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Descriptive analysis of the French NS-Park registry: towards a nation-wide Parkinson's disease cohort?

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ABSTRACT:

Introduction: Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's. The French clinical research network for PD (NS-Park) has created a national patient registry to i)report medical activity of Parkinson Expert Centers (PECs) to the Ministry of Health, ii)facilitate PD patients pre-screening for clinical trials, iii) provide a source for pharmaco-epidemiology studies.

Objective: Assess the French Parkinsonian population at a nation-wide level and discover new clinical characteristics.

Methods: In this feasibility study, PECs prospectively collected clinical data in a standardized manner. The population main clinical characteristics are described, focusing on motor and non-motor symptoms and treatments, assessing its representativeness. By using an unbiased clustering with multiple correspondence analysis (MCA), we also investigate potential relationships between multiple variables like symptoms and treatments, as clues for future studies.

Results: Between 2012 and 2016, among 11,157 included parkinsonian syndromes, 9,454 (85%) had PD. MCA identified various profiles depending on disease duration. Occurrences of motor complications, axial signs, cognitive disorders and Levodopa use increase over time.

Neurovegetative symptoms, psychiatric disorders, sleep disturbances and impulse control disorders (ICDs) seem stable over time.

As expected, ICDs were associated to dopaminergic agonist use but other associations, such as ICDs and sleep disturbances for instance, or anxiety and depression, were found.

Conclusions: Our results report one of the biggest PD registries ever reported and demonstrate the feasibility of implementing a nation-wide registry of PD patients in France, a potent tool for future longitudinal studies and clinical trials' population selection, and for pharmaco-epidemiology and cost-effectiveness studies.

INTRODUCTION:

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. Symptomatic dopaminergic replacement therapy does not prevent debilitating complications occurring during disease course. Development of new symptomatic or disease modifying drugs remains a major challenge in PD.

The French Clinical Research Infrastructure network (F-CRIN; www.F-CRIN.org/en) is the French counterpart of ECRIN, the pan-European support infrastructure for multinational clinical trials (www.ecrin.org). The missions of F-CRIN are to: (i) promote French clinical research abroad, (ii) support large academic multicenter clinical trials under French coordination, (iii) encourage early and innovative studies such as proof of concept studies in partnership with industries. In 2013, F-CRIN supported national clinical research networks focusing on specific diseases. Meanwhile, the French Government labeled 24 Parkinson expert centers (PECs) through the 2012-2016 plan for PD[1]. The pre-existing network of 16 clinical investigation centers involved in PD research was extended to the 24 PECs to create the French clinical research network for PD and movement disorders (NS-Park) which was retained for funding by F-CRIN.

The objective of NS-Park is to promote clinical research in PD and movement disorders in order to (i) understand underlying disease mechanisms, and (ii) develop innovative therapeutic strategies. To achieve these scientific objectives, one of the initiative planned by NS-Park was to create a patient registry to i) report the PECs' medical activity to the Ministry of Health, ii) facilitate clinical trials pre-screening of PD patients, and iii) provide a source of "real-life" clinical data for epidemiology and pharmaco-epidemiology studies.

Here, we describe the main clinical characteristics of the population included into the registry during the implementation phase. In addition to classic descriptive statistics, we investigate potential relationships between variables using MCA, an additional descriptive clustering analysis tool. We demonstrate the feasibility of implementing a nation-wide PD registry, globally representative of the PD population reported in clinical studies. Based on these results, NS-Park is now moving towards a longitudinal cohort supported by a web-based solution.

PATIENTS AND METHODS

Study participants

This was an observational cross-sectional study performed between January 2012 and January 2016 in 11 French PECs (Bordeaux, Caen, Lille, Limoges, Lyon, Montpellier, Paris, Reims, Rouen, Strasbourg and Toulouse). Subjects included into the database were patients with a parkinsonian syndrome referred to the Movement Disorders clinics of the aforementioned PECs. Eligibility criteria were all consecutive patients diagnosed with any cause of Parkinsonism by one of the Movement Disorder specialist of the PECs. Movement disorders specialists were then asked to characterize the patients according to international criteria for diagnosis of PD, multiple system atrophy (MSA), supranuclear palsy (PSP), Lewy body dementia, corticobasal syndrome (CBS), or as “other”. Patients were assessed at the time of their first visit since the PEC creation. Diagnosis of PD, MSA, PSP, CBS or LBD was made according to UK Parkinson’s Disease Society Brain Bank Criteria for PD[2], and usual criteria [3–6]. Patients diagnosed with PD were then further assessed.

