

UC San Diego

UC San Diego Previously Published Works

Title

Cognitive performance and neuropsychiatric symptoms in early, untreated Parkinson's disease.

Permalink

<https://escholarship.org/uc/item/27v642qn>

Journal

Movement disorders : official journal of the Movement Disorder Society, 30(7)

ISSN

0885-3185

Authors

Weintraub, Daniel
Simuni, Tanya
Caspell-Garcia, Chelsea
[et al.](#)

Publication Date

2015-06-01

DOI

10.1002/mds.26170

Peer reviewed



Published in final edited form as:

Mov Disord. 2015 June ; 30(7): 919–927. doi:10.1002/mds.26170.

Cognitive Performance and Neuropsychiatric Symptoms in Early, Untreated Parkinson's Disease

Daniel Weintraub, MD^{1,*}, Tanya Simuni, MD², Chelsea Caspell-Garcia, MS³, Christopher Coffey, PhD³, Shirley Lasch, MBA⁴, Andrew Siderowf, MD, MSCE⁵, Dag Aarsland, MD⁶, Paolo Barone, MD, PhD⁷, David Burn, FRCP, MD, MA⁸, Lama M. Chahine, MD⁹, Jamie Eberling, PhD¹⁰, Alberto J. Espay, MD, MSc, FAAN¹¹, Eric D. Foster, PhD³, James B. Leverenz, MD¹², Irene Litvan, MD¹³, Irene Richard, MD¹⁴, Matthew D. Troyer, MD¹⁵, and Keith A. Hawkins, PsyD¹⁶ The Parkinson's Progression Markers Initiative[†]

¹Departments of Psychiatry and Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA; Philadelphia Veterans Affairs Medical Center, Philadelphia, Pennsylvania, USA ²Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA ³Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, Iowa, USA ⁴Institute for Neurodegenerative Disorders (IND) and Molecular Neurolmaging, LLC (MNI), New Haven, Connecticut, USA ⁵Avid Radiopharmaceuticals, Philadelphia, Pennsylvania, USA ⁶Department of Neurobiology, Care Sciences and Society and the Alzheimer Disease Research Centre, Karolinska Institutet, Stockholm, Sweden; Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway ⁷Neurodegenerative Diseases Centre, Neuroscience Section, Department of Medicine, University of Salerno, Italy ⁸Institute for Ageing and Health, Newcastle University, Newcastle, England ⁹Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA ¹⁰Michael J. Fox Foundation for Parkinson's Research, New York, New York, USA ¹¹Department of Neurology, University of Cincinnati Academic Health Center, Cincinnati, Ohio, USA ¹²Lou Ruvo Center for Brain Health, Cleveland Clinic, Cleveland, Ohio, USA ¹³UCSD Movement Disorder Center, Department of Neurosciences, University of California San Diego, San Diego, California, USA ¹⁴Departments of Neurology and Psychiatry, University of Rochester School of Medicine and Dentistry, Rochester, New York, USA ¹⁵Medivation, Inc., San Francisco, California, USA ¹⁶Department of Psychiatry, Yale School of Medicine, New Haven, Connecticut, USA

Abstract

This study was undertaken to determine the prevalence and correlates of cognitive impairment (CI) and neuropsychiatric symptoms (NPS) in early, untreated patients with Parkinson's disease (PD).

*Correspondence to: Dr. Daniel Weintraub, MD, Associate Professor of Psychiatry and Neurology, Perelman School of Medicine at the University of Pennsylvania, 3615 Chestnut Street, #330, Philadelphia, PA 19104-2676, USA, daniel.weintraub@uphs.upenn.edu.

[†]Parkinson's Progression Markers Initiative authors are listed in the Appendix.

Relevant conflicts of interest/financial disclosures: Nothing to report.

Full financial disclosures and author roles may be found in the online version of this article.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Background—Both CI and NPS are common in PD and impact disease course and quality of life. However, limited knowledge is available about cognitive abilities and NPS.

Methods—Parkinson’s Progression Markers Initiative (PPMI) is a multi-site study of early, untreated PD patients and healthy controls (HCs), the latter with normal cognition. At baseline, participants were assessed with a neuropsychological battery and for symptoms of depression, anxiety, impulse control disorders (ICDs), psychosis, and apathy.

Results—Baseline data of 423 PD patients and 196 HCs yielded no between-group differences in demographic characteristics. Twenty-two percent of PD patients met the PD-recommended screening cutoff for CI on the Montreal Cognitive Assessment (MoCA), but only 9% met detailed neuropsychological testing criteria for mild cognitive impairment (MCI)-level impairment. The PD patients were more depressed than HCs ($P < 0.001$), with twice as many (14% vs. 7%) meeting criteria for clinically significant depressive symptoms. The PD patients also experienced more anxiety ($P < 0.001$) and apathy ($P < 0.001$) than HCs. Psychosis was uncommon in PD (3%), and no between-group difference was seen in ICD symptoms ($P = 0.51$).

Conclusions—Approximately 10% of PD patients in the early, untreated disease state met traditional criteria of CI, which is a lower frequency compared with previous studies. Multiple dopaminergic-dependent NPS are also more common in these patients compared with the general population, but others associated with dopamine replacement therapy are not or are rare. Future analyses of this cohort will examine biological predictors and the course of CI and NPS.

Keywords

anxiety; apathy; cognition; depression; impulse control disorder; Parkinson’s disease; psychosis

Cognitive impairment and neuropsychiatric symptoms (NPS) are frequent in patients with Parkinson disease (PD), negatively impacting patients’ quality of life and increasing caregiver burden.¹ Approximately 25% of non-demented PD patients have mild cognitive impairment (MCI),² and up to 80% of all PD patients will eventually develop dementia.³ Psychosis, depression, anxiety, apathy, and impulse control disorders (ICDs) are the most frequent and problematic NPS.¹

To what extent cognitive impairment and NPS are attributable to the neurodegenerative process, psychosocial, demographic or clinical factors, or a complication of dopamine replacement therapy (DRT) is unclear. The contribution of each factor may differ by disease stage and other variables.

