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Patterns of motor and non-motor features in Parkinson's disease

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ABSTRACT

Objective: To evaluate the presence and nature of patterns of coherency among the motor and non-motor domains in Parkinson's disease (PD) and to examine which clinical parameters are related to the potential patterns.

Methods: A cohort of 397 PD patients was randomly divided into two samples. Exploratory factor analysis (EFA) was performed on the motor and non-motor symptoms in PD in the first sample. Findings of the EFA were used to construct a model which was tested in the second sample by confirmatory factor analysis. Multiple regression analyses on the resulting factors were performed to evaluate the influence of clinical parameters upon these factors.

Results: Four factors were identified. The first and strongest factor (cognitive impairment, autonomic dysfunction, psychotic symptoms, depression, daytime sleepiness, and axial symptoms) reflected advancing disease. Another factor largely reflected motor complications of therapy and was related to dopaminergic medication. The other two factors reflected sleep/depression and tremor/bradykinesia/rigidity, and were only marginally related to disease severity or medication.

Conclusions: The motor and non-motor features in PD can be characterized by four distinct patterns of coherency, which provide insight in the contributions of the primary disease process and anti-parkinsonian medication to the broad clinical spectrum of PD. One factor, consisting of predominantly non-motor symptoms together with axial features, clearly reflected disease severity and may provide a new basis for monitoring disease progression in PD.

INTRODUCTION

Parkinson's disease (PD) encompasses not only a variety of well-known motor features, but also a broad spectrum of non-motor symptoms, including cognitive impairment, psychotic symptoms, depression, sleep disorders, and autonomic dysfunction.[1] However, when considering the full spectrum of the disease, there is still limited information on the coherency of the various motor and non-motor symptoms. This may be partly due to the fact that past research mainly focused on the motor signs of PD as well as to the limited availability of PD specific and clinimetric sound measurement instruments to assess the non-motor impairments.[2] From more recent studies that characterized specific domain interrelations, it is apparent that differential relations exist between the various motor and non-motor domains.[1,3-5] However, in these studies not all impairment domains were studied simultaneously, which is required to unravel domain coherency. Knowledge on the coherency of motor and non-motor domains is important because it may suggest underlying constructs that provide new insight in the contributions of the primary disease process and anti-parkinsonian medication to the broad clinical symptom profile of PD.

In the PROPARK study valid and reliable instruments for each of the relevant impairment domains have been applied simultaneously in a large cohort of patients with PD (www.scopa-propark.eu). As this approach allows a more comprehensive view of domain interrelations, the aim of this study is to evaluate the presence and nature of patterns of coherency among the motor and non-

motor domains in PD and to examine which clinical parameters are related to the potential patterns.

METHOD

Study design

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. Findings obtained from the first annual evaluation of 415 patients who were assessed between May 2003 and March 2006 were used for the present analysis.

Study participants

All patients fulfilled the United Kingdom Parkinson’s Disease Society Brain Bank criteria for idiopathic PD.[6] Patients were recruited from outpatient neurology clinics of university and regional hospitals in the western part of The Netherlands. The majority of the patients were assessed at the Leiden University Medical Center (LUMC); patients who were unable to come to the hospital were assessed at home. Age at onset and disease duration are important determinants of disease course in PD and are related to various manifestations of the disease.[7,8] To obtain an adequate distribution of these characteristics across the cohort, we aimed to construct four strata of 100 patients each, based on age at onset (onset of the first symptoms as perceived by the patient; $\leq$ / > 50 years) and disease

duration (≤ / > 10 years). The study was approved by the medical ethical committee of the LUMC and all participants gave informed consent.

Outcome measures

Information on clinical and sociodemographic variables was obtained and included age, age at onset, disease duration, disease severity (measured with the Hoehn and Yahr (H&Y) scale),[9] and medication. Levodopa equivalent units were calculated for levodopa and dopamine agonists.[10]

