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Title: Validation of a non-motor fluctuations questionnaire in Parkinson's disease

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For the NS-Park/FCRIN Network

Validation of a non-motor fluctuations questionnaire in Parkinson's disease

Abstract

Introduction

Non-motor fluctuations (NMF) in Parkinson's disease (PD) remain poorly recognized but have a high impact on patients' quality of life. The lack of assessment tools limits our understanding of NMF, compromising appropriate management.

Our objective was to validate a hetero-questionnaire for NMF in PD patients at different stages of the disease: without treatment, without motor fluctuations, with motor fluctuations.

Methods

We included patients in 15 centers in France. Our questionnaire, NMF-Park, resulted from previous studies, allowing us to identify the more pertinent NMF for evaluation. Patients reported the presence (yes or no) of 22 selected NMF, and their link with dopaminergic medications. The assessment was repeated at one and two years to study the progression of NMF. We performed a metrological validation of our questionnaire.

Results

We included 255 patients (42 without treatment, 88 without motor fluctuations and 125 with motor fluctuations). After metrological validation, three dimensions of NMF were found: dysautonomic; cognitive; psychiatric. The sensory/pain dimension described in the literature was not statistically confirmed by our study.

Discussion

Our questionnaire was validated according to clinimetric standards, for different stages of PD. It was clinically coherent with three homogeneous dimensions. It highlighted a link between fatigue, visual accommodation disorder, and cognitive fluctuations; and the integration of sensory/pain fluctuations as part of dysautonomic fluctuations. It focused exclusively on NMF, which is interesting considering the described differences between non-motor and motor fluctuations.

Conclusion

Our study validated a hetero-questionnaire of diagnosis for NMF for different stages of PD.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, with an annual incidence of 14 per 100,000 people in the total population, and 160 per 100,000 people aged 65 years or older (1). One of the difficulties in the management of PD consists in its motor complications, occurring often after some years of progression. Motor complications include efficacy fluctuation or involuntary abnormal movement. Non-motor fluctuant symptoms also exist, and can occur concomitantly or independently with motor fluctuations (MF) (2). These non-motor fluctuations (NMF) have been described for more than 20 years but are, however, less well recognized (3). They include psychiatric, cognitive, dysautonomic and pain/sensory fluctuations (3). Psychiatric fluctuations include for instance anxiety, sadness, or hyperactivity. Cognitive fluctuations are mostly slowness of thinking. Dysautonomia can concern drenching sweats, tachycardia, urinary or digestive disorders. Sensory and pain fluctuations are also frequent, they include sensations of constriction, burn or akathisia (4). According to a precedent study based on a structured questionnaire, all investigated patients with PD and MF presented at least one NMF, and up to 28% of patients were more disabled by NMF than by MF (4). Their severity and frequency is bound to the progression of PD, as their number increases with disease duration (5).

Clinicians have no basic guidelines for the management of NMF. This partly results from the fact that these fluctuations often go unrecognized, as well as from the lack of controlled clinical trials dedicated to NMF. Indeed, NMF are generally improved by dopaminergic treatments or deep brain stimulation (DBS) of the subthalamic nuclei (STN) (6). However recent studies have showed that any improvement is highly dependent on the type of NMF (7). The natural history of NMF is not clearly defined. Thereby, as has been observed for depression, anxiety, fatigue and pain (8), other fluctuating symptoms may potentially precede or appear with characteristic motor symptoms of PD. Different scales have been developed to study non-motor symptoms (NMS) and the wearing-off phenomenon (symptom fluctuations linked to the effective period of treatment) (9–11). Our study was designed to investigate not only wearing-off, but a broader spectrum of NMF related and unrelated to motor state and treatments.

The objective of this study was thus to develop and validate, in accordance with psychometric standards, a hetero-questionnaire to be used as a diagnostic tool for these frequent and little recognized NMF.

Materials and Methods

General context

The questionnaire was developed using a three-step process proposed by Juniper (12): item generation; item reduction; validation. Each step was guided by a steering committee composed of 10 neurologists, two epidemiologists, and a biostatistician.

Questionnaire development

▪ 1/Item generation

Starting from a review of the literature (3,13–15), we tested an initial questionnaire of 54 items (each item corresponding to one specific fluctuation) on 90 patients across two studies (6,16). After analysis of the results, we created an intermediary questionnaire based on 29 statistically and clinically relevant yes-or-no items that corresponded to the presence or not of the NMF at certain moments of the day during the three months preceding the evaluation.

