported increased FC between the posterior cingulate cortex and the middle frontal gyrus, the posterior cerebellar lobe, the middle temporal gyrus, and the left precuneus in PD-MCI compared to PD-NC. Interestingly, their PD-MCI group had language, memory, and visuospatial deficits, and the authors suggested that increased FC could reflect resource recruitment to address cognitive impairment. Recently, Li and colleagues[39] found increased FC between the thalamus and the cingulate cortex in PD-MCI compared to PD-NC along with reduced thalamic volume. The increased FC was negatively correlated with global cognitive efficiency, suggesting that the more the FC increased between these regions, the worse the cognitive performance was. Finally, Lang and colleagues[9] reported a significant association between a posterior cortical factor and increased intra-network FC within the temporo-limbic network in PD patients but no significant result regarding the basal ganglia network. In addition to the methodological discrepancies between this study and ours mentioned earlier, it is noteworthy that results regarding the temporo-limbic network should be interpreted with caution given that it includes brain regions that are highly sensitive to magnetic resonance susceptibility.[40] Therefore, given the structural changes in the caudate nuclei and the right thalamus found in PD-PC,[23] the increased FC within the basal ganglia network in our PD-PC patients may potentially be explained as a compensatory mechanism preventing this subtype from having frontostriatal deficits. Such mechanisms may also explain why PD-PC patients had no reduced FC compared with HCs and PD-NC patients.

Frontostriatal Deficits Are Associated with Reduced Inter-Network FC

Our results revealed reduced FC in PD-FS compared to HC, PD-NC, or PD-PC and in PD-MS compared with HC. This mainly concerned inter-network connections. As in the meta-analysis by Wolters and

colleagues,[6] we found reduced FC in the default-mode, the frontoparietal, and the sensorimotor networks in PD-FS and PD-MS compared with HC and/or PD-NC but no significant results regarding PD-PC. These results particularize those of Wolters and colleagues[6] and suggest that reduced FC in these networks may be present in PD patients with frontostriatal deficits only. We did not find a pattern of reduced FC specific to PD-FS or PD-MS. Although the proportions of significant connections *per* network differed between both subtypes, all networks were systematically involved. Lang and colleagues[9] reported a significant association between a dysexecutive factor and decreased intra-network FC within the sensorimotor network. Although we also found significantly reduced FC in this network in PD-FS and PD-MS patients, most significant connections were inter-network connections. However, Lang and colleagues[9] did not assess inter-network connectivity in their study. Regarding location of the involved regions, our results are inconsistent with our hypothesis. Indeed, significant results in PD-FS and PD-MS compared with HC and/or PD-NC concerned mainly connections with posterior brain regions, whereas anterior regions could have been expected given their frontostriatal deficits. Furthermore, Dubbelink and colleagues[41] reported that reduced FC in posterior brain regions was associated with subsequent cognitive decline in PD after a 3-year follow-up, suggesting a core role of these regions regarding the risk of developing dementia.

Interestingly, we found significant differences between PD-FS and PD-PC in several resting-state networks, whereas, using the same population, we found only slight structural differences between these subtypes.[23] Our results suggest that resting-state FC can discriminate the two cognitive subtypes described in the dual syndrome hypothesis.[4] The basal ganglia network seems to be a network of interest as about one quarter of the significant inter-network connections between PD-FS and PD-PC concerned this network.

Finally, we found reduced FC in a fewer number of connections in PD-MS than in PD-FS compared with HC. As we found in a previous study that patients with posterior cortical deficits, especially in patients with a mixed subtype, had more abundant and more extensive structural alterations,[23] we expected to find reduced FC in more connections in PD-MS patients. Besides, this subtype had lower global cognitive efficiency, and cognitive decline is associated with FC alterations.[6,41] Given the major presence of both executive and visuospatial deficits, the PD-MS subtype seems to overlap with the PD-FS and PD-PC subtypes, having reduced FC as the former but in fewer connections, which may potentially be explained by the same compensatory mechanism at play in the latter. Further studies are needed to decipher the pathophysiological mechanisms associated with each cognitive subtype in PD-MCI.

Strengths and Limitations

The main strength of our study was to use several methods to investigate FC brain modifications in PD-MCI subtypes. Moreover, we used consensual international diagnostic criteria for PD-MCI, which facilitates inter-study comparisons. Finally, confounding variables were strictly controlled in our functional MRI analyses.

