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Neurodegeneration Across Stages of Cognitive Decline in Parkinson Disease

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Abstract

Objective—To assess regions and patterns of brain atrophy in patients with Parkinson disease (PD) with normal cognition (PD-NC), mild cognitive impairment (PD-MCI), and dementia-level cognitive deficits (PDD).

Design—Images were quantified using a region-of-interest approach and voxel-based morphometry analysis. We used a high-dimensional pattern classification approach to delineate brain regions that collectively formed the Spatial Pattern of Abnormalities for Recognition of PDD.

Setting—The Parkinson's Disease and Movement Disorders Center at the University of Pennsylvania.

Subjects—Eighty-four PD patients (61 PD-NC, 12 PD-MCI, and 11 PDD) and 23 healthy control subjects (HCs) underwent magnetic resonance imaging of the brain.

Results—The PD-NC patients did not demonstrate significant brain atrophy compared with HCs. Compared with PD-NC patients, PD-MCI patients had hippocampal atrophy ($\beta=-0.37$; $P=.001$), and PDD patients demonstrated hippocampal ($\beta=-0.32$; $P=.004$) and additional medial temporal lobe atrophy ($\beta=-0.36$; $P=.003$). The PD-MCI patients had a different pattern of atrophy compared with PD-NC patients ($P=.04$) and a similar pattern to that of PDD patients ($P=.81$), characterized by hippocampal, prefrontal cortex gray and white matter, occipital lobe gray and white matter, and parietal lobe white matter atrophy. In nondemented PD patients, there was a correlation between memory-encoding performance and hippocampal volume.

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Conclusions—Hippocampal atrophy is a biomarker of initial cognitive decline in PD, including impaired memory encoding and storage, suggesting heterogeneity in the neural substrate of memory impairment. Use of a pattern classification approach may allow identification of diffuse regions of cortical gray and white matter atrophy early in the course of cognitive decline.

Patients with Parkinson disease (PD) are at an increased risk of developing dementia (PDD), with cumulative prevalence rates of up to 80%.¹ Approximately 25% of nondemented PD patients meet neuropsychological criteria for mild cognitive impairment (PD-MCI),² which converts to PDD in many cases,³ and even mild cognitive deficits in PD are associated with functional impairments⁴ and worse quality of life.⁵ Biomarkers of PD-MCI would improve diagnostic accuracy, identify those at highest risk of developing PDD, and predict response to cognitive-enhancing treatments.⁶

There has been extensive biomarker research concerning PDD. For structural imaging, the most consistent findings have been parietal-temporal lobe and prefrontal cortex atrophy compared with healthy control subjects (HCs) and PD patients without dementia.⁷⁻⁹ The neural substrate of MCI in PD is not well known, and studies of nondemented PD patients often include a mixture of PD-MCI patients and those with normal cognition (PD-NC).¹⁰

A pattern classification approach has been developed^{11,12} that integrates structural measurements from the entire brain and determines the brain regions that collectively form a Spatial Pattern of Abnormality for Recognition of Early Alzheimer's Disease (SPARE-AD score). The MCI patients with higher SPARE-AD scores demonstrated greater decline in MiniMental State Examination scores during long-term follow-up¹¹ and increased rates of conversion to AD.¹² To our knowledge, such a structural pattern of atrophy has not been developed for PDD.

Given the limited research on neurodegenerative biomarkers at the initial stage of cognitive decline in PD, we report (1) structural imaging findings from a cohort of PD patients with a range of cognitive abilities and (2) preliminary findings from the generation and application of a high-dimensional pattern classification method to identify PDD. We hypothesized that PD-MCI patients would (1) demonstrate hippocampal and prefrontal cortex atrophy and (2) have a spatial pattern of atrophy similar to that of PDD patients.

METHODS

PARTICIPANTS

Data were obtained as part of the University of Pennsylvania Center of Excellence for Research on Neurodegenerative Diseases, which evaluated a convenience sample of individuals at risk for late-life dementia (AD and PD) with a range of neuro-pathologically linked biomarkers. The diagnosis of PD was based on British Brain Bank criteria,¹³ and movement disorders specialists (including A.D.S. and J.E.D.) administered the motor subscale (part III) of the Unified Parkinson's Disease Rating Scale,¹⁴ determined Hoehn and Yahr stage,¹⁴ and provided a clinical impression of PDD (yes/no).

Eighty-four PD patients and 23 HCs underwent structural magnetic resonance imaging and neuropsychological testing within 6 months of each other. Levodopa and dopamine agonist dosages are presented as levodopa equivalent daily dosage.¹⁵ Demographic and clinical characteristics are presented in the Table.

The institutional review board at the University of Pennsylvania approved this research, and written informed consent was obtained from all study participants.

