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 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.

**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.

Arch Neurol. 2011;68(12):1562-1568

**Patients with Parkinson disease (PD) are at an increased risk of developing dementia (PDD), with cumulative prevalence rates of up to 80%.**

Approximately 25% of nondemented PD patients meet neuropsychological criteria for mild cognitive impairment (PD-MCI), which converts to PDD in many cases, and even mild cognitive deficits in PD are associated with functional impairments and worse quality of life. Biomarkers of PD-MCI would improve diagnostic accuracy, identify those at highest risk of developing PDD, and predict response to cognitive-enhancing treatments.

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. 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).

A pattern classification approach has been developed 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 Mini-Mental State Examination scores during long-term follow-up and increased rates of conversion to AD. 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 cogni-
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 (UPDRS), 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 discriminant...
The clinical impression of dementia was assigned to 10 (83%) PDD patients, 60 (98%) PD-NC, and 10 (83%) PD-MCI patients. Assignments of regional brain volumes are performed through an automated segmentation technique that labels the brain areas (gray and white matter and cerebrospinal fluid) after a sequence of preprocessing steps (including spatial normalization. The RAVENS approach generates 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]).

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 $2.0 \times 2.0 \times 2.0$ 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, $t^2$ tests, $t$ tests, nonparametric tests to compare medians, and a test 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.

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. 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 ($r=0.41; P=.005$).
addition, more than half of PD patients have AD-related
tween the PD-NC and HC groups (\(P = .81\)). In addition, there was no difference be-
therefore, MCI populations can vary widely in terms of cognitive
these studies\(^4^4\)\(^\text{--}\)\(^4^5\) reported mixed results for the presence of atrophy at the stage of PD-MCI.
Patients with only MCI demonstrated hippocampal at-
the entorhinal cortex, perirhinal cortex, and posterior parahippocampal gyrus). This suggests that hip-
medial temporal lobe structures.
The positive correlation between memory perfor-
ence specifically (ie, memory subscales of the DRS-2
unrelated PD patients extend the aforementioned re-
neuropathologic changes on autopsy.\(^2^9\)\(^\text{--}\)\(^3^1\) including in the hippocampus.\(^2^9\)\(^\text{--}\)\(^3^2\) Thus, the neurodegeneration that con-
ations that depend on frontostriatal circuitry.

The relationship between the neurodegenerative pro-
Regarding neuropathologic features, PDD is associated with
diffuse Lewy body disease manifestations, including in the transentorhinal and entorhinal cortices, hippocam-
other limbic cortex regions, and neocortex.\(^2^8\)\(^\text{--}\)\(^2^9\) In addition, more than half of PD patients have AD-related

**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.

**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 (\(P = .51\)). 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.

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.

The positive correlation between memory perfor-
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**COMMENT**

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Our preliminary results using a pattern classification approach to identify patterns of atrophy associated with dementia in PD suggest that it is possible to differenti-
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ing). 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,

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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. 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 decline—and specifically memory—decline in PD.

Accepted for Publication: April 13, 2011.
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Financial Disclosure: None reported.
Funding/Support: This study was supported by health research grant SAP 4100027296 from the Department of Health of the Commonwealth of Pennsylvania from the Tobacco Master Settlement Agreement under Act 2001-77, by P50 NS053488 from the National Institute of Neurological Disorders and Stroke (Penn Udall Center); and by grants R01-14971 and P30-AG10124 from the National Institute on Aging.

Role of the Sponsors: The funding sponsors only provided monetary support and did not participate in the design and conduct of the study; in the collection, management, analysis, and interpretation of data; or in the preparation, review, or approval of the manuscript.

Online-Only Material: The eTables and eFigure are available at http://www.archneurol.com.

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