NS-Park data collection

Data were prospectively collected using a structured questionnaire including demographic data and a physical examination form. Data were obtained during a regular outpatient visit at the PEC. Data were collected by a Movement Disorders specialist interviewing patients and/or their caregivers. Patient characteristics were captured on a standardized paper form which included: age, diagnosis, disease duration, sex, geographical origin, presence or absence of motor and non-motor symptoms, and current PD treatments. Patients were also asked if they would agree or not to be contacted for future clinical trials or studies. Motor and non-motor symptoms were systematically assessed as present or absent as per the opinion of the Movement Disorders specialist, and classified as follows: (i) motor complications (motor fluctuations and dyskinesia); (ii) axial signs (falls or postural instability, freezing of gait, camptocormia, dysarthria, swallowing difficulties); (iii) neurovegetative symptoms (gastro-intestinal, sphincter or erectile dysfunction, postural hypotension); (iv) sleep disturbances (daytime sleepiness, insomnia, REM-sleep

behavioral disorder (RBD), restless leg syndrome (RLS), periodic movements, obstructive sleep apnea syndrome (OSAS)); (v) cognitive disorders (apathy, and dementia); (vi) psychiatric disorders (depression, anxiety, psychosis); (vii) hallucinations; (viii) impulsive-compulsive disorders (ICDs) (pathological gambling, pathological shopping, hypersexuality, binge eating, addiction to L-Dopa, punning). Treatments were assessed as antiparkinsonian medication subtypes (L-dopa, dopamine agonists, monoamine oxidase (MAO) or catechol-O-methyltransferase (COMT) inhibitors, anticholinergic drugs), psychiatric medication subtypes (antidepressants, antipsychotics, anxiolytics). Presence/absence of deep-brain stimulation (DBS) and its target (Subthalamic nucleus (STN), Ventral intermediate medial nucleus (VIM) of the thalamus or the internal Globus pallidus (GPi)) were also assessed.

Standard Protocol Approvals, Registrations, and Patient Consents

According to French regulations at the time this study was conducted, the database was registered at the French National Commission for Data Protection and Liberties (CNIL) and the proposed analysis of the database received approval from the CNIL after a positive advisory opinion from the CCTIRS (the French Advisory Board regarding data processing in Health Research), the medical and scientific section of the CNIL, on the 17th of November 2016. Oral consent was obtained for all patients by the movement disorder specialist entering the data in the database.

Statistical analysis

Extraction of individual data was performed locally at each center, and then centralized for a pooled data monitoring and analysis. Centralized analyses were done using anonymized data to protect privacy. Individual anonymized data were made available for age at examination and disease duration from which age at onset was calculated. For categorical variables, centers were asked to provide summary statistics with the total number of patients with a positive (Yes), negative (No), or missing data (MD) for each symptom. Data management on missing data and outliers was centrally performed on the pooled dataset, and queries were sent to each center for corrections. For the MCA performed only on data from the Paris center, individual data were

made available for all variables. We performed a descriptive analysis for each variable.

Categorical variables are expressed as the ratio of the number of patients presenting the symptom to the total number of patients assessed and as percentages [n/N (%)] so missing data were reported for each item; and continuous variables as mean \pm SD.

To further explore and describe relationships between variables, individual data were extracted from one center (Paris center), and a more detailed analysis was performed. The relationship between categorical variables was summarized by cross-tabulations and analyzed by multiple correspondence analyses (MCA) which studies cross-frequency tables (contingency tables). MCA explores the simultaneous relationships between variables in an n-dimensional space, and then uses the distance between the variables in each dimension to establish the similarity degree of variables. The position of the category-points in MCA maps is the basis for revealing the relationship among the investigated variables. MCA was chosen because as compared to other methods, it allows a description of the structure of the data without assuming their underlying distribution. With most techniques for cross-classification methods [7] categorical data analysis relies on the use of models. In log-linear analysis (one of the most widely used methods), for example, a distribution is assumed under which the data are collected, then a model for the data is hypothesized and estimations are made under the assumption that this model is true. In MCA, it is claimed that no underlying distribution has to be assumed and no model has to be hypothesized, but a decomposition of the data is obtained to study the 'structure' in the data [8]. Numerical variables such as "Disease duration" were transformed into categorical values and used as a supplementary quantitative descriptive variable not included in the MCA calculations. For the MCA analysis, the 14 main variables were chosen using the heads of each clinical complications category from the standardized form, and the treatments. The 14 variables were motor complications, axial signs, neurovegetative symptoms, sleep disturbances, cognitive disorders, psychiatric disorders, ICDs, L-DA, dopaminergic agonists, MAO-B-I, COMT-I, DBS, antidepressants and antipsychotics. All 35 variables were including all subcategories of symptoms from the standardized form, for a more detailed description : motor fluctuations, dyskinesia, falls or postural instability, freezing of gait, camptocormia, dysarthria, swallowing difficulties, gastro-intestinal dysfunction, sphincter or erectile dysfunction, postural

hypotension, daytime sleepiness, insomnia, RBD, RLS, periodic movements, OSAS, apathy, dementia, depression, anxiety, psychosis, hallucinations, pathological gambling, pathological shopping, hypersexuality, binge eating, addiction to L-DA, punning, L-DA, dopaminergic agonists, MAO-B-I, COMT-I, DBS, antidepressants, antipsychotics. Missing values were taken into account as “missing data” in the MCA analysis.