NEUROPSYCHOLOGICAL TESTING AND COGNITIVE CLASSIFICATION

The Dementia Rating Scale–2 (DRS-2)¹⁷ has been validated as an assessment instrument for PDD,¹⁸ including discriminating PD-MCI from PDD.¹⁹ The DRS-2 total score is constructed from the following 5 subscores: attention, initiation, construction, conceptualization, and memory. Because formal assessments of self-reported cognitive decline and functional impairment were not performed, cognitive categorization of patients was solely on the basis of their DRS-2 performance, and the terms *PD-NC*, *PD-MCI*, and *PDD* were retained for descriptive purposes. Cognitive categories were defined on the basis of the following recommended age-standardized DRS-2 scores¹⁷: (1) for PD-NC, a DRS-2 score of greater than 8, which corresponds to greater than the 28th percentile (n=61); (2) for PD-MCI, a DRS-2 score of 6 to 8 inclusive, which corresponds to the 6th through 28th percentiles (n=12); and (3) for PDD, a DRS-2 score of less than 6, which corresponds to less than the 6th percentile (n=11). A subset of PD patients (n=60) underwent assessment with the Hopkins Verbal Learning Test–Revised (HVLTR),²⁰ and HVLTR subscale scores (immediate free recall, delayed free recall, and recognition discrimination) are reported.

The agreement between DRS-2 categorization and the clinicians' clinical impression of dementia diagnosis was high, with 60 (98%) PD-NC and 10 (83%) PD-MCI patients assigned a clinical impression of no dementia, and 9 (82%) PDD patients assigned a clinical impression of dementia.

STRUCTURAL IMAGING AND ANALYSES

Image Acquisition—The data sets included standard T1-weighted magnetic resonance images acquired sagittally using volumetric 3-dimensional magnetization prepared rapid gradient echo with 1.25×1.25-mm in-plane spatial resolution and 1.2-mm-thick sagittal sections (flip angle, 8°; echo time, 3.55 milliseconds; repetition time, 3000 milliseconds; and imaging frequency, 63.64 Hz) performed on 1.5-T scanners.

Image Analysis—We based the Center of Excellence for Research on Neurodegenerative Diseases magnetic resonance imaging analysis on an image-processing protocol developed at the Section of Biomedical Image Analysis of the Department of Radiology at the University of Pennsylvania.²¹ Global volumes were obtained via an automated segmentation technique that labels the brain into white matter (WM), gray matter (GM), cerebrospinal fluid, and ventricles after a sequence of preprocessing steps that remove extracranial material and align each scan with the anterior commissure–posterior commissure plane. Quantification of regional brain volumes is performed through an elastic atlas warping algorithm that coregisters a template of brain anatomy with each scan.²² The template has 97 regions of interest (ROIs) based on the Montreal Neurological Institute template, which are transferred to individual scans, after which regional volumetric and functional measurements can be obtained. These ROIs were then collapsed into 14 larger ROIs, including primarily left and right lobar GM and WM volumes, hippocampi, and ventricles (eTable 1; <http://www.archneuro.com>). To limit the number of variables presented, we calculated the average of the right and left volumes for each ROI. We performed ROI analyses with statistical parametric mapping software (SPM5; <http://www.fil.ion.ucl.ac.uk/spm/software/spm5>).

To further characterize local atrophy in the brain, we performed a voxel-based morphometry (VBM) analysis (Regional Analysis of Volumes Examined in Normalized Space [RAVENS]).²³ This approach computes GM, WM, and ventricle tissue density maps separately in a common coordinate system after spatial normalization. The RAVENS approach bears similarities with the optimized VBM approach except that it uses a high-dimensional image-warping algorithm (termed *HAMMER* [hierarchical attribute matching

mechanism for elastic registration]).^{22,23} It uses tissue-preserving transformations, which ensure that image warping absolutely preserves the amount of GM, WM, and cerebrospinal fluid tissue present in an individual's scan. Voxel dimensions were 2.0×2.0×2.0 mm.

Statistical Analysis and Pattern Classification—We compared PD-NC and HC groups using linear regression models with age, sex, education, and intracranial volume (ICV) as covariates. For cognitive comparisons within the PD groups, χ^2 tests, *t* tests, nonparametric tests to compare medians, and analysis of variance with post hoc analyses (Tukey tests) were used for between-group comparisons on clinical, demographic, and ROI variables. For ROI variables that were significant on bivariate analysis, an additional linear regression model was run with age, sex, educational level, ICV, and disease severity (Hoehn and Yahr stage) as covariates. To examine the association between brain atrophy and neuropsychological test performance, raw DRS-2 scores were analyzed using a Pearson partial correlation controlling for age, sex, educational level, ICV, and disease severity. Normality assumptions were checked whenever required by the tests. All statistical tests were 2-sided with statistical significance set at the .05 level. Analyses were conducted with commercially available software (PASW Statistics, version 18.0; SPSS, Inc, Chicago, Illinois).

