Published in final edited form as:

Parkinsonism Relat Disord. 2016 December ; 33: 107–114. doi:10.1016/j.parkreldis.2016.09.025.

Cognitive impairment in Parkinson's disease: association between patient-reported and clinically measured outcomes

Kelly A. Mills, MD^{A,*}, Zoltan Mari, MD^{A,B}, Gregory M. Pontone, MD^{A,B}, Alexander Pantelyat, MD^{A,B}, Angela Zhang^B, Nadine Yoritomo, RN^B, Emma Powers^B, Jason Brandt, PhD^C, Ted M. Dawson, MD, PhD^{A,B,D,E,F}, and Liana S. Rosenthal, MD^{A,B}

^AMovement Disorders Division, Dept. of Neurology, Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Meyer 6-181, Baltimore, MD, 21287 United States

^BMorris K. Udall Parkinson's Disease Research Center, Johns Hopkins University School of Medicine, 10751 Fall Road, Suite 250, Lutherville, MD 21093 Baltimore, MD, United States

^CDivision of Medical Psychology, Dept. of Psychiatry and Behavioral Science, Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Meyer 218, Baltimore, MD, 21287 United States

^DNeuroregeneration and Stem Cell Programs, Institute for Cell Engineering, Johns Hopkins University School of Medicine, Baltimore, 21205, United States

^ESolomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, 21205, United States

^FDepartment of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, 21205, United States

Abstract

Background—In Parkinson's disease, the association between objective and patient-reported measures of cognitive dysfunction is unknown and highly relevant to research and clinical care.

Objective—To determine which cognitive domain-specific Montreal Cognitive Assessment (MoCA) subscores are most strongly associated with patient-reported cognitive impairment on question 1 (Q1) of the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS).

Methods—We analyzed data from 759 PD participants and 481 persons without PD with in a retrospective, cross sectional analysis using data from the NINDS Parkinson's Disease Biomarkers Program (PDBP), a longitudinal, multicenter biomarker study. The relationship between a patient-reported cognitive rating (MDS-UPDRS q1.1) and objective cognitive assessments (MoCA) was

*Corresponding Author: Kelly Mills, MD, Johns Hopkins Dept. of Neurology, 600 N. Wolfe Street, Meyer 6-181D, Baltimore, MD 21287, 410-502-0133, kmills16@jhmi.edu.

Conflicts of Interest: None

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assessed using multinomial logistic regression modeling and the outcomes reported as conditional odds ratios (cOR's) representing the relative odds of a participant reporting cognitive impairment that is "slight" versus "normal" on MDS-UPDRSq1.1 for a one unit increase in a MoCA sub-score, adjusted for age and education.

Results—In PD participants, changes in visuospatial-executive performance and memory had the most significant impact on subjective cognitive impairment. A 1-point increase in visuospatial-executive function decreased the chance of reporting a MDS-UPDRS Q1 score of "slight" versus "normal" by a factor of 0.686 ($p<0.001$) and each 1 point improvement in delayed recall decreased the odds of reporting "slight" cognitive impairment by a factor of 0.836 ($p<0.001$).

Conclusions—Conversion from a PD patient's report of "normal" to "slight" cognitive impairment may be associated with changes in visuospatial-executive dysfunction and memory more than other cognitive domains.

Keywords

Parkinson's; cognition; patient-reported; mild cognitive impairment

Introduction

Parkinson's disease is a multisystem neurodegenerative disease with motor, autonomic, and neuropsychiatric symptoms. Cognitive impairment is observed in up to 24% of newly diagnosed PD patients [1], with up to 46% of patients developing dementia by 10 years of disease [2] and up to 80% of patients develop dementia after 20 years of PD [3]. Even in the absence of frank dementia, early, mild cognitive impairment is an independent contributor to poorer quality of life [4, 5] and disability even when motor symptoms are controlled with medications [6].

Fortunately, there are interventions that may potentially address early, mild cognitive deficits in PD. Effective treatment of motor symptoms can sometimes exacerbate cognitive dysfunction [7, 8], so adjustments in motor therapy may mitigate these deficits to a certain extent. Furthermore, cognitive enhancers, such as cholinesterase inhibitors have shown some efficacy in treating inattention and executive dysfunction in PD [9, 10]. Cognitive rehabilitation, possibly effective in Alzheimer's disease [11], is now being explored in PD [12]. Early identification of cognitive deficits may also influence recommendations regarding employment, financial decision-making, and even driving.