Based on the results of MCA, we applied hierarchical clustering on variables combined with a heat map representation to identify different profiles. Clustering techniques allow classifying patients or variables within homogeneous subsets (clusters) through the definition of a distance between individuals on the basis of their characteristics. The score (coordinates) obtained on the factorial axes identified through the MCA was used to calculate distances.

The classic descriptive analysis was performed using Microsoft Excel and Graphpad Prism softwares. For MCA, statistical analysis were implemented with R (3.3.0) with FactoMineR and ClustOfVar packages.

RESULTS

Patients' inclusion and case demographics

Between 2012 and 2016, 11,157 patients with a parkinsonian syndrome were included into the database, among which 9,454 (85%) had PD (Figure 1). The rate of recruitment of PD patients was of 197 new patients per month. The distribution of PD patients from the 11 French PECs was 690 from Bordeaux, 334 from Caen, 1,347 from Lille, 350 from Limoges, 1,532 from Lyon, 432 from Montpellier, 2,553 from Paris, 188 from Reims, 529 from Rouen, 413 from Strasbourg and 1086 from Toulouse.

Demographic data of PD patients are shown on Table 1a. Mean age at examination was 67.8 ± 10.5 years and mean disease duration at examination was 9.3 ± 7.2 years, with a sex ratio of 1.4:1 (Table 1a). There was no more than 10% of missing data for all parameters but two (RBD and periodic movements), in which data were particularly missing (Table 1a).

Motor and non-motor symptoms

Table 1a describes the motor and non-motor symptoms observed in the PD population. The most frequent complications reported were Levodopa-induced motor complications in 4,620 (51%) patients, followed by sleep disturbances in 4,307 (48%) and axial signs in 3,690 (42%). Neurovegetative symptoms and psychiatric disorders were reported in a third of the patients (Table 1a), cognitive disorders in 1,584 (18%) and hallucinations in 1,045 (12%) patients. ICDs were present in 8% of the patients.

Regarding Levodopa-induced motor complications, fluctuations were more frequent than dyskinesia.

Treatments

Table 1a shows the various treatments under which patients were at their first visit since the PEC creation. Half of the patients received L-DOPA associated with dopaminergic agonists. L-DOPA monotherapy was given to 2,686 (28%) patients. Only 7% of the patients received dopaminergic agonists as monotherapy. MAO and COMT inhibitors were respectively taken in 26% and 15% of patients. Anticholinergic drugs were used in 2% of the patients.

Antidepressants (15%) and anxiolytics (10%) were the most frequently used psychiatric medications. 850 (9%) of the patients underwent deep brain stimulation. The main target was the STN and more rarely the VIM nucleus of the thalamus or the GPi.

Detailed analysis of Paris Center data

To describe in more detail how the clinical data may capture the relationship between variables, we further analyzed individual data from the Paris center. Characteristics, complications and treatments of the 2,553 PD patients from Paris center were similar to the general population of the global dataset (see Table 1b and Supplementary Table 1).

Among the 2,553 patients from this center, 536 had disease durations below one year (21%) and 1,248 below five years (49%) (Table 1b). Overall, 309 patients were drug naive “de novo” patients. Ages at examination were between 25 and 94 years and their distribution is shown in Supplementary Figure 1, with a mean age of 66.2 years. Early onset PD was observed in 165 (6.5%) patients with an age at diagnosis below 40 years (Table 1b). Age at diagnosis was below

50 years in 592 (23%) of the patients (Table 1b). One hundred and ninety (7%) patients had late-onset PD with an age at diagnosis above 75 years (Table 1b).

A large majority of patients (71%) was not opposed to being contacted to participate into a forthcoming clinical study. Further detailed characteristics of this NS-Park population fitting the profile as a potential clinical study population are summarized in Table 1b.

The clustering approach of the 14 main variables identified various association of variables depending on disease duration as shown in Figure 2 and Supplementary Figures 2-4. The contribution of each individual to each parameter is available to the readers upon request. The respective positions of the variables on the map or on the dendrogram, close to one variable or the other, reflects if there is a stronger association with these variables than the others. Short disease duration of less than 1 year, was more closely correlated to the absence of treatment with L-dopa and neither motor complications nor axial signs as the closest variables were the absence of treatment by L-dopa (L-DA_N) and the absence of motor complications or axial signs (motor complications_N, axial signs_N) (Figure 2, Supplementary Figure 2). Patients with disease duration from 1 to 5 years were likely treated by MAO-B inhibitor and showed strong correlations to having none of the complications and no other treatments (amantadine, dopaminergic agonists, antipsychotic or antidepressants). Disease duration between 5 and 10 years were associated with L-dopa treatment. Disease duration over 10 years showed closer correlations to motor and non-motor complications, deep brain stimulation and treatments for complications (antidepressants, antipsychotics, antidyskinetic drugs as amantadine and against fluctuations as COMT Inhibitors) (Figure 3, Supplementary Table 2). Presence of ICDs was closely related to dopaminergic agonist use (Supplementary Figure 2). An analysis of all 35 variables showed very similar characteristics (Supplementary Figure 3; Supplementary Table 3) and other associations between subcategories of symptoms such as ICDs and sleep disturbances for instance, or anxiety and depression. As an example, the association of anxiety and depression can be seen on the MCA map, as both Anxiety-Yes and Depression-Yes are close to each other, and in the same way, Anxiety-No and Depression-No are close to each other (Supplementary Figure 3).