To better understand cognition and NPS in PD, patients need to be studied soon after diagnosis, before initiation of DRT. Preliminary studies have shown that a significant percentage (10%–30%) of new (sometimes treated) PD patients have cognitive deficits at rates higher than healthy controls (HCs).^{4–8} Others have shown that a range of NPS are more common in early PD patients compared with HCs,^{8–10} with non-motor symptoms predominating in 25% of newly diagnosed, untreated patients.¹¹

The Parkinson's Progression Markers Initiative (PPMI) is the largest ongoing, prospective, longitudinal study of early untreated (at enrollment) PD patients and HCs.¹² Here we report the frequency and correlates of cognitive impairment (CI) and NPS at baseline.

Methods

Participants

Newly diagnosed, untreated PD patients (n = 423) and age- and sex-matched HCs (n = 196) were enrolled in PPMI. The PD participants were required to (1) have an asymmetric resting tremor or asymmetric bradykinesia, or two of bradykinesia, resting tremor, and rigidity; (2) have a recent PD diagnosis; (3) be untreated; (4) have a dopamine transporter (DAT) deficit on imaging; and (5) not have dementia as determined by the site investigator. Healthy controls were required to have: (1) no significant neurologic dysfunction; (2) no first-degree family member with PD; and (3) a Montreal Cognitive Assessment (MoCA) score greater than 26. The aims and methodology of the study have been published elsewhere¹² and are available at www.ppmi-info.org/study-design. The study was approved by the institutional review board at each site, and participants provided written informed consent.

Assessments

Cognitive Abilities—Global cognition was assessed with the MoCA¹³; no MoCA cutoff was applied for PD patients. The HCs were excluded for MoCA scores less than 27, resulting in the exclusion of approximately 10% of HC. The exclusion criterion for HCs precluded a direct comparison of PD patients and HCs on cognitive assessments, so the analyses for cognitive measures examined PD patients only.

The following cognitive tests were administered and categorized into these domains: memory: Hopkins Verbal Learning Test—Revised (HVLTR)¹⁴; visuospatial function: Benton Judgment of Line Orientation¹⁵ 15-item (split-half) version; processing speed-attention: Symbol-Digit Modalities Test¹⁶; and executive function and working memory: Letter-Number Sequencing¹⁷ and semantic (animal) fluency.¹⁸ Language abilities were not assessed. Published norms (referenced previously) were applied.

Cognitive impairment was defined at three levels: (1) at the screening level, the recommended MoCA cutoff was greater than 26^{13,19}; (2) using psychometric tests, CI categorization was reached through a cognitive test-based classification, requiring impairment (>1.5 standard deviations below the standardized mean score, which is the halfway point of the recommend range [>1.0 – 2.0] of standard deviations below the mean to establish a cutoff point for MCI diagnosis²⁰) on any *two* cognitive test scores (using immediate recall and recognition recall from the HVLTR and single scores from each of the other tests); and (3) applying the MDS Task Force Level I (ie, based on abbreviated assessment) criteria for MCI,²⁰ which requires a report of cognitive decline and absence of significant functional impairment based on guidelines provided to each site investigator. This formal cognitive categorization process was instituted after study initiation; thus, results from the MDS Task Force Level I MCI criteria were available for only a subset of patients (n = 247).

Neuropsychiatric Symptoms—Depressive symptoms were assessed using the 15-item Geriatric Depression Scale (GDS-15),²¹ with a cutoff score of 5 or more indicating clinically significant symptoms.²² Anxiety symptoms were assessed with the State-Trait Anxiety Inventory²³; cutoff scores greater than 39 on each subscale, based on the general population, were applied to indicate clinically significant symptoms,²⁴ because the State-Trait Anxiety Inventory has not been validated in PD patients specifically.²⁵ The short version of the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease screened for impulse control disorders (gambling, sexual, buying, and eating) and related behaviors (punding, hobbyism, and walkabout).²⁶ In addition, psychosis and apathy were assessed with single items from the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)²⁷ Part I. Any nonzero score was considered presence of a given symptom for these two items.

Disease Severity—The MDS-UPDRS motor score assessed disease severity. Given previous associations between motor subtypes and cognitive impairment in PD,^{28,29} patients were classified as having tremor-dominant (TD) versus non-TD subtypes (previously described as postural instability and gait disturbance; indeterminate motor subtypes were combined into one group because of concern regarding consistency of postural instability and gait disturbance classification in early PD³⁰).

Statistical Analysis

T tests and chi-squared tests were used for comparisons of demographic, clinical, and neuropsychiatric variables between PD participants and controls. Raw cognitive test scores were converted to standardized scores based on available norms for each test (referenced previously). The effects of common demographic and clinical variables on specific NPS and cognitive variables were examined in univariate and multivariate logistic or linear regression models. Any variables that had univariate associations with *P*-values less than 0.20 were considered in a multivariate model. Variables were removed one at a time from the multivariate models in a backwards selection process until all variables were significant at the 0.10 level. Not significant (NS) variables listed in the results tables had a *P* value greater than 0.10 and were removed from the final model.

Results

Demographic and Clinical Characteristics

Baseline demographic and clinical characteristics for PD patients and HCs are listed in Table 1. No significant between-group differences were seen on any demographic characteristics.