▪ 2/ Item reduction

The 29-item questionnaire was proposed to 69 patients. The steering committee examined the statistical analysis of these patients' response distribution for each item and removed seven items due to low response rate (<20%), low index discrimination (<0.70), or high inter-item correlation (>0.80). Items which were ambiguous or misunderstood were rewritten. The steering committee retained a 22-item final version called NMF-Park questionnaire.

Initially, our questionnaire investigated the link between NMF, motor states and treatment intake. However, with increasing evidence of disconnections between these elements of PD, the final version did not require a link with treatment intake, or a connection with motor symptoms to define an NMF. In the final questionnaire, for an item to be accepted as an NMF, the investigators insisted on the fluctuating nature of the item during the day.

Validation

The validation process was carried out in 15 French hospitals within departments of neurology participating in the NS-Park/FCRIN Network. Patients were included during outpatient visits or hospital stays. The NMF-Park questionnaire was administered to patients, and the following data were recorded: sociodemographic data (gender, age, education level, employment status), disease duration, motor handicap (UPDRS III), complications of therapy (UPDRS IV), dopaminergic treatment status (yes/no), progression of PD (Hoehn & Yahr staging), evaluation of depression (Beck Depression Inventory) (17) and quality of life (French version of Parkinson's Disease Questionnaire) (18). Each patient was assigned a status at the inclusion: de novo – if the patient never had an antiparkinsonian drug; not fluctuant – if the patient had had the disease from 1 to 5 years, had received antiparkinsonian drugs, and was not considered motor fluctuant (UPDRS IV); motor fluctuant – if the patient had had the disease from 5 to 10 years and was considered motor fluctuant (UPDRS IV).

These assessments were made at inclusion and at one year for all the patients included. For the de novo and not fluctuant patients, another assessment was made at two years.

For 30% of the cohort, chosen randomly, the questionnaire was administered by phone 15 days after inclusion to test its reproducibility.

Population

Selection criteria were as followed: subjects over 30 years old with PD according to the UKPDSBB criteria, fluent in French and able to complete the questionnaires. Patients who underwent STN DBS were not included in this study as the evaluation of the effect of this treatment on NMF was beyond the scope of this study.

The sample size for validating a measurement instrument is around 200-300 individuals. We based our sample size calculation on the expected precision for the Cronbach alpha coefficients. A total of 230 individuals were needed to have minimal coefficients at 70% for a 10% degree of precision.

Taking into account a 10% exclusion rate (incomplete questionnaires), we choose to include a total of 260 individuals.

Ethics

Our study was performed with the approval of the French ethics committee (*Comité de Protection des Personnes Sud*). All subjects participated voluntarily. Consent for participation in the study was obtained from all participants.

Scoring

To facilitate the analysis and standardize the results, a score was obtained for each dimension of our questionnaire by computing the mean item of each dimension. All dimension scores were thus linearly transformed to a 0–100 score. A global score for the NMF-Park was computed as the mean of the dimension scores. Higher scores indicate higher levels of NMF.

Statistical analysis

Descriptive statistics of the sample included frequencies and percentages for categorical variables, means and standard deviations for continuous variables. Only the validation of the NMF-Park questionnaire is presented, including construct validity, reliability, and some aspects of external validity. The construct validity was assessed using principal components factor analyses, carried out using varimax rotation, based on tetrachoric matrix correlation. The method was performed to determine the final structure and the number of independent dimensions of NMF. Eigenvalues greater than or equal to 1 were retained. Items were included in the dimensions if they revealed loadings greater than 0.4. In the case of multiple loading of an item on several factors, it was included in the factor that had the more conceptual relationship.

Item internal consistency was assessed by correlating each item with its scale (corrected for overlap) using Pearson's coefficient (correlation of 0.4 recommended for supporting item internal

consistency); item discriminant validity was assessed by determining the extent to which items correlated more highly with the dimensions they were hypothesized to represent than with the other ones. For each dimension scale, internal consistency reliability was assessed with the Kuder-Richardson's coefficient (coefficient of at least 0.7 expected for each scale). The uni-dimensionality of each dimension was assessed using Rasch analysis. The goodness-of-fit statistics (INFIT, ranging between 0.7 and 1.3) ensured that all items of the scale measured the same concept. Floor and ceiling effects were reported assessing the homogeneous spread of the response distribution. Inter-dimension correlations were examined using Pearson's and polychoric coefficients. The discriminant validity was determined by comparing dimension mean scores across patient groups (gender, education level, employment status, disease categories, L-dopa status), and by performing correlations between dimension mean scores and continuous variables (disease duration, UPDRS III, UPDRS IV, Hoehn & Yahr stage, Beck score, PDQ 39).

