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Profiling cognitive and neuropsychiatric heterogeneity in Parkinson's disease

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ABSTRACT

Background: Parkinson's disease (PD) is a highly heterogeneous disease, in which motor symptom subtypes are often-described. While it is recognized that motor, cognitive and affective neuropsychiatric symptoms negatively influence the patients' quality of life, it is currently unknown how these symptoms contribute to phenotypic subtypes. The objective of this study was to assess subtypes of motor, cognitive and affective symptoms in PD.

Methods: A hierarchical cluster analysis was conducted on clinical data of 226 PD patients screened at the VU University Medical Center using comprehensive assessment of cognitive, affective and motor symptoms. Subsequent linear discriminant analyses were conducted to investigate discriminating constructs between clusters.

Results: The cluster analysis yielded four clusters: (1) a young-age (59.9 years), mildly affected cluster (N = 86), (2) an old-age (72.3 years) cluster with severe motor and non-motor symptoms (N = 15), (3) a cluster (age 64.7 years) with mild motor symptoms, below-average executive functioning and affective symptoms (N = 46) and (4) a cluster (age 64.8 years) with severe motor symptoms, affective symptoms and below-average verbal memory (N = 79).

Conclusions: Cluster 1 and 2 seem to represent opposite ends of the PD disease stages. Patients in clusters 3 and 4 had similar age, educational level and disease duration but different symptom profiles – we therefore suggest that these clusters represent different pathways of disease progression, presumably with distinct underlying pathology localization. Future research on the neuropathophysiological characteristics of these two clusters and monitoring of disease progression is required.

1. Introduction

In the past fifteen years, there has been increased interest in identifying subtypes of Parkinson's disease (PD) and understanding the heterogeneity in clinical symptoms [1,2]. Data-driven studies in longitudinal cohorts have identified subtypes of PD [3,4], even in the early stages of the disease [5]. Studies into subtypes of cognitive and neuropsychiatric symptoms in PD are scarce, however, despite a large variability in the presence of cognitive and neuropsychiatric disorders in PD [2,6,7]. Furthermore, these symptoms have a particularly high impact on patients' quality of life [8]. Although cognitive status and neuropsychiatric symptoms are greatly intertwined in the general population [9], the exact relation between these symptoms in PD has still be to unraveled. Only an association between psychotic symptoms and the presence of more severe global cognitive dysfunction, including memory impairment has

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been reported frequently [7,10,11].

Previous studies have distinguished varying clusters. In general, neuropsychiatric symptoms seem to be more prevalent in the non-tremor-dominant subtype of PD [12]. A cluster analysis on cognitive characteristics reported three clusters with increasing severity of cognitive impairment, varying from no or minimal impairment to cognitive impairment across most cognitive domains [13]. Two patterns of executive dysfunction – i.e. attentional control versus abstract reasoning – were identified by Kudlicka and colleagues in patients with mild to moderate PD (Hoehn and Yahr stages I–III) [14]. In addition, a subgroup with specifically attention, visuospatial and logical memory impairment was distinguished from a subgroup with general impaired cognition and a PD dementia subgroup by Liepelt-Scarfone and colleagues [15]. However, these studies did not assess the relationship between cognitive subtypes and neuropsychiatric symptoms.

Given the limitations described above, our aim was to identify symptom profiles in PD patients using a data-driven approach, that not only includes the motor characteristics but also detailed information on cognitive functioning and neuropsychiatric symptoms. We aim to relate profiles of specific cognitive deficits to neuropsychiatric symptoms, principally affective symptoms (i.e. anxiety and depression).

2. Methods

2.1. Patients

For the analyses described in this report, we used data obtained in 226 consecutive patients who were referred to the outpatient clinic for movement disorders of the VU University Medical Center (Amsterdam, The Netherlands) between May 2008 and June 2014. As part of routine clinical practice patients were assessed using a clinical neurological examination, an elaborate neuropsychological assessment, and neuropsychiatric and behavioral questionnaires. Patients were diagnosed clinically with idiopathic PD by movement disorders specialists (H.B. & E.F.). Inclusion criteria were 1) diagnosis of idiopathic PD according to the United Kingdom Parkinson's Disease Society Brain Bank criteria, 2) written informed consent of the patient to use their clinical data for scientific purposes, and 3) a complete set of neurological, neuropsychological, and neuropsychiatric variables after imputation selected for cluster analysis (see *Statistical Analysis*). This study was approved by the medical ethical committee of the VU University Medical Center.