Based on the results of MCA, we applied hierarchical clustering on variables combined with a heat map representation showing the profile of the PD population during disease progression (Figure 3). The frequency of motor complications, falls, cognitive disorders and L-DA use increased over time. Neurovegetative symptoms, psychiatric disorders, sleep disturbances and ICDs seem to be stable over time. Treatments use and their distribution over disease course reflect the frequency of occurrence of the symptoms they are used to treat (Figure 3).

DISCUSSION

This feasibility study including over 11,000 patients of the NS-Park database is one of the largest datasets of PD patients ever reported. The number of PD patients in France is estimated at 150,000[9], thus this initial report of the NS-Park registry represents approximately 10% of the French PD population. A recent review reported the results of 44 studies with a total of 14,666 participants (cohorts' median: 138; range: 23-3.090)[10], hence placing the number of patients in the NS-Park database above any of the cohorts previously reported.

Compared to the literature, our results provide a congruent picture as compared to the general parkinsonian population. The relative frequencies of the various parkinsonian syndromes reported here are in accordance to previous reports[2,11–17]. PD is by far the most frequent parkinsonian syndrome with a male-to-female sex ratio and age as previously reported[2,18]. Rates of complications reported here are also in accordance to previous reports[18–22]. Additionally, depression and anxiety also seem to be closely correlated on the MCA[23–25].

The clustering with MCA shows relevant relationships between disease duration, motor and non-motor symptoms, and treatments. It shows the NS-Park/F-CRIN database can easily provide extended correlation information on a large-scale population as individual level data is made available to the researchers of the NS-Park network in the new computerized version of the NS-Park/F-CRIN database. It is a powerful tool to screen for patients with specific clinical characteristics. The global pooled analysis and the MCA analysis from one center both confirmed that the NS-Park PD population reported here seems representative and congruent

with the literature [2,11–17,26]. Almost all parameters are very similar between the Paris Center and the global dataset from all centers. The percentage of patients with short disease durations is slightly higher at the Paris Center. This may be due to the specific early state outpatient clinics, the “De Novo” consultation, which was set up in this center in order to offer an expert opinion to patients referred by physicians early during disease course[27]. The NS-Park/F-CRIN database may also help identifying or validating novel clinical correlation findings. For instance, we showed an association between ICDs and sleep disturbances, an observation previously suggested by a smaller sample study reporting an association between RBD and pathological gambling [28]. In the same way, we showed an association between OSAS, depression and anxiety, when a previous report failed to show any correlation, probably because of small sample size[29].

MCA was chosen because it allows analyzing all outcomes simultaneously, characterizing the patients’ profiles and considering outcomes together with the other exploratory variables. MCA is a useful tool for investigating the interrelationships among categorical variables. The MCA has several features and some advantages that distinguish it from other techniques of data analysis[26]. This multivariate nature allows revealing relationships, which could occur during a series of pair wise comparisons of variables. As opposed to log-linear analysis, no underlying distribution has to be assumed and no model has to be hypothesized, but a decomposition of the data is obtained to study the 'structure' in the data [29]. Another advantage is related to joint graphical displays. This graphical display produces two dual displays whose row (patients) and column (variables) geometries have similar interpretations. This facilitates the analysis to detect different relationships. In other multivariate approaches to graphical data representation, this duality is not present. MCA helps to describe patterns of relationships distinctively using geometrical methods by locating each variable of analysis as a point in a low-dimensional space. MCA is useful to map both variables and individuals, allowing the construction of complex visual maps, structuring of which can be interpreted. The MCA works effectively for the large data matrix structure either unknown or poorly understood.

A limitation of the results presented here is that they are cross-sectional and not longitudinal yet. Results correlating disease duration with symptoms and treatment has thus to

be taken with caution. However, patients being evaluated at the first visit were of various profiles: de novo, short or long disease duration. Hence, a partial picture of the PD population with different disease duration and treatments was already available. In the future version of the NS-Park database, it is planned to prospectively assess patients at each visit at the center, i.e. usually once to twice a year. The population referred to PECs, tertiary university-based centers with special expertise in movement disorders, may differ from the general PD population, for instance regarding the age at onset, the percentage of De novo patients with no treatment or the percentage of patients undergoing DBS treatment. Our results here however show congruency with the characteristics of the PD population usually reported in the literature, probably because such results are often reported by similar tertiary centers. Another limitation is that motor and non-motor symptom assessments were not quantitative, and they were based on movement disorder specialists' opinion, not standardized definitions. To prevent both of these limitations, the future NS-Park/F-CRIN cohort will allow further evaluation of each parameter by using the international validated scoring of the MDS-UPDRS scale [30]. A web-based interface has been implemented for easier collection by the Movement Disorder specialist to limit missing data.