Detection of the earliest cognitive deficits in PD can be difficult given the heterogeneous cognitive phenotypic presentations [13] (executive dysfunction vs. visuospatial etc.) due to the influence of multiple pathological [14] processes affecting normal cognitive function. In a large cohort of newly diagnosed PD participants in the Parkinson's Progression Markers Initiative, 22% of participants scored in the "impaired" range on the Montreal Cognitive Assessment (MoCA) [15] while verbal memory and processing speed were found to be the most frequently impaired domains when "impairment" was defined as a score 1.5 standard deviations below normative values.

Despite significant knowledge regarding the earliest objectively measured cognitive impairments in PD, the literature regarding patients' subjective experience with early cognitive symptoms is limited and most studies show discordance between subjective and objective cognitive impairment. While Dujardin et al. showed that subjective cognitive complaints were more commonly detected with the Cognitive Complaint Interview (CCI) in patients with significant cognitive impairment (Mattis dementia rating scale <130) [16], the CCI score was not a good predictor of performance on the Mattis dementia rating scale and the study did not evaluate objective deficits in *early* cognitive impairment. A more recent publication suggested that subjective (patient- and caregiver-reported) and objective deficits in specific domains are usually disocordant [17] due to the tendency to describe most cognitive deficits as difficulty with "memory" (ie "forgetting" how to program a new remote control rather than recognizing this as an executive function task). Exploring the specific impairments that drive patients to first report even slight cognitive impairment will create a greater understanding of the degree of patient awareness and direct the use of patient-oriented outcomes in therapeutic research targeting cognition in early PD. Recognition of the domain-specific cognitive deficits that underly the earliest subjective experience of overall cognitive decline will also help clinicians respond to early cognitive complaints with recommendations specific for the domains most likely to be affected. To this end, we evaluated the association between the subjective report of slight overall cognitive impairment (MDS-UPDRS question 1.1) and objective deficits as measured by MoCA sub-scores in a large cohort of well-characterized PD patients and controls.

METHODS

Setting

Objective and subjective cognitive assessments and demographic variables were extracted from the NIH Parkinson's Disease Biomarker Program (PDBP) dataset. The PDBP is a consortium of 11 centers, each with its own research project related to biomarker development. Five of the PDBP sites enroll participants, each collecting longitudinal data on elderly control participants without parkinsonism, PD participants, and atypical parkinsonism syndromes using common data elements [18]. Participants were enrolled at academic centers but are followed by either academic or community neurologists, in Dallas, TX, Hershey, PA, Baltimore, MD, Boston, MA, and Birmingham, AL. Data collection began in 2012 and data for this study were initially extracted on March 17, 2016.

Patients and data

Participants' data were extracted from the PDBP database if they 1) had a diagnosis of "probable or possible idiopathic Parkinson's disease" or "Control" and 2) had at least one visit with both a MoCA and a Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) reported. Subjects with a diagnosis of "parkinsonism" were excluded because the focus of our study was on subjective cognitive complaints in idiopathic PD and we would expect different results in atypical parkinsonian disorders given the differential cortical and subcortical pathology. Diagnosis of probable or possible PD was defined by the UK Brain Bank Criteria [19]. Inclusion and exclusion criteria for PD participants and controls have been previously published [20], but generally, volunteers were

enrolled as controls if they had “no evidence of a clinically significant neurological disorder” and were often spouses of PD participants. Neither controls nor PD subjects were excluded based on the presence of cognitive impairment (PD-MCI or PD dementia) or comorbid psychiatric conditions. Psychiatric conditions are likely to co-occur with cognitive impairment in PD, and excluding patients with psychiatric disease would limit generalizability of our findings to the larger population of PD patients. Each PDBP Center’s local IRB has approved the protocol, and all participants were consented for the study. Aggregate data are released immediately and are publically available.