The following domains were assessed: motor signs and motor complications (SPES/SCOPA, sections motor evaluation (ME) and motor complications (MC)),[11] cognitive impairment (SCOPA – COG),[12] psychotic symptoms (SCOPA-PC, items 1-5),[13] autonomic dysfunction (SCOPA – AUT, items 4-6, 8-16),[14] depressive symptoms (Beck Depression Inventory (BDI))[15], nighttime sleep problems (NS) and daytime sleepiness (DS) (SCOPA-SLEEP sections NS and DS).[16] Cognitive impairment, autonomic dysfunctioning, and motor signs were evaluated as either total or subscores. Subdomains of the SCOPA-COG include memory, attention, executive functioning, and visuospatial functioning. From the SCOPA-AUT, subscores were calculated for constipation (items 4-6), urinary dysfunction (items 8-13), and cardiovascular dysfunction (items 14-16). We excluded domains from the SCOPA-AUT that were less relevant (pupillomotor), were composed of opposite items (thermoregulatory) or yielded too many missing values (sexual dysfunction, because patients indicated these items were “not applicable”). Motor signs were evaluated by subdomains,

resulting from a previously performed factor analysis on the SPES/SCOPA-motor,(unpublished data, van Rooden 2008) and included tremor (rest and postural tremor), bradykinesia and rigidity, axial symptoms (rise, gait, postural instability), and a second axial factor (freezing, swallowing, speech). Instruments were either self-completed (SCOPA-AUT, BDI, SCOPA-SLEEP) or administered by trained research associates (SCOPA-COG, SCOPA-PC, SPES/SCOPA). Domains and subdomain scores of the SCOPA-COG were inversed to arrange that all scores were in the same direction, with higher scores reflecting more severe impairment. For reasons of comparability, all patients who used anti-parkinsonian 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.

Statistical analysis

The total group was randomly divided into two subgroups. In the first sample, the impairments were subjected to an exploratory factor analysis (EFA) with oblique rotation. Since factors emerging from the spectrum of PD domains are expected to be correlated, an oblique rotation, which allows for correlation of factors, was applied. [17] The results of the EFA in the first sample were next used to construct a model that was tested for model fit in the second sample, using confirmatory factor analysis (CFA). To evaluate how well the data fitted the model measures estimating the lack of fit (the root means square error of approximation (RMSEA) and the standardized root mean square residual

(SRMR)) were calculated, supplemented with a measure to estimate the model's goodness of fit (comparative fit index (CFI)).[18] RMSEA values >0.1 indicate poor fit, whereas values <0.08 and <0.05 indicate reasonable and good fit, respectively. The SRMR reflects a good fit if the value is <0.08. A CFI close to 0.95 is indicative of a good fit.[18,19] Factor loadings >0.32 were considered poor, >0.45 fair, >0.55 good, >0.63 very good, and >0.71 excellent, which correspond with squared variances of 0.1, 0.2, 0.3, 0.4, and 0.5, respectively.[20] Multiple forward linear regression analysis with two blocks was used to explore the relation between the different factors and the disease process and medical therapy, while removing all variation due to demographic characteristics by entering age and sex separately in block 1 (block 1: age, sex; block 2: disease duration, Hoehn and Yahr stage (H&Y), levodopa dose (LDE LDOPA), agonist dose (LDE DA)). Age at onset was not entered in the regression model, because it is determined by including age and disease duration and thus could have resulted in collinearity.

Statistics were performed with SPSS 14.0, except for CFA which was carried out with EQS 6.1 for Windows.[21]

RESULTS

Eighteen patients who underwent stereotactical surgery were excluded from the analysis. Characteristics of the 397 patients who remained for analysis, and of the subsamples used for exploratory and confirmatory analysis, are presented in

table 1. The two subsamples did not significantly differ on any of the characteristics (all p-values >0.05).

Table 1: Patient characteristics.

Characteristics	Total group	Sample EFA	Sample CFA	P
N	397	196	201	-
men/women, N (% men)	253/144 (64%)	134/62 (68%)	119/82 (59%)	0.06 [a]
Age, yrs, mean (SD)	61.2 (11.5)	60.9 (10.9)	61.6 (12.0)	0.58 [b]
Age onset, yrs, mean (SD)	51.0 (11.8)	50.8 (11.5)	51.2 (12.2)	0.71 [b]
Disease duration, yrs, median (IQR) [d]	9.2 (5.2-14.0)	9.6 (5.2-14.1)	8.9 (5.0-13.9)	0.86 [c]
H&Y stage, median (IQR)	2 (2-3)	2 (2-3)	2 (2-3)	0.66 [c]
Patients on LDOPA, N (%)	264 (67 %)	131 (67 %)	133 (67%)	0.89 [a]
Patients on DA, N (%)	276 (70 %)	144 (74 %)	132 (66 %)	0.09 [a]
LDE-LDOPA, mg, median (IQR) [d]	300 (0-540)	300 (0-600)	300 (0-500)	0.70 [c]
LDE-DA, mg, median (IQR) [d]	188 (0-375)	200 (0-400)	180 (0-329)	0.27 [c]

[a]) Chi-square

[b]) Independent samples t-test

[c]) Mann-Whitney U-test

[d]) Data were not normally distributed, therefore median (IQR) is presented.