We demonstrate here the feasibility to implement, at a national level, a unique homogenous multicenter database, a potent tool for future longitudinal studies and clinical trials' population selection. Since this feasibility study reporting the feasibility of the recruitment of a large registry, NS-Park/F-CRIN has moved towards a more structured cohort of PD patients involving all PECs in France, using semi-quantitative items for motor and non-motor symptoms, a web-based interface for collecting data, and a quality management plan. The perspective of this new longitudinal cohort will have to be reported in a future study to confirm the feasibility of the prospective evaluation. This initiative is in agreement with precompetitive data sharing to address unmet needs in PD encouraged by others[31,32]. Pairing with national Health insurance databases will soon be available and will allow for pharmaco-epidemiology and cost-effectiveness studies in the French population as it has also been recently reported in the Netherlands[33]. The future NS-Park/F-CRIN cohort should be a tremendous and compelling

opportunity to acquire nation-wide information in terms of epidemiological, pharmacological and clinical data in PD. The perspective of such clinical cohorts in the long term will be to aggregate biological and brain imaging information to clinical data in order to become suitable platforms for precision clinical trials and personalized medicine.

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TABLE/FIGURE LEGENDS:

Table 1: Description of patients with Parkinson's disease

Table 1a: Parkinson's disease patients' demographics, complications and medications

Categorical variables are expressed as the ratio of the number of patients presenting the symptom to the total number of patients assessed and as percentages [n/N (%)] and continuous variables as mean \pm SD [range] (percentage of patients assessed). Different symptoms can be present in the same patient.

Abbreviations: COMT: Catechol-O-methyl-transferase; DBS: Deep brain stimulation; MAO: Monoamine oxidase; REM-sleep: Rapid Eye Movement sleep; SD: Standard Deviation; Vim: Ventral intermediate medial nucleus

Table 1b: Parkinson's disease patients from the Parkinson Expert Center in which Multiple Correspondence Analyses was performed

Categorical variables are expressed as the number of patients and as percentages [n (%)] and continuous variables as mean \pm SD [range] (number of patients assessed).

Figure 1: Flow chart of the patients with a parkinsonian syndrome included in the NS-Park/F-CRIN database.

Abbreviations:

PSP: Progressive Supranuclear Palsy, MSA: Multiple System Atrophy, CBS: Cortico-Basal Syndrome, LBD: Lewy Body Dementia.

Figure 2: Multiple correspondence analysis map showing the positions and the association between 14 variables

Multiple correspondence analysis map showing the positions and the association between 14 variables for patients with Parkinson's disease in the Expert Center where MCA was performed (N=2553).

The horizontal and vertical axes represent the first and second principal dimensions, respectively. The first two axes accounted for 20.4% and 12.1% of inertia. Contribution from the third dimension was only 7.2 %. Motor complications, axial signs, neurovegetative symptoms and sleep disturbances are the most important variables contributing to the variance accounted for by axis 1. Axial signs, motor complications, cognitive disorder and disease duration are the most important variables contributing to the variance accounted for by axis 2 (See Supplementary Table 2). The modalities of categorical variables are specified as a suffix for Yes “_Y” colored in blue and No “_N” colored in black.

Abbreviations: COMT-I: Cathechol-O-methyl-transferase inhibitor; DBS: Deep Brain Stimulation; L-DA: L-DOPA; MAO-I: Monoamine oxidase inhibitor.

Figure 3: Heatmap of the similarity matrix of the Parkinson's disease “patients' stratifications”

Heatmap of the similarity matrix of the “patients' stratifications” of patients with Parkinson's disease in the Expert Center in which MCA was performed. Each row and column means a patient and categorical variable respectively. In the heat map, the blue, white and red colors reflect the modalities of categorical variables (Yes, No and Missing Data respectively).

Abbreviations: COMT-I: Cathechol-O-methyl-transferase inhibitor; DBS: Deep Brain Stimulation; L-DA: L-DOPA; MAO-I: Monoamine oxidase inhibitor, MD: Missing Data, N: No, Y: Yes.

SUPPLEMENTARY DATA:

Online-only figures:

Supplementary Figure 1: Distribution of ages at examination

Distribution of ages at examination of patients with Parkinson's disease in the Expert Center where MCA was performed.

Histogram showing the distribution of the ages at examination of the 2553 patients with Parkinson's disease, fitted with the Gaussian distribution curve. Note the bell-shaped appearance of the histogram with a slight skew (-0.463 ± 0.048) and Kurtosis (0.123 ± 0.097). Number and percentage are figured on top of each bar of the bar chart.

Supplementary Figure 2: The dendrogram represents the results from the hierarchical clustering analysis performed with the four components obtained from the multiple correspondence analyses. The homogeneity criterion of a cluster is defined as the sum of correlation ratios. The modalities of categorical variables are specified as a suffix for Yes “_Y”, No “_N” and Missing Data “_MD”.

