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Parkinson's Disease Is Associated with Hippocampal Atrophy

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Abstract: Patients with Parkinson's disease (PD) may have hippocampal atrophy compared with controls. We compared hippocampal, and extra-hippocampal volumes between PD, PDD (patients with PD who have mild cognitive impairment or dementia), Alzheimer's disease (AD) and controls using volumetric magnetic resonance imaging (MRI). Participants (10 patients with PD, 10 with PDD, 11 with AD, and 12 control subjects) had an informant interview, neurological examination, and psychometric testing. Established, reliable methods were used to measure the hippocampus, parahippocampal gyrus, temporal, frontal, and parieto-occipital lobes. Correction for intracranial volume was carried out before comparison. There was no age difference between groups (mean age, 74 years). On the Clinical Dementia Rating scale (CDR) cognitive impairment was mild (CDR = 0.5) in the majority of PDD and AD patients. Hippocampal ($P < 0.0004$) volumes were smaller in the patient groups. Effect sizes compared with the control group were: PD, 0.66; PDD, 1.22; and AD, 1.81. The other volumes did not differ significantly. Among PD and PDD patients, recognition memory ($r = 0.54$, $P = 0.015$) and Mini-Mental State Examination scores ($r = 0.56$, $P = 0.01$) correlated with left, but not right hippocampal volume. In conclusion, hippocampal volume showed a pattern (Control > PD > PDD > AD) suggesting progressive hippocampal volume loss in PD. Volumetric MRI imaging might provide an early marker for dementia in PD.

Key words: Parkinson's disease; dementia; Alzheimer's disease; MRI; hippocampus; atrophy

Patients with Parkinson's disease (PD), the most common neurodegenerative movement disorder, are at high risk for the development of dementia. Incidence rates for dementia range from 4.2 to 9.5% per year.[1,2] The prevalence of dementia in PD ranges from 10 to 30%. Thus, PD with dementia may represent the second most common cause of dementia after Alzheimer's disease (AD). Dementia in PD is associated with a high risk of nursing home placement[3] and death.[4] Early intervention in PD patients who are at risk for dementia would be ideal, but accurate diagnosis and prediction is necessary.

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Prediction of dementia is imperfect. Incidence studies have identified risk factors, which include older age, male gender, longer duration of symptoms, specific aspects of cognitive dysfunction (e.g., decreased verbal fluency)[5,6] and axial motor impairment (which responds poorly to dopaminergic treatment).[7] A structural or functional neuroimaging marker might complement other clinical and neuropsychological predictors.

Two previous studies demonstrated that hippocampal atrophy is evident in PD with or without dementia.[8,9] Similar findings are observed in dementia with Lewy bodies (DLB), where diffuse Lewy bodies and, in many cases, the pathologic features of AD co-occur.[10–12] These changes overlap with those seen in PD with dementia (PDD),[13,14] but DLB is distinguished by overlapping onset of dementia and parkinsonism within 12 months along with hallucinations and fluctuations.[15] Except for fluctuations, none of the core features are distinctive for DLB. Visual hallucinations, for example, are common in PD, especially in

patients with coexistent dementia, highlighting the clinical overlap of DLB and PDD.[16–18]

We sought to confirm that hippocampal atrophy was evident in an independent sample of patients with PD with very mild cognitive impairment or dementia compared with healthy elderly and non-demented PD using whole-brain volumetric imaging. Specifically, we examined hippocampal and extrahippocampal regions to discern if the pattern of atrophy differed between PD and AD. Based on previous work, we hypothesized that hippocampal atrophy would be present at an early stage in older patients with PD, but would be of lesser severity than that seen in AD. Furthermore, we predicted that the pattern of atrophy would differ between PDD and AD.

