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Short communication

Non-motor symptoms in Parkinson's disease: An explorative network study

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ABSTRACT

Research on the association between non-motor symptoms (NMS) of Parkinson's disease (PD) and patients' quality of life (QoL) has given insight into the burden of NMS. Most studies investigate NMS by assessing the contribution of individual symptoms to QoL. However, symptoms could also have an interactive relationship, which might not be fully taken into account when only studying these individual contributions. Recently, a network approach has been developed that treats symptoms as nodes and associations between symptoms as edges in a network, providing the opportunity to investigate the dimensional spectrum of NMS. In the current cross-sectional study, we investigated NMS with both approaches: first, we assessed individual contributions of NMS to QoL. Second, we aimed to assess NMS using a network approach. Seventy PD patients completed questionnaires on NMS and QoL. Our primary analysis shows that the domains Mood and Pain are significant contributors to QoL. Our secondary network analysis suggests that Mood and Sleep play central roles in the NMS-network, and that Mood and Cognition are strongly related. Because of power issues, the generalizability of our explorative results is limited. However, complementary information from the network analysis does suggest that focusing on sleep problems might help both mood and pain symptoms, which negatively affect QoL. Investigating symptoms not only as individual and independent entities but rather as part of a connected network could show how treating one symptom affects other symptoms.

1. Introduction

Non-motor symptoms (NMS) of Parkinson's disease (PD), such as cognitive dysfunctioning, depressive symptoms and pain, play a major role in the disease next to the characteristic motor symptoms. There is ample evidence of the negative association between NMS and quality of life (QoL) [1–3]. Despite the large body of work investigating NMS and QoL in PD, there is only a small number of NMS consistently showing an association with patients' QoL, namely depression and cognitive impairment. Different studies show different results, which might be explained by hidden symptom-to-symptom interactions that complicate the interplay between NMS towards QoL.

A contemporary method adapted from the field of psychology is a network approach [4] that treats symptoms as nodes and the relations between symptoms as edges in a network. Network theory has been applied to many areas of research, such as sociology and neuroscience. A major difference between networks in neuroscience and networks in psychology, or in our case neurology, is that the entities that make up the network are not based on physical matter [4]. To put it differently, a connection between two brain areas can be physically measured, but the association between two symptoms cannot: it is determined by the behavior of those two symptoms with respect to one another, and to other symptoms present in the network at group level. What we *can* deduct from this type of analysis is which symptoms play a central role in the disease, and thus which symptoms might be most effective to treat in order to improve other symptoms in the network.

The aim of our cross-sectional study is twofold. First, we aim to assess the association of non-motor symptoms with QoL in PD patients, to find which NMS contribute most to QoL in our sample. As a second exploratory analysis, we aim to investigate symptom-to-symptom

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relationships in our sample by making use of the network approach for NMS, and examine which NMS play a central role in the NMS-network.

2. Methods

2.1. Participants and procedure

Participants were recruited from local hospitals in the Amsterdam area (The Netherlands). Inclusion criteria were a diagnosis according to the UK Brain Bank criteria, and ability to sign informed consent form and to finish all tests. The study was approved by the medical ethical committee of OLVG Hospital (Amsterdam, The Netherlands). Patients were invited to participate in our study either after their hospital appointment, or at home if so desired. All participants provided written informed consent. All methods were carried out in accordance with the relevant guidelines and regulations. Trained assistants administered the Non-Motor Symptom Scale (NMSS), King's Parkinson's Disease Pain Scale (KPPS) and Montreal Cognitive Assessment (MoCA). The Numeric Rating Scale (NRS), EQ-5D-3L and Hospital Anxiety and Depression Scale (HADS) were filled out by participants at a time convenient to them. The researchers were available to aid in case of questions regarding the questionnaires by participants. On average, the interval between the patient-completed questionnaires and assessment by the researchers was 2.75 ± 5.44 days around the date of assessment (range: 10 to 24 days, based on data from 55 patients).

