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Journal
Journal of Clinical and Experimental Neuropsychology, 43(5)

ISSN
1380-3395

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Publication Date
2021-05-28

DOI
10.1080/13803395.2021.1927995

Peer reviewed

HHS Public Access

Author manuscript

J Clin Exp Neuropsychol. Author manuscript; available in PMC 2022 August 06.

Published in final edited form as:

J Clin Exp Neuropsychol. 2021 July ; 43(5): 469–480. doi:10.1080/13803395.2021.1927995.

Semantic fluency and processing speed are reduced in non-cognitively impaired participants with Parkinson's disease

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Abstract

Introduction: Parkinson's disease (PD) is associated with a range of cognitive deficits. Few studies have carefully examined the subtle impacts of PD on cognition among patients who do not meet formal criteria for MCI or dementia. The aim of the current study was thus to describe the impact of PD on cognition in those without cognitive impairment in a well-characterised cohort.

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Declaration of interest

The authors report no conflict of interest.

Methods: Non-cognitively impaired participants (122 with PD and 122 age- and sex-matched healthy volunteers) from multiple sites underwent extensive cognitive testing. Linear regression analyses compared diagnostic group performance across cognitive measures. For cognitive tasks that were significantly different between groups, additional analyses examined group differences restricting the group inclusion to PD participants with mild motor symptoms or disease duration less than 10 years.

Results: Processing speed and semantic verbal fluency were significantly lower in the PD group (B = −3.77, 95% CIs [−5.76 to −1.77], p <.001, and B = −2.02, 95% CIs [−3.12, −0.92], p <.001, respectively), even after excluding those with moderate to severe motor symptoms (B = −2.73, 95% CIs [−4.94 to −0.53], p = .015 and B = −2.11, 95% CIs [−3.32 to −0.91], p < .001, respectively) or longer disease duration (B = −3.89, 95% CIs [−6.14 to −1.63], p <.001 and B = −1.58, 95% CIs [−2.78 to −0.37], p = .010, respectively). Semantic verbal fluency remained significantly negatively associated with PD diagnosis after controlling for processing speed (B = −1.66, 95% CIs [−2.79 to −0.53], p =.004).

Conclusions: Subtle decline in specific cognitive domains may be present among people diagnosed with PD but without evidence to support a formal cognitive diagnosis. These results suggest the importance of early awareness of the potential for diminishing aspects of cognition in PD even among those without mild cognitive impairment or dementia.

Keywords

Aging; Cognition; Healthy Volunteers; Neuropsychological Assessment; Parkinson’s disease

Introduction

It is well-established that Parkinson’s disease (PD) is associated with a heterogenous cognitive profile that includes a broad range of intellectual dysfunction (Goldman & Sieg, 2020; Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007). PD is known to lead to cognitive impairment in most people, with at least 80% progressing to dementia during the course of the disease (Hely, Reid, Adena, Halliday, & Morris, 2008). Mild cognitive impairment (MCI) is common throughout the disease, including in patients with *de novo* PD (Aarsland et al., 2009; Yarnall et al., 2014). The trajectory to dementia in PD varies considerably, although the speed of decline is associated with an increasingly predictable set of characteristics (e.g., male sex, genetic factors, age at diagnosis) (Davis et al., 2016) (Phongpreecha et al., in press).

Despite increased awareness and deepening knowledge surrounding cognitive impairment in PD in recent years, few studies have closely examined the subtle impacts of PD on cognition among patients who do not meet formal criteria for MCI or dementia. Two large-scale meta-analyses that reviewed studies of cognition and PD found consistent dysfunction in non-demented PD participants relative to age-matched controls across executive, visuospatial, and verbal memory domains. The majority of these studies, however, included groups with either poorly defined cognitive inclusion/exclusion criteria, use of non-sensitive screening measure cutoffs to exclude cognitive impairment, or exclusion on the basis of dementia only (thus including participants with MCI) (Curtis, Masellis, Camicioli, Davidson, & Tierney,

2019; Kudlicka, Clare, & Hindle, 2011). In the studies that included careful diagnostic evaluation criteria, direct comparisons between HVs and non-cognitively impaired PD participants were not made (Bezdicek et al., 2017; Weintraub et al., 2015). Results from a large online study demonstrated differences in learning and memory, processing speed, attention, and working memory between participants with PD and non-PD participants who did not report a diagnosis of cognitive impairment (B. Cholerton et al., 2019); however, cognitive and motor diagnoses were limited to self-report. Early subtle differences in cognition in PD may be related to factors such as disease duration, motor disability, surgical history, or depression (Curtis et al., 2019; Goldman & Sieg, 2020). However, many of these studies had small sample sizes and/or poorly characterised cognitive status, and thus were limited in generalisability. Overall, the extent and nature of relative deficits in PD patients without a formal diagnosis of cognitive impairment is not currently well-described.