SUBJECTS AND METHODS

Subjects

Subjects were recruited from the Parkinson Center of Oregon Movement Disorders Clinic, the Oregon Aging and Alzheimer Disease Clinic, and the Oregon Brain Aging Study.[19] Parkinson's disease was defined by the presence of two signs among resting tremor, rigidity, and bradykinesia, consistent with the UK Brain Bank criteria.[20] Parkinson's disease with dementia patients required a diagnosis of PD to have preceded the diagnosis of dementia or cognitive impairment by at least one year. This information was collected by history obtained from an informant, and was used to operationally exclude DLB cases where dementia and parkinsonism occurred within one year.[14]

Dementia was defined according to DSM-IV criteria.[21] Cognitive impairment was staged using the Clinical Dementia Rating Scale (CDR),[22] which has been used previously in staging dementia in PD.[23] A rating of 0.5, termed questionable or very mild dementia, indicates persistent memory impairment, or mild cognitive or functional change, representing a change from a previous level of function and was the minimal criterion for cognitive impairment. Some patients at this stage may not meet strict criteria for dementia in that functional decline was not required for the present study. Nevertheless, all cognitively impaired and demented PD patients were referred to as PDD. Higher stages on the CDR represent more severe dementia: 1, mild dementia; 2, moderate dementia; 3, severe dementia. Those with AD met criteria for probable AD according to the NINCDS-ADRDA.[24]

Methods used for the Oregon Brain Aging Study, a longitudinal study of healthy aging, have been described previously.[25] All patients and controls underwent an interview with an informant that was used to provide information to diagnose dementia and obtain a CDR staging. Cognitive testing was used as supportive evidence for cognitive impairment. All non-demented PD patients and controls had no persistent cognitive or functional complaints or cognitive problems reported by the patient or the informant.

Behavioral–Cognitive Assessment

Twenty PD patients had cognitive and motor assessments. Three additional PD patients were recruited and assessed, but the scans could not be analyzed for technical reasons. Their data was not included in this report. Baseline cognitive abilities were characterized by the Wide-Range Achievement Test–Reading, version 2 (WRAT-R2).[26] The Mini-Mental State Examination (MMSE) was carried out with all subjects.[27] Depression was assessed in the PD patients and controls using the Geriatric Depression Scale (GDS).[28] Behavioral problems were documented using the Neuropsychiatric Inventory (NPI).[29] Cognitive assessments carried out for the PD patients included the CERAD word list recall and recognition test.[30]

Controls and patients with AD were assessed as described previously and were age, gender and dementia severity (CDR) matched to the PD subject from a pool of available MRI scans. Cognitive tests reported represent those administered to subjects in all groups.

Motor Assessment

Standard clinical assessments were used to rate tremor, bradykinesia, rigidity, gait, and balance.[31] The Unified Parkinson's Disease Rating Scale (UPDRS) was used to rate PD patients who entered the study. This was only available for the PD patients. None of the control subjects and AD patients exhibited parkinsonism clinically.

MR Imaging

MRI scans were obtained on a 1.5-Tesla GE scanner, with the following image parameters: multi-echo, multiplanar, 4-mm coronal slices, 24-cm^2 FOV, 256 $\times$ 256 matrix, NEX = 0.5, TR = 3000 msec, TE = 30 and 80 msec as described previously.[32] Image analysis was carried out by semiautomated recursive segmentation using the program REGION, and by manual tracing using *NIH Image v. 1.5* on Macintosh computers. Total pixel counts for each region were summed for each slice and multiplied by the slice thickness to convert areas to volumes. Hippocampal and parahippocampal volumes were measured by manually tracing the hippocampal areas on serial slices located between the red nucleus and the superior colliculus as described previously.[32] Intracranial (suparatentorial) volume was defined as non-bone pixels

TABLE 1. *Demographic and baseline clinical features*

	Controls (n = 12)	PD (n = 10)	PDD (n = 10)	AD (n = 11)	*P*
Age (yr)	73.9 (6.7)	73.3 (5.7)	74.7 (7.3)	74.4 (7.3)	0.97
Gender (M/F)	5/7	8/2	4/6	4/7	0.16
Duration (yr)	NA	5.1 (1.3)	7.3 (3.2)[c]	3.5 (1.8)[d]	0.0025
Education (yr)	14.8 (2.6)	15.8 (3.0)	15.6 (3.1)	14.4 (2.8)	0.85
GDS	2.1 (2.1)	11.4 (19.1)	10.5 (6.4)	NA	0.12
MMSE	28.7 (1.1)	28.1 (1.6)	26.3 (3.5)[a]	25.0 (2.1)[b]	0.01
CDR	All 0	All 0	0.82 (0.46)[b]	0.75 (0.49)[b]	<0.0001

Values are expressed as mean (SD), unless otherwise indicated.

