Behavior/Neuropsychology Working Group

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Cognitive and behavioral assessments in PPMI

Cognitive

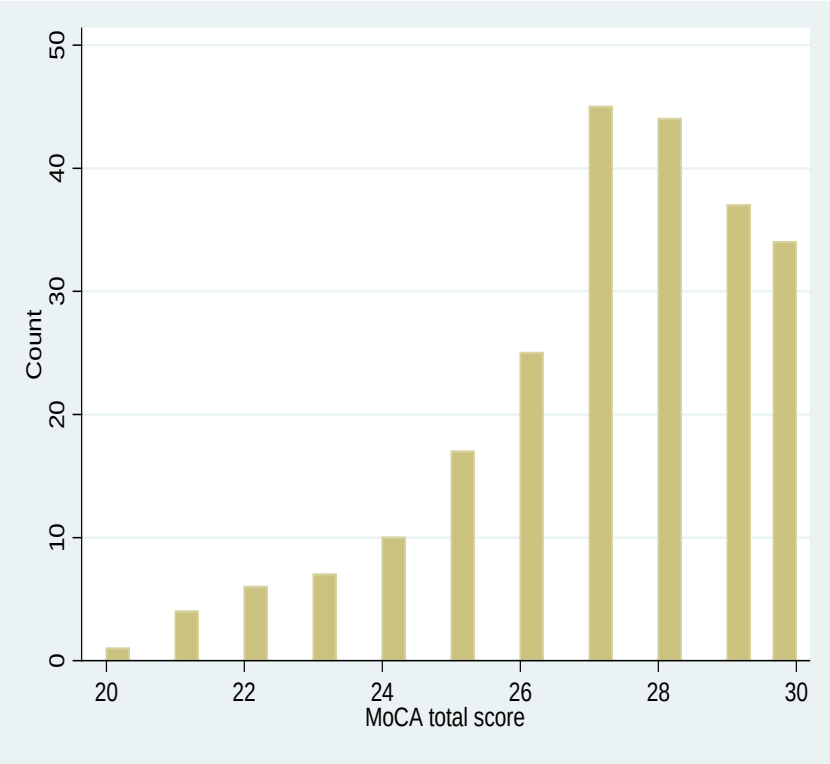
- Montreal Cognitive Assessment (MoCA)
- Hopkins Verbal Learning Test
- Benton Judgment of Line Orientation
- Letter-number sequencing
- Semantic fluency (animals, fruits, vegetables)
- Symbol-digit modalities test

Behavioral

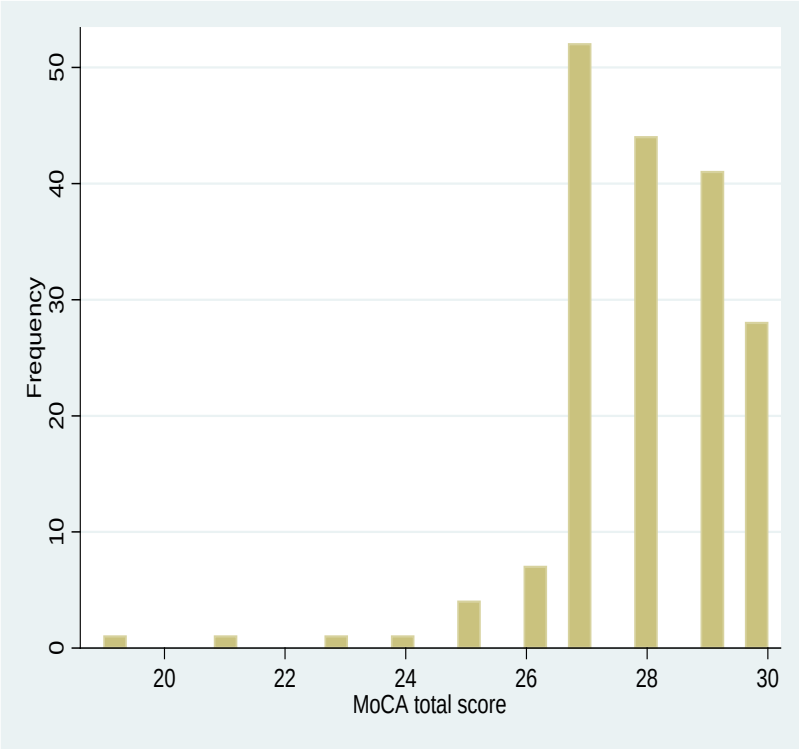
- UPSIT
- Epworth Sleepiness Scale
- REM Sleep Disorder Questionnaire
- Geriatric Depression Scale (GDS-15)
- State-Trait Anxiety
- Impulse control (QUIP)
- SCOPA-AUT