Abbreviations: COMT-I: Catechol-O-methyl-transferase inhibitor; DBS: Deep Brain Stimulation; L-DA: L-DOPA; MAO-I: Monoamine oxidase inhibitor.

Supplementary Figure 3: Multiple correspondence analysis map showing the positions and the association between the 35 variables for patients with Parkinson's disease of the Expert Center in which MCA was performed (N=2553).

The horizontal and vertical axes represent the first and second principal dimensions, respectively. The first two axes accounted for 24.3% and 6.5% of inertia. Contribution from the third dimension was 4.4%. Motor fluctuations, dyskinesia, falls or postural instability, freezing of gait, camptocormia, dysarthria and swallowing difficulties are the most important variables contributing to the variance accounted for by axis 1. Falls or postural instability, dysarthria,

freezing of gait, hallucinations, dementia, motor fluctuations and disease duration are the most important variables contributing to the variance accounted for by axis 2 (See Supplementary Table 3). The modalities of categorical variables are specified as a suffix for Yes “_Y” colored in blue and No “_N” colored in black.

Abbreviations: COMT-I: Catechol-O-methyl-transferase inhibitor; DBS: Deep Brain Stimulation; L-DA: L-DOPA; MAO-I: Monoamine oxidase inhibitor, OSAS: obstructive sleep apnea syndrome, RBD: REM-sleep behavioral disorder, RLS: restless leg syndrome.

Supplementary Figure 4: Multiple correspondence analysis map showing the positions and the association between the 14 variables for patients with Parkinson’s disease of the Expert Center in which MCA was performed (N=2553) with all modalities (Yes, No and Missing Data) represented.

The modalities of categorical variables are specified as a suffix for Yes “_Y” colored in blue and No “_N” colored in black, Missing Data “MD”.

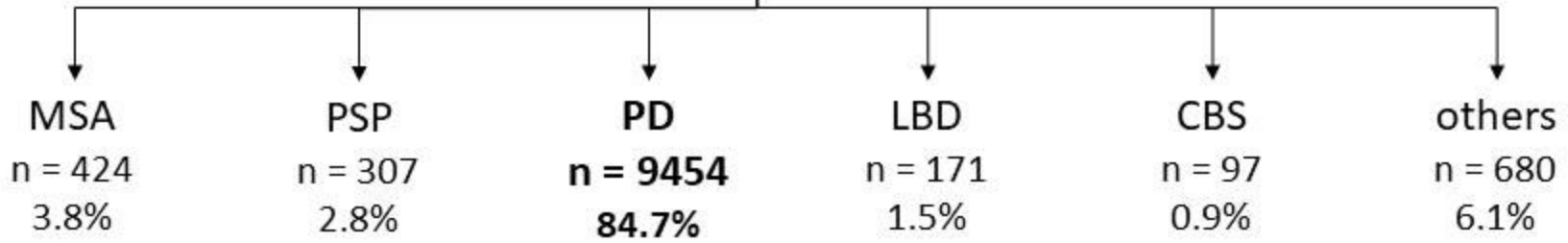
Abbreviations: COMT-I: Catechol-O-methyl-transferase inhibitor; DBS: Deep Brain Stimulation; L-DA: L-DOPA; MAO-I: Monoamine oxidase inhibitor.

Online-only text: Listing of the coinvestigators from the NS-Park study group.