[a]$P < 0.05$ compared to controls; [b]$P < 0.02$ compared to controls and PD; [c]$P < 0.05$ compared to PD; [d]$P < 0.001$ compared to PDD.

GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating scale.

beginning with the first slice in which the frontal poles were present and ending at the occipital poles; excluding brainstem and cerebellar structures. Intracranial volumes were determined by recursive segmentation using REGION. In this semiautomated program, representative pixels of tissue types of interest (bone, brain, and cerebrospinal fluid) are sampled on each slice using predetermined sampling guidelines. The recursive segmentation is completed automatically by applying a discriminant function to identify all non-bone pixels contiguous to the intracranial sample points. Any manual tracing required to correct the automated segmentation is carried out according to strict atlas-based rules. Subsequent segmentation allows measurement of brain and cerebrospinal fluid in a similar manner. These analysis techniques have been shown previously to be reliable: hippocampal volume, intraclass correlation (ICC) = 0.90; parahippocampal volume, ICC = 0.81; temporal lobe volume, ICC = 0.93; frontal lobe volume, ICC = 0.91; parieto-occipital lobe volume, ICC = 0.93; and intracranial volume, ICC = 0.98.[33] The sum of the right and left hemisphere volumes was examined because we did not hypothesize that hippocampal degeneration would be lateralized.

Statistical Analysis

Groups were compared using χ^2 tests, *t*-tests or analysis of variance (ANOVA) for direct comparisons and multivariate analysis of variance (MANOVA) for simultaneous examination of all brain regions and cognitive function; ANOVA and Fisher's PLSD test were used for post hoc comparisons. Total amount of levodopa (L-dopa) equivalents were calculated for the patient groups according to the formula: Total equivalents = regular L-dopa dose × 1 + L-dopa continuous release dose × 0.75 + pramipexole dose × 67 + ropinirole dose × 16.67 + pergolide dose × 100 + bromocriptine dose × 10 + [regular L-dopa dose + (continuous release L-dopa dose × 0.75)] × 0.25 if taking tolcapone or entecapone.[34] Untransformed raw data are presented in the tables. Although there was no significant group difference in intracranial volume (ICV), groups were compared after dividing the volume by the intracranial volume as described previously.[35] To assure that the disease group differences were not related to the statistically insignificant increased number of males in the cognitively intact PD group, analyses were repeated after excluding that group. Right and left hemisphere volumes were combined for all between-group comparisons because we did not hypothesize that one side would be more likely to be associated with cognitive impairment; moreover, right and left hippocampal volumes did not differ from each other ($t = 0.61$, $P = 0.55$). Correlation between memory and MMSE scores and left and right hippocampal volumes were examined among the patients with PD to determine if cognitive function might be associated specifically with focal hippocampal atrophy and to test the hypothesis that verbal memory would be associated with left and not right hippocampal atrophy. Post hoc ANCOVA comparing directly the AD and PDD was carried out, after adjusting for MMSE, to determine if dementia severity might account for any trend in parahippocampal volumes observed. Effect sizes were calculated for each of the patient groups by subtracting the mean brain volume in the disease group from the mean volume in the control group and then dividing by the overall standard deviation. A *P* value of 0.05 was used for as the threshold for statistical significance.

RESULTS

Data regarding the baseline characteristics of the subjects are presented in Table 1. Groups were matched for age and education. Although there were more men in the PD without cognitive impairment, there was no statisti-

TABLE 2. *Cognitive measures and behavioral problems*

	Controls (n = 12)	PD (n = 10)	PDD (n = 10)	AD (n = 11)	*P**
WRAT-R2	72.7 (9.8)	55.5 (7.0)[b]	54.8 (9.6)[b]	64.9 (9.9)[c,d]	0.0002
WRECALL	6.9 (1.9)	5.3 (1.4)[a]	4.5 (2.0)[b]	2.2 (1.5)[b,c,d]	<0.0001
WRECOG	19.7 (1.2)	19.0 (0.94)	17.1 (3.4)[a]	16.5 (3.1)[b,c]	0.005
NPI	ND	3 (2.7)	14.8 (18.8)	ND	0.07

Values are expressed as mean (SD) unless otherwise noted.