Reproducibility and responsiveness

Reproducibility was assessed using the intraclass correlation coefficient (ICC) to compare scores obtained at inclusion and two weeks later for 30% of the study population. ICC was defined as good between 0.60 and 0.74 and as excellent between 0.75 and 1.00.

To study responsiveness, a comparison was needed between the time courses of the questionnaire score and a marker of disease progression. Since there is no validated marker for the progression of NMF in PD, we chose to test the responsiveness of our score to the progression of levodopa equivalent daily dose (LEDD). This choice was supported by the fact that LEDD may be modified because of motor or non-motor symptoms, and that increased LEDD is associated with an increased number of NMF (19). De novo and not fluctuant patients were then defined as worsened or non-worsened based on progression in LEDD from baseline to month 24. The worsened patient group was characterized by an increase in LEDD over the 24 months; all other patients were defined as non-worsened.

Responsiveness was assessed by comparing the questionnaire score at baseline, month 12 and month 24 in worsened and non-worsened patients with a non-parametric Mann-Whitney U-test. Data analysis was performed using SPSS 20.0, M-PLUS, and R-packages (ltm, psych, and TAM).

Results

Sample characteristics

The participating centers included 255 patients with PD. Their main characteristics are displayed in Table 1.

Validity

1/Internal structural validity

The structure of the questionnaire was established by principal component factor analysis, identifying a 3-factor structure that accounted for 42% of the total variance. This model showed a good fit, and all the indices from the confirmatory LISREL model were satisfactory (RMSEA=0.036 [0.021-0.048], CFI=0.95). Two items were removed at this step (euphoria and excessive salivation) because they did not fit the model obtained with the principal component analysis and were less frequently reported. The dimensions were named according to their constitutive items as the following: dysautonomia (DYS, 12 items), cognition (COG, 5 items), psychiatric (PSY, 3 items).

The 20-item final structure is presented in Appendix 1 and 2 (French formulation, English item general meaning, factor, dimension). Item and dimension scales characteristics are summarized in Table 2. The floor effect ranged from 5.7 to 26.4% and the ceiling effect from 0.4 to 22.4%. Alpha coefficients were 72, 66, and 59% for DYS, COG, and PSY respectively. The correlation of each item with its contributive dimension was higher than with the others (item discriminant validity) for DYS, but not for COG and PSY dimensions. The inter-dimension correlations were all significant (all p-values <0.01); they ranged from 0.29 to 0.79 (data not provided).

2/External validity

The correlation between our index and the characteristics of our patients are reported in Table 3. Women reported significantly higher levels of NMF in the global score and two dimensions. Age and educational level were not related to NMF. Patients with an occupational activity reported less often NMF (global score and dysautonomia dimension). Patients with MF and taking L-dopa most often reported higher NMF in the three dimensions and the global score. Higher NMF scores were associated with higher levels of depression and worsened quality of life. NMF were correlated with disease duration, but not with the UPDRS III score.

Reproducibility and responsiveness

At 15 days post-inclusion, 30% of the study population were tested to validate the questionnaire reproducibility. This sample was representative of the study population regarding PD staging: 15.1% de novo patients; 40.7% not fluctuant patients; 44.2% motor fluctuant patients. Reproducibility was good for COG and PSY dimensions (ICC = 0.73 and 0.64 respectively) and excellent for the DYS dimension and for the global questionnaire (ICC = 0.76 and 0.77 respectively).

The questionnaire tended to show responsiveness to disease progression (quantified by LEDD): the score was higher at months 12 and 24 for patients in the worsened group compared with patients in

the non-worsened group ($p=0.085$ and $p=0.271$ respectively). These groups did not show differences for scores at baseline ($p=0.569$).

Discussion:

NMF are frequent and disabling complications of PD. They are increasingly recognized as an important factor of impaired quality of life among patients. But the understanding of their natural history remains limited.