The aim of the current study was to provide a deeper understanding of the impact of PD on cognition in those who do not meet formal criteria for cognitive impairment (either MCI or dementia) in a large, well-characterised cohort. Specifically, the goals of the study were to (1) compare non-cognitively impaired participants with PD and age- and sex-matched healthy volunteer participants on cognitive measures that assess a range of abilities; and (2) determine whether any identified cognitive differences persisted in those with only mild motor symptoms or shorter symptom duration.

Materials and Methods

Participants

Participants aged 50–85 with and without PD were drawn from the Pacific Udall Center of Excellence in PD Research, which enrolls participants from three sites (University of Washington/Veterans Affairs Puget Sound Health Care System, Oregon Health and Sciences University/Veterans Affairs Portland Health Care System, and Stanford University), and from Johns Hopkins University. Participants with PD were included if they met the United Kingdom PD Society Brain Bank clinical diagnostic criteria for idiopathic PD (Gibb & Lees, 1988) and were found to have no cognitive impairment during a diagnostic consensus conference (n = 247). Neurologically healthy volunteer (HV) participants were included if they had no evidence of neurologic disease, including PD, did not have a pathogenic mutation in leucine-rich repeat kinase 2 (*LRRK2*, G2019S or R1441C/G/H/S) or a risk variant in *GBA*, and were found to have no cognitive impairment during a consensus diagnosis case conference (n = 146). Seven participants with PD were excluded for missing one or more of the primary covariates: the 15 item Geriatric Depression Scale (GDS-15) (Yesavage et al., 1982) (n = 3), apolipoprotein E ε4 (*APOE* ε4) allele status (n = 2), or Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) (n = 1). An additional 11 participants were excluded due to a history of deep brain stimulation (DBS) surgery prior to the visit, three were excluded for missing DBS information, and 18 were excluded due to missing cognitive test scores or extreme outliers (total n = 210). Nine HV participants were excluded for missing GDS-15 (n = 5) or *APOE* ε4 status (n = 4), and three were excluded for missing cognitive test scores or extreme outliers (total n = 135). Participants were matched for age (in bins of five years) and sex, for a total sample of 122 with PD and

122 HV. The institutional review boards at all sites provided formal approval for the study. All participants provided written informed consent prior to study participation.

Clinical measurements and covariates

A movement disorder specialist assessed the presence and severity of motor symptoms using Part III of the Unified PD Rating Scale, Movement Disorders Society revision (MDS-UPDRS) (Goetz et al., 2008). Levodopa equivalent daily dose was calculated using methods described by Tomlinson et al. (Tomlinson et al., 2010). PD symptom duration was assessed from the time of participant reported motor symptom onset. Global cognitive status was assessed using the MoCA. Depression symptoms were measured using the GDS-15 (Yesavage et al., 1982). DNA sequencing was performed as described below. The presence of an *APOE* ε4 allele was included in analyses due to previous associations with cognitive decline in older adults with and without PD (Mata et al., 2014).

Cognitive diagnosis

All participants were assigned motor and cognitive diagnoses at a clinical diagnostic consensus conference attended by at least two movement disorder specialists and a neuropsychologist. Participants were determined to have no cognitive impairment if there were no impairments on cognitive tests in the presence of subjective cognitive complaints (by self, collateral, or clinician), no tests equal to or greater than two standard deviations below published normative data and no more than one test equal to or greater than 1.5 standard deviations below published normative data. Thus, participants did not meet published diagnostic criteria for MCI or dementia (Emre et al., 2007; Litvan et al., 2012) as previously described (B. A. Cholerton et al., 2013). In addition, participants were excluded if there was cognitive impairment present on tests that was likely due to factors other than MCI or dementia (e.g., depression, medication effects) or due to unknown causes. Extensive neuropsychological (Table 1) and clinical assessments were available for determination of cognitive diagnosis.

Cognitive variables

Cognitive variables that were consistent across all sites were selected for analyses in the current study: (1) verbal learning and memory (Hopkins Verbal Learning Test-Revised (Benedict, Schretlen, Groninger, & Brandt, 1998) immediate total recall across trials and delayed recall trial), (2) auditory working memory (Letter-Number Sequencing subtest from the Wechsler Adult Intelligence Scale – III) (Wechsler, 1997), (3) processing speed (Digit Symbol subtest from the Wechsler Adult Intelligence Scale-Revised) (Wechsler, 1987), (4) visuospatial working memory/switching (Trail Making Test, Part B) (Strauss, Sherman, & Spreen, 2006), (5) semantic verbal fluency (animals) (Strauss et al., 2006), (6) phonemic verbal fluency (letters F-A-S or C-F-L) (Strauss et al., 2006), and (7) visuospatial functioning (15 item Benton Judgment of Line Orientation) (Benton, Sivan, Hamsher, Varney, & Spreen, 1994). Participants with PD were rated in the ON state if they were taking medications for PD.