Scores were not available for all subjects. The NPI was not completed for the controls and AD patients (ND).

**P*-value refers to the comparison between the PD groups.

[a]$P < 0.05$ compared to controls; [b]$P < 0.005$ compared to controls; [c]$P < 0.05$ compared to PD; [d]$P < 0.05$ compared to PDD.

cally significant difference in gender distribution between groups ($\chi^2 = 0$ 5.1, $P = 0.16$). Years since onset of symptoms differed between patient groups (F[2,28] = 7.5, $P = 0.003$); PDD patients had a longer duration of symptoms than both the AD ($P = 0.0006$) and the non-demented PD patients ($P = 0.04$). No subjects had clinical depression and the GDS did not differ between groups (F[3,29] = 1.55, $P = 0.22$). By definition, only the cognitively impaired groups were rated >0 according to the CDR (for PDD, n = 7, CDR = 0.5; n = 2, CDR = 1; n = 1, CDR = 2; for AD, n = 6, CDR = 0.5; n = 4, CDR = 1; n = 1, CDR = 2). Non-impaired PD and controls had a CDR = 0. As expected, the CDR score differed significantly between groups (F[3,38] = 20.6, $P < 0.0001$); the demented groups differed from the others, but not from each other ($P = 0.50$). There was no difference between PD groups in total L-dopa equivalent use (PD = 560 mg/day and PDD = 568 mg/day, $t = -0.07$, $P = 0.95$).

Results of available cognitive tests are shown in Table 2. A MANOVA that included the cognitive variables (Education, WRAT-R2, MMSE score, word list recall, and word list recognition), was significant: Wilks's $\lambda = 0.184$, $F(15,78) = 4.4$, $P < 0001$. Post hoc tests revealed that education level did not differ between groups (F[3,32] = 0.26, $P = 0.85$). Premorbid cognitive ability, measured by the WRAT-R2, differed between the groups (F[3,32] = 8.9, $P = 0.0002$). The two PD groups did not differ from each other ($P = 0.46$), but had lower WRAT-R2 scores than the AD patients ($P < 0.05$, for both) and controls ($P < 0.005$, for both). MMSE scores differed between groups (F[3,32] = 6.46, $P = 0.01$). Patients with PDD ($P < 0.05$) and AD ($P = 0.003$) were more impaired than the controls, whereas AD patients ($P = 0.01$) were more impaired than the non-impaired PD patients. There was no statistically significant difference between non-impaired PD and the PDD patients ($P = 0.17$), the non-impaired PD patients and controls ($P = 0.52$) and the AD and the PDD patients ($P = 0.21$).

Groups differed on the CERAD word list recall task (F[3,32] = 10.3, $P < 0.0001$). PD groups did not differ ($P = 0.46$) from each other, but both groups performed significantly worse than controls (PD, $P = 0.02$; PDD, $P = 0.005$). The AD patients had poorer recall compared with the control ($P < 0.0001$) and PD subjects (PD, $P = 0.0005$; PDD, $P = 0.005$). Differences were also observed on the recognition format (F[3,32] = 4.0, $P = 0.005$): the PDD ($P = 0.02$) and AD ($P = 0.001$) both performed worse than the controls did, but did not differ from each other ($P = 0.19$). The AD patients performed worse than did the cognitively intact PD patients ($P = 0.009$), who did not differ from the controls ($P = 0.37$). Only 6 AD patients were available for these comparisons.

Groups did not differ significantly on the NPI (F[3,18] = 1.6, $P = 0.22$), but few non-PD subjects were available for comparison.