2.2. QoL

The EQ-5D-3L questionnaire is validated in Parkinson's patients [5], and assesses health related QoL with five questions, and three levels per question. Total sum score was used as an outcome measure [6].

2.3. Non-motor symptoms

The NMSS assesses all non-motor symptoms in 30 questions, subdivided into domains: Cardiovascular, Sleep/Fatigue, Mood/Apathy, Perceptual problems, Attention/Memory, Gastrointestinal tract, Urinary, Sexual function, Miscellaneous. Patients are asked to evaluate frequency and severity of each symptom, which is then multiplied (range from 0, indicating no symptoms present, to 12, indicating maximum frequency and severity) [7]. The KPPS was used to measure pain [5]. The KPPS is developed to capture pain experience specifically in patients with Parkinson's disease. A Dutch version of the KPPS was not yet available, therefore the English version of this questionnaire was translated into Dutch according to an internationally approved procedure and in close cooperation with the authors of the original publication, rendering a validated Dutch version of the KPPS [5]. Approved bilingual translators performed all translations. A graphical overview of the procedure is depicted in Supplementary Figure I. Additionally, the Numeric Rating Scale (NRS) was used to measure the severity of patients' pain during the last month on a scale from 0 (no pain) to 10 (worst pain imaginable). The MoCA, a brief cognitive screening tool, was used as an indication of cognitive functioning [8]. The HADS was used to assess depression and anxiety [9]. Two scores were calculated: one for depression and one for anxiety.

Domains will be indicated with a capital throughout the paper. Three domains were removed, either due to lack of variance (Perceptual problems/Hallucinations and Sexual Function) or due to low reliability (Miscellaneous). Supplementary Table I provides an overview of all domains with concomitant Crohnbach's α, included items and the procedure of calculation of domains. The seven included domains are Cardiovascular, Sleep, Mood, Cognition, Intestinal, Urinary and Pain.

2.4. Statistical analysis

All individual items were converted to z-scores before they were used to calculate a mean for their domain. For our primary analysis, a stepwise forward multiple linear regression was performed to test the association between NMS and QoL, with QoL as dependent variable, and the seven domains as independent variables. Specifically, in order to get insight into individual contributions of significant predictors to the model, the separate forward steps with added significant predictors were provided. QoL was normally distributed, but domain scores were not. Residuals of the regression analysis were normally distributed. Alpha level was set at 0.05. We used SPSS version 23.

RStudio, version 1.1.383 was used for our secondary analysis. A correlation network was calculated with the *qgraph* package [10]. A regularized partial correlation network was calculated using a graphical LASSO with EBIC model selection [11]. Regularized partial correlation networks estimate a large number of parameters and thus require a large set of participants. The sample on which our network was based is quite small, which makes network estimation unstable. The EBIC hyperparameter γ was therefore set to 0 (by default set to 0.5), with a higher γ indicating a sparser network (with fewer edges). This low hyperparameter implies a larger risk of false positives, therefore the second part of our analyses is of exploratory nature [11]. Centrality of nodes was estimated by the following three measures: betweenness centrality indicates the number of times a shortest path between two nodes passes a give node, closeness quantifies a node's connections to other nodes and a node's strength is the sum of connections from that node to other nodes. The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

3. Results

3.1. Participant characteristics

Seventy patients were included in the final analysis, of whom 34 were female (48.6%). Average age was 71.6 years ± 9.72; average disease duration was 6.0 years ± 5.6 and average MoCA score was 22.90 ± 4.58 (median = 24, mode = 25). When asked about dopaminergic fluctuations ('on-off state'), 62 patients indicated feeling 'on' (89%) and three patients (4%) felt 'off' (7% missing).See Supplementary Table II for an overview of medication, and Supplementary Table III for level of education.

