Behavior/Neuropsychology Working Group
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Cognitive and behavioral assessments in PPMI

**Cognitive**
- Montreal Cognitive Assessment (MoCA)
- Hopkins Verbal Learning Test
- Benton Judgment of Line Orientation
- Letter-number sequencing
- Semantic fluency (animals, fruits, vegetables)
- Symbol-digit modalities test

**Behavioral**
- UPSIT
- Epworth Sleepiness Scale
- REM Sleep Disorder Questionnaire
- Geriatric Depression Scale (GDS-15)
- State-Trait Anxiety
- Impulse control (QUIP)
- SCOPA-AUT
MoCA scores for patients and healthy controls

Patients

Healthy Controls

MoCA total score

Count

MoCA total score

Frequency

MoCA total score
Analysis of QUIP in PPMI

• QUIP is self-rated screening questionnaire for ICDs (compulsive gambling, sex, buying, and eating) and related behaviors (punding, hobbyism, walkabout) in PD
  – Short form used in PPMI

• Goal was to determine frequency and correlates of ICD and related behavior symptoms in de novo, untreated PD patients (N=168) and healthy controls (HCs) (N=143)
## Frequencies of Symptoms in PD Patients and Controls

<table>
<thead>
<tr>
<th>ICD Type (percentage)</th>
<th>PD Patients (N=168)</th>
<th>Healthy Controls (N=143)</th>
<th>Statistic (chi-square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gambling</td>
<td>1.2%</td>
<td>0.7%</td>
<td>0.20 (1), p=0.66</td>
</tr>
<tr>
<td>Sex</td>
<td>4.2%</td>
<td>3.5%</td>
<td>0.09 (1), p=0.76</td>
</tr>
<tr>
<td>Buying</td>
<td>3.0%</td>
<td>2.1%</td>
<td>0.24 (1), p=0.63</td>
</tr>
<tr>
<td>Eating</td>
<td>7.1%</td>
<td>10.5%</td>
<td>1.09 (1), p=0.30</td>
</tr>
<tr>
<td>Any ICD</td>
<td>10.7%</td>
<td>13.3%</td>
<td>0.49 (1), p=0.49</td>
</tr>
<tr>
<td>Funding</td>
<td>4.8%</td>
<td>2.1%</td>
<td>1.61 (1), p=0.21</td>
</tr>
<tr>
<td>Hobbyism</td>
<td>5.4%</td>
<td>11.9%</td>
<td>4.30 (1), p=0.04</td>
</tr>
<tr>
<td>Walkabout</td>
<td>0.6%</td>
<td>0.7%</td>
<td>0.01 (1), p=0.91</td>
</tr>
<tr>
<td>Any ICD or related behavior</td>
<td>18.5%</td>
<td>20.3%</td>
<td>0.17 (1), p=0.68</td>
</tr>
</tbody>
</table>
## Multivariable Analyses in Entire Population

<table>
<thead>
<tr>
<th></th>
<th>Any ICD^a (N=37)</th>
<th>Punding or Hobbyism^b (N=33)</th>
<th>ICD or Related Behavior^c (N=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis (PD versus HC)</td>
<td>-0.48 (0.39), p=0.23</td>
<td>-0.70 (0.42), p=0.10</td>
<td>-0.43 (0.33), p=0.19</td>
</tr>
<tr>
<td>Age</td>
<td>-0.02 (0.02), p=0.20</td>
<td>-0.02 (0.02), p=0.40</td>
<td>-0.01 (0.01), p=0.37</td>
</tr>
<tr>
<td>Sex</td>
<td>0.07 (0.39), p=0.86</td>
<td>0.14 (0.41), p=0.74</td>
<td>0.01 (0.32), p=0.97</td>
</tr>
<tr>
<td>MoCA</td>
<td>-0.08 (0.11), p=0.46</td>
<td>-0.17 (0.11), p=0.10</td>
<td>-0.14 (0.09), p=0.11</td>
</tr>
<tr>
<td>GDS-15</td>
<td>0.18 (0.06), p=0.002</td>
<td>0.09 (0.07), p=0.17</td>
<td>0.17 (0.06), p=0.002</td>
</tr>
</tbody>
</table>

^a Chi-square=12.6 (df=5), p=0.03 for model. B (SE), p value presented for each variable.

^b Chi-square=6.8 (df=5), p=0.24 for model.

