Data Availability Statement

Brain samples used in this study, with corresponding results, can be made available by formal application directly to the Queen Square Brain Bank.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

It Is as It Was: MDS-UPDRS Part III Scores Cannot Be Combined with Other Parts to Give a Valid Sum

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ABSTRACT: Background: Original clinimetric analyses by the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) developers did not confirm the validity of summing the scores of its parts. Recent studies used the summed score of Part III and other parts as efficacy outcomes.

Objective: The aim of this study was to establish whether summing scores of MDS-UPDRS parts can be recommended.

Methods: Using 7466 full MDS-UPDRS scores, we applied two-step factor analysis as in the original article to reassess the validity analysis with the threshold criterion set at comparative fit index ≥0.9.

Results: All comparative fit indexes of any combination including Part III were lower than 0.90.

Conclusions: Summing Part III MDS-UPDRS scores with other parts is not clinimetrically sound. The MDS-UPDRS is a validated four-part scale with corresponding individual part scores and needs to be used within the limits originally presented. © 2022 International Parkinson and Movement Disorder Society.

Key Words: clinimetrics; total score; factor analysis; Parkinson's disease

Introduction

The Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is the most widely used clinical rating tool in Parkinson's disease (PD).[1-4] The scale includes patient and investigator ratings in distinct parts and assesses both motor and non-motor aspects of PD. Regulatory recommendations favor outcomes combining objective rater-based scores and patient input,[5] but original clinimetric analyses by the MDS-UPDRS developers failed to confirm the validity of summed scores of its parts.[1] To this end, most prior studies have followed the original recommendations and analyzed each part of the scale individually, providing a separate report of the patient's voice, along with rater-based motor measurements, without reporting an invalid summed score.[4] Recently, however, some studies have used the combined scores of all or selected MDS-UPDRS parts as efficacy outcomes. Specifically, a summed score of Part II (patient-based "Motor Experiences of Daily Living") with Part III (rater-based "Motor Examination") has been used as both a primary and a secondary outcome.[6,7] More recently, two randomized clinical trials used the sum of Parts I + II + III as the primary outcome.[8,9] Given this newly observed interest in summing Part III with other MDS-UPDRS part scores, we reassessed the validity analysis applied in the original clinimetric program in an expanded cohort to establish whether our original recommendation against summing parts could be reconsidered and modified.

Patients and Methods

Study Population

The MDS-UPDRS translation program, sponsored by the International Parkinson and Movement Disorder Society (MDS), is an ongoing cross-sectional, multinational, multicenter study designed to develop and validate the translation of the MDS-UPDRS.[10] The original dataset included 8927 MDS-UPDRS ratings from patients with PD, diagnosed using UK Brain Bank Criteria[11] representing all Hoehn and Yahr stages with assessments performed in the patient's native language (24 international languages, not including English) by raters who successfully completed the MDS-UPDRS training program. We excluded 1461 patients with missing scores in MDS-UPDRS Parts I, II, III, or IV, resulting in a total of 7466 patients included for analysis.

Statistical Analyses

We considered seven combinations of Part III (33 items) with other MDS-UPDRS parts: combination 1, Parts I (13 items) + III; combination 2, Parts II (13 items) + III; combination 3, Parts III + IV (6 items); combination 4, Parts I + II + III; combination 5, Parts I + III + IV; combination 6, Parts II + III + IV; and combination 7, Parts I + II + III + IV. We adopted the same two-step factor analysis methodology as the original article.[1] Specifically, for each combination, we first ran an exploratory factor analysis (EFA) to set the number of factors as the number of eigenvalues being at least 1 in the Scree plot and determined the factor structure by using a factor loading cutoff of 0.4. We then ran a confirmatory factor analysis (CFA) based on the identified factor structure to determine the construct validity. All analyses were conducted using the M-plus, Version 7.4.[12] For factor estimation, we used an adjusted weighted least square method that minimizes the weighted sum of squared differences between observed and estimated correlation matrices, excluding diagonal elements.[13] We used an orthogonal rotation (with option CF-VARIMAX) that forces the factors to be uncorrelated to aid in factor interpretation.

Construct Validity Criterion

To assess the model fit, we computed the comparative fit index (CFI) as the goodness-of-fit index. A CFI ≥0.90 suggests an acceptable fit[14,15] and matches the criterion used for the initial validation of the MDS-UPDRS.[1]

Results

Of the total 7466 subjects, 4133 (55.7%) were male. Hoehn and Yahr stages ranged from stage 0 to stage 5 with the proportion of 0.6%, 13.4%, 48.4%, 26.8%, 8.6%, and 2.3%, respectively. The mean scores for MDS-UPDRS Parts I, II, III, and IV were 12.02, 14.91, 34.31, and 4.67, respectively (Table 1).