The main limitation was the fact that HC data were collected in only one center (Lille), whereas PD data were collected in two centers (Lille and Maastricht). Therefore, the control of this variable in our statistical analyses may have prevented some differences from being significant. Moreover, the number of subjects in the PD-FS patient group was relatively small (n = 14). However, differences between this subtype and the others were significant, suggesting that this small sample size did not prevent from significant results.

Conclusions and Perspectives

In PD-MCI, patients with posterior cortical deficits have increased intra-network FC within the basal ganglia network, whereas patients with frontostriatal deficits have reduced inter-network FC between various resting-state networks. This implies that resting-state FC may potentially be able to discriminate the cognitive subtypes as determined by the dual syndrome hypothesis.[4] Confirmation is needed from longitudinal studies to determine the predictive power of these functional modifications regarding the risk of developing PDD.

Data Availability Statement

Data supporting the findings of this study are available from the corresponding author, upon reasonable request. ●

References

1. Litvan I, Aarsland D, Adler CH, Goldman JG, Kulisevsky J, Mollenhauer B, et al. MDS Task Force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. Mov Disord 2011;26(10):1814–1824.

2. Lawrence BJ, Gasson N, Loftus AM. Prevalence and subtypes of mild cognitive impairment in Parkinson's disease. Sci Rep 2016; 21(6):33929

3. Williams-Gray CH, Evans JR, Goris A, Foltynie T, Ban M, Robbins TW, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. Brain 2009; 132(Pt 11):2958–2969.

4. Kehagia AA, Barker RA, Robbins TW. Cognitive impairment in Parkinson's disease: the dual syndrome hypothesis. Neurodegener Dis 2013;11(2):79–92.

5. Williams-Gray CH, Mason SL, Evans JR, Foltynie T, Brayne C, Robbins TW, et al. The CamPaIGN study of Parkinson's disease:

10-year outlook in an incident population-based cohort. J Neurol Neurosurg Psychiatry 2013;84(11):1258–1264.

6. Wolters AF, van de Weijer SCF, Leentjens AFG, Duits AA, Jacobs HIL, Kuijf ML. Resting-state fMRI in Parkinson's disease patients with cognitive impairment: A meta-analysis. Parkinsonism Relat Disord 2019;62:16–27.

7. Chung SJ, Park Y-H, Yun HJ, Kwon H, Yoo HS, Sohn YH, et al. Clinical relevance of amnestic versus non-amnestic mild cognitive impairment subtyping in Parkinson's disease. Eur J Neurol 2019; 26(5):766–773.

8. Kawabata K, Watanabe H, Hara K, Bagarinao E, Yoneyama N, Ogura A, et al. Distinct manifestation of cognitive deficits associate with different resting-state network disruptions in non-demented patients with Parkinson's disease. J Neurol 2018;265(3):688–700.

9. Lang S, Hanganu A, Gan LS, Kibreab M, Auclair-Ouellet N, Alrazi T, et al. Network basis of the dysexecutive and posterior cortical cognitive profiles in Parkinson's disease. Mov Disord 2019; 34(6):893–902.

10. Baggio H-C, Segura B, Sala-Llonch R, Marti M-J, Valldeoriola F, Compta Y, et al. Cognitive impairment and resting-state network connectivity in Parkinson's disease. Hum Brain Mapp 2015;36(1): 199–212.

11. Peraza LR, Nesbitt D, Lawson RA, Duncan GW, Yarnall AJ, Khoo TK, et al. Intra- and inter-network functional alterations in Parkinson's disease with mild cognitive impairment. Hum Brain Mapp 2017;38(3):1702–1715.

12. Putcha D, Ross RS, Cronin-Golomb A, Janes AC, Stern CE. Altered intrinsic functional coupling between core neurocognitive networks in Parkinson's disease. Neuroimage Clin 2015;27(7):449–455.

13. Dujardin K, Moonen AJH, Behal H, Defebvre L, Duhamel A, Duits AA, et al. Cognitive disorders in Parkinson's disease: confirmation of a spectrum of severity. Parkinsonism Relat Disord 2015; 21(11):1299–1305.

14. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51(6):745–752.

