

Item Response Theory modelling to leverage data from historical Parkinson's Disease trials while integrating data from a newer version of the clinical endpoint

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Objectives

To develop a framework that can leverage historical Unified Parkinson's Disease (PD) Rating Scale (UPDRS) clinical data, while integrating with a newer version - Movement Disorder Society sponsored revision (MDS-UPDRS) through the application of Item Response Theory (IRT) methodology

Background

- The main assumption in IRT is that the probability of response (0, 1, ...k, .. K) to each item (j) depends on an unobserved variable 'disability' of each subject (i) [1]. A two parameter logistic model was used to characterise this relationship (Eq. 1 & 2).
- Item Response Model (IRM) parameters are classified into:
 - Item specific parameters: discrimination/slope (a_j) and difficulty/location (b_j), are modelled as fixed effects
 - Subject specific parameter: disability (D_i), is modelled as random effects

$$P(Y_{ij} \geq k) = \frac{e^{a_j(D_i - b_j)}}{1 + e^{a_j(D_i - b_j)}} \quad \dots (Eq. 1)$$

$$P(Y_{ij} = k) = P(Y_{ij} \geq k) - P(Y_{ij} \geq k + 1) \quad \dots (Eq. 2)$$

- A longitudinal IRM using MDS-UPDRS data of De Novo cohort from the Parkinson's Progression Markers Initiative database [2] was developed previously [3]:
 - It included three latent variables, whose assignment and choice was in good agreement with how the questionnaire was set up and also based on model-based diagnostics

Methods

Data and Patients

- There are 44 items in parts I - III of UPDRS scale, each of which is rated between 0 (normal) and 4 (severely affected).
- Either (a) "total" score calculated as sum of parts I - III or (b) just one individual part is commonly used clinical endpoint in PD trial analyses.
- This work was performed using the UPDRS data from two clinical trials:
 - 12-week crossover Phase III clinical study in 161 early PD patients treated with at least one dose of controlled- and/or extended-release formulations of ropinirole [4].
 - 24-week parallel-group Phase III clinical study in 393 advanced PD patients that were inadequately controlled by L-Dopa and treated with at least one dose of placebo or ropinirole [5]
- The same structural model (excluding the longitudinal aspects) developed previously was assumed and all the item specific parameters were fixed to their final estimates
- In the current work, baseline IRM was developed using UPDRS assessments before the start of the treatment (baseline) from these studies by adapting the previously developed model (based on MDS-UPDRS data)

Model Adaptation Workflow

Step 1 Mapping - strategy outlined by Goetz et al [6] (Fig. 1 & 2)

- Direct-mapping: no additional parameter estimation was necessary
- Indirect-mapping: for the items which do not map one-to-one, additional parameters reflecting the re-assignment of the probabilities were estimated (E.g., Item 29 in Fig. 2)
- Only in UPDRS: item-specific parameters were estimated based on UPDRS data only as these items showed little to no-parallelism with MDS - UPDRS scale

Figure 1. Mapping mechanisms. Listed numbers are the items in UPDRS scale; highlighted in bold are items which were evaluated for different parts and/or sides (e.g., left, right) of the body and number of these evaluations are shown in parentheses with *

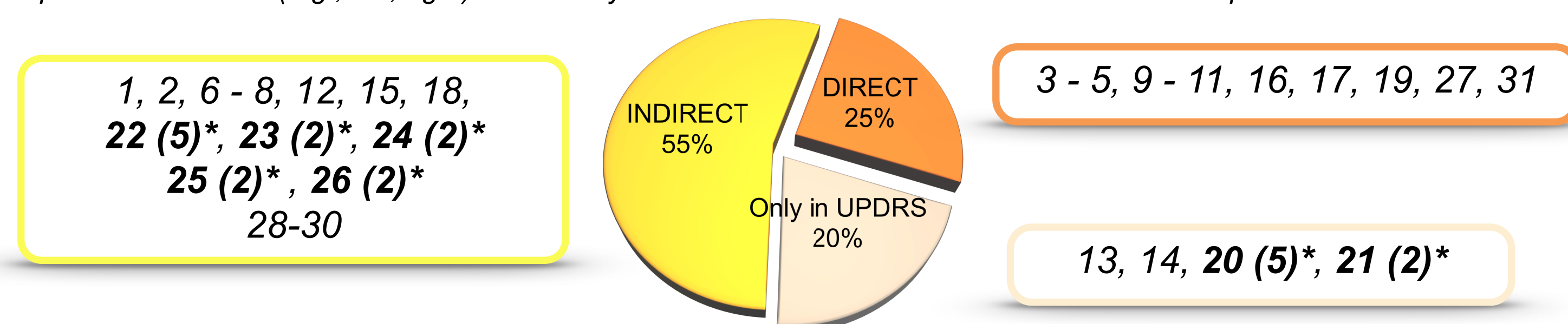


Figure 2. Mapping strategy for item 29. Suggested scheme mapped from UPDRS to MDS - UPDRS: 0 - 0; 1 - 1, 2 - 2, 3 - 2, 4 - 3 or 4; indicated in bold are two additional parameters (FR2, FR4) that are estimated based on the adapted model