Genotyping

Genomic DNA was extracted from peripheral blood samples using standard techniques. *APOE* rs429358 and rs7412 (which define the ε2, ε3, and ε4 alleles) and *LRRK2* G2019S were genotyped using commercially available TaqMan assays (Applied Biosystems) (Mata et al., 2014), and the *LRRK2* R1441C/G/H/S mutational hotspot was assayed by Sanger sequencing exon 31 as described elsewhere (Zabetian et al., 2009). The entire *GBA* coding region was screened by Sanger sequencing using previously published techniques (Mata et al., 2016). *GBA* PD risk variants were defined as the E326K polymorphism (rs2230288) and mutations that have been reported as "pathogenic" for Gaucher disease.

Statistical Analyses

For the purpose of presenting descriptive group features, group differences (PD and HV) on demographic (age, education, sex, *APOE*) and basic clinical (MoCA, GDS-15) variables were assessed using t-tests for continuous variables or chi-square tests for categorical variables. To test associations between diagnostic group and cognitive test performance, multiple linear regression analyses coupled with the robust variance estimator were conducted for each cognitive variable (entered as the dependent variable), with group (PD, HV) and potential confounders as the independent variables. Covariates were chosen *a priori* based on prior work by this group and others (Barbosa et al., 2019; B. Cholerton et al., 2018; Mata et al., 2014; Phongpreecha et al., 2020), and include: age, education, sex, *APOE* ε4 status, depression (GDS-15), global cognition (MoCA), and study site. Raw cognitive test scores were used for linear regression analyses. Z-scores based on published normative data (used primarily for diagnostic purposes) are provided for reference; use of these scores in the regression analyses did not provide substantially different results and thus are not reported. The Shapiro-Francia test for normality was performed on the residuals of each dependent variable. The normality assumption was violated for multiple tests (Trail Making, Part B, Letter-Number Sequencing, semantic verbal fluency, and the Judgment of Line Orientation); to amend this problem, we used the robust variance estimation of the estimated regression coefficients in conducting the linear regression analysis. This method of variance estimation is equivalent to the bootstrap variance estimator based on bootstrapping individual observations and is thus robust to the non-constant residual variance appreciated across cognitive measures; in this case the standard ordinary least squares regression estimator may produce a biased estimate. For analyses that included Digit Symbol or Trail Making, Part B as the dependent variable, Trail Making, Part A was included as a covariate to mitigate the impact of motor symptoms on test performance. To check for multicollinearity among predictors, we examined the variance inflation factors and tolerances. To minimize likelihood of Type I error, α level was set at 0.01. Secondarily, the same analyses were conducted excluding participants with any cognitive test scores that fell 1.5 standard deviations below demographically-corrected normative data to determine whether our results were primarily driven by scores in these lower ranges (total $n = 206$). Finally, linear regression analyses were performed on those cognitive tests with significant group associations in the overall analyses that excluded those with (1) moderate PD motor symptoms (MDS-UPDRS ≥ 33, $n = 19$) (Martinez-Martin et al., 2015; Skorvanek et al., 2017), and (2) PD duration longer than 10 years ($n = 27$) (>75th percentile in the sample)

(Hassan et al., 2012; Hely et al., 1999) and their matched HVs. All analyses were performed in Stata 15.1.

Results

Demographic and basic clinical data are provided in Table 2. Groups were matched for age and sex; thus these variables did not differ significantly between groups. MoCA scores, years of education, and percent of participants with an *APOE* e4 allele also were not significantly different across groups. Mean GDS-15 scores were slightly higher among participants with PD.

Descriptive data for raw cognitive test scores and z-scores based on demographically based normative data for each cognitive test are provided in Table 3.

Linear regression analyses demonstrated significantly poorer performance on tasks of processing speed (Digit Symbol subtest) and semantic verbal fluency in the PD group as compared to the HV group (Table 4). HV participants also performed better on word recall (HVLT-R delayed recall) and visuospatial working memory/switching (Trail Making Test, Part B), however these did not meet our more stringent criteria for statistical significance. There were no statistically significant differences across tasks of verbal learning, visuospatial function, phonemic verbal fluency, or auditory working memory. Mean variable inflation factor was 1.25, and predictor variable tolerances were acceptable (range 0.53– 0.98). For unadjusted models, please refer to the supplement, Table A1. Secondary analyses that excluded participants with any raw cognitive test scores −1.5 standard deviations or more as compared to normative data did not result in substantial differences in the pattern of results (supplement, Table A2).

Reduced performance on both processing speed and semantic verbal fluency remained significantly associated with PD diagnosis after excluding participants with moderate or severe motor impairment ($B = -2.73$, 95% confidence intervals [CIs] [−4.94 to −0.53], p = .015 and $B = -2.11$, 95% CIs [−3.32 to −0.91], p < .001, respectively). Similarly, worse performance on both processing speed and semantic verbal fluency remained significantly associated with PD diagnosis after excluding participants with greater than 10 years disease duration ($B = -3.89$, 95% CIs [−6.14 to −1.63], p < .001 and $B = -1.56$, 95% CIs [−2.78 to −0.37], p = .010, respectively).