Other imaging comparisons were performed via voxelbased statistical analysis of RAVENS maps that were downsampled, normalized by ICV, and smoothed using an 8-mm full-width at half-maximum smoothing kernel. Group comparisons involved voxel-by-voxel *t* tests applied by AFNI software (available at <http://afni.nimh.nih.gov/>). Comparison for multiple corrections used the false discovery rate method.²⁴

Because VBM analysis is not suitable for deriving diagnostic biomarkers on an individual patient basis, we used an individual-patient, high-dimensional pattern approach to classify individual scans belonging to PD-NC or PDD patients.²⁵⁻²⁷ This approach considers all brain regions jointly and identifies a minimal set of regions in which volumes jointly and maximally differentiate between the 2 groups under consideration on an individual scan basis. The leave-one-out cross-validation tests this classification scheme on data sets not used for training to obtain a relatively unbiased estimate of the generalization power of the classifier to new patients. The pattern classification method provides a structural phenotypic score, herein called the SPARE-PDD score. For a classifier constructed from the PD-NC and PDD groups, a positive SPARE-PDD score implies PDD-like brain structure, and a PDD-like brain structure implies a positive SPARE-PDD score. For the SPARE-PDD score, we plotted the receiver operating characteristic curve, with the area under the curve determining its discriminant validity for detecting PDD, and we calculated the sensitivity, specificity, and negative and positive predictive values (NPVs and PPVs) for different cutoff points. The classifier that was determined to maximally distinguish between PD-NC and PDD patients was subsequently applied to the PD-MCI group. The software used to generate SPARE-PDD scores is available through the Section of Biomedical Image Analysis at the University of Pennsylvania at <http://www.rad.upenn.edu/sbia>.

RESULTS

PD-NC PATIENTS COMPARED WITH HCS

The ROI volumes for all subject groups are presented in eTable 1. After controlling for age, sex, education, and ICV, there were no between-group differences in regional brain volumes for PD-NC patients and HCs (eTable 2). When we examined the HCs only, there was no association between total DRS-2 score and any regional brain volumes (data not shown).

ATROPHY IN PD-MCI PATIENTS

Within PD, there were cognitive group-level differences in hippocampal ($F_{2,81}=14.91$; $P<.001$) and medial temporal lobe ($F_{2,81}=6.79$; $P=.002$) volumes. The PD-MCI ($P=.001$) and PDD patients ($P<.001$) had smaller hippocampal volumes compared with PD-NC patients, with no difference between PD-MCI and PDD patients ($P=.79$). The PDD patients, but not PD-MCI patients, also had medial temporal lobe atrophy compared with PD-NC patients ($P=.006$). There were no between-group differences for other brain regions.

Using linear regression analyses to control for possible confounding variables, we continued to find smaller hippocampal volumes in the PD-MCI ($\beta=-0.37$; $P=.001$) and PDD ($\beta=-0.32$; $P=.004$) patients compared with PD-NC patients. Likewise, PDD patients continued to have a smaller medial temporal lobe volume compared with PD-NC patients ($\beta=-0.36$; $P=.003$).

VBM ANALYSES

In complementary VBM analyses not based on ROIs, controlling for age and using an uncorrected $P=.01$, PD-MCI patients had greater atrophy in the hippocampus, insula, and putamen compared with PD-NC patients (areas in yellow-red in Figure 1). When using a more stringent $P=.05$ corrected for multiple comparisons, PD-MCI patients demonstrated greater head of the hippocampus, inferior globus pallidus, and superior-posterior amygdala atrophy (areas in yellow-red in Figure 2).

NEUROPSYCHOLOGICAL TESTING AND HIPPOCAMPAL ATROPHY IN NONDEMENTED PD PATIENTS

When we examined all PD patients, there were positive correlations between hippocampal size and total DRS-2 score ($r=0.44$; $P<.001$), as well as the attention ($r=0.31$; $P=.005$), initiation ($r=0.40$; $P<.001$), and memory ($r=0.41$; $P<.001$) subscale scores. When we examined nondemented PD patients (ie, the PD-NC and PD-MCI groups), there were positive correlations between hippocampal size and total DRS-2 score ($r=0.38$; $P=.008$) and DRS-2 memory subscale score ($r=0.31$; $P=.04$) but no correlation with any of the other DRS-2 subscale scores.

In the subset of PD patients undergoing assessment with the HVLIT ($n=60$), there was a positive correlation between hippocampal size and recognition discrimination performance ($r=0.27$; $P=.05$) but no correlation with immediate or delayed free recall. When we examined only nondemented PD patients ($n=51$), the correlation between hippocampal size and recognition discrimination remained ($r=0.41$; $P=.005$).

GENERATION OF SPARE-PDD

The SPARE-PDD score had an area under the receiver operating characteristic curve of 0.79 for differentiating PDD from PD-NC patients (eFigure). At the optimal SPARE-PDD cutoff score (ie, the point of maximum combined sensitivity and specificity), the psychometric properties for identifying PDD were sensitivity of 91% and specificity of 61%. At this cutoff point, the NPV was 97% and the PPV was 29%.

When we applied the SPARE-PDD score to PD-MCI patients, there were overall differences between the cognitive subgroups ($F_{2,81}=6.92$; $P=.002$). We noted a difference between the PD-NC and PD-MCI groups in mean SPARE-PDD score ($P=.04$), with the PD-MCI group mean (SD) score (0.40 [0.87]) falling between those of the PD-NC (-0.13 [0.64]) and PDD (0.58 [0.69]) groups (Figure 3). There was no difference between the PD-MCI and PDD groups ($P=.81$). In addition, there was no difference between the PD-NC and HC groups ($t_{82}=-0.67$; $P=.51$).