3.2. Predictors of QoL

For our main analysis, the final model included Mood and Pain as significant predictors for QoL. The first model included only Mood, and had an explained variance (R^2) of 19.6%. The final model included Mood and Pain, with R^2 of 28%. See Table 1.

Table 1. Multivariate regression analysis, using a stepwise forward model, both steps are shown. QoL was used as a dependent variable. Predictors in the model were Cardiovascular, Sleep, Mood, Cognition, Intestinal, Urinary and Pain.

3.3. The NMS network

Applying a network approach requires a large set of data, because many parameters need to be estimated. Our secondary analysis will therefore be of an exploratory nature with a predominantly qualitative interpretation. For our secondary analysis, all seven domains were entered as nodes both in a full correlation network as well as in a regularized partial correlation network. Fig. 1a shows a correlation network controlled for spurious connections, and each association was corrected for all other associations in a regularized partial correlation network. Cognition and Mood were most strongly connected in both

Table 1
Multiple regression analysis, using a stepwise forward model, quality of life was used as dependent variable.

	R^2 of the model	Included variables	Unstandardized Coefficients		Standardized Beta	Significance
			Beta	Std Error		
Step 1	.196	Mood	-.620	.162	-.433	$p < .001$
Step 2	.280	Mood	-.537	.158	-.384	$p = .001$
		Pain	-.439	.168	-.295	$p = .011$

networks. Correlation coefficients can be found in Supplementary Table IV. Fig. 1b shows centrality measures of each node in from the regularized partial correlations network. Mood and Sleep had the highest betweenness centrality, indicating their central role in the network.

4. Discussion

With this cross-sectional study, we aimed to investigate NMS of PD with two approaches: to examine how each NMS contributes to patients' QoL quantitatively, and to examine how NMS relate to each other qualitatively, the latter with a network approach.

Our primary analysis shows that mood and pain both contribute majorly to QoL. These results are in line with earlier findings. First, depression is a factor consistently associated with QoL in PD [1]. Second, although pain has less consistently been associated with QoL [12], we suggest that the use of the KPPS gives a more robust measure of PD-related pain than other more generic pain measures, resulting in a stronger association with QoL. Additionally, analysis of the NMS-network indicates that mood and sleep play central roles (Fig. 1c), and that mood and cognitive problems are tightly linked (Fig. 1b). Together with the results on our primary analysis, this paper emphasizes the importance of mood problems, both for QoL as well as within the network of NMS. Also, treatment of sleep problems could be beneficial for QoL in PD: improvement of sleep might coincide with a change in pain and mood based on our network analysis (see Fig. 1b). Longitudinal data should be able to add information on directionality when multiple time points are taken into account. The current network analysis cannot shed light on any causal relations between symptoms: it is an undirected network based on correlations [4]. Nonetheless, a network approach to symptoms could provide suggestions as to which symptoms to target, i.e. those that play a central role in the network, in order to achieve amelioration of a symptom that might be more difficult to treat. Amelioration would then follow indirectly. Moreover, a network analysis approaches the multifaceted and thus complex nature of PD more than when only investigating one or two variables at a time. Our results contribute to this notion because both analyses provided different information, which we interpret as complementary. The use of this approach in longitudinal and cohort studies could therefore shed new light on that type of data. In clinical practice, it can provide suggestions on which symptoms to focus.

Because of aforementioned power issues, we would first like to emphasize that our results should be replicated. Another consideration is the choice of nodes in our network: the variables that make up the nodes in our network are an aggregate of measures of the same construct (e.g. the node 'mood' encompasses symptoms of depression as well as anxiety). This makes the measure on the one hand more robust, but on the other hand reduces specificity. In general, nodes in a network are dependent on the items from the clinical instruments on which they are based. A network might therefore never be 'complete' (i.e. include all symptoms of the disease). Nonetheless, although influences that cannot be accounted for will remain in every dataset, such as within-person variability or influence of medication, even a near-complete network of symptoms and its interactions will greatly aid in the treatment of NMS of PD.