To measure the influence of processing speed on the relationship between semantic fluency and diagnostic group, Digit Symbol was included as a covariate in secondary analyses. Poorer performance on semantic verbal fluency remained associated with PD diagnosis over and above processing speed ($B = -1.66$, 95% CIs [−2.79 to −0.53], p = .004), even when the analyses were restricted to participants with only mild motor symptoms ($B = -1.99$, 95% CIs [−3.20 to −0.77], p = .002). However, when participants with longer disease duration were excluded, this association was no longer statistically significant ($B = -1.19$, 95% CIs [−2.45 to 0.07], p = .065).

Discussion

In the current study, we describe reduced performance in processing speed and semantic verbal fluency in non-cognitively impaired participants with PD as compared to HV participants. In this large, well-characterised cohort, these differences endured despite controlling for depressive symptoms and global cognitive status, and after excluding those with longer disease duration and more severe motor symptoms. Despite mean cognitive scores that fall largely within the expected range for age, our results suggest that patients with PD who are not diagnosed with cognitive impairment nonetheless may have subtle declines in specific cognitive domains.

Lower performance on semantic fluency in PD compared to HV participants has potential implications for disease outcome. Reduced semantic verbal fluency is associated with a range of negative disease outcomes in PD, including dementia or impending dementia (De Roy et al., 2020; Wilson et al., 2020), rapid eye movement behavior disorder symptoms (Yan, Lei, Li, Liu, & Chang, 2019), and hallucinations (Ramirez-Ruiz, Junque, Marti, Valldeoriola, & Tolosa, 2006; Santangelo et al., 2007). Higher verbal fluency scores are associated with better quality of life and lower caregiver burden in PD (Rosenthal et al., 2017). At face value, the group differences reported here may not appear to represent clinically meaningful differences. However, recent work suggests that even early subtle changes may impact real-world functioning. Interestingly, although the mean difference between HV and PD participants on the semantic fluency measure is ~two words, recent work suggests suggest that the threshold for detecting “real” change at the group level is two to four words in a clinical population, although with the caveat that this may be different for each group studied (Magnin, Sagawa, Moulin, & Decavel, 2020). Further, lower performance on measures of both processing speed and semantic verbal fluency may negatively impact caregiver perception of overall executive abilities in PD patients, even when scores are within the expected range for age and there are no overall significant differences between HV and PD groups (Lanni et al., 2014). Finally, semantic verbal fluency test performance is a significant predictor for subsequent cognitive decline even among newly diagnosed, medically untreated patients with PD (Wilson et al., 2020). Importantly, there is emerging evidence that exercise, cognitive training, and enhancing social relationships may help improve semantic fluency performance, thus pointing to potential candidates for future intervention programs (Bahar-Fuchs, Martyr, Goh, Sabates, & Clare, 2019; Holthoff et al., 2015; Kelly et al., 2017; Nocera, McGregor, Hass, & Crosson, 2015; Paris et al., 2011).

Prior studies that compared verbal fluency in non-demented PD and HV participants produced conflicting results. Piatt et al. (Piatt, Fields, Paolo, Koller, & Troster, 1999) described no differences in verbal fluency between non-demented PD and HV participants. Participants in this study were matched in terms of age, education, and global cognition, however specific diagnosis information (e.g., MCI) was missing and the study was relatively small (59 HV and 57 PD). Similarly, Scholtissen et al. (Scholtissen, Dijkstra, Reithler, & Leentjens, 2006) found no differences in overall performance or retrieval strategies in a small study (25 PD and 15 HV participants), although again, MCI diagnoses was not explicitly excluded. In another small study of 32 PD and 32 HV participants, those

with PD performed more poorly on name fluency but not animal fluency. However, two of the participants with PD were taking cholinesterase inhibitors, suggesting some level of cognitive impairment was present in the sample (Fine, Delis, Paul, & Filoteo, 2011). Conversely, other studies with similarly small samples demonstrated that both phonemic and semantic fluency are worse in participants with PD as compared to HVs; however, overall global cognitive status was either lower in the PD group (Obeso, Casabona, Bringas, Alvarez, & Jahanshahi, 2012) or unreported (Dadgar, Khatoonabadi, & Bakhtiyari, 2013), thus the relative impact of the inclusion of participants with MCI is unclear. Here, we provide evidence for differences in semantic verbal fluency in a large, multisite cohort, limited to those with no formal cognitive impairment following careful assessment and diagnostic protocols.