Online-only tables

Supplementary Table 1, Supplementary Table 2, Supplementary Table 3

Parkinsonian syndromes
n = 11 157



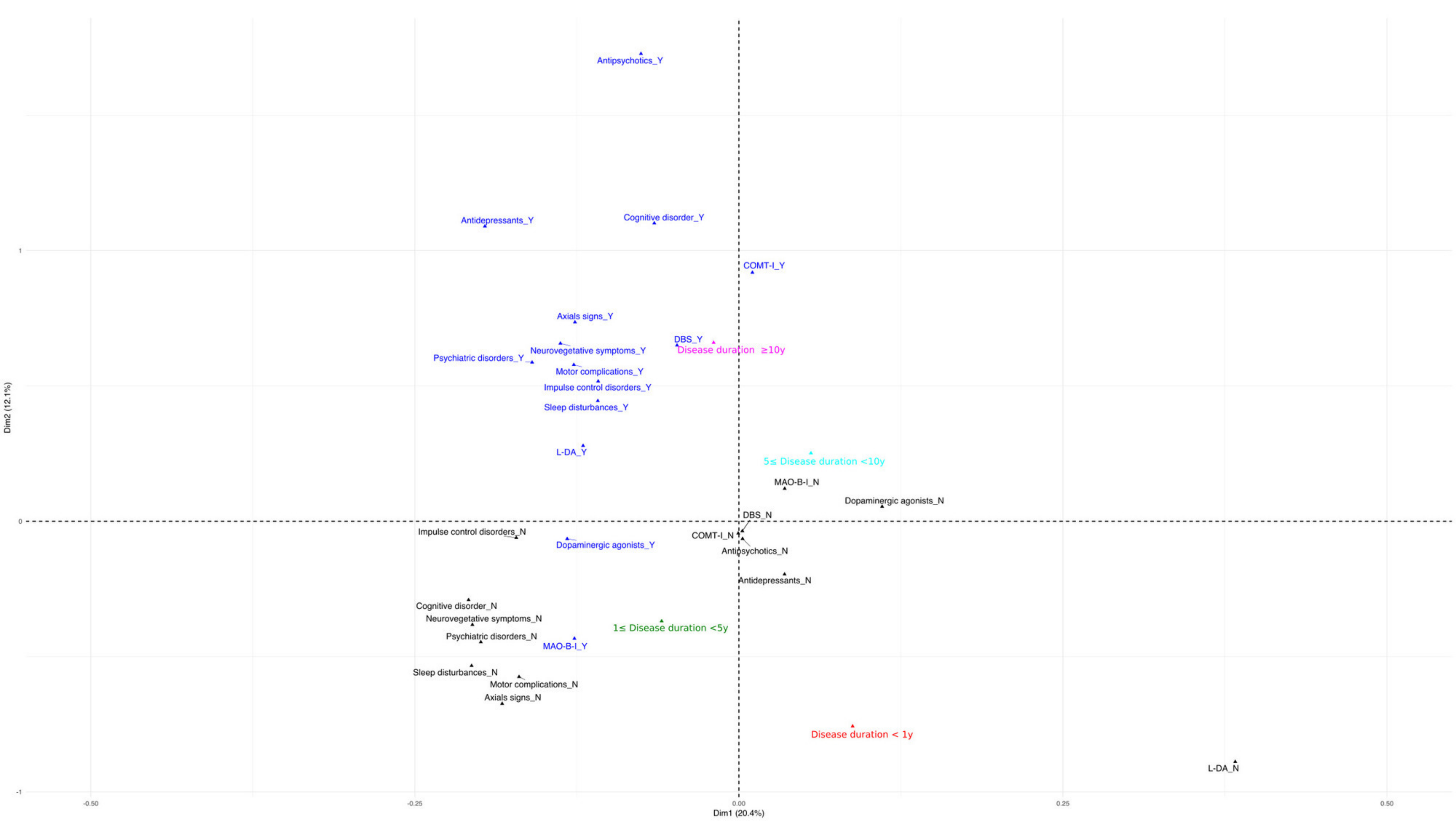


TABLE : Table 1: Description of patients with Parkinson's Disease**Table 1a:** Parkinson's disease patients demographics, complications and medications

	N	9,454	Missing data
Age at examination (years)		67.9 ± 10.4 [25-99] (100)	0
Age at onset (years)		58.5 ± 11.4 [25-94] (95)	474 (5)
Disease duration (years)		9.2 ± 6.9 [0-39] (95)	474 (5)
Males / Females		5,489 (58) / 3,964 (42)	0
Sex ratio (M:F)		1.4:1	
Clinical manifestations and complications		Yes	No
			Missing data
Motor complications		4,620/9,119 (51)	4,499/9,119 (49)
Motor fluctuations		4,179/8,710 (48)	4,531/8,710 (52)
Dyskinesia		3,039/9,060 (34)	6,021/9,060 (66)
Axial signs		3,690/8,806 (42)	5,116/8,806 (58)
Falls or postural instability		2,338/8,722 (27)	6,384/8,722 (73)
Freezing of gait		1,974/8,717 (23)	6,743/8,717 (77)
Camptocormia		750/8,769 (9)	8,019/8,769 (91)
Speech disturbances, Dysarthria		1,823/8,792 (21)	6,969/8,792 (79)
Swallowing difficulties		768/8,712 (9)	7,944/8,712 (91)
Neurovegetative symptoms		3,008/8,940 (34)	5,932/8,940 (66)
Diarrhea and/or constipation		1,175/8,758 (13)	7,583/8,758 (87)
Sphincter or erectile dysfunction		1,602/8,947 (18)	7,345/8,947 (82)
Postural hypotension		817/8,620 (9)	7,803/8,620 (91)
Sleep disturbances		4,307/9,010 (48)	4,703/9,010 (52)
Excessive daytime sleepiness		1,705/8,645 (20)	6,940/8,645 (80)
Insomnia		2,046/8,639 (24)	6,593/8,639 (76)
REM-sleep behavioral disorder		1,343/8,272 (16)	6,929/8,272 (84)
Restless leg syndrome		348/8,558 (4)	8,210/8,558 (96)
Periodic movements		55/7,476 (1)	7,421/7,476 (99)
Obstructive sleep apnea syndrome		294/8,504 (3)	8,210/8,504 (97)
Cognitive disorder		1,584/8,860 (18)	7,276/8,860 (82)
			594/9,454 (6)