EFA; exploratory factor analysis, CFA; confirmatory factor analysis, IQR; interquartile range, H&Y; Hoehn and Yahr, LDOPA; levodopa, DA; dopamine agonists

Exploratory analysis

An initial EFA of all domains, including the subdomains of cognitive impairment (memory, attention, executive and visuospatial functioning) autonomic dysfunctioning (constipation, urinary dysfunction, cardiovascular dysfunction) and motor signs (tremor, bradykinesia/rigidity, two axial factors), showed that the subdomains of cognition and autonomic impairment grouped together, but the motor subdomains did not. Therefore a second EFA was performed in which the total scores of cognitive impairment and autonomic dysfunction, and the subdomain scores of motor signs were included.

Four factors with an eigenvalue >1 were identified, which together explained 62% of the variance (Table 2). These factors were similar to the factors resulting from the first EFA. The first factor, explaining 31% of the variance, comprised psychotic symptoms, daytime sleepiness, autonomic dysfunction, and cognitive impairment, depression and both axial symptoms. Nighttime sleep problems, motor fluctuations and depression clustered in the second factor, and explained 12% of the variance. The third factor, comprising dyskinesias, motor fluctuations, and axial symptoms 2 (freezing, swallowing, speech), explained 11% of the variance. Factor four explained 9% of the variance and included the remaining

motor subdomains, that is, tremor and bradykinesia/rigidity. Three domains showed dual loadings, namely depression (factor 1 and 2), axial symptoms 2 (factor 1 and 3) and motor fluctuations (factor 2 and 3).

Table 2: Exploratory factor analysis of impairment domains

	Factor 1	Factor 2	Factor 3	Factor 4
Psychotic symptoms	0.75			
Autonomic dysfunction	0.72			
Daytime sleepiness	0.62			
Cognitive impairment	0.62			
Axial symptoms1 *	0.61		0.45	
Axial symptoms2 **	0.60		0.56	
Depression	0.60	0.61		
Nighttime sleep problems		0.84		
Motor fluctuations		0.60	0.65	
Dyskinesias			0.83	
Tremor				0.83
Bradykinesia/ rigidity				0.62
% of variance	31	12	11	9

Structure matrix of exploratory factor analysis with oblique rotation. Factor loadings <0.45 have been omitted. Four factors with eigenvalue >1, explaining 61.9% of the variance.

* Axial symptoms 1: Rise, gait, postural instability;

** Axial symptoms 2: Freezing, speech, swallowing.

Confirmatory analysis

A model for CFA was constructed, based on the results from the second EFA (factor loadings >0.55). The fit of this model was insufficient. A model with good fit was obtained when cognitive impairment was allowed to load on factor 2 and axial symptoms 2 was allowed to load on factor 4 (Figure 1). The CFI of this model was 0.95, while the SRMR was 0.05 and the RMSEA 0.06 (95% CI 0.03-0.08). The factor loadings of axial symptoms 2 on factor 1 and 4, and the factor loading of motor fluctuations on factor 2 had a positive, albeit non-significant, contribution to the fit of the model. The factor loadings of the variables loading on factor 1 were in a similar range of very good (psychotic symptoms, autonomic dysfunction, and axial symptoms 1) to excellent (cognitive impairment). The loading of depression on factor 1 was fair while the loading of daytime sleepiness on this factor was poor. Factor 2 was mainly determined by sleep, which had an excellent factor loading, while depression and cognition poorly loaded on this factor. Notably, cognitive impairment had a negative loading on factor 2. Of the three variables loading on factor 3, the loading for dyskinesias was excellent, while these were good for motor fluctuations, and nearly fair for axial symptoms 2. Rigidity and bradykinesia most strongly determined factor 4 with an excellent factor loading, whereas the factor loading of tremor was poor.