The basis for verbal fluency decline in early PD is not fully understood, but may be related in part to diminishing processing speed caused by reductions in striatal dopamine that is characteristic of PD (Bayram, Kaplan, Shan, & Caldwell, 2020; Sawamoto et al., 2007; Vriend et al., 2020). In the current study, we found the expected strong association between processing speed and PD diagnosis. Both cognitive and motor slowing occurs early in the disease, thus it is plausible that declining performance on other cognitive (particularly executive) tasks prior to significant cognitive impairment may be principally related to reduced psychomotor speed. Indeed, there are reports that semantic verbal fluency performance may be more influenced by psychomotor speed than by cognitive flexibility, executive function efficiency, or semantic knowledge, particularly in the early stages of the disease (Koerts et al., 2013; McDowd et al., 2011). Given these reports, we ran secondary analyses controlling for processing speed and found that performance on semantic verbal fluency was still significantly reduced in PD compared to HV participants. Consistent with these prior reports, our results also show that processing speed may have a greater impact on semantic verbal fluency in those with shorter motor disease duration.

Our findings and the above discussion suggest that it is unlikely that pathology underlying the specific semantic verbal fluency deficit in those with early cognitive disease is limited solely to the striatum. Indeed, temporal lobe structures are thought to predominantly influence semantic fluency, knowledge, and retrieval, with frontal cortical regions primarily involved in organisational and search strategies (Henry & Crawford, 2004). In support of this, Pereira et al. (Pereira et al., 2009) demonstrated that higher semantic verbal fluency performance in non-demented participants with PD was positively associated with gray matter density in the temporal, frontal, and cerebellar lobes, while none of these were related to phonemic fluency performance. PET (18)F-DOPA uptake in both the striatum and middle frontal gyrus was associated with a verbal fluency factor, although this was not specific to semantic fluency (Picco et al., 2015).

Other potential influences on semantic verbal fluency performance in PD have been reported. For example, longitudinal decline in verbal fluency is associated with longer PD duration, older age, and more severe motor function (Rosenthal et al., 2017). Others have reported that worse semantic fluency in PD was most strongly associated with depression (Tremblay, Monchi, Hudon, Macoir, & Monetta, 2012; Troster, Stalp, Paolo, Fields, & Koller, 1995), although the depressed group in at least one study appears to have had

generally lower cognitive status. While these variables may impact overall semantic verbal fluency performance in PD, our results after controlling for depressive symptoms and including those with only mild PD motor symptom and shorter disease duration suggest that there are persistent differences in semantic verbal fluency between PD and HV participants over and above these factors.

We did not find differences between non-cognitively impaired PD participants and HVs in other cognitive domains that have been previously shown to be impaired in nondemented PD patients, including visuospatial functions, working memory, and switching (Curtis et al., 2019; Kudlicka et al., 2011). However, as described above, these studies typically included participants with likely or verified MCI. As MCI generally represents the largest cognitive group in most PD populations (Phongpreecha et al., 2020), these samples are likely enriched with cognitively impaired individuals. Thus, direct comparison of the results in the current study with previous studies is difficult. Replication studies are needed to determine whether these findings are generalisable to other populations.

Limitations of the current study include lack of follow up available data for the HV sample; as a result we were not able to compare trajectories or subsequent cognitive decline. For example, we previously showed potential sex differences in longitudinal analyses of the PD cohort, such that non cognitively impaired females with PD who performed relatively worse on semantic verbal fluency were more likely to subsequently progress to MCI (B. Cholerton et al., 2018). We were not able to examine subsequent cognitive decline among HV participants to determine whether this was a disease-specific finding. Further, we enrolled a prevalent PD sample rather than an incident sample, thus our PD participants were not *de novo*. An advantage of this approach is that it permitted inclusion of a broader range of PD participants, including those who remain not cognitively impaired for many years, and is thus potentially more generalisable to the larger PD population. Finally, we did not have measures available that allowed us to compare semantic verbal fluency to assessments of functional change in PD and HV participants; future research will be necessary to determine whether the consistent statistically significant differences noted in the current study translate to real-world impacts.

The current study demonstrates that processing speed and semantic verbal fluency are reduced in non-cognitively impaired participants with PD as compared to age- and sex-matched HV participants. These differences were noted even after eliminating those with prior DBS surgery, controlling for depression and global cognitive status, and excluding those with moderate or severe motor symptoms or longer disease duration. Semantic verbal fluency performance is likely influenced by multiple factors that extend beyond the impact of slowed processing speed related to early striatal changes. The current standard of care in PD is primarily treatment of motor symptoms, with more obvious non-motor symptoms treated as they arise. However, subtle early changes in cognition may be overlooked in the absence of a clinical cognitive diagnosis. Our results thus serve as a reminder to clinicians that cognitive decline may be present, even in seemingly cognitively normal participants, thus warranting closer query and monitoring of these symptoms and their potential impact.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Institutes of Neurological Disorders and Stroke grant P50 NS062684, Department of Veterans Affairs grant 101 CX001702, and the Scully Initiative Fund. L.S.R. and T.M.D were supported by P50 NS38377 and U01 NS082133. The funding sources did not provide scientific input for the study. This material is the result of work supported with resources and the use of facilities at the Veterans Affairs Puget Sound Health Care System. We sincerely thank our research participants for their participation in this study.