Raw MRI volumes and effect sizes are shown in Table 3. The overall MANOVA examining the corrected brain volumes (hippocampal, parahippocampal, temporal, frontal, and parieto-occipital) as dependent variables was significant: Wilks's $\lambda = 0.325$, $F(15,97) = 3.25$, $P = 0.0002$. Corrected hippocampal volumes differed between groups (F[3,39] = 7.7, $P = 0.0004$): PD ($P = 0.004$), PDD ($P = 0.003$), and AD ($P < 0.0001$) were smaller than the controls, although these groups did not differ from each other. Differences in adjusted parahippocampal volumes were of borderline significance (F[3,39] = 2.85, $P = 0.05$, see Fig. 1). Between-group differences in corrected temporal (F[3,39] = 2.5, $P = 0.08$), frontal (F[3,39] = 1.4, $P = 0.24$), parieto-occipital lobe (F[3,39] = 2.7, $P = 0.06$), or total brain volumes (F[3,39] = 1.9, $P = 0.15$) were not significant. Results of the overall MANOVA remained similar after excluding the non-impaired PD group (that included more males, Wilks's $\lambda = 0.351$, F[10,52] = 3.5, $P = 0.001$). After adjusting for MMSE, there was no significant

TABLE 3. *Raw brain volumes by group*

Region	Controls	PD	PDD	AD	*P**
Hippocampus	1.41 (0.13)	1.29 (0.14) 0.66[a]	1.19 (0.12) 1.22[a]	1.08 (0.16) 1.81[a]	0.0004
Parahippocampus	3.16 (0.53)	3.76 (0.60) 1.0	3.42 (0.56) 0.43	2.84 (0.34) 0.53	0.05
Temporal lobe	123.6 (15.4)	130.1 (16.0) 0.35	118.2 (16.6) 0.29	110.3 (22.1) 0.72	0.08
Frontal lobe	443.1 (73.9)	434.2 (68.5) 0.14	428.2 (58.5) 0.23	433.4 (59.8) 0.15	0.24
Parieto-occipital	312.4 (56.4)	382.4 (62.1) 1.1	306.8 (46.1) 0.09	303.4 (65.7) 0.14	0.06
Total brain	978.6 (85.8)	1045.0 (131.5) 0.58	940.5 (86.4) 0.33	940.8 (129.9) 0.33	0.15
Intracranial	1199.9 (116.7)	1310.1 (133.7) 0.86	1204.0 (114.7) 0.03	1238.4 (133.5) 0.30	0.15

Values are expressed as mean (SD) absolute effect size. Volumes in mm^3.

**P*-values refer to comparisons using volumes divided by intracranial volume, except for the comparison of intracranial volumes where raw volumes were compared.

[a]$P < 0.005$ compared to controls.

difference between the AD and PDD groups with respect to parahippocampal volumes ($F[1,17] = 0.21$, $P = 0.65$).

Recognition memory ($r = 0.54$, $P = 0.015$) and MMSE scores ($r = 0.56$, $P = 0.01$) correlated with left hippocampal volume; right hippocampal correlations were all insignificant ($P > 0.2$).

DISCUSSION

Our data confirm that PD patients with or without cognitive impairment have more hippocampal atrophy than healthy age-matched control subjects, with volumes similar to that in patients with mild AD. Differences in parahippocampal volumes were of borderline significance, and trends observed were related to dementia severity. Differences in temporal and frontal lobe volume and parieto-occipital lobes were not significant in this sample. Thus, hippocampal atrophy is evident in older PD patients before the onset of dementia. Effect sizes observed were modest for all comparisons, with a trend for hippocampal atrophy of AD > PDD > PD, compared with controls.

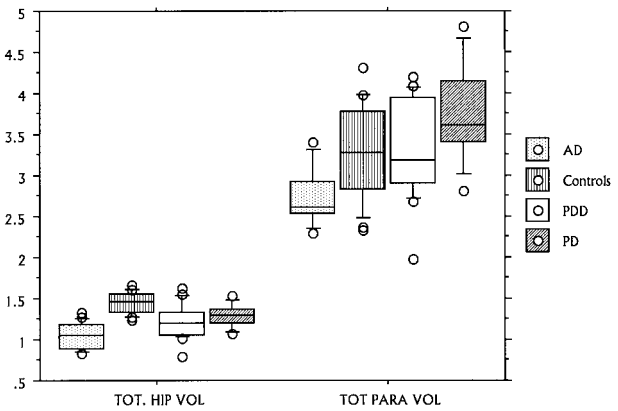

FIG. 1. Box plot showing hippocampal (hip) and parahippocampal (para) volumes in cubic millimeters. Parkinson's disease subjects without (PD) and with cognitive impairment (PDD) showed smaller hippocampal volumes. Parahippocampal volumes did not differ between groups after adjustment for MMSE scores.