We assessed the construct validity of the factor structures of all combinations of MDS-UPDRS parts, including Part III. We determined the number of factors based on the Scree plots in Fig. 1. Specifically, four factors were selected in combinations 1, 2, and 3; five factors were used for combinations 4, 5, and 6; and six factors were selected for combination 7. The EFA results are in Supporting Information Table S1. The CFA results (Table 2) suggest that all CFIs from combinations 1 to 7 were lower than 0.90, which is less than the prespecified validity threshold.

TABLE 1 *Baseline demographic and disease characteristics of the dataset*

Characteristics	All
Sample size, N	7466
Education years, mean (SD) (n = 6306)	11.26 (5.86)
Sex (n = 7421)	
Female, n (%)	3288 (44.3%)
Male, n (%)	4133 (55.7%)
PD diagnosis (n = 6969), mean (SD), years	7.63 (5.74)
Dyskinesias presence (n = 7410)	
Yes (%)	2131 (28.8%)
Hoehn and Yahr stage (n = 7395), n (%)	
0	43 (0.6%)
1	988 (13.4%)
2	3579 (48.4%)
3	1981 (26.8%)
4	635 (8.6%)
5	169 (2.3%)
MDS-UPDRS Part I sum, mean (SD)	12.02 (7.43)
MDS-UPDRS Part II sum, mean (SD)	14.91 (9.73)
MDS-UPDRS Part III sum, mean (SD)	34.31 (19.09)
MDS-UPDRS Part IV sum, mean (SD)	4.67 (4.82)

Abbreviations: MDS-UPDRS, Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; SD, standard deviation.

Discussion

The original MDS-UPDRS was envisioned to focus on motor and non-motor components of PD and to honor both the patient's perspective and the judgment of trained raters. Acknowledging that the data sources were purposefully different and the clinical items evaluated in the scale were divergent for the two potential raters, the developers never prespecified a plan to generate a single total score based on the sum of the four parts. Nonetheless, the original analyses did test the various combinations of MDS-UPDRS parts and reported, "The combined results preclude using a total MDS-UPDRS score or scores based on combinations of parts."[1] As a result, the MDS-UPDRS scores are reported separately for Part III rater-based motor scores alongside, but separate from, Part I (patient perceptions of non-motor elements), Part II (patient perceptions of motor activities), and Part IV (complications of therapy).

Regarding the cutoff point of CFI, some reports[16-18] accept 0.80 for an adequate fit. However, these articles[16-18] also comment on the limitations of setting 0.80 as the threshold. For example, $0.8 \le CFI < 0.90$ was defined as an adequate but marginal fit, which may lead to a lack of construct validity of the summing strategy. In contrast, some studies[19-21] considered a variety of simulation settings involving different sample sizes and item numbers. They recommended to use CFI ≥0.90 as the threshold when there are more than 30 items and the sample size is larger than 250. Accepting that there is no absolute rule, in the original clinimetric analyses by the MDS-UPDRS developers,[1] they defined CFI ≥0.90 as the threshold, and we aimed to replicate this exercise. Our goal was to reassess the validity of various combinations of Part III with other parts without any methodology change. Hence we set CFI ≥0.90 as the threshold of pass versus no pass. Although some combinations, e.g., Parts II + III and Parts II + III + IV, had CFI very close to 0.9, this statistic is either met or not met, and therefore those values fail.

Whereas combining parts by summing the component items may seem clinically logical, the MDS-UPDRS parts do not have the same calibration or the same number of items, leaving a simple summation fraught with statistical liabilities. The standard two-step validation process with an initial EFA based on factor structure followed by CFA and the calculation of a CFI with a predetermined success threshold of ≥0.9 failed for all combinations of MDS-UPDRS parts with Part III. This failure with a sample size of nearly 7500 subjects with PD mimicked that found with our original