Relations with disease and medication related variables

In the multiple regression analyses controlling for age and sex, 45% of the variance of factor 1 was explained, with H&Y stage contributing 23%. A total of 44% of the variance of factor 3 was accounted for, with LDE LDOPA explaining 31% and disease duration 9%. Only 10% of the variance of factor 2 and 13% of factor 4 was explained. (Table 3)

Table 3. Regression analyses of the factors.

	Independent variables *	Beta ‡	P-value beta	R^2
Factor 1 [a,b]	Age	0.21	0.00	0.18
	H&Y stage	0.43	0.00	0.23
	LDE LDOPA	0.14	0.00	0.03
	Disease duration	0.14	0.00	0.01
	Total	-		0.45
Factor 2 [a,c]	Age	-0.20	0.00	0.03
	Sex	-0.14	0.01	0.02
	LDE DA	0.15	0.01	0.03
	LDE LDOPA	0.15	0.01	0.02
	Total	-		0.10
Factor 3 [a,d]	Age	-0.08	0.06	0.02
	LDE LDOPA	0.44	0.00	0.31
	Disease duration	0.26	0.00	0.09
	LDE DA	0.14	0.00	0.01

	H&Y stage	0.13	0.00	0.01
	Total	-		0.44
Factor 4 [a,e]	Age	0.01	0.82	0.02
	Sex	0.19	0.00	0.01
	H&Y stage	0.30	0.00	0.08
	LDE DA	-0.13	0.01	0.02
	Total	-		0.13

* 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: sex, age; block 2: levodopa dose equivalent levodopa, levodopa dose equivalent dopamine agonists, Hoehn and Yahr stage, disease duration.

[b] Factor 1, including psychotic symptoms, autonomic dysfunction, daytime sleepiness, axial symptoms (rise, gait, postural instability), cognitive impairment, depressive symptoms.

[c] Factor 2, including nighttime sleep problems, depressive symptoms, cognitive impairment.

[d] Factor 3, including motor fluctuations, dyskinesias, axial symptoms (freezing, speech, swallowing).

[e] Factor 4, including bradykinesia and rigidity, tremor.

LDE; levodopa dose equivalent, LDOPA; levodopa, DA; dopamine agonists, H&Y; Hoehn and Yahr.

DISCUSSION

Identification of factors among motor and non-motor impairment domains may aid in unraveling the nature of underlying constructs. Using EFA, we identified four factors in the spectrum of motor and non-motor symptoms in our sample of patients with PD. With only minor modifications, this factor structure was confirmed by CFA in an independent sample, thereby strengthening the results. The first and strongest factor comprised most of the non-motor domains. The main contributors to this factor were cognitive impairment, autonomic dysfunction, psychotic symptoms and the axial symptoms that reflect Postural Instability Gait Difficulty (PIGD; rise, gait and postural instability). Daytime sleepiness and depressive symptoms had a smaller contribution to this factor. The second factor was mainly characterized by sleep disturbances and showed a moderate contribution of depressive symptoms and cognitive impairment. The third factor comprised both types of motor complications with a smaller additional contribution of the axial symptoms freezing, speech, and swallowing. The classical motor features of PD (tremor, bradykinesia and rigidity) grouped together in the fourth factor.

In trying to understand the nature of the encountered patterns, multiple regressions analysis was used to evaluate relations between the factors and variables that reflect disease severity and duration as well as dopaminergic treatment. This approach revealed H&Y stage as the variable most strongly related to factor 1 with negligible contributions of LDE LDOPA and disease duration (1-3%). LDE LDOPA was the variable most strongly related to factor 3

with disease duration showing a small (9%) contribution. Notably, for both factors, more than half of the variance is unexplained.The variables in the regression model together explained only a negligible proportion (10-13 %) of the variance of factors 2 and 4.

The coherence of the domains in factor 1 corroborates the results from previous studies.[22] The relation with H&Y stage and to a lesser extent disease duration most likely indicate that symptoms in this factor cumulate with increasing disease severity or Lewy body pathology.[23] The load of Lewy body pathology is related to the alpha-synuclein gene dosage, which in turn is also influenced by aging.[24] In earlier studies, visual hallucinations, frequent falls, and cognitive impairment have all been found to occur at a similar time to death, which was not proportional to disease duration.[22,25] If, in the development of these symptoms, time to death is a more important determinant than disease duration, age is expected to be more closely related to these symptoms than disease duration. We indeed found that age explained 18% of the variance in factor 1, while the relation with disease duration was negligible.

