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Speech difficulties in early *de novo* patients with Parkinson's disease

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ABSTRACT

Introduction: Speech difficulties are a common debilitating feature of Parkinson's disease and we aimed to investigate whether speech difficulties are associated with striatal dopaminergic deficits and faster disease progression.

Methods: Using the Parkinson's Progression Markers Initiative database, 143 early *de novo* Parkinson's disease patients with speech difficulties were identified and matched 1:1 with 143 Parkinson's disease patients without speech difficulties for age, disease duration and motor symptom severity. We investigated differences in clinical features and striatal [^{123}I]FP-CIT single photon emission computed tomography (SPECT) uptake in Parkinson's disease patients with and without speech difficulties. Cox proportional hazards analysis was carried out to investigate whether speech difficulties were predictive of a faster motor progression and cognitive decline.

Results: Speech difficulties were more common in patients with an akinetic-rigid motor phenotype compared to those with a tremor-dominant phenotype. Parkinson's disease patients with speech difficulties had lower resting tremor ($P = 0.027$), higher autonomic dysfunction ($P = 0.034$), increased daytime sleepiness (ESS; $P = 0.048$), and a higher prevalence of REM sleep behaviour disorder (RBD) symptoms ($P = 0.007$) compared to those without speech difficulties. Parkinson's disease patients with speech difficulties had significantly lower [^{123}I]FP-CIT uptake in the striatum ($P < 0.001$), caudate ($P = 0.003$) and putamen ($P = 0.003$) compared to those without speech difficulties. The presence of speech difficulties was a predictor of cognitive decline [Hazard Ratio (HR): 0.341, 95% Confidence Interval (CI): 0.153–0.759; Wald: 6.945; $P = 0.008$), whereas it had no influence on motor progression (HR: 0.885, 95% CI: 0.662–1.183; Wald: 0.680; $P > 0.10$).

Conclusion: Speech difficulties are associated with greater autonomic dysfunction, sleep disturbances and striatal dopaminergic deficit, and can serve as a predictor of faster cognitive decline in early Parkinson's disease.

1. INTRODUCTION

Speech difficulties are very common and debilitating features of Parkinson's disease (PD), occurring in up to 90% of the patients over the course of the disease, and significantly affecting their social interactions and quality of life [1]. Changes in voice and speech have been reported in early drug-naïve PD patients [2,3] and even as early as five years prior to PD diagnosis [4,5]. It has been suggested that speech difficulties in PD arise as a result of bradykinesia and rigidity of the laryngeal muscles, due to dopaminergic deficits [6–11]. However, previous studies investigating the influence that dopamine replacement therapy has on speech performance in PD have yielded inconsistent results, reporting that dopamine replacement therapy either has no effect on speech performance, or ameliorates it in PD patients [7,12–15]. Thus, the mechanisms underlying speech abnormalities in PD remain poorly understood and little is known about their prognostic value in PD progression. Here, we investigated whether speech difficulties are associated with presynaptic dopaminergic deficits using [^{123}I]FP-CIT single photon emission computed tomography (SPECT) molecular imaging and whether speech difficulties are linked to progression of symptoms in early *de novo* PD patients.

2. METHODS

2.1. Participants and clinical evaluation

From the 412 PD patients included in the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data), a total

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of 353 early *de novo* PD patients had a complete three-year follow-up and were included in the analysis. All PD patients were recruited between 2010 and 2015, diagnosed with PD less than two years prior to a screening visit, never treated with dopamine replacement therapy and presented with two among bradykinesia, resting tremor and rigidity or with asymmetric resting tremor/bradykinesia at screening. The diagnosis was confirmed by the presence of dopaminergic deficit using [^{123}I]FP-CIT SPECT imaging.

The presence of speech difficulties was defined according to the Unified PD Rating Scale Part-III (UPDRS-III), Item 3.1 (Speech) ≥ 1. This item is a clinician-based scale consisting of 5 scores, rating between 0 (normal) and 4 (most severe impairment). Using propensity scores, 143 PD patients with speech difficulties were matched 1:1 with 143 PD patients without speech difficulties for age, disease duration and UPDRS-III. All matching variables were balanced after propensity scores.