Cognitive Performance in PD

The mean (standard deviation [SD]) MoCA score for PD patients at baseline was 27.1 (2.3). In individual cognitive tests, using a cutoff score of greater than 1.5 SD below the standardized mean to define impairment, the highest frequencies of impairment were seen on verbal memory (9%–17% impaired on the four HVLT-R subtests) and processing speed–attention (14%) (Table 2). Low levels of impairment were seen on executive abilities–working memory (semantic fluency [5%] and Letter-Number Sequencing [4%]) and

visuospatial abilities (3%). See Table 2 for number of participants meeting less (>1 SD) and more (>2 SD) stringent criteria for impairment.

Frequency of Cognitive Impairment in PD

Level 1—Using the prespecified MoCA cutoff score of less than 26, 22.0% of the subjects met criteria for cognitive impairment, including 1% who met criteria for dementia-level impairment (ie, MoCA score < 21)¹⁹ (Table 2).

Level 2—Based on the detailed cognitive tests, 8.9% (37/415) of patients met threshold for CI. Of these, 51.4% (19/415) were impaired on two tests, 37.8% (14/415) on three tests, and 10.8% (4/415) on four tests. Nearly all (89.2%) CI patients had impairment on at least one memory test. Four patients (10.8%) were impaired on executive abilities/working memory and attention/processing speed tasks, without amnesic impairment. Given the limitations of the cognitive battery, the frequencies of amnesic versus non-amnesic or single- versus multiple-domain CI, according to MDS Task Force Level II criteria, were not calculated.²⁰

The agreement between MoCA and cognitive test categorization of CI was low (kappa = 0.092). Of the 89 subjects who scored less than 26 on the MoCA and also had detailed cognitive test results, 14.6% had two or more abnormal cognitive test scores. Of the 37 participants who met cognitive test criteria for CI, 35.1% scored less than 26 on the MoCA.

Level 3—Investigators recorded cognitive decline in only 2.4% (6/247) participants. Using this variable and applying the more stringent MDS Task Force–recommended criteria yielded an MCI rate of only 0.4% (1/247). Subsequent to this finding of infrequent documentation of cognitive decline using the specific cognitive decline question, we substituted a nonzero score on the MDS-UPDRS Part I cognitive impairment item for the specific cognitive decline question to determine whether investigators were more likely to document cognitive impairment on this instrument, and this increased the frequency of MCI slightly, to 4.1% (17/415).

Predictors of Cognitive Impairment in PD Patients

On univariate analysis, predictors of worse MoCA performance in PD patients were older age, male sex, being nonwhite, and greater motor impairment (Table 3). On multivariate analysis, all four factors remained statistically significant, with the greatest effect for older age.

Using the MoCA screening cutoff, increasing age, being nonwhite, and higher MDS-UPDRS motor score predicted presence of CI (data not shown). In contrast, using the cognitive test–based diagnosis, CI was predicted by a higher MDS-UPDRS motor score and a trend effect for being non-white (Supplementary Table 1). Applying the MDS-UPDRS Task Force Level I MCI criteria using the MDS-UPDRS Part I cognitive impairment question to capture cognitive decline, in a multivariate model being nonwhite and lower education (trend effect) were associated with an MCI diagnosis (data not shown).

Psychiatric Symptoms

The PD patients had significantly higher depression scores compared with HCs; twice as many PD patients met criteria for clinically significant depressive symptoms (14% vs. 7%) (Table 4). No association was seen between depression and global cognition in PD patients (Supplementary Table 2).

The PD patients also had significantly more state and trait anxiety symptoms, and the frequency rates of clinically significant anxiety symptoms (PD patients vs. HCs) were 24.6% versus 7.7% ($P < 0.001$) for state anxiety and 20.1% versus 9.7% for trait anxiety ($P = 0.001$). There was no association between anxiety and global cognition in PD patients (Supplementary Table 3).

Regarding ICDs and related behaviors symptoms, no statistically significant between-group differences in symptoms were found for any of the four ICDs, hobbyism, or walkabout. A trend effect for punning was found to be more common in PD patients (5% vs. 2%). Apathy (17% vs. 5%) and psychosis (3% vs. 1%) were more common in PD patients per the MDS-UPDRS Part I items.

Predictors of Psychiatric Symptoms

The PD patients remained more likely to meet the GDS cutoff score for depression compared with HCs when controlling for demographic characteristics (odds ratio [95% confidence interval] = 2.30 [1.23, 4.33], $df = 1$, $P = 0.009$). Examining raw GDS scores in PD patients only, being non-white, higher MDS-UPDRS motor scores, and non-TD motor subtype were associated with increasing severity of depression (Supplementary Table 2). Using the GDS cutoff score in PD patients only, being non-white and having non-TD motor subtype was associated with depression, with a trend effect for higher MDS-UPDRS motor score (data not shown).

In a multivariate model, having PD was not associated with presence of ICD symptoms when controlling for demographic factors (odds ratio [95% confidence interval] = 0.87 [0.56, 1.33], $df = 1$, $P = 0.51$). Examining only PD patients, no demographic or clinical factors predicted a positive QUIP (data not shown).

Younger age, higher MDS-UPDRS motor scores, shorter duration of disease, and non-TD motor subtype were associated with more severe *state* anxiety in a multivariate model (Supplementary Table 3). *Trait* anxiety was associated with younger age, higher MDS-UPDRS motor scores, non-TD motor subtype, being non-white, and female sex (data not shown).

No demographic or clinical predictors of a positive psychosis score were seen on the MDS-UPDRS item in PD patients. Increasing disability (Hoehn & Yahr stage) (odds ratio [95% confidence interval] = 1.97 [1.13, 3.45], $df = 1$, $P = 0.02$) and non-TD motor subtype (odds ratio [95% confidence interval] = 2.14 (1.26, 3.66), $df = 1$, $P = 0.005$) predicted a positive apathy score. The PD patients with apathy had higher depression scores than patients without apathy (3.89 vs. 2.01, t test = -6.17 , $df = 421$, $P < 0.001$), but there was no association with global cognition (data not shown).