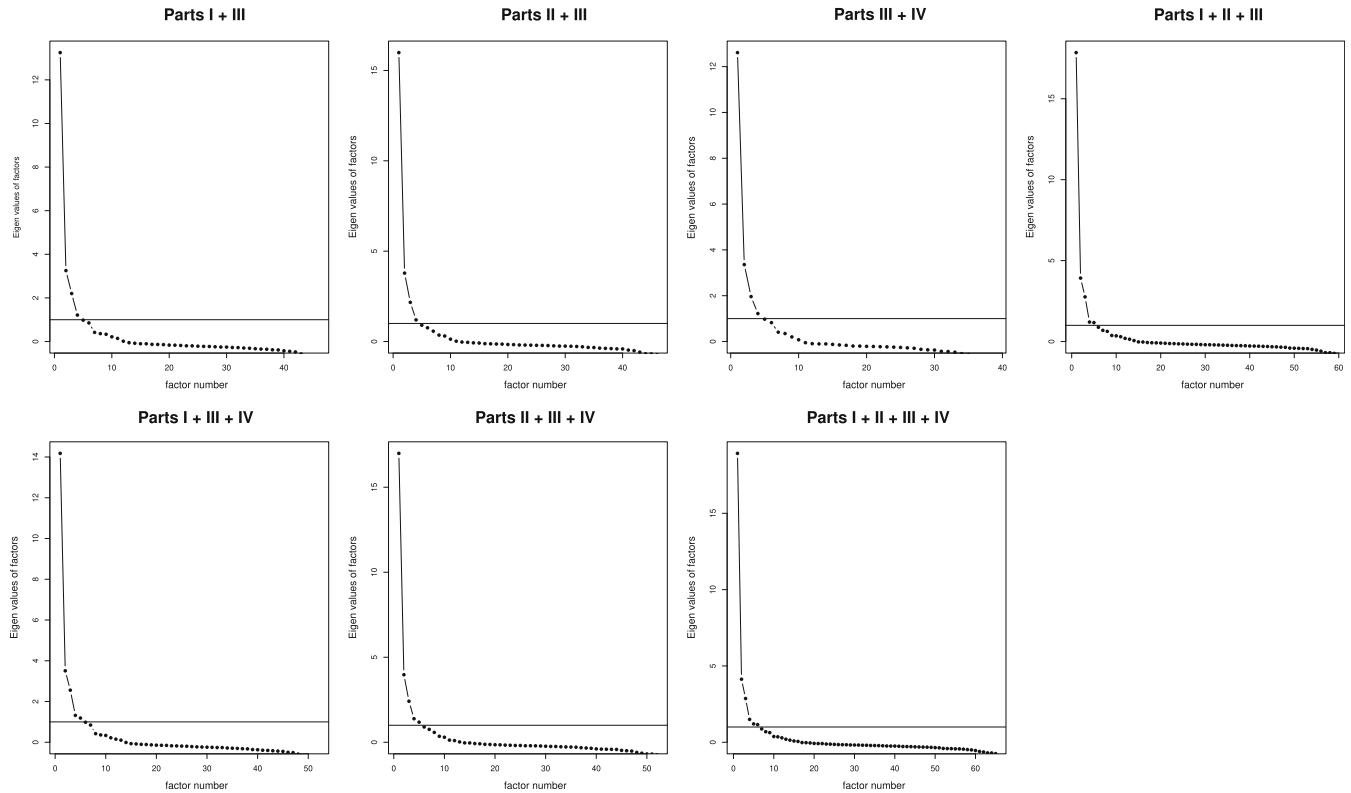

FIG. 1. Scree plots of seven combinations of Part III (33 items) with other Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) parts.

TABLE 2 *Confirmatory factor analysis results from seven combinations of Part III with other MDS-UPDRS parts*

Combination number	Combinations	CFI	Acceptance (≥0.90)
1	Parts I + III	0.862	No
2	Parts II + III	0.893	No
3	Parts III + IV	0.877	No
4	Parts I + II + III	0.865	No
5	Parts I + III + IV	0.852	No
6	Parts II + III + IV	0.890	No
7	Parts I + II + III + IV	0.873	No

Abbreviations: CFI, comparative fit index; MDS-UPDRS, Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale.

sample of 877, so we are confident that sample size limitations had no impact on the negative results. Without hesitation, we state to all colleagues using the MDS-UPDRS that the scale must be used as validated and originally presented: summing Part III scores with those of any one or several other parts is not scientifically sound.

Cognizant of the regulatory pressures, however, we have used other statistical techniques to use the item information from the MDS-UPDRS in innovative ways that can incorporate patient and rater estimates into pertinent outcomes. When this process is limited to motor elements of PD, we have taken the individual items of Parts II and III and considered them as a simple list of 46 combined items. With EFA and Item Response Theory applications,[22] we identified two salient motor domains, tremor and non-tremor, within the combined two parts, and we could generate valid summation scores for Part II + III tremor (1 item from Part II and 10 items from Part III) and Part II + III non-tremor (12 items from Part II and 23 items from Part III) (unpublished data)). This strategy culls material from the patient and rater on the given domain and statistically provides a solid manner to weave Parts II and III together. It provides a valid measure of MDS-UPDRS tremor and non-tremor severity but still results in two primary motor outcomes.