Motor symptom severity was assessed with the UPDRS-III and staged with the Hoehn and Yahr (H&Y) scale. UPDRS-III score was calculated excluding Item 3.1 (Speech). Each motor domain (bradykinesia, resting tremor, rigidity, postural instability) was calculated using specific UPDRS-III sub-items as follows: bradykinesia (Total score range 0–52) = sum of Item 3.4 finger tapping, item 3.5 hand movements, item 3.6 pronation-supination movements of hands, item 3.7 toe tapping, item 3.8 leg agility, item 3.9 arising from chair, item 3.13 posture and item 3.14 body bradykinesia; rigidity (Total score range 0–20) = sum of Item 3.3 rigidity (neck, upper limbs and lower limbs); resting tremor (total score range 0–24) = sum of item 3.17 rest tremor amplitude (lip/jaw, upper limbs and lower limbs) and item 3.18 constancy of tremor; axial (total score range 0–12) = sum of item 3.10 gait, item 3.11 freezing of gait and item 3.12 postural stability [16]. UPDRS-II score was calculated excluding Item 2.1 (Speech).

PD motor phenotypes were identified as either tremor-dominant or akinetic-rigid using the numerical ratio, which was derived from a patient's mean tremor score and mean akinetic-rigidity score [17]. Tremor global score was derived from the mean of nine items from UPDRS, rated in the OFF state: 1. By history left arm tremor; 2. By history right arm tremor; 3. On exam, tremor at rest of face, lips or chin/jaw; 4. On exam, tremor at rest of right upper extremity (RUE); 5. On exam, tremor at rest of left upper extremity (LUE); 6. On exam, tremor at rest of right lower extremity (RLE); 7. On exam, tremor at rest of left lower extremity (LLE); 8. On exam, presence of action or postural tremor in RUE; 9. On exam, presence of action or postural tremor in LUE. Kinetic-rigid gobal score was derived from the mean of 12 UPDRS items, rated in the OFF state: 1. Rigidity in neck; 2. Rigidity in RUE; 3. Rigidity in LUE; 4. Rigidity in RLE; 5. Rigidity in LLE; 6. Hand movements; 7. Finger taps; 8. Arising from chair; 9. Posture; 10. Gait; 11. Postural instability; 12. Body bradykinesia. Patients with ratio < 0.8 were classified as akinetic-rigidity phenotype, patients with ratio > 1.0 were classified as tremor-dominant phenotype and patients with ratio between 0.8 and 1 were classified as mixed subtype. Non-motor symptoms were assessed using UPDRS-I and the Scale for Outcomes for PD–Autonomic function (SCOPA-AUT). Neuropsychiatric symptoms were assessed with the short version of the 15-item Geriatric Depression Scale (GDS) and the State Trait Anxiety Total scale (STAI). Sleep disorders were assessed with the Epworth Sleeping Scale and REM sleep behavior disorder questionnaire (RBDQ). Cognitive impairment was measured using the Montreal cognitive assessment (MoCA). Olfactory dysfunction was measured by the University of Pennsylvania Smell Identification Test (UPSIT). Disability was estimated using the Modified Schwab & England Activity of Daily Living (ADL).

This study is registered with ClinicalTrials.gov (No: NCT01141023). Each PPMI site has received approval from an ethical committee on human experimentation before the study's initiation. Written informed consent for research was obtained from all individuals participating in the study. The present study was written according to the STROBE guidelines [18].