Discussion

The PPMI is the most comprehensive multicenter, international biomarker study to date in early, untreated PD patients and unaffected controls. Our primary findings were that, at the time of diagnosis, 20% of PD patients reach a screening threshold for CI, 10% meet cognitive test–based criteria for CI, and a very low rate of cognitive decline is reported by participants or site investigators. Multiple NPS (eg, depression, anxiety, and apathy) are more common in PD patients at the time of diagnosis compared with the general population; although these differences may have been impacted by the slight cognitive differences between the two groups, no association was found between either depression or anxiety symptoms and cognitive performance in the PD group. Rates of NPS associated with DRT (eg, psychosis and ICDs) are either low or similar to controls. The statistically significant findings were despite the potential for self-exclusion of patients with clinically significant cognitive impairment or NPS given the demands of this study.

The estimated rates of CI were higher when using a screening instrument versus a cognitive test battery (22% vs. 9%), because recommended cutoff scores for screening instruments prioritize sensitivity over specificity.¹⁹ The rates of CI based on the cognitive battery were lower than the rates reported in previous studies of early, untreated PD patients.^{4,7} Potential causes include a highly educated (82% of the PD patients reported having formal education beyond high school, and only two tests adjusted for education) and relatively young (mean age of PD patients at baseline was 61.7 years) PPMI cohort. To compare, a recent study examining nonmotor symptoms in early (mean disease duration = 4.4 mo) PD patients reported a mean MoCA score of 25.1,³¹ 2 points below PPMI PD patients. Our interpretation of the cognitive data is limited by an inability to directly compare PD patients with HCs on cognitive performance because of the MoCA exclusion criterion.

When applying the recommended MDS MCI Task Force criteria for MCI,²⁰ 2% of PD patients met criteria for MCI, because of low recording of cognitive decline by the site investigators. The discrepancy between the reporting of cognitive decline and actual performance on cognitive tests may be attributable to lack of awareness of early, mild cognitive changes in PD, or that the chosen cutoff points on neuropsychological tests over-identify patients as having cognitive impairment. The low reporting rate of cognitive decline raises questions regarding the value of including this criterion when diagnosing PD-MCI, a concern that has been considered previously.^{4,32} It also raises the question about how best to document significant cognitive functional impairment—an essential determinant between dementia and MCI. Finally, the low agreement between the MoCA and cognitive battery results demonstrates that the two methods of assessing cognition are not interchangeable. Perhaps a lower screen positive cutoff point on the MoCA may need to be applied in the PPMI and other early PD cohorts to better match the results of the detailed cognitive testing, and this can be explored in future analyses.

Our data are limited by the limited cognitive battery that lacked coverage of certain domains (ie, language) and unevenly covered the included domains. Memory was the most affected cognitive domain, with free recall being more affected than recognition recall, the typical pattern reported in PD, and supporting the idea that memory deficits in PD relate more to

retrieval rather than encoding deficits, although impairments in both can occur.³³ This is consistent with research showing that memory is affected in PD, even at the stage of MCI.² The next most affected domain was processing speed–attention, with sparing of the executive abilities–working memory and visuospatial skills. The difference between cognitive domains should be interpreted with caution, because the tests may have differential sensitivities and the number of tests varied across domains.

Predictors of worse cognitive performance included being older, male, and nonwhite, and having more severe motor symptoms. Most of these factors predict the development of dementia,³⁴ suggesting that clinical and demographic risk factors for cognitive decline manifest themselves at disease onset. The mean duration of illness was approximately 6 months, which precluded detecting an effect of disease duration. Future analyses can examine baseline predictors of long-term cognitive decline, because PPMI participants are assessed annually.

Increasing research on nonmotor symptoms can predict PD, including depression, anxiety, Rapid Eye Movement behavior disorder, impaired olfaction, and autonomic disturbances.³⁵ Our results support the notion that a range of NPS are already common at diagnosis. Formal diagnostic criteria were not used, and there are limitations in using single items from the MDS-UPDRS to document presence of symptoms (ie, for psychosis and apathy) or their correlates (eg, cognitive impairment), so these findings require replication. Depression, anxiety, and apathy were more common in PD patients compared with controls, with 15% to 25% meeting criteria for clinically significant symptoms. No association was found between cognitive performance and either depression, anxiety, or apathy severity in PD patients, suggesting that worse cognitive performance in PD patients did not play a role in elevated rates of NPS in PD patients compared with HCs. The elevated prevalence of these symptoms in early untreated PD and their inclusion as part of the premotor syndrome³⁶ suggests that early PD-related neuropathophysiological changes in key neurotransmitter systems (eg, norepinephrine, serotonin, and dopamine) and involvement of specific brain regions (eg, locus coeruleus) contribute to the development of depression, anxiety, and apathy, although psychological factors also likely contribute once a formal diagnosis is made.

The relatively high rates of NPS in early PD have clinical implications. First, NPS have a significant impact on function, quality of life, and caregiver burden,¹ and the initiation of DRT.³⁷ The NPS remain underrecognized and undertreated in PD.^{38,39} Our findings highlight the importance of early, routine screening for a range of highly prevalent NPS to initiate optimal treatment. The most consistent predictors of NPS were non-TD motor subtype, increasing severity of motor symptoms, and being non-white. A clear relationship between motor subtype and NPS has not been reported previously, but our findings need to be verified through longitudinal analyses because of possible instability in motor subtyping in early PD. The association between race and NPS or cognition in PD has not been well explored, although some evidence exists that cognitive deficits⁴⁰ and dementia⁴¹ are more common in nonwhite PD patients, and that non-whites receive lower quality of depression treatment compared with whites.⁴² No difference was found between white and nonwhite PD patients for age, sex, education, MDS-UPDRS Part III score, TD versus non-TD

subtype, or PD duration that would have helped explain the differences in NPS (data not shown).