After examining the data maps for the features used most frequently by the classifier, we identified the following regions, all smaller in the PDD compared with PD-NC patients: (1) for GM: hippocampus, medial and lateral prefrontal cortex, medial orbitofrontal cortex, occipital lobe, and pericentral sulcus; and (2) for WM: internal and external capsules, inferior temporal lobe and gyrus, medial orbitofrontal cortex, occipital lobe, and precuneus.

COMMENT

The relationship between the neurodegenerative process and cognitive decline in PD remains unclear. Regarding neuropathologic features, PDD is associated with diffuse Lewy body disease manifestations, including in the transentorhinal and entorhinal cortices, hippocampus, other limbic cortex regions, and neocortex.^{28,29} In addition, more than half of PD patients have AD-related neuropathologic changes on autopsy,^{30,31} including in the hippocampus.^{29,32} Thus, the neurodegeneration that contributes to cognitive decline in PD, particularly in regions predisposed to AD pathologic changes (eg, the hippocampus), is likely due to a complex interaction of different diseases.³³

Patients with PDD are reported to have decreased hippocampal, temporal, and parietal lobes and decreased prefrontal cortex volumes compared with HCs and nondemented PD patients.^{7-9,34-37} Nondemented PD patients are reported to have varying degrees of atrophy compared with HCs,^{8,36,38,39} with mixed evidence of a correlation between atrophy and neuropsychological test performance or conversion to PDD.^{7,40-42} However, nondemented PD patients are a heterogeneous group that includes PD-NC and PD-MCI patients, thus blurring any distinctions between the 2 groups. In addition, there are no consensus diagnostic criteria for PD-MCI; therefore, MCI populations can vary widely in terms of cognitive abilities. One study of PD patients with amnesic MCI reported GM atrophy in the precuneus and the left prefrontal and left primary motor cortices compared with HCs,⁴³ and other studies^{44,45} reported mixed results for the presence of atrophy at the stage of PD-MCI.

After separating nondemented PD patients into PD-NC and PD-MCI groups purely on the basis of cognitive performance, we found that PD-NC patients had regional brain volumes similar to those of HCs. This suggests that significant regional brain atrophy does not occur in PD in the absence of comorbid cognitive impairment.

Patients with only MCI demonstrated hippocampal atrophy using ROI and VBM analyses and basal ganglia (putamen and globus pallidus), amygdala, and insula atrophy using VBM analyses. The putamen and globus pallidus are associated with learning, executive abilities, and attention in PD patients,^{46,47} and the amygdala has been shown to subservise memory and attention.⁴⁸ At the stage of PDD, we found additional medial temporal lobe atrophy (ie, in the entorhinal cortex, perirhinal cortex, and posterior parahippocampal gyrus). This suggests that hippocampal neurodegeneration is associated with the initial stages of cognitive decline in PD, with more severe cognitive impairment associated with additional atrophy in medial temporal lobe structures.

The positive correlation between memory performance specifically (ie, memory subscales of the DRS-2 and the HVLT-R) and hippocampal volume in nondemented PD patients extends the aforementioned results. On the HVLT-R, the correlation was with recognition discrimination ability, which requires memory encoding and storage abilities subserved by medial temporal lobe structures and has been shown to be impaired in a subset of nondemented PD patients.^{49,50} There was no correlation between hippocampal volume and free recall performance, which in part reflects retrieval abilities that depend on frontostriatal circuitry.

Our preliminary results using a pattern classification approach to identify patterns of atrophy associated with dementia in PD suggest that it is possible to differentiate PDD and PD-NC patients with high sensitivity and NPV (ie, good for screening), although the specificity and PPV were suboptimal (ie, not adequate for diagnosing). However, the relatively low specificity (ie, high false-positive rate) may indicate patients who are at increased risk of future cognitive decline. We anticipate that, with a larger sample of PDD patients and additional clinical characterization (ie, application of formal diagnostic criteria to support neuropsychological test results), the psychometric properties of the pattern classifier will improve.

The PD-MCI patients demonstrated a pattern of atrophy different than that of the PD-NC patients and similar to although less severe than that of the PDD patients. This suggests that a diffuse pattern of GM and WM brain atrophy can be detected at an early stage of cognitive decline in PD if sensitive imaging analyses are used. Because the use of traditional imaging methods in PD patients has produced mixed results regarding the correlation between atrophy and current and future cognitive performance,^{40,41} additional research is needed to determine whether the pattern classifier for PDD is able to predict cognitive decline in nondemented PD patients, as has been reported for individuals with MCI in the general population.²⁷

Our study has a number of limitations. First, the classification of patients into cognitive groups was based solely on neuropsychological test results because formal MCI and PDD diagnostic criteria were not applied. However, there currently are no commonly accepted diagnostic criteria for PD-MCI, and the validity of self-reporting of nonmotor symptoms in PD has been called into question.⁵¹ Second, the DRS-2 was the primary neuropsychological test; consequently, sensitivity may have been suboptimal. In addition, the recommended standardized DRS-2 cutoff scores for MCI and PDD have not been validated in PD, and the mean standardized DRS-2 scores for all 3 cognitive groups were lower than those reported in previous research using formal diagnostic criteria for PD-MCI and PDD.⁵² Third, the PD sample was predominantly male, and there was a sex imbalance between HCs and PD-NC patients. Finally, the sample sizes of PDD and PD-MCI patients were relatively small, which may affect the reproducibility of our findings.