Elaboration:

After an exhaustive literature review, we achieved a first questionnaire which allowed us to study NMF among 90 parkinsonian patients (6,16). With the analysis of these results, we were able to refine our scale and select the most pertinent items. The questionnaire presented in this work is the outcome of many years of study of NMF. We evaluated the correlation to motor state and the improvement with antiparkinsonian drugs for each item, but these factors were not required to define an NMF in our questionnaire. This made sense since some NMF are known not to be synchronized with motor state and not to respond to antiparkinsonian drugs. This also made it possible to identify NMF in de novo patients who were not taking any treatment for their disease. Moreover, from a therapeutic point of view, NMF related to MF has to be differentiated from NMF unrelated to MF. NMF related to MF implies adaptation of dopaminergic treatment and may lead to continuous dopaminergic stimulation treatment (20), whereas NMF unrelated to MF will require more specific symptomatic treatment (7). Thus, for our questionnaire, we insisted on the fluctuant nature of each item during the day.

Dimensions

The validation of our scale highlighted that NMF exhibit three separate dimensions, which can be described as dysautonomic, cognitive, and psychiatric. This arose from the principal component analysis and was not decided a priori. We thus noted that fluctuations previously considered to be sensorial (pain, tingling, akathisia) did not form a distinct dimension, but were correlated to dysautonomic fluctuations. This was not the separation we had expected to obtain because since the first descriptions, NMF have usually been classified into cognitive/psychiatric, dysautonomic and sensory categories (3). But this commonly used classification of NMF results from empirical similarities existing between symptoms of a same category.

Our study brought a statistical validation to a separation of NMF by dimensions, which is supported by clinical findings. These dimensions indeed do not always exhibit the same course in relation to

motor progression and may have different treatment responses. For instance, dysautonomic symptoms do not fluctuate with motor state, contrary to other NMF (7). Cognitive and psychiatric symptoms are more often present and severe in motor OFF condition than in motor ON (7). Although STN DBS improves behavioral aspects of PD (21), concomitant evaluation of the dimensions of NMF shows that cognitive, dysautonomic and sensorial fluctuations are more improved by this treatment than psychiatric fluctuations (6).

Our work also brought new elements of reflection for some difficult-to-classify NMF. Pain in PD is classically assigned to a sensory/pain dimension (3,13), however it remains a heterogeneous and multifactorial symptom. In our study, pain was related to dysautonomic fluctuations. Similar correlations have been described by other works. Pain and dysautonomic symptoms both tend to fluctuate little during the day, regardless of motor state (7,11), and PD patients with primary central pain can show worse autonomic evaluations than patients without pain (22). Fatigue is as well very common in PD (7); it was correlated with cognitive fluctuations in our study. Such an association has been described by other authors (23). Fatigue also distinguishes itself from psychiatric fluctuations by being more frequently improved by DBS (6). Another interesting finding is the inclusion of visual accommodation disorders in the cognitive category. Although this type of NMF is difficult to relate empirically to one of our dimensions, relationships between visual and cognitive impairments in PD have been described in the past (24,25).

Differences between motor and non-motor aspects

In addition to the distinction of dimensions, we studied correlations between NMF and disease progression markers. NMF were related to disease duration, but not to UPDRS III. Other studies indeed found moderate correlation or no correlation between UPDRS and NMS frequency, severity and their fluctuations (7,11,26). Thus, even if UPDRS III is a good marker of disease progression, it only reflects the motor aspects of PD. Hoehn & Yahr stages also give no information on non-motor aspects of PD, and it often takes more than two years to see a stage transition (27). LEDD may conversely be increased in response to motor and non-motor progression of PD and can be an assessment criterion for both aspects. Our questionnaire was indeed not sensitive to progression in Hoehn & Yahr staging, but it was to LEDD progression.

Aside from the distinction of motor progression and NMF, the link between MF and NMF is also questioned. MF and NMF share common risk factors (28), and some NMF can be improved with dopaminergic treatments (29). But recent studies however showed that NMF can occur independently of MF (19) and a large proportion are not correlated with MF in terms of severity (7)

and timing (26,30). Thus, NMF cannot be considered as a homogeneous group of symptoms which vary according to motor state or dopaminergic treatments.

Existing questionnaires

Another non-motor fluctuations questionnaire (NoMoFA) was recently proposed by Kleiner et al. (31). NoMoFA is a 27-item US-Canadian questionnaire based on the patient's point of view. The questionnaire differs from ours in its content. It was developed with a very small sample of patients (n=11) compared to our approach (n=90). Its initial version contained 33 items reported by patients (32) while we based our initial questionnaire on 54 items from an exhaustive review of the literature on NMF. The structures also differ since NoMoFA only provides a global score while ours provides dimension scores. Responsiveness assessment is lacking for the NoMoFA questionnaire, while this property is essential in the global process of validating a measurement instrument.

