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Motor Patterns in Parkinson's Disease: A Data-Driven Approach

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Abstract: To identify patterns of motor disturbances in Parkinson's disease (PD) and evaluate their relation with other PD domains. A cohort of 399 PD patients was randomly divided into two samples. Factors within the motor section of the SPES/SCOPA were identified by exploratory factor analysis on data from the first sample and next tested by confirmatory factor analysis in the second sample. Relations with other PD domains were evaluated by regression analyses. A four factor model was found to be valid. This included a tremor, a bradykinetic-rigid, and two axial factors. One axial factor ("rise", "gait", "postural instability") was associated with age and cognition, while the other axial factor ("freezing", "speech", "swallowing") was related to dopaminergic medication and complications of therapy. Both other factors showed no relevant associations with demographic and clinical characteristics. The identification of motor factors and their relation with other domains of the disease may help to elucidate the mechanisms responsible for these associations and provide an objective base for further research on subtypes in PD. © 2009 Movement Disorder Society

Key words: Parkinson's disease; motor impairment; factor analysis; structural equation modeling

INTRODUCTION

In Parkinson's disease (PD) is considerable heterogeneity in the expression of clinical manifestations and progression of the disease, suggesting the existence of subtypes. Several motor subtypes of the disease have been suggested, mostly based on clinical observations: a tremor dominant subtype, associated with mild disease progression[1–3]; an akinetic-rigid subtype, associated with more severe cognitive impairment and depressive symptoms than patients with tremor[4,5]; a subtype in which postural instability and gait dysfunction (PIGD) are most prominent, associated with cognitive impairment and a more progressive disease course.[1,3,6,7]

When studying subtypes through a more data-driven approach, studies have analyzed the motor domain in various ways such as a total score,[8] as a ratio of tremor and nontremor items,[9] and as subscores of tremor, hypokinesia/rigidity, PIGD.[10] An objective determination of groups of variables that group together as manifestations of an underlying construct may provide a stronger basis for classification into subtypes and enhance our understanding of the underlying pathophysiology. Exploratory factor analysis (EFA) is a method that can be used in this respect; it identifies groups of closely related variables ("factors") among a larger set of variables.[11] Several studies applied EFA on the items of the motor section of the Unified PD Rating Scale (UPDRS)[12–15] and the Short Parkinson's Evaluation Scale (SPES).[12] These studies yielded inconsistent results, likely because of differences in scale content and size and composition of samples. Confirmatory factor analysis (CFA) is a method to test hypotheses on constructs that underlie a set of variables and is more powerful than EFA. Only one study performed CFA on the motor items of the UPDRS, which resulted in five main factors (rigidity; tremor; bradykinesia; axial impairment; speech/hypomimia), as well as two separate factors reflecting laterality.[16]

As the first step in a data-driven determination of subtypes, this study aimed to identify patterns of motor impairments in PD by both exploratory and confirmatory factor analysis. Secondly, the relation between

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motor factors and nonmotor impairments of PD were evaluated.

METHODS

The study is part of the "PROfiling PARKinson's disease" (PROPARK) study, a longitudinal cohort study of patients with PD, who are profiled on phenotype, genotype, disability, and global outcomes of health using valid and reliable assessment instruments for PD (www.scopa-propark.eu). Findings obtained from the first annual evaluation of 417 patients, assessed between May 2003 and March 2006, were used for analysis. The study was approved by the medical ethical committee of the Leiden University Medical Center and all patients gave informed consent.

All patients fulfilled the United Kingdom PD Society Brain Bank criteria for idiopathic PD, with the exception that positive family history was not regarded as an exclusion criterion.[17] Patients who underwent stereotactic surgery were excluded from analysis. The recruitment procedure has been described elsewhere.[18]

To assess the motor impairments of patients, the motor section of the SPES/SCOPA rating scale was used.[19] This scale has a good balance between items reflecting motor features of early and late stage disease, and has good metric properties.[19] The SPES/SCOPA-motor consists of 10 items with response options ranging from 0 to 3, where higher scores reflect poorer motor function. For the current study, data obtained for cognition (SCOPA-COG),[20] autonomic symptoms (SCOPA-AUT),[21] depressive symptoms (Beck Depression Inventory (BDI)),[22] psychotic symptoms (SCOPA-Psychiatric Complications (SCOPA-PC), items 1–5),[23] nighttime sleep problems and excessive daytime sleepiness (SCOPA-SLEEP),[24] and motor complications (SPES/SCOPA-Motor Complications)[19] were used for post-hoc analyses. In all scales higher scores also reflect more severe symptoms, except for the SCOPA-COG. For reasons of comparability, these scores were inversed. Instruments were either self-completed (SCOPA-AUT, BDI, SCOPA-SLEEP) or administered by trained research associates (SCOPA-COG, SCOPA-PC, SPES/SCOPA motor and motor complications). All patients who used antiparkinsonian medication were assessed while they benefited from their medication. When exhaustion or off-periods were detected, patients were allowed to take a break or medication. For each patient, a levodopa dose equivalent (LDE) was calculated.[25]