MDS - UPDRS Model	DV = 0 (MD) P0	DV = 1 (MD) P1	DV = 2 (MD) P2	DV = 3 (MD) P3	DV = 4 (MD) P4
UPDRS Data	DV = 0 (U) P0	DV = 1 (U) P1	DV = 2 (U) P2	DV = 3 (U) P3	DV = 4 (U) P4
Adapted Final Model	DV = 0 P0	DV = 1 P1	DV = 2 P2*FR2	DV = 3 P2*(1-FR2) + P4*FR4	DV = 4 P3 + P4*(1-FR4)

Step 2 Estimation of the mean & variance of latent variable distributions with shifts

- The mean and variance of the latent variable distributions for the early PD subjects (used as the reference population), and the variances, shifts in the means for the study with advanced PD subjects were estimated

Step 3 Model evaluation: simulation based diagnostics

Conclusions

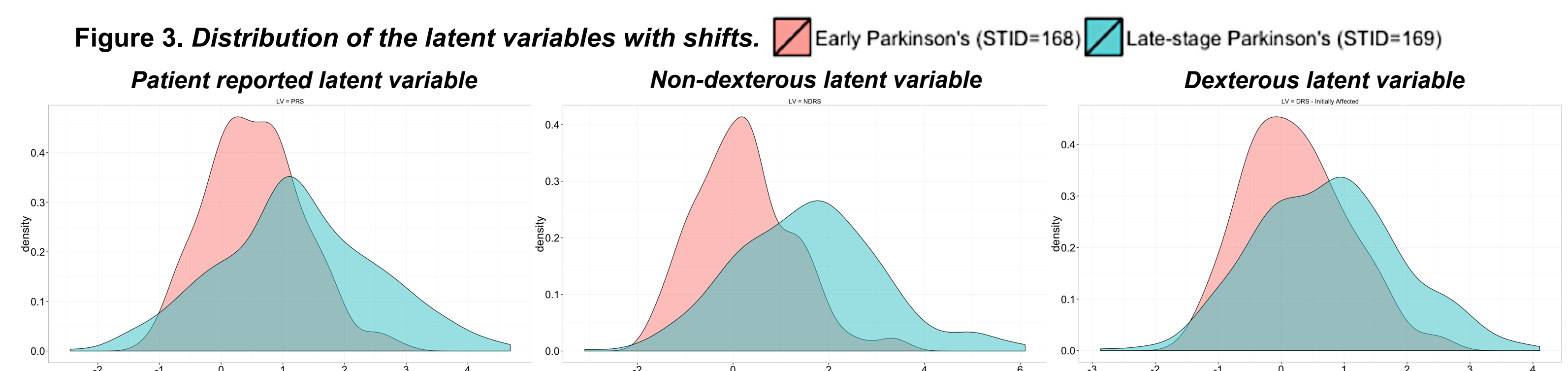
- IRT methodology allowed for integration of two versions of main clinical endpoints used in PD trial analyses into one unique framework, provided they are mapped on to the same underlying latent variable(s) continuum.
- This can facilitate improved utilization of data from diverse sources and also different disease populations (e.g., early vs. advanced PD), potentially leading to better characterization of disease progression and drug effects in PD.

Results

- Parameters characterising the re-assignment of the probabilities for the indirectly mapped items and the parameters for items unique to UPDRS were estimated successfully.
- The estimates for mean and variance for each of the latent variable distribution is shown in Table - 1 and plotted in Figure 3 (each panel representing a latent variable).