We have extended previous research by examining a mild spectrum of disease using quantitative, whole brain neuroimaging. Previous pathological [36–39] and imaging-based volumetric studies[8,9] that have examined more advanced patients with PD are consistent with our study. Hippocampal atrophy also occurs in DLB, which overlaps pathologically with PDD, where hippocampal volume is intermediate between that observed in controls and in those with AD with sparing of the parahippocampal gyrus.[40]

Our study was limited by a small sample size, and by the fact that the non-demented PD group was predominantly male. Nevertheless, the difference in gender distribution between groups was not significant statistically and the other patient groups, including the PDD group, were well matched. A larger intracranial volume in men would bias against our finding of a decreased hippocampal volume in PD, compared with controls, arguing that this finding is valid. A greater number of men in the cognitively intact PD group would bias toward finding larger volumes in that group; however, we have adjusted for intracranial capacity using accepted methods, and the overall MANOVA remained significant after excluding that group. Although we had a small sample size, our current subjects were independent of those reported in our pilot study that showed similar findings, and therefore are confirmatory.[8] Based on our pilot study, we included a number of PD patients similar to those of Laakso and associates.[9]

In DLB the rate of brain atrophy does not differ from that in AD or vascular dementia.[41] In a comparison with controls and patients with progressive supranuclear palsy, patients with PD (on average 5 years younger than those in our study) did not show hippocampal atrophy, raising the possibility that atrophy is accelerated in PD.[42] A recent study demonstrated that cognitive decline was

correlated with global brain atrophy in PD.[43] A previous volumetric study of patients with PD suggested that hippocampal atrophy might be correlated with episodic memory, consistent with our finding of a relationship between cognitive function and left hippocampal volume.[44] Given the high risk of dementia in people with PD and the finding that atrophy precedes the onset of dementia, our study raises the possibility that focal atrophy might provide a presymptomatic marker for dementia risk. Nevertheless, given that atrophy in both cognitively impaired and unimpaired subjects was similar, additional changes must be invoked to explain dementia in PD.

One interpretation of the trend to larger parahippocampal volumes in PDD is that the PDD subjects were at a milder stage of disease. Given that, after adjustment for MMSE, there was no clearly significant difference in parahippocampal volumes between the AD and PDD groups, it is likely that dementia severity accounts for this finding. On the other hand, the PDD and AD groups did not differ in the distribution of CDR levels or on the MMSE, both of which reflect global cognitive function. Although sparing of parahippocampal and temporal lobe structures also has been noted in DLB compared with AD in imaging studies,[45,46] a recent pathological study found that parahippocampal involvement with Lewy body and neuritic pathology was associated with dementia in patients with PD and DLB, consistent with involvement of these regions in PDD.[14] Involvement of the subiculum was shown recently for DLB, but not PD, suggesting that the pattern of atrophy might differ in these two entities.[47]

Our data examining cortical regions, including parieto-occipital lobe volumes, are consistent with a recent study that showed specific sparing of occipital volume in DLB compared with AD and controls.[48] In our study, as in many of the previous imaging studies, there was considerable overlap between patient groups with respect to each of the brain volumes examined (see Fig. 1). Given our small sample size, we did not carry out subgroup analyses to examine the possibility of clinical heterogeneity.

In summary, we have shown that hippocampal atrophy may distinguish PD from healthy controls. Hippocampal changes resemble those seen in patients with mild AD and may correlate with cognitive function. Prospective studies will determine if this provides a presymptomatic marker for dementia in PD and if the evolution of atrophy in PD resembles that seen in other neurodegenerative disorders. Ongoing research using higher resolution MRI scans will allow further, more precise definition of the pattern of brain atrophy, especially in the medial temporal lobes. Pathological correlation with atrophy on MRI will be required to determine if PDD is distinct from DLB.

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