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Table 1

Neuropsychological measures used for cognitive diagnosis across study sites

Cognitive domain	Neuropsychological measures	
	VA Puget Sound Health Care System - University of Washington / VA Portland Health Care System - Oregon Health and Sciences University / Johns Hopkins University	**Stanford University**
Memory	Hopkins Verbal Learning Test-Revised Logical Memory I & II Brief Visual Memory Test-Revised[a]	Hopkins Verbal Learning Test-Revised Craft Story Recall Benson Complex Figure recall
Visuospatial	Judgment of Line Orientation Clock copy Brief Visual Memory Test-Revised copy[a]	Judgment of Line Orientation Clock copy Benson Complex Figure copy
Language	Boston Naming Test Shipley Vocabulary Semantic verbal fluency	Multilingual Naming Test Wechsler Test of Adult Reading Semantic verbal fluency
Executive/ attention/ working memory	Clock Drawing Test Phonemic verbal fluency Trail Making test, parts A & B Letter-Number Sequencing Digit Symbol Digit Span Stroop (Golden version)	Clock Drawing Test Phonemic verbal fluency Trail Making test, parts A & B Letter-Number Sequencing Digit Symbol Number Span Stroop (Victoria version)

[a]Test not administered at the Johns Hopkins University site

Table 2

Demographic and clinical characteristics of PD and HV participants

Variable	PD n = 122	HV n = 122	*p* value [a]
Age, years			
mean (sd)	68.7 (7.2)	69.1 (7.0)	.660
range	51.8 – 84.8	50.9 – 83.9	
Education, years			
mean (sd)	16.4 (2.4)	16.9 (2.3)	.097
range	12 – 20	12 – 20	
Sex			
n, % male	55, 45.1	55, 45.1	1.00
MoCA			
mean (sd)	27.1 (2.0)	27.2 (2.1)	.663
range	22 – 30	20 – 30	
APOE ε4 allele			
n, % ε4+	26, 21.3	30, 24.6	.543
GDS-15 total score			
mean (sd)	5.0 (1.7)	4.6 (1.9)	.038
range	0 – 12	0 – 10	
Motor symptom duration, years [b]			
mean (sd)	6.9 (4.4)		
range	0.5 – 23.3		
MDS-UPDRS part III			
mean (sd)	22.6 (10.6)		
range	5 – 62		
LEDD, mg/d			
mean (sd)	589.2 (493.4)		
range	0 – 2886.9		
% no PD medication	9.0%		
% low dose PD medication (</=400 mg/d)	27.9%		
% medium dose PD medication (>400, <1200 mg/d)	50.8%		
% high dose PD medication (>=1200 mg/day)	12.3%		

[a] *P* values based on t tests for continuous variables and chi-square tests for categorical variables

[b] Motor symptom duration measured from the time the participant reported first motor symptoms

Abbreviations: *APOE*, apolipoprotein E; GDS-15, 15 item Geriatric Depression Scale; HV, healthy volunteers; LEDD, levodopa equivalent daily dose; MDS-UPDRS, United Parkinson's Disease Rating Scale, Movement Disorder Society revision; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; sd, standard deviation

Table 3

Cognitive test scores in PD and HV participants

Cognitive test	Raw score mean (sd) range		z score[a] mean (sd) range	
	PD	HV	PD	HV
HVLT-R immediate	26.4 (3.4) 17 – 35	27.0 (3.6) 19 – 34	0.25 (0.73) −1.35 – 1.87	0.33 (0.87) −1.84 – 2.06
HVLT-R delayed	9.7 (1.6) 6 – 12	10.2 (1.4) 6 – 12	0.33 (0.72) −1.82 – 1.54	0.48 (0.71) −1.65 – 1.38
Trail Making, Part A [b]	31.1 (12.0) 15 – 116	28.5 (8.2) 15 – 51	0.03 (0.84) −4.49 – 1.36	0.23 (0.66) −1.24 – 1.90
Trail Making, Part B [b]	75.0 (25.9) 40 – 138	66.2 (19.4) 26 – 117	0.12 (0.63) −1.60 – 1.31	0.33 (0.45) −0.96 – 1.28
Letter-Number Sequencing	10.4 (2.1) 6 – 16	10.6 (2.2) 6 – 17	0.64 (0.73) −0.67 – 3.00	0.71 (0.74) −1.00 – 3.00
Digit Symbol	48.1 (9.0) 31 – 77	53.2 (8.0) 31 – 75	−0.14 (0.73) −1.87 – 2.30	0.32 (0.73) −1.41 – 2.12
Semantic verbal fluency	21.4 (4.3) 13 – 34	23.4 (4.6) 14 – 36	−0.10 (0.77) −1.70 – 2.22	0.23 (0.87) −1.41 – 2.86
Phonemic verbal fluency	45.7 (11.9) 22 – 77	49.1 (11.1) 22 – 80	0.68 (0.92) −1.09 – 3.29	0.93 (0.92) −1.20 – 3.53
Judgment of Line Orientation	12.7 (2.0) 6 – 15	13.0 (1.8) 7 – 15	1.96 (2.00) −1.88 – 3.99	2.36 (1.93) −1.64 – 3.99