2.2. Dopaminergic imaging

SPECT images were obtained 4 ± 0.5 h after administrating an injection of approximately 185 MBq [^{123}I]FP-CIT. [^{123}I]FP-CIT SPECT scans were analysed following the imaging technical operations manual (http://ppmi-info.org/). Raw SPECT data was acquired into a 128 x 128 matrix stepping each 3° for a total of 120 (or 4° for a total of 90) projections in a window centered on 159 ± 10%KeV. The total scan duration was 30–45 min. A Chang 0 attenuation correction was applied using a customised *Mu* determined empirically from the anthropomorphic brain phantom acquired at each site. A standard Gaussian 3D 6.0 mm filter was applied to each image volume and then normalised to standard Montreal Neurologic Institute space. Each scan was interpreted by two independent readers who were blinded to the subjects' demographics and characteristics. For quantification, SPECT image volumes were spatially normalized to an Ioflupane template. The eight most prominent axial slices containing striatum were summed and then a standardized volume of interest (VOI) template was applied to this image. VOI analyses were performed on the left and right caudate and putamen with the occipital region serving as a reference tissue. Specific binding ratios (SBR) were calculated as the ratio of the caudate or putamen VOI count density divided by count density of the occipital cortex minus 1. This measure approximates the binding potential, BP_{ND}, when the tracer is in equilibrium at the target site and was previously reported with Ioflupane SPECT [19].

2.3. Assessment of motor progression and cognitive decline

Motor progression was defined as a change of 1 point in the H&Y scale at each follow-up visit, measured in the "off" treatment state [20].. Cognitive impairment was defined as MoCA score of ≤22 at the follow-up visits. Follow-up visits took place in the outpatient unit of the reference hospitals once every 12 months. All early *de novo* PD patients were followed up for a three-year period.

2.4. Statistical analysis

Statistical analysis and graph illustration were performed with SPSS (version 20) and GraphPad Prism (version 6.0c) for MAC OS X, respectively. For all variables, variance homogeneity and Gaussianity were tested with Kolmogorov-Smirnov test.

Group comparisons between PD patients with and without speech difficulties were carried out using the Student *t*-test (parametric variables) and Mann-Whitney *U* test (non-parametric variables), as appropriate. Categorical variables were compared using a χ [2] test. *P*-values for each variable were calculated following Bonferroni's multiple comparisons test. We interrogated correlations between the speech scores and imaging data using Spearman's rank correlation and we applied Bonferroni's multiple comparisons test. To investigate whether speech difficulties were predictive of a faster disease progression and development of cognitive impairment, two Cox proportional hazards analyses were carried out investigating the presence of speech difficulties as predictor of: (1) motor progression; (2) cognitive decline. The analyses have been repeated including age and gender as covariate. The time to occurrence of the first event in a category for a given subject was used in the Cox model. All data are presented as mean ± standard deviation (SD), and the level α was set for all comparisons at $P < 0.05$, corrected.

3. RESULTS

3.1. Clinical characteristics

In our population, 137 PD patients exhibited mild speech difficulty (Item 3.1 Speech = 1) and 6 PD patients had moderate speech difficulty (Item 3.1 Speech = 2). There were no PD patients who presented with

Table 1
Demographic and clinical characteristics of early *de novo* PD patients.