The NPS commonly associated with DRT treatment did not differ between PD patients and controls. Psychosis occurred in 3% of patients; follow-up of these patients will determine whether this group has increased risk of cognitive decline. The ICDs and related behavior symptoms were not more common in PD patients than in controls. This additional evidence supports the strong association between DRT use and development of ICDs in PD.^{43,44} Seeing whether the approximately 20% of PD patients with a positive QUIP at baseline have an increased risk of developing an ICD after initiation of DRT will be important.

In conclusion, the PPMI baseline results confirm the high frequency of a range of NPS at disease onset, but significant cognitive impairment may not be common. They also support the hypothesis that some cognitive deficits and NPS are more likely related to the range of brainstem-midbrain monoamine deficiencies prominent in early PD, whereas others are associated with the initiation of DRT or more widely distributed neuropathology. As the PPMI cohort is followed longitudinally, future analyses can examine the long-term course, predictors, and association with biomarkers for these crucial nonmotor symptoms, which will inform future clinical research and be invaluable for patient education and treatment planning.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Corresponding Author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding agencies: The study is funded by the Michael J. Fox Foundation (MJFF). The MJFF designed the study and is overseeing its conduct at the study sites but is not involved in data analysis. The Foundation reviewed and approved this manuscript for submission. Details regarding MJFF's Parkinson Progression Marker Initiative (PPMI) have been previously published (Marek K, Jennings D, Lasch S, Siderowf A, Tanner C, Simuni T, et al. The Parkinson Progression Marker Initiative (PPMI). *Prog Neurobiol* 2011; 95:629–35).

Appendix: PPMI Authors List

Steering Committee

Kenneth Marek, MD⁴ (Principal Investigator); Danna Jennings, MD⁴ (Olfactory Core, PI); Shirley Lasch, MBA⁴; Caroline Tanner, MD, PhD¹⁷ (Site Investigator); Tanya Simuni, MD² (Site Investigator); Christopher Coffey, PhD³ (Statistics Core, PI); Karl Kieburtz, MD, MPH¹⁹ (Clinical Coordination Core, PI); Werner Poewe, MD²⁰ (Site Investigator); Brit Mollenhauer, MD²¹ (Site Investigator); Tatiana Foroud, PhD²⁸ (Genetics Coordination Core, PI); Douglas Galasko, MD³⁸ (Site Investigator); Todd Sherer, PhD¹⁰; Sohini Chowdhury¹⁰; Mark Frasier, PhD¹⁰; Catherine Kopil, PhD¹⁰; Vanessa Arnedo¹⁰

Study Cores

Clinical Coordination Core: Alice Rudolph, PhD¹⁹ *Imaging Core:* John Seibyl, MD⁴ (Principal Investigator); Susan Mendick, MPH⁴; Norbert Schuff, PhD²² *Statistics Core:* Chelsea Caspell,³ Liz Uribe,³ Eric Foster,³ Katherine Gloer, PhD,³ Jon Yankey, MS³; *Bioinformatics Core:* Arthur Toga, PhD²³ (Principal Investigator); *BioRepository:* Dorit Berlin, PhD (Principal Investigator),²⁴ Paola Casalin,²⁵ Giulia Malferrari²⁵; *Bioanalytics Core:* John Trojanowski, MD, PhD¹³ (Principal Investigator), Les Shaw, PhD¹³ (Co-Principal Investigator); *Neuropsychological and Cognitive Assessments:* Keith A. Hawkins, PsyD¹⁶

Site Investigators

David Russell, MD, PhD⁴; Stewart Factor, DO²⁹; Penelope Hogarth, MD³⁰; David Standaert, MD, PhD³¹; Robert Hauser, MD, MBA³²; Joseph Jankovic, MD³³; Matthew Stern, MD⁹; Lama Chahine, MD⁹; Samuel Frank, MD³⁴; Irene Richard, MD¹⁴; Paolo Barone MD, PhD⁷; Klaus Seppi, MD²⁰; Holly Shill, MD³⁵; Daniela Berg, MD³⁷; Zoltan Mari, MD³⁹; Nicola Pavese, MD⁴⁰; Alberto Espay, MD, MSc¹¹; Johnna Devoto¹¹; Dominic Rowe, MD, PhD⁴¹; Melanie Brandabur, MD¹⁷; Roy Alcalay, MD⁴²; Eduardo Tolosa, MD⁴³; Michele York, PhD³³

Coordinators

Laura Leary⁴; Cheryl Riordan⁴; Linda Rees, MPH¹⁷; Alicia Portillo³⁰; Art Lenahan³⁰; Karen Williams¹⁸; Stephanie Guthrie, MSN³¹; Ashlee Rawlins³¹; Sherry Harlan³²; Christine Hunter, RN³³; Baochan Tran²⁶; Cathi-Ann Thomas, RN, MS³⁴; Raymond James, RN³⁴; Fabienne Sprenger, MD²⁰; Diana Willeke²¹; Sanja Obradov³⁵; Jennifer Mule³⁶; Katharina Gauss³⁷; Deborah Fontaine, RN, MS, GNP MS³⁸; Bina Shah, BSc⁴²; Madelaine Ranola⁴³

Working Group and other

John R. Sims⁴⁴

¹⁷The Parkinson's Institute, Sunnyvale, California, USA

¹⁸Northwestern University, Chicago, Illinois, USA

¹⁹Clinical Trials Coordination Center, University of Rochester, Rochester, New York, USA