2.2. Measurement instruments

Some measurements were used for the clustering procedure and some for post-hoc analyses only. Multicollinearity, ceiling performances, limited variation in scores and non-continuous measurement scale impaired the ability to include more measures in the cluster analysis (see *Statistical analysis* for more detail).

2.2.1. Cluster analysis measurements

Measurements used in the cluster analysis assessed motor symptoms, cognitive function, and affective symptoms. Neuropsychological instruments were administered by trained neuropsychology students or professionals. Motor symptom severity was assessed in the "ON" medication state (if applicable) by trained residents in neurology using the Unified Parkinson's Disease Rating Scale (UPDRS)-III. Neuropsychological tasks assessed a wide range of cognitive domains. *Global cognitive functioning*: Mini-mental State Examination (MMSE). *Executive functions/working memory*: the Stroop interference measure (color-word task time corrected for color-only time), the Trail Making Task (TMT) task B time corrected for task A time (B | A), and the backwards digit span subtest of the Wechsler Adult Intelligence Scale (WAIS)-III. *Episodic memory*: the 15-min delayed recall of a 15-word list learning task (15WT – Dutch version of the Rey Auditory Verbal Learning Test). The Beck Anxiety Inventory (BAI) for anxiety symptoms was the only neuropsychiatric symptom measure in the cluster analysis.

2.2.2. Post-hoc analyses measurements

Disease duration was computed by subtracting the subjective age at disease onset – the age at which the patient first noticed signs of motor symptoms related to PD, retrospectively – from age at testing. Educational level was measured by the Dutch 'Verhage' education scale, which ranges from 1 (minimum; primary school not finished) to 7 (maximum; university education and higher). Disease stage was measured by the Hoehn & Yahr (H&Y) scale. The UPDRS was divided in three averaged subscores: a tremor score (item 16, 20, and 21), a hypokinesia/rigidity score (item 22 and 31) and a postural instability/gait disorder (PIGD) score (item 13, 14, 15, 29, and 30) [12]. Dopaminergic medication use was transformed to the 'levodopa equivalent daily dosage' (LEDD), as described elsewhere [16]. Neuropsychological measures used for post-hoc analyses are described in the Supplementary Material. Depressive symptoms were measured by the Beck Depression Inventory (BDI). In addition, we screened for psychotic symptoms and impulse control impairment, using the Scales for Outcomes in Parkinson's Disease – Psychiatric Complications (SCOPA-PC). Sleep disorders were assessed by the SCOPA-SLEEP – item B1 to B5 assessed nighttime sleep quality and item D1 to D6 assessed daytime sleepiness. Autonomic symptoms were measured by the SCOPA-AUT. Finally, the activities of daily living (ADL) were measured using the UPDRS part II and the Schwab and England ADL Scale. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS, Chicago, Il, USA).

Questionnaires were completed by the patient prior to the examination, if necessary with help from the informal caregiver. BAI score >12 and BDI score >14 were considered clinically relevant. An MMSE ≤24 was considered indicative of cognitive impairment.

2.3. Statistical analysis

Cognitive measures were adjusted for sex, age and/or educational level, and transformed to *t*- or percentile scores, using the Dutch norms by Schmand, Houx and De Koning (2012). A summary of the corrected variables with an overview of the qualitative description of norm scores is provided in Table e-1 of the Supplementary Material. BAI, BDI, SCOPA-SLEEP daytime sleepiness and SCOPA-AUT item 1-21 scores were imputed if 1/6 or less of the items were missing using the average score of valid questionnaire items. Cases were excluded from analysis if more than 1/6 of the items was missing. The sex-specific items (item 22-25) and the item concerning medication (item 26) of the SCOPA-AUT were not included in the imputation due to different answer scales within these items. Variables were checked for normality. Skewed distributions were transformed, if necessary, using a square root transformation.

We conducted a hierarchical cluster analysis (HCA) on cognitive, affective and motor symptoms. The adjusted cognitive measures, BAI, UPDRS-III and MMSE were transformed to *z*-scores to equalize the unit of measurement across variables within the HCA. We used the squared Euclidean distance measure, with Ward's clustering method of minimal variance, rendering good clustering qualities. The number of clusters was determined by 1) the 'best cut' dendrogram output, 2) the 'elbow' in the scree plot and 3) the ecological value of the cluster solution. The HCA included the Stroop interference measure, TMT task B time corrected for task A

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