Because the 5 sites recruited participants for different protocols, the study duration and number of serial assessments varied across sites. Though our study evaluated cross-sectional associations between objective and subjective cognitive assessments, visits within the same participant were clustered to correct for repeated measures with a robust standard error. From each patient-visit, the following data were collected: age, diagnosis (PD or control), gender (self-reported: male or female), education level (17 possible responses), MDS-UPDRS (32 subjective cognitive scores, 33 objective motor scores) [21], and MoCA [22] scores. The MoCA contains 10 sections which assess six proposed cognitive domains [22], confirmed by factor analysis [23, 24] to roughly characterize separate cognitive domains with construct validity. Though the positive and negative predictive value of individual MoCA item performance does not replace a detailed cognitive evaluation [25], it is a reasonable screen for individual cognitive domains in a large study sample [15]. In question 1.1 of the MDS-UPDRS, patients are asked, “Over the past week, have you had problems remembering things, following conversations, paying attention, thinking clearly, or finding your way around the house or in town?” Possible answers include that cognition is “normal”, or that cognitive impairment is present and, “slight, mild, moderate, or severe”. This was used as the subjective cognitive measure.

Statistical analysis

Analytic overview—Our aim was to observe relationships between objective and subjective cognitive dysfunction to determine objective cognitive deficits that are most likely to be present when a PD patient first perceives the mildest degree of impairment reportable on the MDS-UPDRS question 1.1. To do this, we used multinomial logistic regression modeling to determine the conditional odds ratio (cOR) of answering “slight” versus “normal” to the question of cognitive impairment over the last week for a change in individual MoCA section scores.

Participant characterization—PD and control participants’ baseline demographics, disease characteristics and cognitive performances were reported as means and compared using unpaired t-tests of means or proportions (Table 1). Because many of the PDBP sites have slightly different follow-up schedules and the study is ongoing, there were a highly variable number of repeat assessments within individual participants (esupp Table 1).

Model fitting and assessment—First, we determined the scale of the individual MoCA predictor variables (Table 2): Visuospatial/executive, naming, digit span, letters, serial 7 subtractions, language repetition, and delayed recall appeared to have a linear relationship

with MDS-UPDRS question 1 (Q1) score. The other MoCA items, letter fluency, abstraction, and orientation were non-linear. Letter fluency (2 levels) and abstraction (3 levels) were treated as categorical variables. Because the distribution of “orientation” was so heavily skewed left, the variable was dichotomized at a cut-point of 5 or below. Education was simplified in a three category variable: no college, at least some college, at least some graduate school. Age was kept as continuous because there was a linear association between age and MDS-UPDRS Q1 score.

Multinomial logistic regression models were fit including all MoCA sections as covariates, adjusting for visit, age, and education level, and with robust estimation of standard error. The primary outcome was the exponentiated coefficients for MoCA sections in the “slight” category, representing the conditional odds of reporting “slight” cognitive impairment versus “normal” (conditional odds ratio) for each unit increase in the subtest rating scale. To assess for confounding, unadjusted multinomial logistic regression models were fit for each MoCA section (objective cognitive measurement) with MDS-UPDRS Q1 (subjective cognitive measurement) as the outcome variable. We also transformed the conditional odds ratios into adjusted probabilities of answering “slight” or “normal” cognitive impairment given a specific MoCA subtest score when all other subtests were at their means.

The model fit the observed data when tested with a goodness of fit assessment using a group by category contingency table, with Pearson’s chi-squared statistic as the test statistic ($p=0.075$ with 10 bins) [26]. Collinearity between MoCA sections was evaluated and variance inflation factor was less than 10 for all covariates. For categorical variables with more than three groups, a constrained Wald test of statistical significance was used across all levels of the variable. Given the concern for effect modification of MoCA score by education level, interactions between age and education level with each MoCA section score were assessed using likelihood ratio tests of nested models with and without the interaction terms. Likelihood ratio testing for models with education interacted with each MoCA sub-score did not show statistical significance; thus no interaction terms were included in the final model. The models were preserved with all variables, even those which did not influence MDS-UPDRS Q1 by a statistically significant conditional odds ratio, as explanatory models to describe the associations between various MoCA sections (representing cognitive domains) and their impact on MDS-UPDRS Q1.1.