Apathy	886/8,651 (10)	7,765/8,651 (90)	803/9,454 (8)
Dementia	854/8,507 (10)	7,653/8,507 (90)	947/9,454 (10)
Hallucinations	1,045/8,473 (12)	7,428/8,473 (88)	981/9,454 (10)
Psychiatric disorders	2,967/8,515 (35)	5,548/8,515 (65)	939/9,454 (10)
Depression	1,740/8,568 (20)	6,828/8,568 (80)	886/9,454 (9)
Anxiety	2,080/8,697 (24)	6,617/8,697 (76)	757/9,454 (8)
Psychosis	160/8,683 (2)	8,523/8,683 (98)	771/9,454 (8)
Impulse control disorders	734/8,963 (8)	8,229/8,963 (92)	491/9,454 (5)
Pathological gambling	151/8,819 (2)	8,668/8,819 (98)	635/9,454 (7)
Pathological shopping	119/8,820 (1)	8,701/8,820 (99)	634/9,454 (7)
Hypersexuality	184/8,819 (2)	8,635/8,819 (98)	635/9,454 (7)
Binge eating	271/8,819 (3)	8,548/8,819 (97)	635/9,454 (7)
Addiction to L-dopa	38/8,996 (0.4)	8,958/8,996 (99.6)	458/9,454 (5)
Punding	59/8,809 (1)	8,750/8,809 (99)	645/9,454 (7)
Treatments (medication, DBS)			
Antiparkinsonian medication			
L-dopa alone	2,686/9,266 (29)	6,580/9,266 (71)	188/9,454 (2)
Dopamine agonists alone	610/9,353 (7)	8,743/9,353 (93)	101/9,454 (1)
L-dopa + Dopamine agonists	4,698/9,101 (52)	4,403/9,101 (48)	353/9,454 (4)
MAO inhibitor	2,426/9,287 (26)	6,861/9,287 (74)	167/9,454 (2)
COMT inhibitor	1,409/9,399 (15)	7,990/9,399 (85)	55/9,454 (1)
Anticholinergic	216/9,450 (2)	9,234/9,450 (98)	4/9,454 (0.04)
Psychiatric medication			
Antidepressants	1,422/9,396 (15)	7,974/9,396 (85)	58/9,454 (0.6)
Antipsychotics	354/9,436 (4)	9,082/9,436 (96)	18/9,454 (0.2)
Anxiolytics	948/9,413 (10)	8,465/9,413 (90)	41/9,454 (0.4)
Deep Brain Stimulation			
Subthalamic nucleus	850/9,378 (9)	8,528/9,378 (91)	76/9,454 (1)
Vim of the thalamus	788/9,387 (8)	8,599/9,387 (92)	67/9,454 (1)
Vim of the thalamus	20/9,452 (0.2)	9,432/9,452 (99.8)	2/9,454 (0.02)
Internal Globus pallidus (GPi)	29/9,447 (0.3)	9,418/9,447 (99.7)	7/9,454 (0.1)

Categorical variables are expressed as the ratio of the number of patients presenting the symptom to the total number of patients assessed and as percentages [n/N (%)] and continuous variables as mean \pm SD [range] (percentage of patients assessed). Different symptoms can be present in the same patient.

Abbreviations: COMT: Catechol-O-methyl-transferase; DBS: Deep brain stimulation; MAO: Monoamine oxidase; REM-sleep: Rapid Eye Movement sleep; SD: Standard Deviation; Vim: Ventral intermediate medial nucleus

Table 1b: Parkinson's disease patients from the Parkinson Expert Center (PEC) in which Multiple Correspondence Analyses was performed and all PECs

	Paris PEC		All PECs	
Parkinson's Disease patients	n = 2,553 (100)		n = 9,454 (100)	
Age at examination (years)	66.2 ± 10.5 [25-94] (n=2,542)		67.9 ± 10.4 [25-99] (n=9,454)	
Age at onset (years)	59.2 ± 11.1 [25-89] (n=2,542)		58.5 ± 11.4 [25-94] (n=8,980)	
Disease duration (years)	7.0 ± 6.4 [0-36] (n=2,542)		9.2 ± 6.9 [0-39] (n=8,980)	
Males / Females	1,450 (56.8) / 1,103 (43.2)		5,489 (58) / 3,964 (42)	
Sex ratio (M:F)	1.3:1		1.4:1	
Clinical study specific populations	Yes	Missing data	Yes	Missing data
Not opposed to future participation in clinical studies	1818 (71)	0	6,589 (77)	863 (9)
De novo (no treatment)	309 (12)	0	703 (9)	1,876 (20)
Disease duration ≤ 1 y.	536 (21)	11 (0.5)	839 (9)	474 (5)
Disease duration ≤ 5 y.	1248 (49)	11 (0.5)	3,156 (35)	474 (5)
Age at onset ≤ 40 y. old	165 (6.5)	11 (0.5)	559 (6.2)	474 (5)
Age at onset ≤ 50 y. old	592 (23)	11 (0.5)	2,177 (24.2)	474 (5)
Age at onset between 50 and 75	1,771 (69)	11 (0.5)	6,077 (67.7)	474 (5)
Age at onset ≥ 75 y. old	190 (7)	11 (0.5)	726 (8.1)	474 (5)

Categorical variables are expressed as the number of patients and as percentages [n (%)] and continuous variables as mean ± SD [range] (number of patients assessed).