²⁰Innsbruck Medical University, Innsbruck, Austria

²¹Paracelsus-Elena Klinik, Kassel, Germany

²²University of California, San Francisco, California, USA

²³Laboratory of Neuroimaging (LONI), University of Southern California, USA

²⁴Coriell Institute for Medical Research, Camden, New Jersey, USA

- ²⁵BioRep, Milan, Italy
- ²⁶University of Pennsylvania, Philadelphia, Pennsylvania, USA
- ²⁷National Institute on Aging, NIH, Bethesda, Maryland, USA
- ²⁸Indiana University, Indianapolis, Indiana, USA
- ²⁹Emory University of Medicine, Atlanta, Georgia, USA
- ³⁰Oregon Health and Science University, Portland, Oregon, USA
- ³¹University of Alabama at Birmingham, Birmingham, Alabama, USA
- ³²University of South Florida, Tampa, Florida, USA
- ³³Baylor College of Medicine, Houston, Texas, USA
- ³⁴Boston University, Boston, Massachusetts, USA
- ³⁵Banner Research Institute, Sun City, Arizona, USA
- ³⁶Cleveland Clinic, Cleveland, Ohio, USA
- ³⁷University of Tuebingen, Tuebingen, Germany
- ³⁸University of California, San Diego, California, USA
- ³⁹Johns Hopkins University, Baltimore, Maryland, USA
- ⁴⁰Imperial College of London, London, UK
- ⁴¹Macquarie University, Sydney, Australia
- ⁴²Columbia University Medical Center, New York, New York, USA
- ⁴³Hospital Clinic of Barcelona, Barcelona, Spain
- ⁴⁴Eli Lilly and Company, Indianapolis, Indiana, USA

References

1. Weintraub D, Burn DJ. Parkinson's disease: the quintessential neuropsychiatric disorder. *Mov Disord.* 2011; 26:1022–1031. [PubMed: 21626547]
2. Aarsland D, Bronnick K, Williams-Gray CH, et al. Mild cognitive impairment in Parkinson's disease: a multicenter pooled analysis. *Neurology.* 2010; 75:1062–1069. [PubMed: 20855849]
3. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sørensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Arch Neurol.* 2003; 60:387–392. [PubMed: 12633150]
4. Aarsland D, Bronnick K, Larsen JP, Tysnes OB, Alves G, ParkWest Study Group. Cognitive impairment in incident, untreated Parkinson disease: The Norwegian ParkWest Study. *Neurology.* 2009; 72:1121–1126. [PubMed: 19020293]

5. Foltynie T, Brayne C, Robbins T, Barker R. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study *Brain*. 2004; 127:550–560. [PubMed: 14691062]
6. Elgh E, Domellöf M, Linder J, Edström M, Stenlund H, Forsgren L. Cognitive function in early Parkinson's disease: a population-based study. *Eur J Neurol*. 2009; 16:1278–1284. [PubMed: 19538208]
7. Poletti M, Frosini D, Pagni C, et al. Mild cognitive impairment and cognitive-motor relationships in newly diagnosed drug-naïve patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2012; 83:601–606. [PubMed: 22492216]
8. Yarnall A, Breen D, Duncan G, et al. Characterizing mild cognitive impairment in incident Parkinson disease: the ICICLE-PD Study. *Neurology*. 2014; 82:1–9.
9. Aarsland D, Brønnick K, Alves G, et al. The spectrum of neuropsychiatric symptoms in patients with early untreated Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2009; 80:928–930. [PubMed: 19608786]
10. Mollenhauer B, Trautmann E, Sixel-Doring F, et al. Nonmotor and diagnostic findings in subjects with de novo Parkinson disease of the DeNoPa cohort. *Neurology*. 2013; 81:1226–1234. [PubMed: 23997153]
11. Erro R, Vitale C, Amboni M, et al. The heterogeneity of early Parkinson's disease: a cluster analysis of newly diagnosed untreated patients. *PLoS ONE*. 2013; 8:e60702. doi:10.1371/journal.pone.0070244
12. Marek K, Jennings D, Lasch S, et al. The Parkinson Progression Marker Initiative PPMI. *Prog Neurobiol*. 2011; 95:629–635. [PubMed: 21930184]
13. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005; 53:695–699. [PubMed: 15817019]
14. Brandt, J.; Benedict, RHB. *The Hopkins Verbal Learning Test-Revised*. Odessa, FL: Psychological Assessment Resources; 2001.
15. Benton AL, Varney NR, Hamsher KS. Visuospatial judgment: a clinical test. *Arch Neurol*. 1978; 35:364–367. [PubMed: 655909]
16. Smith, A. *Symbol digit modalities test: Manual*. Los Angeles: Western Psychological Services; 1982.
17. Wechsler, D. *Wechsler Adult Intelligence Scale*. 4th. San Antonio: Psychological Corporation; 2008.
18. Gladsjo JA, Shuman CC, Evans JD, Peavy GM, Miller SW, Heaton RK. Norms for letter and category fluency: demographic corrections for age, education, and ethnicity. *Assessment*. 1999; 6:147–178. [PubMed: 10335019]
19. Dalrymple-Alford J, MacAskill M, Nakas C, et al. The MoCA: well-suited screen for cognitive impairment in Parkinson disease. *Neurology*. 2010; 75:1717–1725. [PubMed: 21060094]
20. Litvan I, Goldman JG, Troster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force Guidelines. *Mov Disord*. 2012; 27:349–356. [PubMed: 22275317]
21. Sheikh, JI.; Yesavage, JA. Geriatric Depression Scale GDS: recent evidence and development of a shorter version. In: Brink, TL., editor. *Clinical Gerontology: A Guide to Assessment and Intervention*. New York: The Haworth Press; 1986. p. 165-173.
22. Weintraub D, Oehlberg KA, Katz IR, Stern MB. Test characteristics of the 15-Item geriatric depression scale and Hamilton depression rating scale in Parkinson's disease. *Am J Geriatr Psychiatry*. 2006; 14:169–175. [PubMed: 16473982]
23. Spielberger, CD.; Gorsuch, RL.; Lushene, RE. *Manual for the State Trait Inventory*. Palo Alto, CA: Consulting Psychologists Press; 1970.
24. Knight R, Waal-Manning H, Spears G. Some norms and reliability data for the State-Trait Anxiety Inventory and the Zung Self-Rating Depression Scale. *Br J Clin Psychol*. 1983; 22:245–249. [PubMed: 6640176]
25. Leentjens AFG, Dujardin K, Marsh L, et al. Anxiety rating scales in Parkinson's disease: critique and recommendations. *Mov Disord*. 2008; 23:2004–2014. [PubMed: 18709683]