A much more difficult clinimetric exercise involves adding Part I (non-motor) information and rendering a total integration of Parts I, II, and III. If Parts I + II + III in simple summation, as developed and reported recently in two major studies,[8,9] fails clinimetrically, are

there alternate statistical strategies that might lead to a clinimetrically sound integration? The statistical challenge is complex, because it brings together completely different types of symptoms outside of motor disability and impairment, which is corroborated by the lack of statistical support for combining such dissimilar indices. Clearly, a simple sum fails, and despite many attempts to model a composite score for Parts I, II, and III, to date, we have not found ways to consolidate the individual items or parts of the MDS-UPDRS into a valid single solution.

The implications of generating a numeric score without a valid anchor to the disease being measured are many. On the one hand, the value may not change with an intervention, giving a false impression of futility when, in fact, the treatment may be beneficial in some important functional domain. Likewise, a false positive effect may lead clinicians to invest in a treatment that has no ultimate impact. Avoiding this "apples and oranges" dilemma is the foundation of scale validation, so that the numbers reported as outcomes have clinical pertinence.

We are left with the two sober conclusions that we offered when the scale was originally presented to the scientific community.[1] First, the MDS-UPDRS offers a clinimetrically sound and clinically pertinent assessment of the multiple domains of PD impairment and disability, incorporating rater input and patient voice in discrete parts. Second, the data are diverse, and the parts must be considered in their integrity for standard analysis and never summarized with a simple arithmetic sum of Part III with any other part or parts. Although we continue to test alternative statistical modeling that may provide a path forward to address particular questions pertinent to regulatory agencies and clinical trial design, we ask our colleagues to use the MDS-UPDRS as it was envisioned and soundly tested. In short, it is as it was, and a scale should be used only within its clinimetric limits. ■

Ethical Compliance Statement

This study has been approved by Duke Institutional Review Board (Protocol ID: Pro00107266). Informed patient consent was not necessary for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. ■

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Detection and Characterization of a De Novo *Alu* Retrotransposition Event Causing *NKX2-1*-Related Disorder

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ABSTRACT: Background: Heterozygous *NKX2-1* loss-of-function variants cause combinations of hyperkinetic movement disorders (MDs, particularly childhood-onset chorea), pulmonary dysfunction, and hypothyroidism. Mobile element insertions (MEIs) are potential disease-causing structural variants whose detection in routine diagnostics remains challenging.

Objective: To establish the molecular diagnosis of two first-degree relatives with clinically suspected *NKX2-1*-related disorder who had negative *NKX2-1* Sanger (SS), whole-exome (WES), and whole-genome (WGS) sequencing.

Methods: The proband's WES was analyzed for MEIs. A candidate MEI in *NKX2-1* underwent optimized SS after plasmid cloning. Functional studies exploring *NKX2-1* haploinsufficiency at RNA and protein levels were performed.

Results: A 347-bp *Alu*Ya5 insertion with a 65-bp poly-A tail followed by a 16-bp duplication of the pre-insertion wild-type sequence in exon 3 of *NKX2-1* (ENST00000354822.7:c.556_557ins*Alu*541_556dup) segregated with the disease phenotype.

Conclusions: We identified a de novo exonic *Alu*Ya5 insertion causing *NKX2-1*-related disorder in SS/WES/WGS-negative cases, suggesting that MEI analysis of short-read sequencing data or targeted long-read sequencing could unmask the molecular diagnosis of unsolved MD cases. © 2022 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: brain-lung-thyroid syndrome; chorea; dystonia; mobile element insertion; thyroid transcription factor-1

Introduction

NKX2-1 is a homeobox gene encoding thyroid transcription factor-1 (TTF1), a key regulator of tissue-specific gene expression mainly involved in thyroid, lung, and ventral forebrain morphogenesis.[1] Heterozygous *NKX2-1* loss-of-function variants account for a clinical spectrum, including childhood-onset chorea, hypothyroidism, and pulmonary dysfunction, in isolation or any combination, with brain-lung-thyroid (BLT) syndrome being the most severe phenotype.[2,3] Other possible manifestations include motor delay, dystonia,