	PD with speech difficulties (n = 143)	PD without speech difficulties (n = 143)	*P* value*
DEMOGRAPHIC CHARACTERISTICS			
Age (mean ± SD)	63.23 (± 9.0)	63.26 (± 8.6)	> 0.10
Gender male, % (n)	72.0% (103)	61.5% (88)	0.08
Disease duration (months; mean ± SD)	6.68 (± 6.0)	6.19 (± 6.4)	> 0.10
Family history of PD, % (n)	25.2% (36)	25.2% (36)	> 0.10
MOTOR SYMPTOMS			
Motor Subtypes, % (n)	AR: 69.9% (100) TD: 18.9% (27) Mixed: 11.2% (16)	AR: 58.7% (84) TD: 30.1% (43) Mixed: 11.2% (16)	-
Hoehn and Yahr scale (mean ± SD)	1.64 (± 0.4)	1.66 (± 0.5)	> 0.10
UPDRS-II (mean ± SD)	6.79 (± 4.68)	5.57 (± 3.78)	> 0.10
UPDRS-III (mean ± SD)	22.2 (± 7.7)	21.2 (± 7.7)	> 0.10
Bradykinesia subscore (mean ± SD)	11.12 (± 5.1)	10.74 (± 5.5)	> 0.10
Rigidity subscore (mean ± SD)	4.03 (± 2.5)	4.08 (± 2.6)	> 0.10
Postural instability subscore (mean ± SD)	0.92 (± 0.9)	0.86 (± 1.0)	> 0.10
Resting Tremor Amplitude subscore (mean ± SD)	1.33 (± 1.3)	1.67 (± 1.3)	> 0.10
Resting Tremor Costancy subscore (mean ± SD)	1.17 (± 1.1)	1.59 (± 1.2)	**0.027**
Global Tremor subscore (mean ± SD)	4 (± 3.0)	5.08 (± 3.0)	**0.027**
NON-MOTOR SYMPTOMS			
UPDRS-I (mean ± SD)	1.35 (± 1.60)	1.14 (± 1.40)	> 0.10
SCOPA-AUT (mean ± SD)	11.02 (± 6.89)	5.82 (± 9.01)	**0.034**
GDS (mean ± SD)	2.35 (± 2.29)	2.35 (± 2.39)	> 0.10
STAI (mean ± SD)	92.75 (± 7.89)	94.36 (± 8.63)	> 0.10
ESS (mean ± SD)	6.42 (± 3.67)	5.29 (± 3.12)	**0.048**
RBDQ Score, % (n)	44.1% (63)	28.7% (41)	**0.007**
MoCA (mean ± SD)	27.02 (± 2.28)	27.01 (± 2.34)	> 0.10
UPSIT (mean ± SD)	21.75 (± 7.9)	22.30 (± 7.99)	> 0.10
FUNCTIONAL ASSESSMENT			
ADL (mean ± SD)	92.52 (± 5.84)	93.27 (± 5.51)	> 0.10

ADL: Modified Schwab & England Activity of Daily Living; AR: Akinetic-rigid dominant; ESS: Epworth Sleeping Scale; GDS: 15-item Geriatric Depression Scale; MoCA: Montreal Cognitive Assessment Scale; RBDQ: REM sleep behaviour disorder questionnaire; SCOPA-AUT: the scale for outcomes for PD-autonomic function; STAI: state and train anxiety scale; TD: Tremor dominant; UPSIT: University of Pennsylvania Smell Identification Test. **P* values are Bonferroni corrected.

moderate-severe speech difficulty (Item 3.1 Speech = > 3). Speech difficulties were more common in *de novo* PD patients with akinetic-rigid motor phenotype compared to those with tremor-dominant phenotype (100/84; 69.9% *vs* 27/43; 18.9%, $P < 0.05$).

In order to avoid biases, due to motor symptoms severity and disease duration, we performed a case-control analysis where PD patients with speech difficulties were matched for age, disease duration and UPDRS-III with 143 PD patients who did not have any speech difficulties (Item 3.1 Speech = 0). With regards to UPDRS-III motor subscores, PD patients with speech difficulties had lower resting tremor ($P = 0.027$) and global tremor ($P = 0.027$) scores compared to those without speech difficulties. No differences were observed in bradykinesia, rigidity and postural instability subscores between the two groups (all $P > 0.10$; Table 1).

Early *de novo* PD patients with speech difficulties had higher autonomic dysfunction ($P = 0.034$), increased daytime sleepiness (ESS; $P = 0.048$) and a higher prevalence of RBD symptoms ($P = 0.007$) compared to patients without speech difficulties. There were no differences in UPDRS-I, UPSIT scores, anxiety/depressive symptoms, cognitive function and ADL between *de novo* PD patients with and without speech difficulties (all $P > 0.10$; Table 1).