26. Weintraub D, Stewart S, Shea JA, et al. Validation of the Questionnaire for Impulsive-Compulsive Behaviors in Parkinson's Disease QUIP. *Mov Disord.* 2009; 24:1461–1467. [PubMed: 19452562]
27. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale MDS-UPDRS: scale presentation and clinimetric testing results. *Mov Disord.* 2008; 23:2129–2170. [PubMed: 19025984]
28. Alves G, Larsen JP, Emre M, Wentzel-Larsen T, Aarsland D. Changes in motor subtype and risk for incident dementia in Parkinson's disease. *Mov Disord.* 2006; 21:1123–1130. [PubMed: 16637023]
29. Burn D, Rowan E, Allan L, Molloy S, O'Brien J, McKeith I. Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry.* 2006; 77:585–589. [PubMed: 16614017]
30. Stebbins G, Goetz C, Burn D, Jankovic J, Khoo T, Tilley B. How to identify tremor dominant and postural instability/gait difficulty groups with the Movement Disorder Society Unified Parkinson's Disease Rating Scale: comparison with the Unified Parkinson's Disease Rating Scale. *Mov Disord.* 2013; 28:668–670. [PubMed: 23408503]
31. Khoo TK, Yarnall AJ, Duncan GW, et al. The spectrum of nonmotor symptoms in early Parkinson disease. *Neurology.* 2013; 80:276–281. [PubMed: 23319473]
32. Caviness JN, Driver-Dunckley E, Connor DJ, et al. Defining mild cognitive impairment in Parkinson's disease. *Mov Disord.* 2007; 22:1272–1277. [PubMed: 17415797]
33. Weintraub D, Moberg PJ, Culbertson WC, Duda JE, Stern MB. Evidence for both impaired encoding and retrieval memory profiles in Parkinson's disease. *Cogn Behav Neurol.* 2004; 17:195–200. [PubMed: 15622014]
34. Aarsland D, Andersen K, Larsen JP, Lolk A, Nieman H, Kragh-Sorensen P. Risk of dementia in Parkinson's disease: a community-based, prospective study. *Neurology.* 2001; 56:730–736. [PubMed: 11274306]
35. Lang A. A critical appraisal of the premotor symptoms of Parkinson's disease: potential usefulness in early diagnosis and design of neuroprotective trials. *Mov Disord.* 2011; 26:775–783. [PubMed: 21484865]
36. Postuma R, Aarsland D, Barone P, et al. Identifying prodromal Parkinson's disease: pre-motor disorders in Parkinson's disease. *Mov Disord.* 2012; 27:617–626. [PubMed: 22508280]
37. Ravina B, Camicioli R, Como PG, et al. The impact of depressive symptoms in early Parkinson's disease. *Neurology.* 2007; 69:342–347. [PubMed: 17581943]
38. Shulman LM, Taback RL, Rabinstein AA, et al. Non-recognition of depression and other non-motor symptoms in Parkinson's disease. *Parkinsonism Relat Dis.* 2002; 8:193–197.
39. Gallagher D, Lees A, Schrag A. What are the most important non-motor symptoms in patients with Parkinson's disease and are we missing them? *Mov Disord.* 2010; 25:2493–2500. [PubMed: 20922807]
40. Sagliocco L, Bandinin F, Pierantozzi M, et al. Electrophysiological evidence for visuocognitive dysfunction in younger non Caucasian patients with Parkinson's disease. *J Neural Transm.* 1997; 104:427–439. [PubMed: 9295175]
41. Willis A, Schootman M, Kung N, Evanoff B, Perlmutter J, Racette B. Predictors of survival in patients with Parkinson's disease. *Arch Neurol.* 2012; 69:601–607. [PubMed: 22213411]
42. Cheng E, Sidwerowf A, Swartrauber K, et al. Disparities of care in veterans with Parkinson's disease. *Parkinsonism Relat Disord.* 2008; 14:8–14. [PubMed: 17702625]
43. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol.* 2010; 67:589–595. [PubMed: 20457959]
44. Bastiaens J, Dorfman BJ, Christos PJ, Nirenberg MJ. Prospective cohort study of impulse control disorders in Parkinson's disease. *Mov Disord.* 2013; 28:327–333. [PubMed: 23283708]