^c Chi-square=15.2 (df=5), p=0.01 for model.
## Correlates in PD Patients

<table>
<thead>
<tr>
<th>ICD Type</th>
<th>ICD + (N=18)</th>
<th>ICD - (N=150)</th>
<th>Statistic (t test, Mann-Whitney U test, or chi square)</th>
<th>ICD or Related Behavior + (N=31)</th>
<th>ICD or Related Behavior - (N=137)</th>
<th>Statistic (t test, Mann-Whitney U test, or chi square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, [SD])</td>
<td>58.8 (11.2)</td>
<td>61.9 (9.2)</td>
<td>1.3 (166), p=0.19</td>
<td>59.4 (11.0)</td>
<td>62.0 (9.1)</td>
<td>1.4 (166), p=0.15</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>72.2</td>
<td>71.3</td>
<td>0.006 (1), p=0.94</td>
<td>71.0</td>
<td>71.5</td>
<td>0.004 (1), p=0.95</td>
</tr>
<tr>
<td>Race (% white)</td>
<td>94.4</td>
<td>96.7</td>
<td>0.2 (1), p=0.63</td>
<td>96.8</td>
<td>96.4</td>
<td>0.01 (1), p=0.91</td>
</tr>
<tr>
<td>Education (# years)</td>
<td>16.1 (2.0)</td>
<td>15.8 (2.7)</td>
<td>p=0.54</td>
<td>15.7 (2.1)</td>
<td>15.9 (2.8)</td>
<td>p=0.91</td>
</tr>
<tr>
<td>UPDRS motor score (mean, [SD])</td>
<td>21.3 (5.7)</td>
<td>21.7 (8.9)</td>
<td>p=0.80</td>
<td>19.1 (6.0)</td>
<td>22.2 (9.0)</td>
<td>p=0.12</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr stage (median)</td>
<td>2.0</td>
<td>2.0</td>
<td>p=0.51</td>
<td>2.0</td>
<td>2.0</td>
<td>p=0.81</td>
</tr>
<tr>
<td>MoCA (mean, [SD])</td>
<td>27.1 (2.2)</td>
<td>27.1 (2.2)</td>
<td>p=0.75</td>
<td>26.5 (2.4)</td>
<td>27.3 (2.1)</td>
<td>p=0.11</td>
</tr>
<tr>
<td>Semantic Fluency (mean, [SD])</td>
<td>50.1 (11.7)</td>
<td>48.6 (10.9)</td>
<td>p=0.69</td>
<td>48.3 (10.1)</td>
<td>48.9 (11.2)</td>
<td>p=0.68</td>
</tr>
<tr>
<td>Letter Number Sequencing (mean, [SD])</td>
<td>10.2 (2.9)</td>
<td>10.9 (2.4)</td>
<td>p=0.47</td>
<td>10.8 (2.7)</td>
<td>10.8 (2.4)</td>
<td>p=0.81</td>
</tr>
<tr>
<td>GDS-15 (mean, [SD])</td>
<td>3.8 (3.0)</td>
<td>2.0 (2.3)</td>
<td>p=0.004</td>
<td>3.2 (2.7)</td>
<td>2.0 (2.3)</td>
<td>p=0.005</td>
</tr>
<tr>
<td>DaTSCAN striatal :occipital ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right caudate</td>
<td>1.5 (0.5)</td>
<td>1.4 (0.4)</td>
<td>-1.4 (18), p=0.18</td>
<td>1.5 (0.5)</td>
<td>1.4 (0.4)</td>
<td>-1.1 (37), p=0.26</td>
</tr>
<tr>
<td>Left caudate</td>
<td>1.4 (0.5)</td>
<td>1.4 (0.3)</td>
<td>p&gt;0.99</td>
<td>1.4 (0.4)</td>
<td>1.4 (0.3)</td>
<td>p=0.90</td>
</tr>
<tr>
<td>Right putamen</td>
<td>0.7 (0.3)</td>
<td>0.7 (0.3)</td>
<td>p=0.48</td>
<td>0.7 (0.3)</td>
<td>0.7 (0.3)</td>
<td>p=0.47</td>
</tr>
<tr>
<td>Left putamen</td>
<td>0.7 (0.2)</td>
<td>0.7 (0.3)</td>
<td>p=0.54</td>
<td>0.7 (0.3)</td>
<td>0.7 (0.3)</td>
<td>p=0.63</td>
</tr>
</tbody>
</table>
Conclusions

• PD itself does not appear to confer an increased risk for development of ICD or related behavior symptoms
  – Further reinforces the reported association between PD medications and ICDs in PD

• As ≈20% of de novo PD patients screen positive for ICD or related symptoms, long-term follow-up needed to determine if such patients are at ↑ risk for ICD development once PD medications are initiated
Rationale for Assessment of Cognitive Impairment in PPMI

- Cognitive impairment/dementia important outcome in PD

- Movement Disorders Society Criteria for dementia and MCI recently published

- Previously no mechanism for assessment of MCI or dementia as a clinical diagnosis in PPMI
Cognitive decline in early PD: Frequency and risk factors