With growing recognition of PD-MCI as common and clinically significant, it will be important to develop consensus diagnostic criteria, validate assessment instruments for use in clinical care and research, and test treatments for their symptomatic and disease-modifying effects. Validating biomarkers of neurodegeneration associated with MCI and distinguishing PD-MCI from the early stages of dementia with Lewy bodies will inform our understanding of the development, course, profile, and neuropathophysiologic features of the initial stage of cognitive decline in PD. Emerging evidence implicates hippocampal involvement early in the course of cognitive—and specifically memory—decline in PD.

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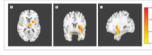
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REFERENCES

1. 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(3):387–392. [PubMed: 12633150]
2. Aarsland D, Bronnick K, Williams-Gray CH, et al. Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis. *Neurology*. 2010; 75(12):1062–1069. [PubMed: 20855849]
3. Janvin CC, Larsen JP, Aarsland D, Hugdahl K. Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. *Mov Disord*. 2006; 21(9):1343–1349. [PubMed: 16721732]
4. Rosenthal E, Brennan L, Xie S, et al. Association between cognition and function in patients with Parkinson disease with and without dementia. *Mov Disord*. 2010; 25(9):1170–1176. [PubMed: 20310053]
5. Marras C, McDermott MP, Rochon PA, Tanner CM, Naglie G, Lang AE. Parkinson Study Group DATATOP Investigators. Predictors of deterioration in health-related quality of life in Parkinson's disease: results from the DATATOP trial. *Mov Disord*. 2008; 23(5):653–659. quiz 776. [PubMed: 18076084]
6. Aarsland D, Ravina B. Biomarkers of PD progression: is CSF the answer? *Neurology*. 2010; 75(12):1036–1037. [PubMed: 20739641]
7. Jokinen P, Brück A, Aalto S, Forsback S, Parkkola R, Rinne JO. Impaired cognitive performance in Parkinson's disease is related to caudate dopaminergic hypofunction and hippocampal atrophy. *Parkinsonism Relat Disord*. 2009; 15(2):88–93. [PubMed: 18434233]
8. Lyoo CH, Ryu YH, Lee MS. Topographical distribution of cerebral cortical thinning in patients with mild Parkinson's disease without dementia. *Mov Disord*. 2010; 25(4):496–499. [PubMed: 20108369]
9. Kenny ER, Burton EJ, O'Brien JT. A volumetric magnetic resonance imaging study of entorhinal cortex volume in dementia with Lewy bodies: a comparison with Alzheimer's disease and Parkinson's disease with and without dementia. *Dement Geriatr Cogn Disord*. 2008; 26(3):218–225. [PubMed: 18781072]
10. Ibarretxe-Bilbao N, Tolosa E, Junque C, Marti MJ. MRI and cognitive impairment in Parkinson's disease. *Mov Disord*. 2009; 24(suppl 2):S748–S753. [PubMed: 19877242]
11. Davatzikos C, Bhatt P, Shaw LM, Batmanghelich N, Trojanowski JQ. Prediction of MCI to AD conversion, via MRI, CSF biomarkers, and pattern classification [published online June 29, 2010]. *Neurobiol Aging*. doi:10.1016/j.neurobiolaging.2010.05.023.
12. Misra C, Fan Y, Davatzikos C. Baseline and longitudinal patterns of brain atrophy in MCI patients, and their use in prediction of short-term conversion to AD: results from ADNI. *Neuroimage*. 2009; 44(4):1415–1422. [PubMed: 19027862]
13. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry*. 1992; 55(3):181–184. [PubMed: 1564476]
14. Fahn, S.; Elton, RL. UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn, S.; Marsden, CD.; Calne, D.; Goldstein, M., editors. *Recent Developments in Parkinson's Disease*. Macmillan Health Care Information; Florham Park, NJ: 1987. p. 153-163.
15. Hobson DE, Lang AE, Martin WR, Razmy A, Rivest J, Fleming J. Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian Movement Disorders Group. *JAMA*. 2002; 287(4):455–463. [PubMed: 11798367]
16. Sheikh, JL.; 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*. Haworth Press; New York, NY: 1986. p. 165-173.
17. Jurica, PJ.; Leitten, SL.; Mattis, S. *Dementia Rating Scale-2 (DRS-2): Professional Manual*. Psychological Assessment Resources; Odessa, FL: 2001.
18. Llebaria G, Pagonabarraga J, Kulisevsky J, et al. Cut-off score of the Mattis Dementia Rating Scale for screening dementia in Parkinson's disease. *Mov Disord*. 2008; 23(11):1546–1550. [PubMed: 18546326]

