OVERVIEW OF BIOMARKERS IN DIVERSE POPULATIONS: SEX DIFFERENCES

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LA
While PD is most commonly associated with motor disturbances, cognitive dysfunction appears in 40% of patients. Cognitive domains include:

- Executive function
- Visuospatial function
- Processing speed
• PD is 1.5 times more common in men than in women
• Symptomatic onset is delayed in women
• Women more often present with the tremor dominant phenotype (67% compared to 48% in men) associated with less severe motor deterioration

• Hypothesis: there are sex differences in cognitive dysfunction in PD
SUBJECTS

PD group
  • N = 89 (39 females)

Control group
  • N = 59 (27 females)

Sex/gender was determined via self-report

Exclusion criteria:
  • MMSE < 24
  • WAIS-III Digit Span Total < 10
  • Hx of Head Injury, Mental Illness, Drug Abuse etc.
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Age (years)</th>
<th>Education (years)</th>
<th>MMSE</th>
<th>ESS</th>
<th>NART-R</th>
<th>GDS *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control (M)</strong></td>
<td>32</td>
<td>65.63 (5.84)</td>
<td>16.53 (3.29)</td>
<td>28.94 (1.01)</td>
<td>7.25 (3.59)</td>
<td>112.03 (9.28)</td>
<td>2.75 (3.07)</td>
</tr>
<tr>
<td><strong>Control (F)</strong></td>
<td>27</td>
<td>65.04 (6.93)</td>
<td>16.59 (3.13)</td>
<td>28.59 (1.39)</td>
<td>6.33 (3.37)</td>
<td>113.83 (5.44)</td>
<td>2.82 (3.89)</td>
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<tr>
<td><strong>PD (M)</strong></td>
<td>50</td>
<td>67.9 (6.52)</td>
<td>15.58 (2.9)</td>
<td>28.42 (1.84)</td>
<td>8.46 (4.08)</td>
<td>112.82 (9.88)</td>
<td>6.36 (5.61)</td>
</tr>
<tr>
<td><strong>PD (F)</strong></td>
<td>39</td>
<td>66.53 (5.97)</td>
<td>16.50 (2.46)</td>
<td>28.84 (1.31)</td>
<td>8.63 (5.07)</td>
<td>115.53 (6.36)</td>
<td>4.76 (3.93)</td>
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</tbody>
</table>
LEVODOPA EQUIVALENTS

Equivalent dose in mg

Male

Female
## Disease Severity

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
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<tbody>
<tr>
<td>H&amp;Y (median)</td>
<td>1.904</td>
<td>2.016</td>
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<tr>
<td>UPRDS I</td>
<td></td>
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<tr>
<td>UPRDS II</td>
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<td>UPRDS III</td>
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<td>UPRDS IV</td>
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<tr>
<td>UPRDS Total</td>
<td></td>
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</table>
### Digit Span

<table>
<thead>
<tr>
<th>Digit Span Forward</th>
<th>Digit Span Backward</th>
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<tbody>
<tr>
<td>• 9-7</td>
<td>• 7-1</td>
</tr>
<tr>
<td>• 6-3</td>
<td>• 3-4</td>
</tr>
<tr>
<td>• 5-8-2</td>
<td>• 6-2-9</td>
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<tr>
<td>• 6-9-4</td>
<td>• 4-7-5</td>
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<tr>
<td>• 7-8-2-6</td>
<td>• 8-2-7-9</td>
</tr>
</tbody>
</table>

- 1-7
- 4-3
- 9-2-6
- 5-7-4
- 9-7-2-8
Condition 1
• Measure of visuospatial function
Condition 2 and 3

• Number and letter connection
Condition 4
- Number/Letter Switching
Condition 5

- Motor Speed correction
TRAIL MAKING TEST

Time (s)

Condition 1  Condition 2  Condition 3  Condition 4  Condition 5  Condition 4 minus 5

PD (M)  PD (F)

*
VERBAL FLUENCY

Condition 1
  • Letter Fluency
    • F A S

Condition 2
  • Category Fluency
    • Animals and Boy’s Names

Condition 3
  • Fruits/ Furniture

Total Switching Accuracy
  • Number of total correct category switches between fruit and furniture
VERBAL FLUENCY

<table>
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<tr>
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<th>PD (F)</th>
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<tr>
<td><strong>Letter Fluency</strong></td>
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<tr>
<td><strong>Category Fluency</strong></td>
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<tr>
<td><strong>Category Switching</strong></td>
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</tr>
<tr>
<td><strong>Total Switching Accuracy</strong></td>
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</table>