RESULTS

Demographic and summary MoCA and MDS-UPDRS data are given in Table 1. The PD group was slightly older and had a greater proportion of caucasians. Education level did not differ between PD and control groups. As expected, ratings of PD disease severity, the MDS-UPDRS and the motor subsection of the MDS-UPDRS, were higher in the PD group. The MoCA was lower by only 1 point in the PD group (26.4 vs. 25.4 for controls vs. PD, $p<0.001$).

Our main analysis results are shown in Table 3, with both adjusted and unadjusted conditional odds ratios comparing the odds of reporting “slight” cognitive impairment relative to “normal” for a one-point change in the corresponding MoCA sections.

Analysis of the conditional odds ratios (cOR) in elderly control (non-PD) participants showed that the greatest magnitude cOR's for answering "slight" cognitive impairment (versus "normal"), while holding the other MoCA sub-scores, age, and education categories constant, were associated with "serial 7 subtractions" and age. For each 1 point increase in the "serial 7 subtraction" score, the odds of answering "slight" relative to the odds of answering "normal" was reduced by about 33.3% (cOR for slight vs. normal =0.667, CI: 0.478–0.931, $p<0.001$). In other words, a lower serial 7 subtractions score made it more likely participants would report slight cognitive impairment (as opposed to no cognitive impairment). When holding all MoCA scores and education constant, an increase in age by one year was associated with an increased odds of answering "slight" versus "normal" to a question about cognitive impairment on the MDS-UPDRS (cOR for slight vs. normal =1.044, CI: 1.022–1.066, $p<0.001$). A relatively large cOR for reporting "slight" versus "normal" cognitive impairment was found for a 1 point increase in auditory vigilance ("tap for letter A's"), a marker of attention, but a wide confidence interval made this finding slightly less reliable (cOR for slight vs. normal =0.414, CI: 0.478–0.931, $p=0.082$). Delayed recall also showed a reasonable magnitude cOR according to the adjusted model, but also had a wide 95% confidence interval (cOR for slight vs. normal =0.865, CI: 0.741–1.01, $p=0.066$).

The pattern of association between MoCA sub-tests and the odds of self-reported cognitive impairment was different in PD than what was found in the control sample. Both the "visuospatial/executive" and the "delayed recall" MoCA subsections showed statistically significant associations with the odds of reporting "slight" versus "normal" cognitive impairment: In PD participants, the adjusted conditional odds ratio of a participant reporting "slight" relative to "normal" when describing cognitive impairment was 31% lower for each 1 point improvement in visuospatial function (cOR=0.686, CI: 0.597–0.788, $p<0.001$) and was 17% lower for each 1 point improvement in delayed recall (cOR=0.836, CI: 0.756–0.924, $p<0.001$). A one-point increase in both "serial 7 subtractions" (cOR=0.833, CI: 0.687–1.01, $p=0.064$) and "orientation >5" (cOR=0.622, CI: 0.382–1.01, $p=0.056$) MoCA sub-scores also decreased the odds of reporting "slight" cognitive impairment to a substantial degree, but with wide 95% confidence intervals that included the chance of no difference in odds. However, unlike in controls, age (cOR slight vs. normal =1.007, CI: 0.988–1.026, $p=0.487$) did not seem to influence the odds of reporting "slight" relative to "normal" cognitive impairment.

Looking more closely at cognitive deficits that are associated with patient-reported cognitive decline specific to PD, we evaluated the adjusted probabilities of reporting "slight" cognitive impairment or "normal" cognitive function based on participants' MoCA visuospatial (Figure 1A.) or delayed recall (Figure 1B.) scores. When adjusting for age and education while holding the other MoCA section scores constant, a score of 5 (out of 5) on the MoCA visuospatial/executive section had a only a 25% chance of reporting "slight" cognitive impairment and a 70% chance of reporting the absence of cognitive impairment in PD participants (Figure 1A). Similarly, the probability of reporting slight cognitive impairment is 25% for a PD patient who scores 5 points on the MoCA delayed recall but is 68% for reporting the absence of cognitive impairment with the same MoCA delayed recall score of

5 when other MoCA section scores are held constant and adjustment for age and education is performed (Figure 1B).

DISCUSSION

Using common data elements pooled from participants in the NINDS PDBP investigation, we established the deficits in objectively measured cognitive domains that substantially impacted the chance of “slight” cognitive impairment, as reported by patients on a scale that ranges from “normal” to “marked”. Interestingly, we found differences between controls and PD participants in the MoCA sub-scores that, when increased by 1 point, had the most substantial influence on the odds of reporting “slight” versus “normal” cognitive impairment.