[a] z scores based on demographically-corrected normative data

[b] Higher scores represent worse performance

Abbreviations: HV, healthy volunteers; HVLT-R, Hopkins Verbal Learning Test-Revised; PD, Parkinson's disease; sd, standard deviation

Table 4

Associations between cognitive test scores and PD diagnosis in participants without cognitive impairment

Cognitive test	Semi-partial correlations	*B* [a]	95% CI	*p* value
HVLT-R immediate (total words recalled)				
Diagnosis				
HV		Reference		
PD	−0.067	−0.49	−1.34, 0.36	.258
Age, years	−0.055	−0.03	−0.09, 0.04	.396
Education, years	0.075	0.12	−0.08, 0.31	.239
Sex				
Female		Reference		
Male	0.121	0.86	0.01, 1.73	.048
APOE ε4		0.57	−0.28, 1.41	.191
MoCA score	0.148	0.26	0.07, 0.45	**.007**
GDS-15 score	−0.079	−0.21	−0.46, 0.05	.109
Site				
VA Puget Sound Health Care System/ University of Washington		Reference		
VA Portland Health Care System/ Oregon Health & Sciences University	−0.122	−1.20	−2.38, -0.02	.046
Stanford University	−0.155	−1.50	−2.71, -0.30	.015
Johns Hopkins University	−0.005	−0.07	−1.72, 1.59	.938
HVLT-R delayed (total words recalled)				
Diagnosis				
HV		Reference		
PD	−0.135	−0.43	−0.80, -0.05	.025
Age, years	−0.909	−0.02	−0.05, 0.00	.103
Education, years	0.101	0.07	−0.01, 0.15	.087
Sex				
Female		Reference		
Male	0.205	0.65	0.27, 1.03	**.001**
APOE ε4 allele	0.023	0.08	−0.30, 0.46	.682
MoCA score	0.128	0.10	0.01, 0.19	.032
GDS-15 score	−0.075	−0.09	−0.22, 0.05	.218
Site				
VA Puget Sound Health Care System/ University of Washington		Reference		
VA Portland Health Care System/ Oregon Health & Sciences University	−0.163	−0.71	−1.23, -0.20	**.007**
Stanford University	−0.062	−0.27	−0.79, 0.26	.323
Johns Hopkins University	−0.012	−0.08	−0.81, 0.66	.841
Trail Making Test, Part B (seconds) [b, c]				
Diagnosis				

Cognitive test	Semi-partial correlations	*B* [a]	95% CI	*p* value
HV		Reference		
PD	0.099	4.84	0.05, 9.63	.048
Trail Making, Part A	0.342	0.83	0.58, 1.09	**<.001**
Age, years	0.211	0.75	0.35, 1.15	**<.001**
Education, years	−0.194	−2.03	−3.17, -0.89	**<.001**
Sex				
Female		Reference		
Male	0.007	0.32	−4.46, 5.10	.896
APOE ε4 allele	−0.037	−1.94	−7.50, 3.63	.496
MoCA score	−0.018	−0.21	−1.46, 1.05	.748
GDS-15 score	0.015	0.26	−1.47, 1.99	.770
Site				
VA Puget Sound Health Care System/ University of Washington		Reference		
VA Portland Health Care System/ Oregon Health & Sciences University	−0.111	−7.33	−12.38, -2.29	**.004**
Stanford University	0.046	2.97	−3.53, 9.47	.371
Johns Hopkins University	0.016	1.63	−7.63, 10.89	.730
Letter-Number Sequencing (total score)				
Diagnosis				
HV		Reference		
PD	−0.010	−0.05	−0.54, 0.45	.858
Age, years	−0.216	−0.07	−0.11, -0.03	**.001**
Education, years	0.171	0.16	0.06, 0.27	**.003**
Sex				
Female		Reference		
Male	−0.041	−0.18	−0.72, 0.36	.512
APOE ε4	0.006	0.03	−0.63, 0.69	.929
MoCA score	0.122	0.13	0.02, 0.24	.025
GDS-15 score	−0.070	−0.11	−0.27, 0.05	.173
Site				
VA Puget Sound Health Care System/ University of Washington		Reference		
VA Portland Health Care System/ Oregon Health & Sciences University	0.067	0.40	−0.38, 1.19	.316
Stanford University	−0.032	−0.20	−0.87, 0.48	.571
Johns Hopkins University	−0.035	−0.31	−1.20, 0.58	.496
Digit Symbol (total score) [b, c]				
Diagnosis				
HV		Reference		
PD	−0.203	−3.77	−5.76, 1.77	**<.001**
Trail Making, Part A	−0.270	−0.25	−0.39, -0.11	**<.001**
Age, years	−0.172	−0.23	−0.37, -0.10	**<.001**