Statistical Analyses

In the SPES/SCOPA, the items rest tremor, postural tremor, bradykinesia and rigidity are separately evaluated for the left and right arm. For the present analyses, scores of both sides were added up, resulting in one score for each symptom.

Exploratory and Confirmatory Factor Analysis

The total group was randomly divided into two samples, which was expected to yield two approximately equally large groups. Next, an EFA with oblique rotation was performed on the first sample, using all 10 items of the SPES/SCOPA-motor. The oblique rotation method was used, because factors emerging from the motor domain were expected to be correlated.[26] The number of factors was determined by inspection of the scree plot and Kaiser's criterion (i.e. eigenvalue$>$1). Data of the second sample were used for cross-validation. In structural equation modeling (SEM), relations between measured and proposed latent variables (factors) can be evaluated. CFA is a special case of SEM and tests how well data fit an a priori hypothesized model of variables that group together in factors.[27] Based on the result of the EFA, a model was constructed. The chi-square test for goodness-of-fit was calculated. This test should be nonsignificant ($P > 0.05$, indicating that the model does not significantly differ from the data), although it should be noted that the test is sensitive to sample size and to small to moderate discrepancies of the data to normality.[26,28] Therefore measures estimating the lack of fit (the root means square error of approximation (RMSEA) and the standardized root mean square residual (SRMR)) were also calculated, supplemented with a measure to test the model's goodness of fit (comparative fit index (CFI)).[29] RMSEA values >0.1 indicate a poor fit, <0.08 reasonable fit, and <0.05 good fit. The SRMR reflects a good fit if the value is <0.08. A CFI close to 0.95 is indicative of a good fit.[28,29]

Regression Analysis

Pearson correlations (r; two-tailed) were calculated to assess the correlation between each of the resulting motor factors and the other impairment domains of PD, and demographic and disease related variables. Correlation coefficients were defined as very weak (r = 0.00–0.19), weak (r = 0.20–0.39), moderate (r = 0.40–0.59), strong (r = 0.60–0.79), or very strong (r = 0.80–1.00).[30] Multiple forward linear regression analysis with separate blocks was used to explore the contribution of the impairment domains to the motor

TABLE 1. *Results of the exploratory factor analysis of the SPES/SCOPA motor section (oblique rotation)*

Motor items SPES/SCOPA	Factor 1	Factor 2	Factor 3	Factor 4
Rise from chair	0.844			
Postural instability	0.851			
Gait	0.588			
Speech		0.744		
Swallowing		0.714		
Freezing during on		0.666		
Postural tremor			0.899	
Rest tremor			0.892	
Rigidity				0.863
Bradykinesia				0.706
% of variance explained by factor	29.1	16.7	11.7	10.5

Factor loadings <0.4 have been omitted from the table.

factors, while taking differences in demographic and disease related variables into account (block 1: age, disease duration, LDE; block 2: impairment domains).

Statistics were performed in SPSS 16.0, except for CFA which was carried out with EQS 6.1 for Windows.[31]

RESULTS

After excluding patients who underwent stereotactical surgery (N = 18), data of 399 patients were available for analysis, of whom 344 had no missing values on any item of the SPES/SCOPA-motor. The mean (SD) age was 60.8 (11.6) years, the mean (SD) disease duration was 10.1 (6.2) years and the mean (SD) LDE was 570 (452) mg. EFA was performed on 171 patients, while CFA was performed on 173 patients. The samples did not differ with respect to age, disease duration, or LDE (age: mean difference, −1.2; 95% CI, −3.7 to 1.2; disease duration: mean difference, −1.6; 95% CI, −4.1 to 0.95; LDE: mean difference 51; 95% CI, −45 to 147).

Exploratory Factor Analysis

The screeplot indicated a four-factor solution. Four factors had an eigenvalue >1, explaining 68.0% of the variance (factor 1: 29.1%, factor 2: 16.7%, factor 3: 11.7%, factor 4: 10.5%; see Table 1). Factor 1 consisted of items that relate to axial motor function, namely "rise from chair", "gait", and "postural instability". A second "axial" factor (factor 2) consisted of the items "freezing during on", "speech" and "swallowing". "Rest tremor" and "postural tremor" grouped in factor 3, whereas "rigidity" and "bradykinesia" formed factor 4.