Factor 3 was predominantly related to LDE LDOPA, whereas a smaller part was explained by disease duration. Total daily dose, duration of exposure, and age at initiation of L-DOPA, together with disease severity, are well known risk factors of motor complications.[26,27] The relation between medication and freezing, speech and swallowing is somewhat unexpected, but in agreement with findings of others.[28,29] In a previous factor analysis on motor signs of PD, axial symptoms presented as two separate factors, namely one reflecting rise, gait and

postural instability, and the other reflecting freezing, speech and swallowing.(unpublished data, van Rooden 2008) Our current findings showed a differential behavior of both axial factors with respect to their contribution to the four factors and thus may indicate that they represent distinct motor components of PD.

The relation between sleep and depression, as found in factor 2, has been found in several studies.[30-32] A negative relation between sleep and cognition has also been reported previously.[4] Of the 10% variance of this factor that could be explained, half was accounted for by LDE LDOPA and LDE DA. The relation between insomnia and dopaminergic medication has been found by others[31,32] and may possibly be due to the negative influence of dopaminergic medication on sleep depth or REM sleep.[33] In line with findings from other studies, no relation emerged between this factor and disease severity.[30-32] Possibly this is explained by the finding that in PD, insomnia is an inconsistent and reversible complaint.[30] The dual loading of depression on factors 1 and 2 is most likely explained by the multifactorial etiology of depression.[34,35]

Factor 4, comprising the motor signs tremor, bradykinesia and rigidity, showed a marginal correlation with DA dose, which is in line with previous findings.[36] A similar marginal correlation was found for disease severity, although others have reported a stronger association.[37] Because bradykinesia and rigidity are responsive to dopaminergic treatment, these marginal correlations may reflect a masking effect of dopaminergic medication.[38] Additionally, our findings again

underscore that tremor has a distinct behavior within the motor spectrum of PD.[37,39]

In the present study, the full spectrum of motor and non-motor symptoms of PD was evaluated in a large cohort, using measurement instruments specifically developed for PD. We found distinct patterns of domain coherency among motor and non-motor symptoms, with the first and strongest factor (cognitive impairment, autonomic dysfunction, psychotic symptoms, PIGD, daytime sleepiness and depressive symptoms) reflecting advancing disease.

Hitherto, the severity and longitudinal course of PD is evaluated by the Hoehn and Yahr staging system, which, from a conceptual point of view, is a peculiar mixture of impairments and disabilities.[9] Stages are determined by the presence of tremor, bradykinesia or rigidity on one or both sides of the body in the early phase of the disease, and by postural instability and the degree of disability in the more advanced stages. In view of the growing awareness that the clinical spectrum of PD is much broader than motor signs only, this staging system does not do justice to the clearly more complicated nature of the disease. In the present study disease severity was found to be best characterized by the non-motor domains and PIGD motor features that constitute factor 1. Together these domains may provide a better basis of a future disease severity staging system. Additionally, motor complications as reflected in the third factor, are an important consequence of the treatment in PD. Since motor complications are only marginally related to disease severity, this domain likely is better evaluated on a separate axis.

Factors 2 (sleep and depression) and 4 (bradykinesia, rigidity and tremor), though distinct, are not related to either disease severity or complications of therapy. Therefore, these domains have limited applicability in a disease severity staging system. However, information of these domains may have important consequences for disease management and for future studies on patient subtypes. Further research in independent samples is needed to confirm our results.

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COMPETING INTEREST

None declared.

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FIGURE LEGENDS

Figure 1. Model of factor structure of all impairment domains of Parkinson's disease.

Standardized factor loadings are indicated next to the arrows. Non-significant factor loadings with a positive contribution to the fit of the model are not displayed in the figure (axial symptoms 2 on factor 1 and 4; motor fluctuations on factor 2).