3.2. Imaging assessment: presynaptic dopaminergic function

Early *de novo* PD patients with speech difficulties had lower [^{123}I] FP-CIT uptakes in the striatum ($P < 0.001$), caudate ($P = 0.003$) and putamen ($P = 0.003$) compared to those without speech difficulties (Table 2; Fig. 1A and C). Worse speech scores, as assessed by the UPDRS-III item 3.1, were associated with lower [^{123}I]FP-CIT uptakes in the striatum ($r_s = -0.24$; $P < 0.001$), caudate ($r_s = -0.21$; $P = 0.006$) and putamen ($r_s = -0.23$; $P < 0.001$; Fig. 1B). These results were confirmed following the inclusion of SCOPA-AUT, ESS, prevalence of RBD symptoms and motor phenotype subtype as covariates.

3.3. Motor progression and cognitive decline

Over a period of three years, 151 (42.8%) *de novo* PD patients exhibited motor progression and 27 (7.6%) patients developed cognitive impairment. Cox proportional hazards analysis showed that the presence of speech difficulties in early *de novo* PD patients predicted cognitive decline at a three-year follow-up [Hazard Ratio (HR): 0.341, 95% Confidence Interval (CI): 0.153–0.759; Wald: 6.945; $P = 0.008$; Fig. 2], whereas it did not influence PD motor progression (HR: 0.885, 95% CI: 0.662–1.183; Wald: 0.680; $P > 0.10$). These results were confirmed after including age and gender as covariates.

4. Discussion

Our findings indicate that early *de novo* PD patients with speech difficulties have greater autonomic dysfunction, excessive daytime sleepiness, RBD symptoms and striatal dopaminergic deficit compared to PD patients without speech difficulties, independently from disease duration, age and severity of overall motor symptoms. Moreover, the presence of speech difficulties in early *de novo* PD patients is linked to an increased risk of cognitive decline.

Speech difficulties was prevalent in 42.8% of our cohort of 353 early *de novo* PD patients, which is in line with previous studies showing that speech difficulties can occur in approximately 40% of early untreated PD patients [3]. Speech difficulties were more common in akinetic-rigid PD patients. Increased bradykinesia and rigidity were the motor symptoms specifically associated with speech difficulties, suggesting that speech impairment in PD may be linked to bradykinesia and rigidity of laryngeal muscles. A recent study investigating longitudinal changes of speech in 55 early *de novo* PD patients has shown that worse speech performance, according to quantitative acoustic vocal evaluation and UPDR-III (Speech) item 3.1, was associated with increased

Table 2
[^{123}I]FP-CIT uptakes in the groups of early Parkinson's disease patients with and without speech difficulties.

Regions of Interest	PD with speech difficulties	PD without speech difficulties	*P* value*	% changes
Striatum (mean ± SD)	1.29 (± 0.3)	1.45 (± 0.3)	< 0.001	−12.4%
Caudate (mean ± SD)	1.84 (± 0.5)	2.05 (± 0.5)	0.003	−11.4%
Putamen (mean ± SD)	0.73 (± 0.2)	0.85 (± 0.2)	0.003	−16.4%