19. Martin RC, Okonkwo OC, Hill J, et al. Medical decision-making capacity in cognitively impaired Parkinson's disease patients without dementia. *Mov Disord.* 2008; 23(13):1867–1874. [PubMed: 18759361]
20. Brandt, J.; Benedict, RHB. *The Hopkins Verbal Learning Test–Revised.* Psychological Assessment Resources; Odessa, FL: 2001.
21. Goldszal AF, Davatzikos C, Pham D, Yan MX, Bryan RN, Resnick SM. An image-processing system for qualitative and quantitative volumetric analysis of brain images. *J Comput Assist Tomogr.* 1998; 22(5):827–837. [PubMed: 9754125]
22. Shen D, Davatzikos C. HAMMER: hierarchical attribute matching mechanism for elastic registration. *IEEE Trans Med Imaging.* 2002; 21(11):1421–1439. [PubMed: 12575879]
23. Shen DB, Davatzikos C. Very high-resolution morphometry using mass-preserving deformations and HAMMER elastic registration. *Neuroimage.* 2003; 18(1):28–41. [PubMed: 12507441]
24. Yekutieli D, Benjamini Y. Resampling-based false discovery rate controlling multiple test procedures for correlated test statistics. *J Stat Planning Inference.* December.1999 82:171–196.
25. Davatzikos C, Fan Y, Wu X, Shen D, Resnick SM. Detection of prodromal Alzheimer's disease via pattern classification of magnetic resonance imaging. *Neurobiol Aging.* 2008; 29(4):514–523. [PubMed: 17174012]
26. Fan Y, Shen D, Gur RC, Gur RE, Davatzikos C. COMPARE: classification of morphological patterns using adaptive regional elements. *IEEE Trans Med Imaging.* 2007; 26(1):93–105. [PubMed: 17243588]
27. Fan Y, Batmanghelich N, Clark CM, Davatzikos C. Alzheimer's Disease Neuroimaging Initiative. Spatial patterns of brain atrophy in MCI patients, identified via high-dimensional pattern classification, predict subsequent cognitive decline. *Neuroimage.* 2008; 39(4):1731–1743. [PubMed: 18053747]
28. Braak H, Rüb U, Jansen Steur EN, Del Tredici K, de Vos RA. Cognitive status correlates with neuropathologic stage in Parkinson disease. *Neurology.* 2005; 64(8):1404–1410. [PubMed: 15851731]
29. Kalaitzakis ME, Pearce RK. The morbid anatomy of dementia in Parkinson's disease. *Acta Neuropathol.* 2009; 118(5):587–598. [PubMed: 19820956]
30. Lieberman AN. Point of view: dementia in Parkinson's disease. *Parkinsonism Relat Disord.* 1997; 3(3):151–158. [PubMed: 18591069]
31. Sabbagh MN, Adler CH, Lahti TJ, et al. Parkinson disease with dementia: comparing patients with and without Alzheimer pathology. *Alzheimer Dis Assoc Disord.* 2009; 23(3):295–297. [PubMed: 19812474]
32. Apaydin H, Ahlskog JE, Parisi JE, Boeve BF, Dickson DW. Parkinson disease neuropathology: later-developing dementia and loss of the levodopa response. *Arch Neurol.* 2002; 59(1):102–112. [PubMed: 11790237]
33. Kurosinski P, Guggisberg M, Götz J. Alzheimer's and Parkinson's disease—overlapping or synergistic pathologies? *Trends Mol Med.* 2002; 8(1):3–5. [PubMed: 11796255]
34. Burton EJ, McKeith IG, Burn DJ, Williams ED, O'Brien JT. Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls. *Brain.* 2004; 127(pt 4):791–800. [PubMed: 14749292]
35. Camicioli R, Moore MM, Kinney A, Corbridge E, Glassberg K, Kaye JA. Parkinson's disease is associated with hippocampal atrophy. *Mov Disord.* 2003; 18(7):784–790. [PubMed: 12815657]
36. Tam CWC, Burton EJ, McKeith IG, Burn DJ, O'Brien JT. Temporal lobe atrophy on MRI in Parkinson disease with dementia: a comparison with Alzheimer disease and dementia with Lewy bodies. *Neurology.* 2005; 64(5):861–865. [PubMed: 15753423]
37. Junqué C, Ramírez-Ruiz B, Tolosa E, et al. Amygdalar and hippocampal MRI volumetric reductions in Parkinson's disease with dementia. *Mov Disord.* 2005; 20(5):540–544. [PubMed: 15645532]
38. Brück A, Kurki T, Kaasinen V, Vahlberg T, Rinne JO. Hippocampal and prefrontal atrophy in patients with early non-demented Parkinson's disease is related to cognitive impairment. *J Neurol Neurosurg Psychiatry.* 2004; 75(10):1467–1469. [PubMed: 15377698]