Cognitive test	Semi-partial correlations	*B* [a]	95% CI	*p* value
Education, years	0.096	0.39	−0.00, 0.77	.052
Sex				
Female		Reference		
Male	0.159	2.90	0.97, 4.83	**.003**
APOE ε4 allele	−0.0002	−0.00	−1.93, 1.92	.997
MoCA score	0.046	0.17	−0.33, 0.68	.499
GDS-15 score	0.019	0.12	−0.48, 0.73	.693
Site				
VA Puget Sound Health Care System/ University of Washington		Reference		
VA Portland Health Care System/ Oregon Health & Sciences University	0.184	4.64	1.73, 7.54	**.002**
Stanford University	0.061	1.51	−1.22, 4.25	.278
Johns Hopkins University	0.009	0.34	−3.34, 4.02	.857
Semantic verbal fluency (total correct words)				
Diagnosis				
HV		Reference		
PD	−0.214	−2.02	−3.12, -0.92	**<.001**
Age, years	−0.268	−0.18	−0.26, -0.10	**<.001**
Education, years	0.137	0.28	0.04, 0.51	.022
Sex				
Female		Reference		
Male	0.031	0.29	−0.78, 1.36	.597
APOE ε4	−0.047	−0.48	−1.61, 0.64	.401
MoCA score	0.078	0.18	−0.06, 0.42	.146
GDS-15 score	0.096	0.33	−0.05, 0.70	.089
Site				
VA Puget Sound Health Care System/ University of Washington		Reference		
VA Portland Health Care System/ Oregon Health & Sciences University	0.046	0.59	−0.88, 2.06	.433
Stanford University	0.013	0.17	−1.22, 1.56	.814
Johns Hopkins University	−0.013	−0.24	−2.30, 1.82	.819
Phonemic verbal fluency (total correct words)				
Diagnosis				
HV		Reference		
PD	−0.107	−2.57	−5.26, 0.12	.061
Age, years	−0.028	−0.05	−0.24, 0.14	.618
Education, years	0.316	1.63	1.06, 2.20	**<.001**
Sex				
Female		Reference		
Male	0.054	1.30	−1.39, 3.98	.345

Cognitive test	Semi-partial correlations	B [a]	95% CI	p value
APOE ε4	0.038	0.99	−2.47, 4.44	.575
MoCA score	0.225	1.31	0.77, 1.86	**<.001**
GDS-15 score	0.140	1.21	0.31, 2.12	.009
Site				
VA Puget Sound Health Care System/ University of Washington		Reference		
VA Portland Health Care System/ Oregon Health & Sciences University	0.096	3.16	−0.81, 7.14	.119
Stanford University	−0.071	−2.30	−5.81, 1.22	.201
Johns Hopkins University	−0.002	−0.12	−5.40, 5.17	.966
Judgment of Line Orientation (total score)				
Diagnosis				
HV		Reference		
PD	−0.081	−0.32	−0.77, 0.14	.171
Age, years	−0.076	−0.02	−0.06, 0.01	.213
Education, years	0.084	0.07	−0.02, 0.16	.115
Sex				
Female		Reference		
Male	−0.331	−1.29	−1.73, -0.84	**<.001**
APOE ε4	−0.036	−0.15	−0.65, 0.34	.545
MoCA score	0.040	0.04	−0.08, 0.16	.546
GDS-15 score	−0.008	−0.01	−0.17, 0.15	.887
Site				
VA Puget Sound Health Care System/ University of Washington		Reference		
VA Portland Health Care System/ Oregon Health & Sciences University	0.019	0.10	−0.43, 0.63	.707
Stanford University	−0.082	−0.43	−1.08, 0.21	.189
Johns Hopkins University	−0.042	−0.33	−1.18, 0.52	.443

[a] Unstandardized beta coefficients derived from linear regression analyses including diagnosis, age, sex, education, *APOE* ε4 allele, GDS-15 total score, MoCA total score, and site

[b] Analyses control additionally for Trail Making, Part A scores to account for motor slowing common among PD participants

[c] Higher scores represent worse performance

[d] Bold font indicates statistical significance ($p < 0.01$)

Abbreviations: *APOE*, apolipoprotein E, CI, confidence interval; GDS-15, 15-item Geriatric Depression Scale; HV, healthy volunteers; HVLT-R, Hopkins Verbal Learning Test-Revised; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; VA, Veterans Affairs