In PD, the associations with patient-reported cognitive impairment were strongest between visuospatial/executive function and delayed recall on the MoCA. Interestingly, an evolving hypothesis in PD cognitive research posits that while early, frontal lobe symptoms such as working memory and executive dysfunction can be mild and stable over time, “posterior” cortical symptoms, such as visuospatial function and verbal memory (measured by delayed recall in this study) may herald the onset of a more rapid cognitive decline to dementia [13, 27]. It is interesting that these same objective measures that may predict subsequent cognitive decline [28] are also the cognitive domains most associated with these patients’ earliest acknowledgement of slight cognitive impairment. This has implications for development of strategies to detect participants who are most at risk for dementia for inclusion in future research targeting PD dementia.

Furthermore, a common question from PD patients is whether their perceived cognitive deficits are part of “normal aging” or PD dementia. Our study suggests that different patterns of objective cognitive deficits drive the report of “slight” cognitive impairment in PD patients versus elderly persons of a similar age without PD. Specifically, the presence of visuospatial deficits seemed particularly associated with patient self-report of cognitive impairment in PD participants but not in controls, allowing clinicians to potentially answer this common question through analysis of objective, point-of-care cognitive testing with a screening tool like the MoCA. This association may also guide recommendations from the physician: when a PD patient reports even slight cognitive impairment, subsequent questioning should specifically involve visuospatial tasks such as getting lost in a familiar environment or issues with driving. These findings may also warrant closer investigation of driving ability in PD participants who report even slight cognitive impairment.

One potential limitation of this study is the fact that subjective cognitive impairment is based on one question, where the patient is asked to globally define “cognition”. Other reports evaluating subjective cognitive impairment in PD participants used a more thorough questionnaire measuring multiple domains [16, 29]. However, one group found discordance between the presence of subjectively perceived and objectively measured cognitive deficits where patients over-reported memory deficits while under-reporting executive dysfunction [29]. The other group found that the subjective cognitive impairment scale used did not have high discriminant power for PD versus PD dementia, and that four of the ten questions had

little bearing on detection of objective deficits [16]. This suggests that the jargon-heavy semantics and concepts of cognitive domains may complicate participants' ability to correctly describe the deficits they perceive and that a more global, patient-reported cognitive measure (such as the one used in our study) is more externally valid. Our study is informative in that with only one question about global cognition, the patient had to sum his or her experiences and give a general response based on the degree of self-assessed severity while avoiding the confusion added by definitions of discrete domains. Also, the MDS-UPDRS is among the most well-validated tools in PD [21]. Another weakness is the retrospective, cross-sectional design such that the associations between objective and subjective cognitive measures cannot be considered causative. The use of the MoCA, rather than a more comprehensive neuropsychological battery, limits the ability to detect changes in some cognitive functions pertinent to PD. However, the MoCA has been shown to detect domains in individual deficits and a more comprehensive assessment would not be feasible in such a large cohort [23, 24]. Lastly, our analysis did not control for the presence or degree of depression, which can mimic or cause cognitive impairment.

As treatments for Parkinson's disease movement symptoms advance and patients maintain an active lifestyle for longer disease duration [30], even the earliest cognitive impairments are an increasing source of disability [6]. Our findings suggest that when a PD patient reports a slight degree of cognitive impairment, declines in visuospatial function and verbal memory are most likely to be driving this complaint relative to other cognitive domains. This pattern is different than what is found in controls given the same battery of objective and subjective assessments, and this indicates that there may be a PD-specific phenotype of "subjective cognitive impairment" that is different than that of "normal aging". This finding may help to focus research on the potential etiologies most likely to cause these deficits in hopes of reducing patient-reported cognitive impairment. It may also inform clinical care of patients reporting this symptom, in that visuospatial and memory domains should be specifically assessed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Data and biospecimens used in preparation of this manuscript were obtained from the Parkinson's Disease Biomarkers Program (PDBP) Consortium, part of the National Institute of Neurological Disorders and Stroke at the National Institutes of Health. Investigators include: Roger Albin, Roy Alcalay, Alberto Ascherio, DuBois Bowman, Alice Chen-Plotkin, Ted Dawson, Richard Dewey, Dwight German, Xuemei Huang, Rachel Saunders-Pullman, Liana Rosenthal, Clemens Scherzer, David Vaillancourt, Vladislav Petyuk, Andy West and Jing Zhang. The PDBP Investigators have not participated in reviewing the data analysis or content of the manuscript.