39. Song SK, Lee JE, Park H-J, Sohn YH, Lee JD, Lee PH. The pattern of cortical atrophy in patients with Parkinson's disease according to cognitive status. *Mov Disord.* 2011; 26(2):289–296. doi: 10.1002/mds.23477. [PubMed: 21370255]
40. Martin WR, Wieler M, Gee M, Camicioli R. Temporal lobe changes in early, untreated Parkinson's disease. *Mov Disord.* 2009; 24(13):1949–1954. [PubMed: 19606493]
41. Aybek S, Lazeyras F, Gronchi-Perrin A, Burkhard PR, Villemure JG, Vingerhoets FJ. Hippocampal atrophy predicts conversion to dementia after STN-DBS in Parkinson's disease. *Parkinsonism Relat Disord.* 2009; 15(7):521–524. [PubMed: 19349206]
42. Dalaker TO, Zivadinov R, Larsen JP, et al. Gray matter correlations of cognition in incident Parkinson's disease. *Mov Disord.* 2010; 25(5):629–633. [PubMed: 20213820]
43. Lee JE, Park H-J, Song SK, Sohn YH, Lee JD, Lee PH. Neuroanatomic basis of amnesic MCI differs in patients with and without Parkinson disease. *Neurology.* 2010; 75(22):2009–2016. [PubMed: 21115956]
44. Beyer MK, Janvin CC, Larsen JP, Aarsland D. A magnetic resonance imaging study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel-based morphometry. *J Neurol Neurosurg Psychiatry.* 2007; 78(3):254–259. [PubMed: 17028119]
45. Apostolova LG, Beyer M, Green AE, et al. Hippocampal, caudate, and ventricular changes in Parkinson's disease with and without dementia. *Mov Disord.* 2010; 25(6):687–695. [PubMed: 20437538]
46. van Beilen M, Leenders KL. Putamen FDOPA uptake and its relationship to cognitive functioning in PD. *J Neurol Sci.* 2006; 248(1-2):68–71. [PubMed: 16782131]
47. Scott RB, Harrison J, Boulton C, et al. Global attentional-executive sequelae following surgical lesions to globus pallidus interna. *Brain.* 2002; 125(pt 3):562–574. [PubMed: 11872613]
48. Schaefer A, Gray JR. A role for the human amygdala in higher cognition. *Rev Neurosci.* 2007; 18(5):355–363. [PubMed: 19544622]
49. Weintraub D, Moberg PJ, Culbertson WC, Duda JE, Stern MB. Evidence for impaired encoding and retrieval memory profiles in Parkinson disease. *Cogn Behav Neurol.* 2004; 17(4):195–200. [PubMed: 15622014]
50. Brønnick K, Alves G, Aarsland D, Tysnes O-B, Larsen JP. Verbal memory in drug-naive, newly diagnosed Parkinson's disease: the retrieval deficit hypothesis revisited. *Neuropsychology.* 2011; 25(1):114–124. [PubMed: 20954781]
51. McKinlay A, Grace RC, Dalrymple-Alford JC, Anderson TJ, Fink J, Roger D. Neuropsychiatric problems in Parkinson's disease: comparisons between self and caregiver report. *Aging Ment Health.* 2008; 12(5):647–653. [PubMed: 18855181]
52. Dalrymple-Alford JC, MacAskill MR, Nakas CT, et al. The MoCA: well-suited screen for cognitive impairment in Parkinson disease. *Neurology.* 2010; 75(19):1717–1725. [PubMed: 21060094]

**Figure 1.**

Hippocampus, insula, and putamen atrophy in patients with Parkinson disease (PD) and mild cognitive impairment compared with PD patients with normal cognition (uncorrected $P=.01$). A, Axial view. B, Coronal view. C, Sagittal view. The color scale indicates the amount of atrophy (in cubic millimeters) per cubic millimeter of tissue in the reference image at that voxel, adjusted by the intracranial volume.

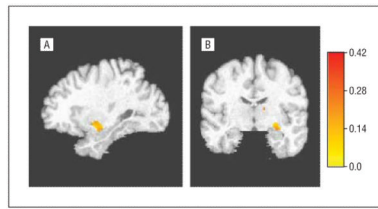


Figure 2. Hippocampus, amygdala, and globus pallidus atrophy in patients with Parkinson disease (PD) and mild cognitive impairment compared with PD patients with normal cognition (corrected $P=.05$). A, Sagittal view. B, Coronal view. The color scale indicates the amount of atrophy (in cubic millimeters) per cubic millimeter of tissue in the reference image at that voxel, adjusted by the intracranial volume.