* Axial symptoms 1: Rise, gait, postural instability;

** Axial symptoms 2: Freezing, speech, swallowing.

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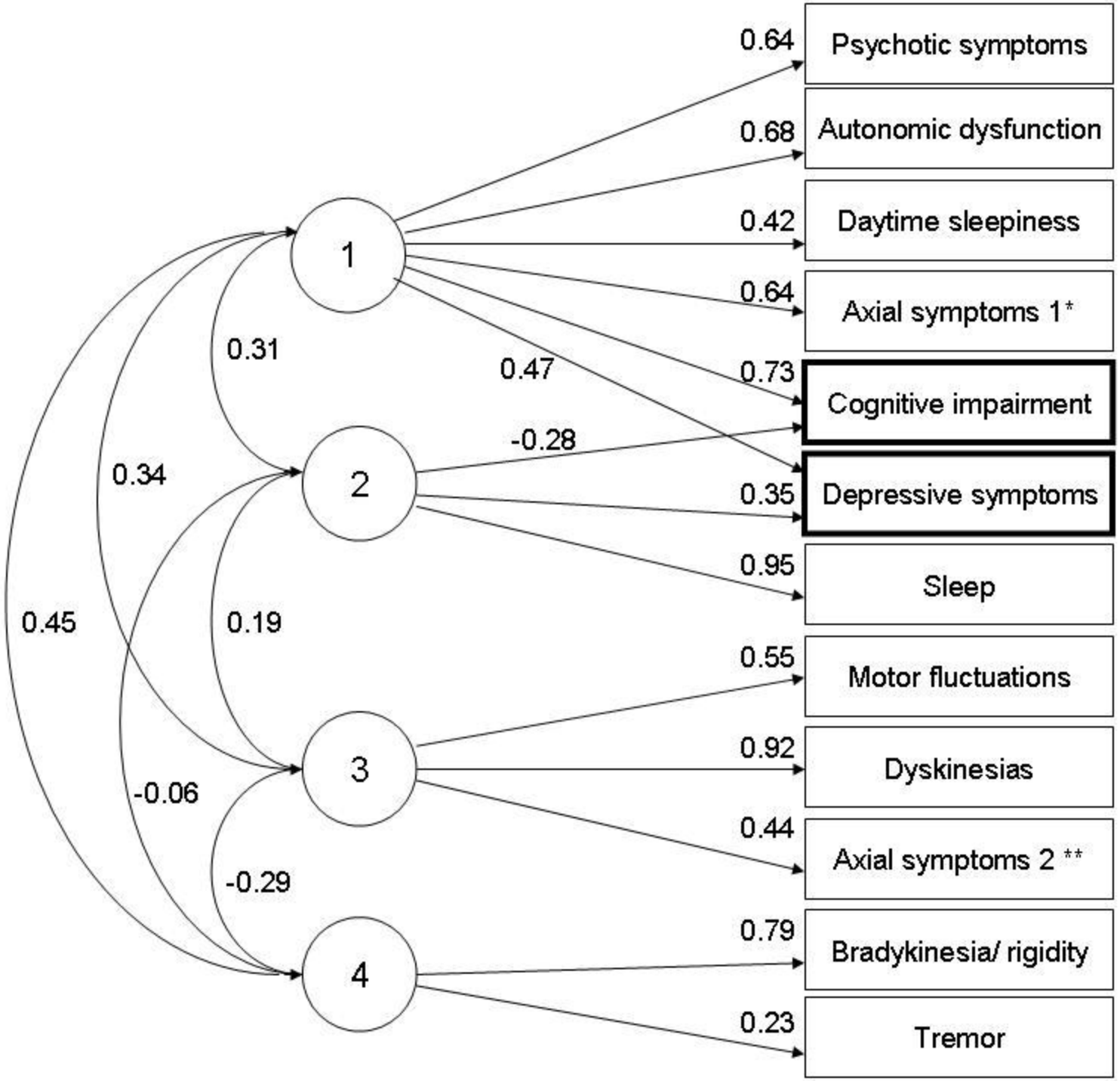
1
2
3
4
0.31
0.34
0.45
0.19
-0.06
-0.29
0.47
-0.28
0.64
0.68
0.42
0.64
0.73
0.35
0.95
0.55
0.92
0.44
0.79
0.23
Psychotic symptoms
Autonomic dysfunction
Daytime sleepiness
Axial symptoms 1*
Cognitive impairment
Depressive symptoms
Sleep
Motor fluctuations
Dyskinesias
Axial symptoms 2 **
Bradykinesia/ rigidity
Tremor