Confirmatory Factor Analysis

Based on the four factors a model was constructed (Fig. 1). The chi-square test was significant (χ^2 = 52.33, degrees of freedom = 29, P = 0.01). Other fit indices reflected a good fit: The CFI was 0.94, the RMSEA 0.07 (90% confidence interval 0.04–0.10) and the SRMR 0.06.

Association Between Motor Factors and Demographic, Clinical and Disease Related Characteristics

Both axial factors showed significant weak to moderate correlations with most of the impairment domains. Both factors moderately correlated with autonomic symptoms. The first axial factor further showed moderate correlations with age, whereas the second axial factor moderately correlated with psychotic symptoms. The bradykinesia-rigidity factor only had weak or nonsignificant correlations, whereas the tremor factor hardly showed any significant correlation. In the multiple regression analysis, a total of 34% of the variance of the first axial factor was accounted for, with 21% being explained by higher age and longer disease duration (block 1), and more autonomic symptoms,

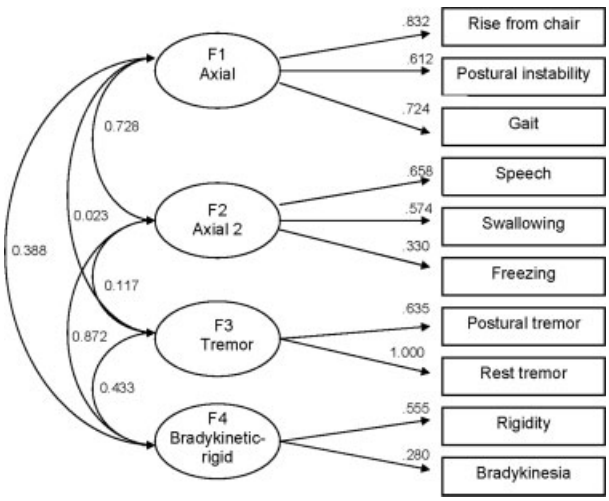

FIG. 1. Model of factor structure of the SPES/SCOPA motor section. Standardized solution of the model as tested in the confirmatory analysis. The circles represent the latent variables or factors; the arrows on the right point at the items (in the rectangles) of which the factors are composed; the numbers above the arrows represent the path coefficients (equivalent of factor loading in exploratory factor analysis); the arrows on the left indicate that intercorrelations between the factors were allowed, and the numbers indicate the magnitude of the intercorrelations.

TABLE 2. *Regression analyses of the motor factors*

Motor factor	Independent variables*	Beta‡	R^2
Axial 1[a,b]	Age	0.21	0.14
	Disease duration	0.17	0.07
	Autonomic symptoms	0.24	0.09
	Depressive symptoms	0.17	0.03
	Cognitive impairment	0.12	0.01
	Total	–	0.34
Axial 2[a,c]	Disease duration	0.15	0.15
	LDE	0.14	0.04
	Autonomic symptoms	0.18	0.09
	Psychotic symptoms	0.14	0.02
	Dyskinesias	0.15	0.02
	Depressive symptoms	0.17	0.01
	Sleep problems	−0.11	0.01
	Total	–	0.34
Tremor[a]	Duration	0.13	0.01
	Sleep problems	−0.12	0.02
	Total	–	0.03
Bradykinetic-rigid[a]	Cognitive impairment	0.23	0.06
	Autonomic symptoms	0.16	0.02
	Dyskinesias	−0.14	0.01
	Total	–	0.09

LDE; levodopa dose equivalent.
*Variables are ordered in the table as they appeared in the model.
‡Standardized beta.
[a]Multiple forward linear regression analysis with variables entered in two blocks: block 1: age, disease duration, levodopa dose equivalent; block 2: cognition, autonomic symptoms, depressive symptoms, psychotic symptoms, sleep problems, daytime sleepiness, motor fluctuations, dyskinesias.
[b]Axial 1: factor consisting of the items "rise", "gait", "postural instability".
[c]Axial 2: factor consisting of the items "freezing", "speech", "swallowing".

more depressive symptoms, and more cognitive impairment together accounting for the other 13% (block 2). A total of 34% of the variance of the second axial factor was explained, with longer disease duration contributing 15% in the first block, and higher LDE, more severe autonomic symptoms, more psychotic symptoms, more severe dyskinesias, more depressive symptoms, and less severe nighttime sleep problems explaining the other 19% (Table 2). Only 3% of the variance of the tremor factor could be explained by longer disease duration and less severe sleep problems. More cognitive impairment, more autonomic symptoms, and less severe dyskinesias together accounted for the 9% explained variance of the bradykinesia-rigidity factor.