Number of Words

*Indicates significant difference.
COLOR WORD INTERFERENCE

Condition One

Condition Two

green red blue green blue red blue green blue green red green red blue green red green blue red green blue

Condition Three

green red blue green blue red blue green blue green red green red blue green red green red blue green red green blue red green blue

Condition Four

green red blue green blue red blue green blue green red green red blue green red green red blue green red green blue red green blue
### SYMBOL DIGIT MODALITIES TEST (SDMT)

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<tr>
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SYMBOL DIGIT MODALITIES TEST (SDMT)

Female

Male

Number Correct
REAL WORLD IMPLICATIONS

How do cognitive deficits impact activities of daily living?
<table>
<thead>
<tr>
<th>Domain</th>
<th>Task</th>
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</thead>
<tbody>
<tr>
<td>Communication</td>
<td>Finding a telephone number</td>
</tr>
<tr>
<td>Finances</td>
<td>Making Change</td>
</tr>
<tr>
<td>Food</td>
<td>Reading the first 3 ingredients on a can of food</td>
</tr>
<tr>
<td>Shopping</td>
<td>Finding 2 items on a shelf</td>
</tr>
<tr>
<td>Medicine</td>
<td>Reading the direction on a medicine bottle</td>
</tr>
</tbody>
</table>
TIMED INSTRUMENTAL ACTIVITIES OF DAILY LIVING (TIADL)

- Female
- Male

Time

0 20 40 60 80 100 120 140 160

Male
REGRESSION

$R^2 = 0.4519$

SDMT Score vs. TIADL

APDA
AMERICAN PARKINSON DISEASE ASSOCIATION
Strength in optimism. Hope in progress.
• Processing speed deficits have been hypothesized to account for the majority of age-related variance for a variety of cognitive tasks. A necessary assumption of this theory is that processing speed is a fundamental part of the cognitive architecture that is common across cognitive domains.

• Limited Time Mechanism: Cognitive performance may decline with decreased speed of processing because relevant operations cannot be successfully completed in a timely manner. If early operations are not completed, then later processes will be less effective.

• Simultaneity Mechanism: Decreased processing speed results in reduced performance on complex tasks because the products of early processing are no longer available when later processing occurs, thus reducing the amount of simultaneously available information.

       Salthouse et al., 1996; Nguyen et al. 2017
MRI BASED BIOMARKERS OF COGNITIVE FUNCTION

- Fluid-attenuated inversion recovery (FLAIR)
- Spectroscopy
- Functional Connectivity
FLAIR: WM Disease

R² = 0.3603

SDMT Score

Fazekas Score

Male  Female
IMAGE METRICS

FLAIR: WM Disease

\[ R^2 = 0.3603 \]

Fazekas Score

SDMT Score

Male
Female

R² = 0.3603
MR Spectroscopy

**Ant. Cing. Cho/Cr**

- **Males**: [Bar graph showing higher values with a standard deviation]
- **Females**: [Bar graph showing lower values with a standard deviation]

**Image Metrics**

- NAA
- CrCho

**Additional Graphs**

- **NAA**, **Cho**, **Cr**

**Statistics**

- $R^2 = 0.1938$
MR Spectroscopy

Ant. Cing. Cho/Cr

SDMT Score

R² = 0.1938
FUNCTIONAL CONNECTIVITY: PD MALE > FEMALE

- AC, Anterior Cingulate Gyrus
- IFG r, Inferior Frontal Gyrus, Right
- SMG l, Supramarginal Gyrus, Left
- IC l, Insular Cortex Left
FUNCTIONAL CONNECTIVITY: PD MALE AND SDMT, SIMPLE EFFECT OF SDMT

- PaHC r, Parahippocampal Gyrus Right
- STG r, Superior Temporal Gyrus Right
- ICC r, Intracalcarine Cortex Right
- IC l, Insular Cortex Left
FUNCTIONAL CONNECTIVITY: PD FEMALE AND SDMT, SIMPLE EFFECT OF SDMT

- SMG r, Supramarginal Gyrus Right
- Hippocampus Left
- ITG r, Inferior Temporal Gyrus Right
- OP r, Occipital Pole Right
- MTG r, Middle Temporal Gyrus Right
- Caudate Right
- TP l, Temporal Pole Left
- Thalamus Left
- HG l, Heschl's Gyrus Left
- Hippocampus L
- PO l, Parietal Operculum Cortex Left
- PaHC l, Parahippocampal Gyrus Left
- Hippocampus L
- TFusC r, Temporal Fusiform Cortex Right
CONCLUSIONS

• Men consistently had poorer performance than women in many cognitive domains
• Processing speed was associated with everyday function
• Brain imaging data is correlated with processing speed in PD
Thank you to the American Parkinson Disease Association!