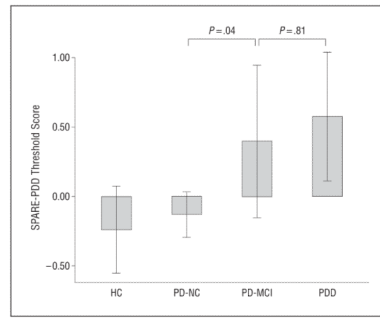


Figure 3. Scores for the Spatial Pattern of Abnormality for Recognition of Parkinson disease with dementia-level cognitive deficits (SPARE-PDD) instrument by cognitive subgroup. Data are presented as mean threshold scores; whiskers represent 95% CIs. HC indicates healthy controls; MCI, mild cognitive impairment; and NC, normal cognition.

Table

Characteristics of the Study Sample^a

Variable	HCs (n=23)	PD Groups		
		PD-NC (n=61)	PD-MCI (n=12)	PDD (n=11)
Clinical and demographic				
Age, y	71.5 (9.2)	69.3 (5.7)	75.7 (7.7) ^b	73.1 (7.2)
Male sex, No. (%)	5 (22)	39 (64) ^c	10 (83)	7 (64)
Education, y	15.8 (2.9)	16.0 (2.8)	15.2 (1.6)	14.4 (2.7)
PD duration, y	NA	7.1 (3.8)	9.3 (6.6)	9.0 (7.1)
Hoeft and Yahr stage, median (IQR)	NA	2.0 (2.0-2.5)	2.0 (2.0-3.0)	3.0 (2.5-3.0) ^d
Levodopa dosage, mg/d ^e	NA	424 (368)	543 (441)	610 (209)
Dopamine agonist dosage, mg/d ^e	NA	101 (164)	75 (145)	45 (101)
UPDRS motor score	NA	20.3 (8.9)	23.6 (11.1)	29.5 (12.7)
GDS-15 score ^f	0.7 (1.4)	2.2 (2.3) ^g	3.3 (3.1)	4.0 (3.1)
Neuropsychological assessment				
DRS-2				
Total score	141.5 (2.5)	139.4 (3.0) ^h	127.8 (3.5)	108.5 (17.1) ⁱ
Total standardized score	13.2 (2.1)	11.5 (2.0) ^j	6.8 (0.9)	3.3 (1.2) ^k
Memory subscale	NA	23.7 (1.3)	20.5 (2.2)	16.4 (4.7)
Attention subscale	NA	36.2 (1.7)	34.9 (1.9)	33.1 (3.4) ^l
Conceptualization subscale	NA	37.3 (1.6)	35.3 (2.1)	31.8 (3.6) ^{l,m}
Initiation/persistence subscale	NA	36.2 (1.7)	31.3 (3.9)	22.8 (6.9) ⁿ
Construction subscale	NA	5.9 (0.3)	5.9 (0.3)	4.4 (2.2) ^o
HVLT-R ^p				
Immediate recall	NA	21.0 (4.8)	13.4 (4.7)	11.7 (7.0) ^q
Delayed recall	NA	6.6 (3.0)	3.8 (2.5)	1.6 (2.1) ^r

Variable	HCs (n=23)	PD Groups		
		PD-NC (n=61)	PD-MCI (n=12)	PDD (n=11)
Recognition discrimination	NA	10.0 (1.5)	8.3 (1.8)	6.3 (4.4) ^l

Abbreviations: DRS-2, Dementia Rating Scale-2; GDS-15, 15-Item Geriatric Depression Scale¹⁶ (a commonly used version as opposed to the original 30-item GDS); HCs, healthy controls; HVLTR, Hopkins Verbal Learning Test-Revised; IQR, interquartile range; NA, not applicable; PD, Parkinson disease; PDD, PD with dementia-level cognitive deficits; PD-MCI, PD with mild cognitive impairment; PD-NC, PD with normal cognition; UPDRS, Unified Parkinson's Disease Rating Scale.

^a Comparisons are between PD-NC and HC groups and among PD-NC, PD-MCI, and PDD groups. Unless otherwise indicated, data are expressed as mean (SD)

^b $P = .01$, PD-NC vs PD-MCI group (Tukey test).

^c $P = .001$, PD-NC vs HC group ($\chi^2_1 = 11.9$).

^d $P = .001$, PDD vs PD-NC group (Tukey test)

^e Includes 83 PD patients.

^f Includes 102 PD patients and HCs.

^g $P = .001$, HCs vs PD-NC group ($t_{67,1} = -3.6$)

^h $P = .005$, PD-NC vs HC group ($t_{82} = 2.9$).

ⁱ $P < .001$ among all PD groups ($F_{2,81} = 105.6$)

^j $P = .001$, PD-NC vs HC group ($t_{82} = 3.3$).

^k $P < .001$ among all PD groups ($F_{2,81} = 114.9$)

^l $P < .001$, PDD vs PD-NC group (Tukey test).

^m $P = .03$, PDD vs PD-MCI group (Tukey test)

ⁿ $P < .001$ among all PD groups ($F_{2,81} = 88.0$).

^o $P < .001$, PDD vs PD-MCI group and PDD vs PD-NC group (Tukey test)

^p Includes 60 PD patients.

^q $P = .001$, PD-NC vs PD-MCI group (Tukey test)

^r $P = .03$, PD-NC vs PD-MCI group (Tukey test).