MoCA scores for patients and healthy controls

Patients



Healthy Controls



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

ICD Type (percentage)	PD Patients (N=168)	Healthy Controls (N=143)	Statistic (chi-square)
Gambling	1.2%	0.7%	0.20 (1), p=0.66
Sex	4.2%	3.5%	0.09 (1), p=0.76
Buying	3.0%	2.1%	0.24 (1), p=0.63
Eating	7.1%	10.5%	1.09 (1), p=0.30
Any ICD	10.7%	13.3%	0.49 (1), p=0.49
Punding	4.8%	2.1%	1.61 (1), p=0.21
Hobbyism	5.4%	11.9%	4.30 (1), p=0.04
Walkabout	0.6%	0.7%	0.01 (1), p=0.91
Any ICD or related behavior	18.5%	20.3%	0.17 (1), p=0.68

Multivariable Analyses in Entire Population

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

[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

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

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

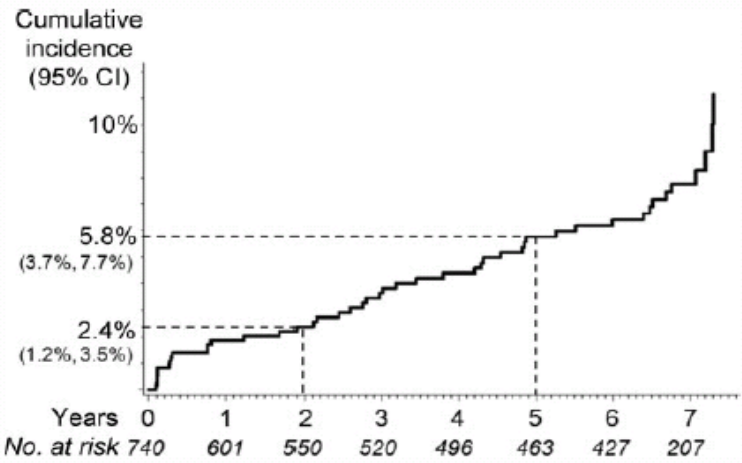
Rationale for Assessment of Cognitive Impairment in PPMI

- 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

Figure 1 Kaplan-Meier curve showing the cumulative incidence of cognitive impairment in the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism cohort



Values below the years indicate the numbers of subjects at risk for cognitive impairment.

From Uc et al, Neurology 2009

PARKINSON'S PROGRESSION MARKERS INITIATIVE
Play a Part in Parkinson's Research

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

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PPMI

1 3 2 COGNITIVE CATEGORIZATION

SUBJECT ID VISIT NO

INITIALS SITE NO VISIT DATE MM DD YYYY

A. Indicate the source of information: A.
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, misplacement 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) 1.

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) 2.

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PPMI

1 3 2 COGNITIVE CATEGORIZATION

SUBJECT ID VISIT NO

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 state: 3.

1 = Normal Cognition (PD-NC)
2 = Mild Cognitive Impairment (PD-MCI)
3 = Dementia (PDD)

4. What is your level of confidence of this cognitive diagnosis? 4.

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) 5.

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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