15. Morris JC. The clinical dementia rating (CDR): current version and scoring rules. Neurology 1993;43(11):2412–2414.

16. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007;22(12):1689–1707; quiz 1837

17. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189–198.

18. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008; 23(15):2129–2170.

19. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.

20. Leentjens AFG, Dujardin K, Pontone GM, Starkstein SE, Weintraub D, Martinez-Martin P. The Parkinson Anxiety Scale (PAS): development and validation of a new anxiety scale. Mov Disord 2014;29(8):1035–1043.

21. Sockeel P, Dujardin K, Devos D, Denève C, Destée A, Defebvre L. The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. J Neurol Neurosurg Psychiatry 2006;77(5):579–584.

22. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010;25(15):2649–2653.

23. Devignes Q, Viard R, Betrouni N, Carey G, Kuchcinski G, Defebvre L, et al. Posterior cortical cognitive deficits are associated with structural brain alterations in mild cognitive impairment in Parkinson's disease. Front Aging Neurosci 2021;13:668559

24. Litvan I, Goldman JG, Tröster AI, Schmand BA, Weintraub D, Petersen RC, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord 2012;27(3):349–356.

25. Varoquaux G, Sadaghiani S, Pinel P, Kleinschmidt A, Poline JB, Thirion B. A group model for stable multi-subject ICA on fMRI datasets. Neuroimage 2010;51(1):288–299.

26. Crossley NA, Mechelli A, Vértes PE, Winton-Brown TT, Patel AX, Ginestet CE, et al. Cognitive relevance of the community structure of the human brain functional coactivation network. Proc Natl Acad Sci U S A 2013;110(28):11583–11588.

27. O'Callaghan C, Bertoux M, Hornberger M. Beyond and below the cortex: the contribution of striatal dysfunction to cognition and behaviour in neurodegeneration. J Neurol Neurosurg Psychiatry 2014;85(4):371–378.

28. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2018.

29. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B Methodol 1995;57(1):289–300.

30. Zalesky A, Fornito A, Bullmore ET. Network-based statistic: identifying differences in brain networks. Neuroimage 2010; 53(4):1197–1207.

31. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. Neuroimage 2010;52(3):1059–1069.

32. Xia M, Wang J, He Y. BrainNet Viewer: a network visualization tool for human brain connectomics. PLoS One 2013;8(7): e68910

33. Tessitore A, Cirillo M, De Micco R. Functional connectivity signatures of Parkinson's disease. J Parkinsons Dis 2019;9(4):637–652.

34. Filippi M, Elisabetta S, Piramide N, Agosta F. Functional MRI in idiopathic Parkinson's disease. Int Rev Neurobiol 2018;141: 439–467.

35. Peraza LR, Colloby SJ, Firbank MJ, Greasy GS, McKeith IG, Kaiser M, et al. Resting state in Parkinson's disease dementia and dementia with Lewy bodies: commonalities and differences. Int J Geriatr Psychiatry 2015;30(11):1135–1146.

36. Chen B, Fan GG, Liu H, Wang S. Changes in anatomical and functional connectivity of Parkinson's disease patients according to cognitive status. Eur J Radiol 2015;84(7):1318–1324.

37. Borroni B, Premi E, Formenti A, Turrone R, Alberici A, Cottini E, et al. Structural and functional imaging study in dementia with Lewy bodies and Parkinson's disease dementia. Parkinsonism Relat Disord 2015;21(9):1049–1055.

38. Zhan Z-W, Lin L-Z, Yu E-H, Xin J-W, Lin L, Lin H-L, et al. Abnormal resting-state functional connectivity in posterior cingulate cortex of Parkinson's disease with mild cognitive impairment and dementia. CNS Neurosci Ther 2018;24(10):897–905.

39. Li M-G, He J-F, Liu X-Y, Wang Z-F, Lou X, Ma L. Structural and functional thalamic changes in Parkinson's disease with mild cognitive impairment. J Magn Reson Imaging 2020;52(4):1207–1215.

40. Yeo BTT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol 2011; 106(3):1125–1165.

41. Olde Dubbelink KTE, Schoonheim MM, Deijen JB, Twisk JWR, Barkhof F, Berendse HW. Functional connectivity and cognitive decline over 3 years in Parkinson disease. Neurology 2014; 83(22):2046–2053.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Author Roles

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