**P* values are Bonferroni corrected.

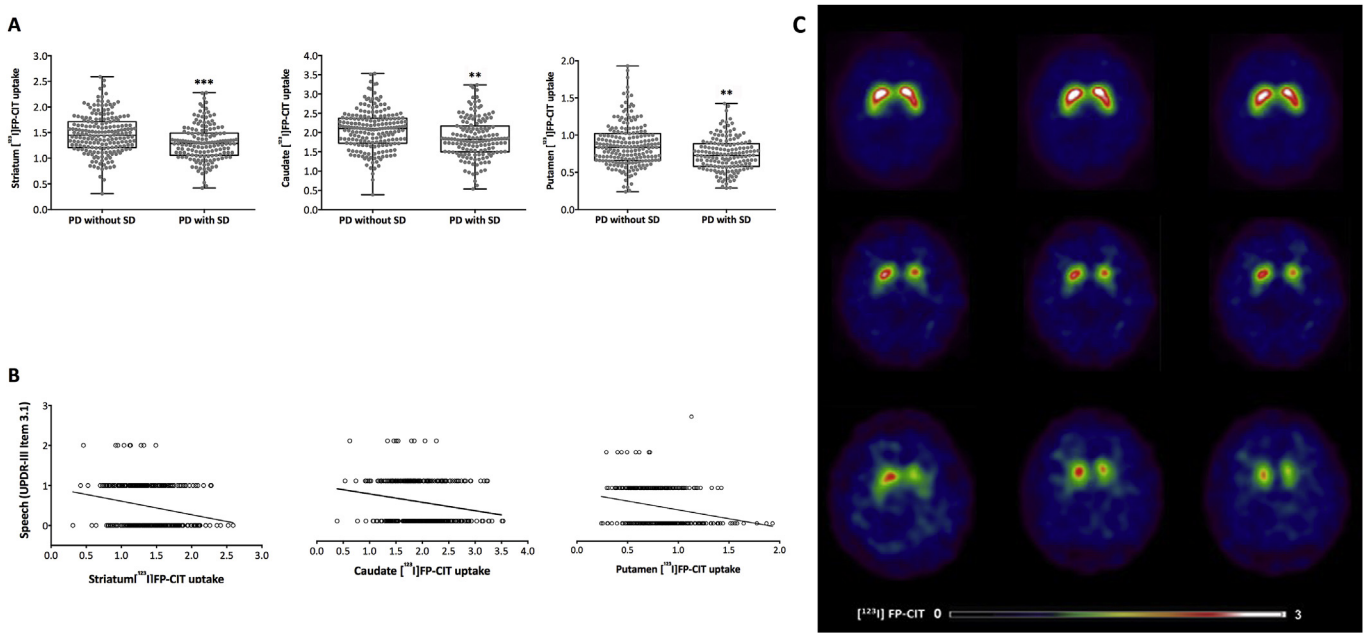

Fig. 1. Presynaptic dopaminergic deficit in the group of early de novo Parkinson's disease patients with speech difficulties. (A) Box-plot showing decreased [^{123}I]FP-CIT uptakes in the striatum, caudate and putamen of early *de novo* PD patients with speech difficulties. **(B)** Correlations between the degree of speech impairment (UPDRS-III, item 3.1) and [^{123}I]FP-CIT uptake in the striatum ($r_s = -0.24$; $P < 0.001$), caudate ($r_s = -0.21$; $P = 0.006$) and putamen ($r_s = -0.23$; $P < 0.001$) of early *de novo* PD patients; ***$P < 0.001$; **$P < 0.01$. **(C)** [^{123}I]FP-CIT SPECT images in Parkinson's disease patients with and without speech difficulties. (Top) 55-year-old healthy control showing typical [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 3.41) and putamen (SBR: 2.49) (Middle) 55-year-old male without speech difficulties exhibiting slight dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 2.43) and putamen (SBR: 1.19); (Bottom) 55-year-old male with speech difficulties demonstrating larger striatal dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 1.22) and putamen (SBR: 0.455).