DISCUSSION

Exploring and characterizing interrelations of assumed different clinical features of disease may contribute to the understanding of shared underlying mechanisms. Four motor factors were identified by EFA and confirmed by CFA in an independent sample. All factors showed different correlation patterns with other characteristics important in PD, thus underscoring their differential nature. Interestingly, two factors related to axial motor symptoms and collectively explained 46% of the variance of the motor items. The factor that explained most of the variance was related to the so-called PIGD component of PD and included "rise from chair", "gait", and "postural instability". Previous studies that applied different rating scales have identified a similar PIGD factor, in spite of the application of different rating scales. The consistency of these findings thus underscores the importance of this motor component of PD.[14–16]

In contrast to the other studies, we also found a second axial factor, consisting of "freezing", "speech", and "swallowing". This contrast may simply be explained by the fact that in the UPDRS these items are part of the ADL section, which was not included in the factor analyses of previous studies. The relation between speech and swallowing most likely reflect a shared impairment of oral-pharyngeal motor control. The association with freezing is less obvious. However, in one study speech in addition to gait, consistently was associated with freezing and with the risk of developing freezing.[32] Additionally, freezing frequency correlated with speech and writing in patients who were "on", while improvement of freezing frequency by levodopa strongly correlated with improvement of tremor and speech.[33] In both studies swallowing was not analyzed.

Both axial factors correlated with each other and showed similar correlations with disease duration, autonomic symptoms, and depression. Although our findings suggest some commonality between both axial factors, regression analyses also showed clear differences. The axial factor with PIGD items was related to higher age and more cognitive impairment, which is in line with previous studies.[6,7,34] The second axial factor showed relations with dopaminergic medication and complications of therapy (psychotic symptoms and dyskinesias). Because dopaminergic treatment may provoke freezing,[35,36] the association between this axial factor and complications of therapy is not unexpected. Consistent with findings of other studies, a tremor factor was identified.[13,15,16] This factor clearly behaved as the most independent component of the motor spectrum, as illustrated by the lower corelations with other factors and the lack of relations with most nonmotor impairments.

Finally we identified a bradykinesia-rigidity factor, which was described in one earlier study.[15] This factor

was marginally explained by other disease related variables. However, relations with other domains may be masked by a generally stronger effect of dopaminergic medication on bradykinesia and rigidity in comparison with other motor features.[37]

Of previous studies that performed factor analysis on motor symptoms in PD, some analyzed tremor, bradykinesia and rigidity separately for each extremity,[14,16] while others did not.[13,15] Stebbins et al. used exploratory factor analysis and found side sensitivity for bradykinesia, but not for tremor and rigidity. Stochl et al. performed a confirmatory factor analysis and found two factors reflecting laterality (right and left) in addition to five factors that reflected symptoms. Since PD may present with an asymmetrical appearance of tremor, bradykinesia, or rigidity, which persists over the disease course,[38] the finding of a laterality factor is not unexpected. To date it is unclear if laterality is informative with respect to distinct motor subtypes or their underlying biological constructs. Anomalies of asymmetry of motor impairments were found in 11% of the patients with PD, including a rest tremor most pronounced in one upper limb and the contralateral lower limb, rest and postural tremor most pronounced in opposite extremities, and unilateral dominance of rigidity, bradykinesia and rest tremor, followed by development of predominance of all three features on the contralateral side.[39] Asymmetric manifestations of the disease have been suggested to be stochastically determined and not by genetic, environmental, structural or neurochemical causes.[38] Aim of our study was therefore to detect patterns of interrelations between the various motor symptoms in PD irrespective of side differences.

Items that involve motor features that are responsive to levodopa will likely have been scored as less severe compared to the situation in which they did not benefit from their medication (i.e., were "off") and this may have altered the strength of the correlations between items. However, the overall effect on the factor structure is probably limited, because Stebbins et al., who performed factor analyses both in the "on" and "off" phase, showed that both situations resulted in an identical factor structure.[14,40]

In conclusion, we identified four distinct components of the motor spectrum of PD through a data-driven approach. Based on their different relations with demographic characteristics and clinical domains of the disease, these components may reflect the different nature of causes, including disease process, aging and dopaminergic treatment. Additionally, these motor components may facilitate future research aiming to identify clinical subtypes of PD.

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