Modeling a Composite Score in Parkinson’s Disease using Item Response Theory

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Parkinson’s Disease

- Parkinson’s disease is a progressive neurodegenerative brain disorder characterized by
  - loss of neurons in substantia nigra
  - decrease in the dopamine levels

- Parkinson’s disease is known to affect approximately 6.3 million people worldwide¹

- Movement Disorder Society (MDS) - sponsored revision² of the Unified Parkinson’s Disease Rating Scale (UPDRS)

¹. European Parkinson’s Disease Association (http://www.epda.eu.com/en/)
². Goetz et al. Move Disord. 2007; 22(1) 41-7
Overall, there are 68 items – 66 ordered categorical and 2 binary

Higher total score (range: 0 – 267) indicates more severe disease

Part I
• Non-motor aspects of experiences of daily living
  • e.g. cognitive impairment

Part II
• Motor aspects of experiences of daily living
  • e.g. tremors

Part III
• Motor examination
  • e.g. finger tapping – right & left hands

Part IV
• Motor complications
  • e.g. functional impact of dyskinesias
Data

- Parkinson Progression Markers Initiative (PPMI) Database:
  - Longitudinal MDS-UPDRS data:
    at baseline(0), up to 12 visits (60 months) ➔ 255023 observations

Healthy Controls
(n = 196)
Age ≥ 30 years
No first degree blood relative with Parkinson’s disease

De Novo Parkinson’s Disease Subjects
(n = 423)
Diagnosed ≤ 2 years
Not taking any medications for Parkinson’s disease

Subjects With Scans Without Evidence of Dopaminergic Deficit (SWEDD)
(n = 64)
Consented as Parkinson’s patients
PPMI – Item Responses
Item 23

Over the past week, have you usually had a shaking or tremor?

0: Normal
Not at all. I have no shaking or tremor

1: Slight
Shaking or tremor occurs but does not cause problems with any activities

2: Mild
Shaking or tremor cause problems with only a few activities

3: Moderate
Shaking or tremor cause problems with many of my daily activities

4: Severe
Shaking or tremor cause problems with most of my activities
Over the past week, have you usually had a shaking or tremor?

0: Normal
1: Slight
2: Mild
3: Moderate
4: Severe
Item Response Theory

It relates the probability of responses to items in an assessment to an underlying latent (hidden) variable.
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It has been applied in:
- Alzheimer's (ADAS-cog)
- Multiple Sclerosis (EDSS)
- Schizophrenia (PANSS)

Aims of the project

- To explore IRT model components and investigate MDS-UPDRS features
- To describe MDS-UPDRS longitudinal changes
- To provide a model for future design and analysis of trials in Parkinson’s Disease
- To explore model building strategies and diagnostics for IRT
Model building strategy

- Subjects of De Novo cohort was used as reference population
  - Healthy controls and SWEDD cohort modeled by shift in (distribution of) disability

- Estimation of ICC with shifts
  - Fix the ICC
  - Estimate the longitudinal changes

- Simultaneous estimation of ICC and longitudinal changes
Structural IRT model

Model parameters divided into
- Item specific parameters \(- a_j, b_j \ldots\) (discrimination and difficulty)
- Subject specific parameters \(- D_i\) (disability)

Ordered categorical \((0 - 4/5)\)

\[
P(Y_{ij} \geq k) = f_j(D_i) = \frac{e^{a_j(D_i - b_j)}}{1 + e^{a_j(D_i - b_j)}}
\]

\[
P(Y_{ij} = k) = P(Y_{ij} \geq k) - P(Y_{ij} \geq k+1)
\]

Binary \((0/1)\)

\[
P(Y_{ij} = 1) = f_j(D_i) = \frac{e^{a_j(D_i - b_j)}}{1 + e^{a_j(D_i - b_j)}}
\]

\[D_i = \eta_i\]

\[D_i(t) = D_{i,0} + \text{Slope}_i \times t\]

De Novo cohort: \(D_{i,0} \sim N(0, 1)\)

Other cohorts:
- Shift in baseline
- Different slopes
Item Characteristic Curve

*Item 23 – Distribution of item responses*
Item Characteristic Curve

*Item 23 – Individual probabilities*
Results

*Shift in baseline disability for a typical individual*

- Healthy Controls
- SWEDD
- De Novo Parkinson's

**16**
Results

Longitudinal changes – *De Novo cohort*
Results

Longitudinal changes – De Novo cohort
Results

Longitudinal changes – De Novo cohort
Results

Longitudinal changes – De Novo cohort
Diagnostics

VPC of longitudinal model – All cohorts

Healthy Controls

De Novo PD Subjects

SWEDD
Diagnostics

*Item 23 - Longitudinal model – De Novo cohort*
For the $i^{th}$ subject, $j^{th}$ (23rd) item, $DV = 1$

Based on ICC
For $i^{th}$ subject, $j^{th}$ (23rd) item, $DV = 1$

Based on ICC

\[ E_{ij} \text{ (weighted prediction)} = P1 \times 1 + P2 \times 2 + P3 \times 3 + P4 \times 4 \]

\[ RES = DV - E_{ij} \]
For $i^{th}$ subject, $j^{th}$ (23rd) item, $DV = 1$

Based on ICC

\[ E_{ij} \text{ (weighted prediction)} = P1 \times 1 + P2 \times 2 + P3 \times 3 + P4 \times 4 \]

\[ = (1.289) \]

\[ RES = DV - E_{ij} \]

\[ (-0.289) \]
Correlation among item responses

• Already handled by the IRT model, all item responses are related to the same latent variable - disability

Certain item responses may be more (/less) correlated than what the model predicts

• Investigate multiple latent variables by exploring correlation of residuals among the item responses
Correlation of residuals

All data from De Novo cohort ONLY – One latent variable
Correlation of residuals

All data from De Novo cohort ONLY – One latent variable

Alternating right & left
(30 – 43) & (50 – 57)
Diagnostics – Residuals

All data from De Novo cohort ONLY – One latent variable
Diagnostics – Residuals

All data from De Novo cohort ONLY – **Four latent variables**
• Simultaneous estimation of IRT parameters with the longitudinal changes described the data well.
  – The IRT model simulations for the total score and at item level were in good agreement with observations

• Model-based diagnostics based on the residuals can be used as a tool to assess the need for multiple latent variables to improve the IRT models
Future direction

Disease/patient population

This framework may be then extended:

– To characterize the disease progression in Parkinson’s
– As a basis for design and analysis of trials in Parkinson’s
– Identifying false positive patients (e.g., misdiagnosed Parkinson’s subjects) such as SWEDD
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