Other questionnaires have previously been developed to study non-motor aspects of PD. The WOQ19 and WOQ9 (9,10) were recommended for screening wearing-off in PD (33). However, these questionnaires focus on detecting wearing-off rather than fluctuations in their totality, and do not include the diversity of NMF. Another study used the NMS Scale, a validated tool for screening NMS, to observe the fluctuation of these symptoms depending on the motor state (11). This scale was developed and validated for NMS and not NMF, with an empirical separation in categories. Ossig and colleagues developed a diary to evaluate the kinetics of some NMS (26,30) and their correlation to motor state. But there is a risk of poor adherence from patients since the diary requires an hour-by-hour rating of NMS.

Limitations and advantages

Several limitations can be retained concerning our study. There is a risk the presence of NMF might be overrated if they are suggested by a hetero-questionnaire. Unlike the preliminary studies, NMF severity was not included in the final measure. This was decided to simplify our scale and facilitate its use among patients. NMF severity and response to treatment are hard to measure precisely retrospectively. Another tool is currently being developed to address this difficult issue by evaluating the severity of selected NMF at the moment of the evaluation, in different treatment conditions. The fact that variations related to the patient's dopaminergic treatment or motor state were not included in the definition of NMF could be a limitation, the risk being to consider as fluctuation any non-motor symptom felt by the patients. If these conditions are not integrated, there is no precise definition of the moment from which NMS can be differentiated from NMF. For a symptom to be accepted as an NMF, we insisted on the fluctuant nature of symptoms during the day. Furthermore, although some non-motor aspects fluctuate more than others, a previous study found that all the

non-motor aspects studied can be described as static by some patients and as fluctuating by others (59). This imposes caution regarding the dichotomy between NMS and NMF. A better understanding of the mechanisms responsible for the fluctuations of NMS might be helpful in advancing progress in our understanding of the pathophysiological causes of these phenomena, and to better adapt propositions for their management.

Since the questionnaire was usually administered during a consultation, patients could be in the ON or OFF state during the assessments. It would be interesting to verify to what extent the patient's motor state when the questionnaire is being administered could affect the patient's answers. Interoception is indeed altered during PD (34) and may be impacted by dopaminergic treatments (35). However, we can assume that this type of variation in interoception would influence more an evaluation of severity than an evaluation of the presence or absence of NMF.

The choice to use LEDD as marker of PD progression to test the responsiveness of our questionnaire could possibly lead to biases due to dose-dependent modifications of the NMF pattern. The wide variation in NMF profile from one patient to another, and with disease progression, makes it difficult to ascertain how much the distribution of NMF might have been altered by the increase in LEDD. It is however known that increased LEDD is linked to increase in the overall number of NMF (19), justifying our choice to use this criterion.

The questionnaire was developed and validated in French. Its translation and use in other languages and among other populations may require further validation.

Our questionnaire has been validated in a multicentric study, on a substantial number of patients (n=255) according to standard metric criteria. We were able to assess the tool's reproducibility and sensitivity to change, which are two core psychometric properties of a measuring instrument. The results presented here demonstrate that our questionnaire is functional, encompassing the diverse range of NMF, and well-adapted to the outpatient setting. It is the only questionnaire that has been validated for screening NMF by including patients at three different stages of PD (de novo, not fluctuant, motor fluctuant). Future work will focus on studying changes in NMF during these stages of PD in order to improve our overall understanding of their natural history.

Conclusion

Our study validated a questionnaire for NMF at different stages of PD. This process highlighted a new categorization of NMF with three statistically robust dimensions (dysautonomic, psychiatric and cognitive). This questionnaire will be helpful in recognizing NMF and could play an important role in

the management of PD patients. A better understanding of NMF will enable more specific characterization of patients through their non-motor profiles.

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Table 1. Main Characteristics of the cohort (N=255)

Demographic characteristics	Number (%)
Age class (years)	
.... Less than 50	14 (5.6)
.... 51 – 69	170 (68.0)
.... More than 70	66 (26.4)
Gender (men)	154 (60.4)
Category	Number (%)
....De novo	42 (16.4)
....Motor fluctuations	125 (49)
....Not fluctuant	88 (34.5)
Disease duration (years)	8 (5)
Scores	Median (IQR)
Hoehn & Yahr (OFF)	2 (1)
UPDRS III	12 (13)
UPDRS IV	1 (4)
PDQ-39	24.7 (21.2)
BDI	9 (9)
Treatments (type)	Number (%)
.... None	42 (16.8)
.... Monotherapy L-Dopa	41 (16.4)
.... Monotherapy dopaminergic agonists	34 (13.6)
.... Bitherapy L-Dopa and dopaminergic agonists	133 (53.2)
Treatments (dose)	Median (IQR)
LEDD	650 (500)