Funding sources: This manuscript was supported, in part, by a grant from the NIH/NINDS U01NS082133, P50 NS 38377 (Drs. Dawson and Rosenthal) and the Johns Hopkins Institute for Clinical and Translational Research (ICTR) which is funded in part by Grant Number KL2TR001077 from the National Center for Advancing Translational Sciences (NCATS) a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the Johns Hopkins ICTR, NCATS or NIH.

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Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution
2. Statistical analysis: A. Design, B. Execution, C. Review and Critique
3. Manuscript: A. Writing of the first draft, B. Review and Critique

K.M. – 1A, B, C; 2A, B; 3A

Z.M. – 1A, 2C, 3B

G.P – 1A, 2C, 3B

A.P. – 2C, 3B

A.Z. – 1B, C; 3B

N.Y. – 1B, C

E.P. - 1A, B, C

J.B. – 2C, 3B

T.D. – 2C, 3B

L.R. – 1A, C; 2C; 3B

Full Financial Disclosure (previous 12 months)

K.M.: He receives salary support through the NIH/NCATS (KL2TR001077, PI Daniela Ford). Dr. Mills has received funding from Northwestern University and Adamas Pharmaceuticals for involvement in clinical trials.

Z.M.: Dr. Mari is supported by the National Parkinson's Foundation with a Center of Excellence Grant and is supported by NIH/NINDS U01 NS082133.

G.P.: Dr. Pontone receives funding through the NIH/NIA as part of a K23 award (AG044441-01A1).

A.P.: Dr. Pantelyat is supported for this project by NIH/NINDS U01 NS082133, and is also supported by NIH/NINDS P50 NS38377.

A.Z.: Nothing to report.

E.P.: Nothing to report

J.B.: Dr. Brandt receives financial support from the NIH (RO1HG008045, RO1NS091139, and RO1AG041633), as well as the Douglas Hospital Research Center, the William and Ella Owens Medical Research Foundation and the BrightFocus Foundation. He is a compensated consultant to MedAvante, Inc.

T.D.: Dr. Dawson acknowledges the Adrienne Helis Malvin and Diana Henry Helis Medical Research Foundations and their direct engagement in the continuous active conduct of medical research in conjunction with The Johns Hopkins Hospital and The Johns Hopkins University School of Medicine and the Foundation's Parkinson's Disease Programs. His work is also supported by Sanofi- Aventis Recherche and Development, NIH/NINDS P50NS038377, NIH/NINDS U01NS082133, NIH/NINDS R37NS067525, NIH/NIDA P50 DA00266, the JPB Foundation, the MDSCRF 2015-MSCRFE-1782, the Michael J. Fox Foundation and Abbvie Pharmaceuticals. Dr. Dawson is the Leonard and Madlyn Abramson

Professor in Neurodegenerative Diseases. Dr. Dawson is chair of the Dystonia Prize committee of the Bachmann Strauss Dystonia and Parkinson's Disease Foundation and the Michael J. Fox Foundation and a member of the Board of Directors of the Bachmann Strauss Dystonia and Parkinson's Disease Foundation. Dr. Dawson is a member of Scientific Advisory Board of CurePSP. Dr. Dawson is a member of American Gene Technologies International Inc., advisory board. The terms of this arrangement are being managed by The Johns Hopkins University in accordance with its conflict of interest policies. Dr. Dawson is a founder of Valted, LLC and holds an ownership equity interest in the company. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies.

L.R.: Dr. Rosenthal also received support in the previous 12 months from NIH/NINDS P50 NS038377, NIH/NINDS P50NS38377, Marilyn and Edward Macklin Foundation, and the Michael J. Fox Foundation. She also received an honorarium from the Edmond J. Safra Foundation, Functional Neuromodulation, and Biohaven Pharmaceuticals.