TABLE 1

Demographic and Clinical Characteristics in PD Patients and Controls

Variable	Enrolled Subjects		P Value
	PD Subjects (N = 423)	Healthy Controls (N = 196)	
Age			0.33
Mean	61.7	60.8	
(Min, Max)	(33, 85)	(31, 84)	
Sex			0.77
Male	277 (65%)	126 (64%)	
Female	146 (35%)	70 (36%)	
Education			0.30
<13 y	77 (18%)	29 (15%)	
13 y or more	346 (82%)	167 (85%)	
Ethnicity			0.62
Hispanic/Latino	9 (2%)	3 (2%)	
Not Hispanic/Latino	414 (98%)	193 (98%)	
Race			0.85
White	391 (92%)	182 (93%)	
Non-white	32 (8%)	14 (7%)	
Family history			<.001
Positive PD	102 (24%)	10 (5%) ^a	
MDS-UPDRS Part III score			<.001
Mean	20.9	1.2	
(Min, Max)	(4, 51)	(0, 13)	
TD/Non-TD classification			NA
TD	299 (71%)	NA	
Non-TD	123 (29%)	NA	
Side most affected			NA
Left	180 (43%)	NA	
Right	233 (55%)	NA	
Symmetric	10 (2%)	NA	
PD duration			NA
Mean (SD) months	6.65 (6.50)	NA	NA

^aHealthy controls were excluded for having 1st-degree relative with PD.

TABLE 2

Cognitive Performance in PD Subjects

Cognitive Domain	Variable	Mean (SD) or N (%)
Global	MOCA score (N = 423)	27.1 (2.3)
	30–26	330 (78%)
	21–25	89 (21%)
	<21	4 (1%)
Visuospatial	Benton Judgment of Line Orientation Score (N = 422)	12.8 (2.1)
	Mild impairment ^a	30 (7%)
	Moderate impairment ^b	14 (3%)
	Severe impairment ^c	2 (0%)
Memory	HVLT Immediate Recall (N = 422)	24.4 (5.0)
	Mild impairment	131 (31%)
	Moderate impairment	73 (17%)
	Severe impairment	29 (7%)
	HVLT Delayed Recall (N = 422)	8.4 (2.5)
	Mild impairment	139 (33%)
	Moderate impairment	70 (17%)
	Severe impairment	26 (6%)
	HVLT Retention (N = 422)	0.9 (0.2)
	Mild impairment	89 (21%)
	Moderate impairment	47 (11%)
	Severe impairment	21 (5%)
	HVLT Discrimination Recognition (N = 421)	9.6 (2.6)
	Mild impairment	102 (24%)
	Moderate impairment	38 (9%)
	Severe impairment	13 (3%)
Executive abilities—working memory	Letter Number Sequencing Raw Score (N = 422)	10.6 (2.7)
	Mild impairment	28 (7%)
	Moderate impairment	19 (4%)
	Severe impairment	4 (1%)
	Semantic Fluency Total Score (N = 422)	48.7 (11.6)
	Mild impairment	61 (14%)
	Moderate impairment	22 (5%)
	Severe impairment	9 (2%)
Processing speed—attention	Symbol Digit Modalities Score (N = 422)	41.2 (9.7)
	Mild impairment	110 (26%)
	Moderate impairment	60 (14%)
	Severe impairment	27 (6%)

^a <1.0 SD below standardized mean score. The rows within a given test are cumulative from bottom up (e.g., mild impairment = severe impairment + moderate impairment + mild impairment).

^b <1.5 SD below standardized mean score (used to classify patients as impaired for MCI categorization).

^c <2.0 SD below standardized mean score.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

TABLE 3

Demographic and Clinical Predictors of MoCA Score in PD Subjects

Variable (Affected Group)	Univariate Analysis ^a		Multivariate Analysis ^b	
	Regression Coefficient	P Value	Regression Coefficient	P Value
Age (older age)	-0.047	<.001	-0.043	<.001
Sex (male)	0.635	0.007	0.590	0.01
Education (>12 y)	-0.108	0.71	—	—
Ethnicity (Hispanic/Latino)	1.043	0.18	—	NS
Race (non-white)	-1.090	0.01	-1.327	0.001
Family history of PD (no)	-0.042	0.87	—	—
MDS-UPDRS Part III (greater motor impairment)	-0.033	0.01	-0.025	0.047
Hoehn & Yahr stage (stage 2 or above)	-0.263	0.24	—	—
Duration of disease (longer duration)	-0.026	0.13	—	NS
TD/Non-TD classification (TD)	0.133	0.59	—	—
Side most affected (left)	0.045	0.83	—	—

^aDegrees of freedom = 1.^bDegrees of freedom = 422.

TABLE 4

Psychiatric Symptoms in PD Patients and Controls

Variable	Enrolled Subjects		P Value
	PD Subjects (N = 423)	Healthy Controls (N = 196)	
GDS-15 score			<0.001
Mean	2.3	1.3	
(Min, Max)	(0.0, 14.0)	(0.0, 15.0)	
GDS-15 cutoff			0.008
Not depressed (<5)	364 (86%)	183 (93%)	
Depressed (≥ 5)	59 (14%)	13 (7%)	
STAI—State score			<.001
Mean	33.0	28.0	
(Min, Max)	(20.0, 76.0)	(20.0, 58.0)	
STAI—Trait score			<.001
Mean	32.4	29.1	
(Min, Max)	(20.0, 63.0)	(20.0, 53.0)	
QUIP disorders			
Any 1 or more disorders	87 (21%)	36 (18%)	0.51
Gambling	4 (1%)	1 (1%)	0.57
Sex	12 (3%)	5 (3%)	0.84
Buying	11 (3%)	4 (2%)	0.67
Eating	36 (9%)	18 (9%)	0.78
Hobbyism	31 (7%)	19 (10%)	0.31
Punding	21 (5%)	4 (2%)	0.09
MDS-UPDRS Part I Apathy item			<.001
Negative	352 (83%)	186 (95%)	
Any positive score	71 (17%)	9 (5%)	
MDS-UPDRS Part I Psychosis item			0.047
Negative	410 (97%)	194 (99%)	
Any positive score	13 (3%)	1 (1%)	