SD : standard deviation ; IQR : interquartile range ; UPDRS = Unified PD Rating Scale ; BDI Beck

depression inventory (higher score indicates higher level of depression); PDQ-39 Parkinson's Disease

Questionnaire (higher scores indicate worst level of QoL) ; LEDD (Levodopa equivalent daily dose)

Table 2. Dimension characteristics of NMF-Park

Dimension (number of items)	Mean	SD	IIC min-max	IDV min-max	Floor (%)	Ceiling (%)	Alpha ^a	INFIT min-max
DYS (12)	35.09	23.23	0.21-0.43	0.00-0.37	5.7	0.4	0.72	0.94 - 1.11
COG (5)	48.72	29.76	0.25-0.56	0.14-0.59	8.6	9.5	0.66	0.90 - 1.07
PSY (3)	49.05	36.97	0.26-0.49	0.09-0.59	26.4	22.4	0.59	0.93 - 1.10

DYS Dysautonomic ; COG Cognition ; PSY Psychiatric ; SD Standard deviation ; IIC Item-internal consistency ; IDV Item discriminant validity ; ^a Alpha (Kuder-Richardson coefficient) ; ICC Intraclass correlation coefficient

Table 3. Relationships between sociodemographic and clinical data and the dimension/total scores of NMF-Park.

	DYS	COG	PSY	Global
Gender				
Men (n=154)	32.2 ± 22.1	47.5 ± 29.3	44.8 ± 36.5	42.0 ± 22.0
Women (n=101)	39.6 ± 24.4	50.6 ± 30.6	55.8 ± 36.9	48.9 ± 22.1
Anova	<0.05	NS	<0.05	<0.05
Age classes				
≤ 50 years (n=14)	28.6 ± 22.3	55.7 ± 36.1	59.5 ± 37.4	47.9 ± 22.9
51-69 years (n=170)	36.1 ± 23.7	47.0 ± 28.9	46.8 ± 36.9	43.9 ± 22.8
≥ 70 years (n=66)	33.9 ± 22.3	51.6 ± 30.4	52.6 ± 37.0	46.0 ± 20.8
Anova	NS	NS	NS	NS
Education level				
Bachelor degree (n=121)	33.8 ± 22.2	49.8 ± 27.6	49.9 ± 37.1	45.0 ± 22.1
Other (n=125)	36.6 ± 24.3	47.5 ± 31.7	48.9 ± 36.7	44.7 ± 22.6
Anova	NS	NS	NS	NS
Employment				
Yes (n=51)	26.8 ± 20.6	41.6 ± 27.4	46.4 ± 34.7	38.5 ± 19.7
No (n=195)	37.5 ± 23.5	50.5 ± 30.1	50.2 ± 37.4	46.5 ± 22.7
Anova	<0.01	NS	NS	<0.05
Group category				
DN (n=42)	27.7 ± 21.9	34.4 ± 26.5	44.1 ± 36.1	36.8 ± 20.7
NF (n=88)	25.5 ± 18.9	41.2 ± 28.5	38.3 ± 36.8	35.1 ± 21.4
MF (n=125)	44.2 ± 23.0	58.3 ± 28.5	58.2 ± 35.2	53.8 ± 19.6
Anova	<0.001	<0.001	<0.001	<0.001
L-dopa				
Yes (n=174)	39.0 ± 23.6	54.2 ± 29.4	54.0 ± 37.0	49.2 ± 21.3
No (n=74)	25.5 ± 19.6	35.1 ± 26.4	38.1 ± 34.2	33.5 ± 20.7
Anova	<0.001	<0.001	<0.01	<0.001
Disease duration	0.310*	0.144*	0.038	0.201*
UPDR III Total	0.039	0.011	0.105	0.094
Hoehn et Yahr	0.232*	0.189*	0.218*	0.284*
BDI	0.493*	0.475*	0.617*	0.727*
Quality of life (PDQ-39)	0.317*	0.403*	0.600*	0.627*

DYS: Dysautonomic; COG: Cognitive; PSY: Psychiatric (higher score indicates higher level of non-motor fluctuations); BDI: Beck depression inventory (higher score indicates higher level of depression); PDQ-39: Parkinson's Disease Questionnaire (higher scores indicate worst level of QoL); DN: De Novo; MF: Motor Fluctuant; NF: Not Fluctuant; * : Significant results