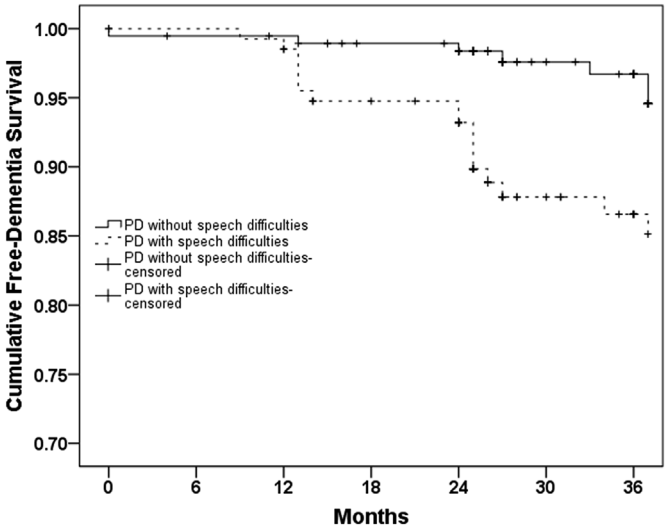

Fig. 2. Overall survival curves for the development of cognitive impairment regarding to the presence of speech difficulties. Patients with speech difficulties had an increased risk of developing cognitive impairment compared to those without speech difficulties (Log Rank (Mantel-Cox) = 7.702; HR: 0.341, 95% CI: 0.153–0.759; Wald: 6.945; $P = 0.008$).

UPDRS-III motor scores and bradykinesia subscores [21]. At follow-up assessment, improvements in speech performance were closely related to dopamine replacement therapy and antiparkinsonian treatment-related improvements in motor symptoms, specifically in bradykinesia subscores [21].

Other studies have found a significant correlation between speech abnormalities and axial symptoms, in particular freezing of gait, in moderate PD patients who were on dopamine replacement therapy [15,22,23] as well as advanced disease stages [24] where speech dysfluency represents a motor speech control disorder and possibly shares common pathophysiological mechanisms with the freezing of gait.

We did not find significant differences in axial subscores between early *de novo* PD patients with and without speech difficulties. However, our axial subscores included gait, freezing of gait and postural stability and we did not assess direct associations between speech difficulties and freezing of gait.

We found that early *de novo* PD patients with speech difficulties had significantly lower striatal [^{123}I]FP-CIT uptake compared to those without speech difficulties, with lower striatal presynaptic dopaminergic function being associated with higher speech impairment. The differences in dopaminergic integrity between patients with and without speech difficulties did not appear to be associated with the worse clinical symptoms or motor phenotype exhibited by PD patients with speech difficulties, given that these variables were included as covariates in the statistical model, and the results remained consistent. To our knowledge, this is the first study showing a link between striatal presynaptic dopaminergic deficits and speech impairment in PD. Previous positron emission tomography (PET) [25–28] and functional magnetic resonance (fMRI) studies [29,30] that have investigated neuronal substrates of speech difficulties in PD have shown abnormal activation of the basal ganglia–cerebellum–cortex circuit with altered recruitment of the orofacial motor cortex, supplementary motor cortex and cerebellum, as well as increased involvement of the premotor and prefrontal cortices in moderate PD patients on dopamine replacement therapy [29,30].

A recent fMRI study investigating the impact of levodopa on resting state functional connectivity in the ON and OFF medication states and speech prosody control, revealed that there is an association between levodopa-induced changes in the caudate-dorsolateral prefrontal cortex connectivity and speech improvement in PD patients, thus suggestive of a link between dopamine deficits and speech impairment in PD [29]. Conversely, another study that evaluated the influence of levodopa on

speech, using a syllable repetition paradigm reported there to be no association between levodopa administration and vocal pace performance. These findings suggest that dysfunctional basal ganglia circuits responsible for the maintenance of the speech motor programs do not respond to short-term dopaminergic stimulation [31]. Further studies are required to investigate the role of levodopa on all the components of speech. The re-evaluation of our population at a later follow-up might give us a better understanding of the effect, if any, levodopa has on speech difficulties in PD.

