Neurodegeneration Across Stages of Cognitive Decline in Parkinson Disease

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**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 PD.

**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.

**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.

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tive 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 neuropathologically linked biomarkers. The diagnosis of PD was based on British Brain Bank criteria, 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 determined Hoehn and Yahr stage, 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. 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) has been validated as an assessment instrument for PDD, including discriminat...
ing PD-MCI from PDD.19 The DRS-2 total score is constructed from the following 5 subcores: 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 scores21: (1) for PD-NC, a DRS-2 score of greater than 8, which corresponds to greater than the 28th percentile (n=11); (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 (HVLT-R),22 and HVLT-R 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 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 for 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.23 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.archneurol.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, χ² 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 voxel-based 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 ($r=0.31; P=.005$) but no correlation with any of the other DRS-2 subscale scores.

In the subset of PD patients undergoing assessment with the HVLT (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 ($r=0.41; P=.005$).

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.
The relationship between the neurodegenerative process and cognitive decline in PD remains unclear. Regarding neuropathologic features, PD is associated with diffuse Lewy body disease manifestations, including in the transentorhinal and entorhinal cortices, hippocampus, other limbic cortex regions, and neocortex.30,31 In addition, more than half of PD patients have AD-related neuropathologic changes on autopsy.30,31 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 nonmented PD patients.7-9,34-37 Nonmented 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, nonmented 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 amnestic MCI reported GM atrophy in the precuneus and the left prefrontal and left primary motor cortices compared with HCs,33 and other studies44,45 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 subserve 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 nonmented 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 diagnos-
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, 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.31 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.32 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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Online-Only Material: The eTables and eFigure are available at http://www.archneurol.com.

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