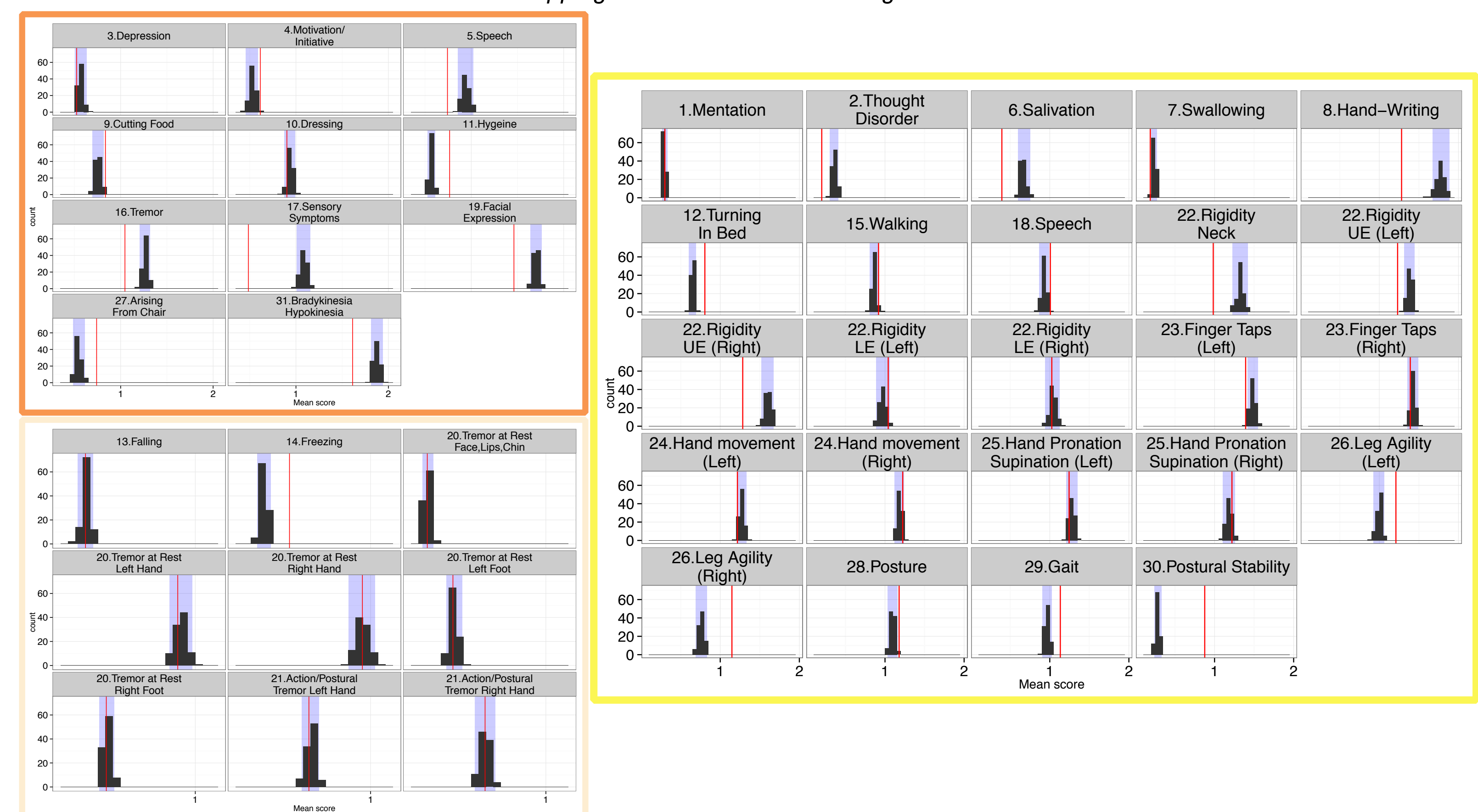
Table 1. Mean & variances of latent variable distributions. Number following '+' is the shift; Items 20* and 22* were evaluated for tremor at rest of face, lips, chin and rigidity of neck respectively, among the right and left sides of the body and therefore they appear in both the non-dexterous as well as dexterous latent variable

Parameter	Values for Study with Early PD Subjects	Shift value for Study with Late PD Subjects
Mean (Variance)		
Latent variable 1: Patient reported items (1 - 17)	0.535 (0.774)	+ 0.697 = 1.23 (1.88)
Latent variable 2: Non-dexterous items (18, 19, 20*, 22*, 27 - 31)	0.219 (1.23)	+ 1.36 = 1.58 (2.63)
Latent variable 3: Dexterous items (20*, 21, 22*, 23 - 26)	0.353 (0.821)	+ 0.32 = 0.734 (1.50)



- The simulation based diagnostics (Figure. 4) suggest:
 - very good agreement with observations for items unique to UPDRS
 - varying degree of agreement for direct/indirectly-mapped items
- Although not all the IRM parameters were re-estimated, which allowed to use prior information and gain run-times, adequacy between the data and simulations was satisfactory.

Figure 4. Simulation based diagnostics. The red line is the calculated mean of all the observed scores for each item; black histogram represent the distribution of the mean of simulated scores (based on 100 simulations of the final baseline model) and purple shaded area shows 5th and 97.5th percentiles for each item based on the simulations; U/LE - Upper/Lower Extremity. Panels show the stratification based on the mapping mechanisms shown in Figure 1.



References

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Disclosures:

Uppsala University, the institution of G. Gottipati, M.O. Karlsson, and E. L. Plan, has received contract analysis fee from GlaxoSmithKline, London, UK

A. C. Berges, S. Yang, C. Chen are employees of GlaxoSmithKline, London, UK.