Highlights

- Subjective and objective cognitive impairment in Parkinson's disease are compared
- Early cognitive complaints associate with posterior cortical deficits in Parkinson's
- Visuospatial deficits underlie early cognitive complaints in Parkinson's disease

Figure 1.

Probabilities of subjective report by PD participants of “slight” cognitive impairment or “normal” cognitive function for each potential MoCA visuospatial sub-score (A), or delayed recall sub-score (B), when other MoCA scores are constant, adjusting for age and education.

Table 1
Demographic & clinical characteristics of Parkinson's disease and control groups

Characteristic	Control		Parkinson's disease		p
Age (mean in years (sd))	62.7	10.8	65.4	9.16	<0.001*
Race (N, %)					
Caucasian	447	93.3%	728	96.4%	.014*
Black	28	5.9%	18	2.4%	0.58
American indian	2	42.0%	3	0.4%	1.00
East asian	2	0.6%	6	1.0%	0.96
Non-Caucasian	34	7.1%	31	4.1%	0.60
Education (N, %)					
6th – 12th grade	71	14.8%	123	16.2%	0.78
Any college	273	56.8%	396	52.2%	0.26
Any graduate school	137	28.5%	237	31.2%	0.56
Total MoCA (mean, sd)	26.4	2.54	25.39	3.41	<0.001*
Total MDS-UPDRS (mean, sd)	6.65	6.38	49.5	25.6	<0.001*
MDS-UPDRS Motor III (mean, sd)	1.72	3.51	25.48	14.57	<0.001*
Disease Duration (mean years, sd)	-	-	6.09	5.17	

Table 2

Variable list for multinomial logistic regression models

Variable	Treatment in model	Number of levels
Age	continuous	-
Race	categorical	4
Caucasian		-
Black		-
American Indian		-
East Asian		-
Education	categorical	3
6th – 12th grade		-
Any college		-
Any graduate school		-
MoCA items		-
visuospatial/executive	continuous	6
naming	continuous	4
digits	continuous	3
letter vigilance	continuous	2
serial 7 calculations	continuous	4
language repetition	continuous	3
language fluency	categorical	1
abstraction	categorical	3
delayed recall	continuous	6
orientation *	categorical	2

* originally 6 levels, dichotomized due to skewed distribution

Table 3

Results from multinomial logistic regressions. Relative risk ratio for response of “slight” versus “none” cognitive impairment in PD patients

Variables	Controls				Parkinson's disease			
	cOR unadjusted	95% CI	p	cOR adjusted	95% CI	p	cOR adjusted	95% CI
Cognitive assessments								
Visuospatial-executive	0.81	0.64	1.02	0.077*	0.97	0.76	1.25	0.838
Naming	0.77	0.11	1.47	0.433	1.05	0.51	2.20	0.888
Digits	1.11	0.58	2.13	0.752	1.22	0.61	2.45	0.577
Auditory vigilance	0.24	0.10	0.61	0.002*	0.41	0.15	1.12	0.082
Serial 7 subtractions	0.64	0.48	0.85	0.002*	0.67	0.48	0.93	0.017*
Sentence repetition	1.03	0.71	1.49	0.891	1.15	0.77	1.72	0.504
Letter fluency	0.67	0.41	1.11	0.121	0.89	0.50	1.58	0.694
Abstraction [‡]								0.913 [‡]
One correct	0.77	0.15	4.07	0.761	0.92	0.20	4.35	0.921
Two correct	0.77	0.16	3.60	0.735	1.08	0.25	4.61	0.92
Delayed recall	0.82	0.71	0.94	0.004*	0.87	0.74	1.01	0.066
Orientation = 6	1.34	0.39	4.53	0.664	1.56	0.47	5.25	0.47
Demographic variables								
Age (years)	1.05	1.03	1.07	<0.001*	1.04	1.02	1.07	<0.001*
Education [‡]								0.666 [‡]
Any college	0.73	0.40	1.31	0.286	0.75	0.40	1.41	0.376
Any graduate	0.81	0.42	1.54	0.517	0.84	0.40	1.77	0.644

*
p < 0.05.[‡]
relative to zero abstractions correct.[‡]
relative to at least some high school.[‡]
Constrained Wald test. Adjusted = visit and other variables in model held constant.