Among the non-motor symptoms, PD patients with speech difficulties had worse autonomic dysfunction, more severe daytime somnolence and a higher prevalence of RBD symptoms compared to patients without speech difficulties, with no differences in anxiety, depression or cognitive function. Interestingly, we found that the presence of speech difficulties was associated with an increased risk of cognitive decline, but did not influence motor progression over a three-year follow-up period. A recent study found that early drug-naïve PD patients with RBD have higher risk of cognitive decline, though they did not investigate the presence of speech difficulties, which may have driven their results [20]. However, given the well-documented association between RBD and cognitive decline, the higher prevalence of RBD may have influenced our results. Nevertheless, RBD, together with autonomic dysfunction, excessive daytime sleepiness and motor phenotype, were included as covariates in the statistical model, and speech difficulties remained to be a predictor of cognitive decline. Two studies have investigated the role of PD-related speech difficulties in predicting cognitive dysfunction in smaller cohorts of PD patients [32,33]. Gago and colleagues [32] found that speech impairment progression, as measured by the UPDRS-III (Speech) was the strongest predictor of dementia over a six-year period in 24 early stage PD patients without axial motor impairment at baseline. PD patients with speech difficulties appeared to decline more rapidly when completing the Mini Mental Status Examination, Clock Drawing, Semantic Verbal Fluency and Block Design neuropsychological tests [32]. Subsequently, a more recent study, using quantitative acoustic vocal assessment, showed that variation in the range of the fundamental voice frequency and in specific the speech index of rhythmicity can predict changes in cognitive status as measured by the Addenbrooke's cognitive examination with 73.2% accuracy over a 2-year period [33]. Our study extends previous preliminary observations and provides robust evidence for the link and predictive role of speech impairment in the development of cognitive decline in a large cohort of early stage patients with PD.

A limitation of our study includes the absence of quantitative acoustic vocal assessments to assess speech difficulties in PD patients. However, utilising clinician-based scales, such as the UPDRS-III (Speech) item 3.1, means clinicians are equipped with a simple tool to monitor the progression of speech difficulties. It is important to note, however, that UPDRS-III (Speech) item 3.1 does not distinguish between hypokinetic and iterative speech disorders (stuttering dysarthria), which has been related to more severe disease progression in previous studies [24,31]. Thus, future studies using acoustic analysis and perceptual assessment of speech by a speech and language therapist must confirm these findings, which are rather preliminary because of this limitation.

Additional limitations of this study relate to the fact that the population of Parkinson's disease patients included in the PPMI are characterized by early drug-naïve patients. Therefore, 137 patients of our speech-impaired PD cohort exhibited speech difficulties categorised to be of mild severity (Item 3.1, Speech = 1), with only 6 patients exhibiting speech difficulties categorised to be of moderate severity (Item 3.1, Speech = 2). We were, therefore, unable to evaluate whether patients with different speech phenomenology have a different progression. Further studies including patients with Item 3.1 scores ≥ 3, which refers to patients with severe speech difficulty, are needed to clarify this issue.

Our findings demonstrate that speech difficulties are associated with higher striatal dopaminergic deficits and worse symptomatology in early PD. Speech difficulties can also serve as a predictor of faster cognitive decline.

5. Financial disclosure statement

Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org. PPMI – a public-private partnership - is sponsored by the Michael J. Fox Foundation for Parkinson's Research (MJFF) and is co-funded by MJFF, Abbvie, Avid Radiopharmaceuticals, Biogen Idec, Bristol-Myers Squibb, Covance, Eli Lilly & Co., F. Hoffman-La Roche, Ltd., GE Healthcare, Genentech, GlaxoSmithKline, Lundbeck, Merck, MesoScale, Piramal, Pfizer and UCB. PPMI. Industry partners are contributing to PPMI through financial and in-kind donations and are playing a lead role in providing feedback on study parameters through the Industry Scientific Advisory Board (ISAB). Through close interaction with the study, the ISAB is positioned to inform the selection and review of potential progression markers that could be used in clinical testing. Mr Polychronis, Dr. Niccolini, Dr. Pagano, Ms Tayyabah Yousaf and Dr. Politis report no disclosures.

6. Potential conflicts of interest

No potential conflict of interest relevant to this article was reported.

Authorship

S.P. and M.P. conceived the study and conceptualized the experimental design. F.N., and G.P. gave input to experimental design. F.N. and S.P. wrote the first draft and prepared the manuscript. G.P., F.N. and S.P. performed the statistical analysis. F.N., S.P. and T.Y. generated the figures. F.N., M.P., S.P., G.P. interpreted the data. All authors revised and gave input to the manuscript.

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