- Age
- Education
- “Bulbar” UPDRS
- Frontal cognitive tests
- Hallucinations

From Uc et al, Neurology 2009
MDS definitions of MCI and dementia

**PD-MCI**
- Report of cognitive decline from premorbid status
- No significant functional impairment resulting from cognitive decline
- Impaired cognitive performance
  - At least 2 test scores >1.0 SD below the standardized mean, regardless of domain

**PD-dementia**
- Presence of cognitive decline from premorbid status
- Significant functional impairment resulting from cognitive decline
- Impaired cognitive performance
  - At least one test score from 2 domains >1.5 SD below the standardized mean
Goals of Cognitive Determination in PPMI

• Standardized assessment

• Implement Movement Disorders Society (MDS) definitions of PD-dementia and PD-MCI

• Limited site burden
Steps for determination of MCI/dementia

1. Investigator determines whether there has been cognitive decline from pre-morbid baseline based on clinical interview and knowledge of patient

2. Investigator determines whether there is functional impairment based on cognitive deficits interfering with performance of routine instrumental activities of daily living (IADLs)

3. Subject has neuropsychological testing at study visit

4. Categorization of MCI/dementia is made centrally based on investigator determinations of #1 and #2 and results of neuropsychological testing

5. Investigator impression of whether MCI or dementia is present is assessed, but is not primary
Case Report Form

PPMI

DRAFT

COGNITIVE CATEGORIZATION

<table>
<thead>
<tr>
<th>SUBJECT ID</th>
<th>SITE NO</th>
<th>VISIT NO</th>
</tr>
</thead>
</table>

INITIALS

<table>
<thead>
<tr>
<th>VISIT DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM DD YYYY</td>
</tr>
</tbody>
</table>

A. Indicate the source of information:
1 = Subject, 2 = Caregiver, 3 = Subject and Caregiver

Determining Report of Cognitive Decline

Based on information provided by the subject, the informant, and/or based on the Site Investigator's judgment, determine whether the subject has experienced a decline in cognition compared with pre-morbid abilities (i.e., pre-PD). The following cognitive abilities should be considered:

Attention: Ability to sustain and direct attention, lapses

Memory: Registration, recall of recent events or important dates, new learning ability, displacement of items, forgetting items

Orientation: Forgetting appointments, estimating time, spatial or geographical orientation

Executive abilities: Reasoning ability, making decisions, following instructions, difficulty with calculations

Praxis: Constructional or mechanical cognitive ability, such as use of tools and appliances

Language: Word finding problems, problems with naming or comprehension

1. Has the subject experienced cognitive decline? (0 = No, 1 = Yes)

Determining Functional Impairment

Based on information provided by the subject, the informant, and/or based on the Site Investigator's judgment, determine whether the subject has experienced a decline in functional abilities (from a cognitive standpoint) to the extent of demonstrating impairment in performing instrumental activities of daily living, examples of which include: driving, managing finances, managing medications, shopping, food preparation, participation in hobbies and employment.

2. Does the subject have functional impairment as a result of cognitive impairment? (0 = No, 1 = Yes)

Determining Cognitive Diagnosis

Based on your impression of the subject's current cognitive function, which may include performance on neuropsychological testing, as well as your knowledge of his/her pre-morbid cognitive function and the degree to which cognitive deficits impact his/her ability to carry out daily activities, please rate the subject's current cognitive status. The determination of dementia implies (1) cognitive function that is impaired in more than one cognitive domain, (2) decline from pre-morbid function, and (3) impact of cognitive impairment on daily function. The determination of MCI is based on (1) impairment in at least one cognitive domain, (2) decline from pre-morbid function, and (3) lack of significant impact of cognitive impairment on daily function.

3. Based on your clinical impression, which of the following categories best describes the subject's cognitive status:
   1 = Normal Cognition (PD-NC)
   2 = Mild Cognitive Impairment (PD-MCI)
   3 = Dementia (PD3)

4. What is your level of confidence of this cognitive diagnosis?
   1 = 90 - 100%
   2 = 50 - 89%
   3 = 10 - 49%
   4 = 0 - 9%

5. Did you review any neuropsychological tests (including MoCA scores) in making this determination? (0 = No, 1 = Yes)
Rationale for Emphasizing testing over investigator impression

• Investigator impression still central
  – Cognitive decline
  – Functional impairment

• Minimize site burden
  – Calculate normalized scores
  – Feed back information to PI in real time

• Maintain consistency with MDS definitions
What about completed visits

• If the subject is not MCI or demented at current visit, a category of normal will be assigned to prior, missing visits

• If the subject is MCI or demented at next visit, determination will be made retrospectively

• Retroactive determinations will be noted in database