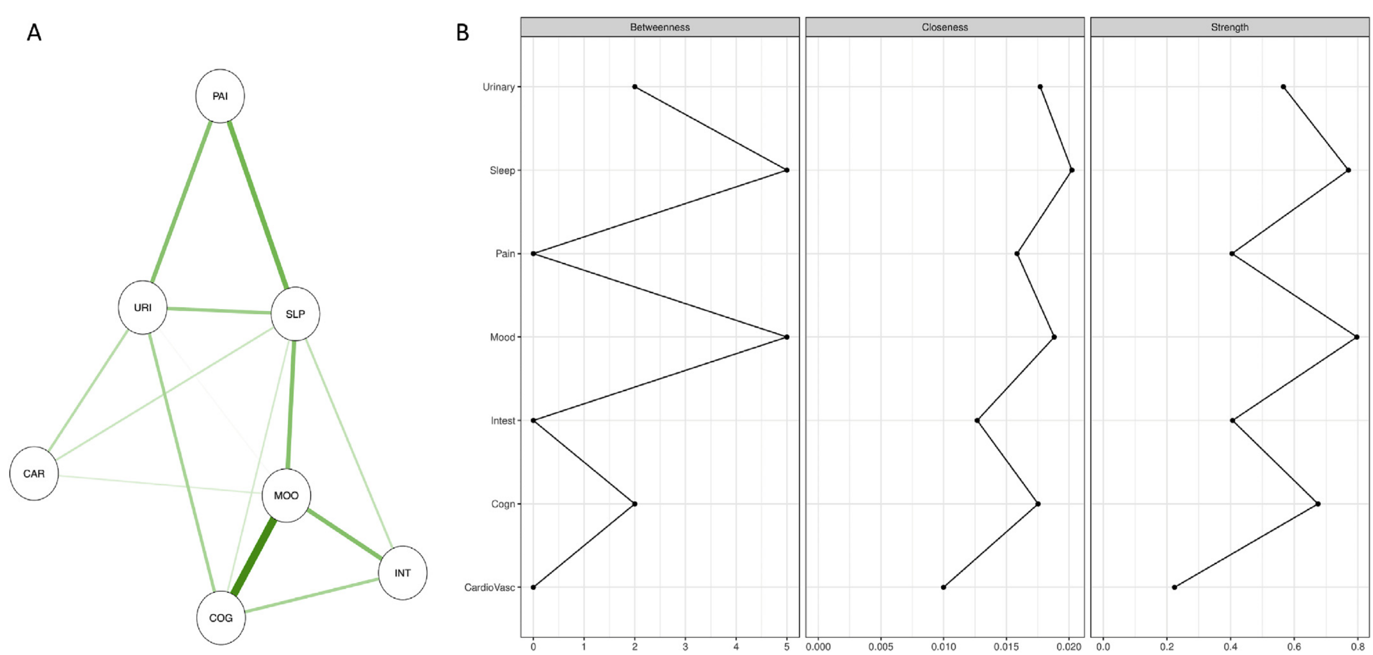

Fig. 1. Exploratory network analysis of the seven non-motor domains of PD, preformed on all subjects (n = 70). Thickness of connecting lines indicates strength of correlations. All correlations are positive. Fig. 1a: Regularized partial correlation network; Fig. 1b: Betweenness centrality, closeness and strength per node. PAI = Pain, URI = Urinary, SLP = Sleep, CAR = Cardiovascular, MOO = Mood, COG = Cognition, INT = Intestinal.

Declaration of interest

GE received funding from Stichting Parkinson Fonds. LD received funding from the Branco Weiss Fellowship (Society in Science).

Contributors

GE, YK, HW, ES and AV contributed to the conception of the design of the study. GE, YK and AV carried out data acquisition. GE, LD and ES performed the analyses. GE drafted the article, LD, YK, HW, ES and AV have critically revised the article. All authors have approved the final article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.08.002.

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