Cerebral atrophy and its relation to cognitive impairment in Parkinson disease

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Abstract—*Objective:* Voxel-based morphometry was used to compare the amounts of gray matter in the brains of patients with Parkinson disease (PD) and normal control subjects (NCs) and to identify the specific regions responsible for cognitive dysfunction in PD. *Methods:* Patients were classified into nondemented (ND) and demented (D) groups according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (4th ed.), and a group comparison was performed. In the ND patients, a correlation was also performed between local gray matter density and the score on Raven Colored Progressive Matrices (RCPM), a test of executive and visuospatial function. *Results:* In patients with advanced ND-PD vs NCs, atrophic changes were observed in the limbic/paralimbic areas and the prefrontal cortex. In D vs ND patients, atrophic change was observed widely in the limbic/paralimbic system, including the anterior cingulate gyrus and hippocampus as well as the temporal lobe, dorsolateral prefrontal cortex, thalamus, and caudate nucleus. The RCPM score was positively correlated with the gray matter density in the dorsolateral prefrontal cortex and the parahippocampal gyrus. *Conclusions:* In patients with Parkinson disease (PD), atrophic changes occur mainly in the limbic/paralimbic and prefrontal areas. These atrophic changes may be related to the development of dementia in PD.

Cognitive impairment is relatively frequent in Parkinson disease (PD), especially at an advanced stage. In its severe form, it may be global and meet the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM- IV) criteria for dementia.[1] The prevalence of dementia in PD is estimated to be 20 to 40%.[1,2] Moreover, even in the absence of dementia, specific impairments in executive function, visual memory, and visuospatial abilities are often present.[3,4] Raven Colored Progressive Matrices (RCPM), which was initially developed as a nonverbal intellectual test,[5] has been shown to be sensitive to cognitive deficits in PD[6] and can be considered to rely on at least two cognitive factors: visuospatial and executive functions.[7]

A small number of MRI studies have related brain atrophy to cognitive dysfunction in PD. There have been reports, among nondemented PD (ND-PD) patients, of major correlations between verbal learning or frontal lobe function scores and ventricular enlargement[8] and between annual reductions in brain volume and reductions in performance and full-scale IQ.[9] In another study of ND-PD patients, hippocampal atrophy was found to correlate with memory impairment.[10] Finally, reduced gray matter volume in demented PD (D-PD) patients was observed in widespread cortical (temporal, occipital, lateral prefrontal) and subcortical (caudate, putamen, thalamus) areas vs control subjects using voxel-based morphometry (VBM).[11] However, as far as we know, there have been no reports on the relation between gray matter atrophy and cognitive impairment in ND-PD using VBM.

The aim of this study was to identify the gray matter atrophic changes that are associated with specific cognitive impairment and dementia in PD. We used VBM to assess focal brain atrophy in the whole brain of PD patients with and without dementia and matched healthy control subjects. We also correlated gray matter density to performance on the RCPM in the ND-PD patients.

Methods. *Subjects.* Fifty-eight patients with PD who fulfilled the clinical criteria for the diagnosis of PD[12] were recruited. Detailed interview with patients and their families and neurologic examination were used to determine cognitive status. Nine patients were diagnosed as D-PD according to the DSM-IV criteria. All of them had impairments in memory function affecting their daily life and had experienced visual hallucinations. One patient had cognitive fluctuation and, as a result, also fulfilled the criteria of the Consortium on Dementia with Lewy Bodies International Workshop.[13] In all D-PD, the onset of parkinsonism preceded the development of dementia by at least 2 years, and significant cognitive impairment involving executive function and/or visuospatial abilities preceded the memory difficulties. Among the

Table 1 *Clinical features of normal subjects and patients*

Group category	Comparison	No.	Age, y	H-Y Scale	UPDRS motor score	Disease duration, y	MMSE score
NC	NC vs all ND-PD NC vs advanced ND-PD	31	63.5 ± 8.8				29.2 ± 1.2
ND-PD	NC vs all ND-PD	39	61.8 ± 8.1	2.3 ± 0.9	25.5 ± 16.1	3.5 ± 3.4	28.4 ± 1.9
	NC vs advanced ND-PD	19	62.6 ± 7.9	3.1 ± 0.5	37.4 ± 15.3	4.9 ± 4.3	28.1 ± 2.0
	Advanced ND-PD vs D-PD	17	65.4 ± 6.4	3.1 ± 0.6	38.7 ± 15.7	5.2 ± 4.5	27.9 ± 2.0
	Regression analysis	38	61.9 ± 8.2	2.3 ± 0.9	26.0 ± 16.0	3.6 ± 3.4	28.4 ± 1.9
D-PD	ND-PD vs D-PD	9	67.3 ± 5.4	3.3 ± 0.7	45.7 ± 10.9*	9.3 ± 5.4	16.1 ± 5.7

* n = 6.

H-Y = Hoehn and Yahr; UPDRS = Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; NC = normal control; ND-PD = nondemented Parkinson disease; D-PD = demented Parkinson disease.

remaining PD patients, none fulfilled the DSM-IV criteria for delirium or amnesic disorder. After excluding patients with a history of hallucination, severe depression, severe autonomic failure, or resistance to dopaminergic medications, 39 PD patients remained to form the ND-PD group. All patients were rated using the Hoehn and Yahr (H-Y) Scale and the Mini-Mental State Examination (MMSE). All patients except three D-PD patients were rated using the Unified Parkinson's Disease Rating Scale (UPDRS), and all ND-PD patients except one underwent the RCPM Test. Thirty-one normal control subjects (NCs), who were neurologically intact and age matched to the ND-PD patients, were also recruited. Permission to perform these studies was obtained from the Ethical Committee of the National Center for Geriatrics and Gerontology.

MRI and VBM. High-resolution volumetric MRI was performed on a 1.5 T Visart MRI scanner (Toshiba, Tokyo, Japan) using a three-dimensional field echo sequence (repetition time 20 milliseconds, echo time 7 milliseconds, flip angle 35°), generating T1-weighted contiguous sagittal slices with a pixel size of 0.89 × 0.89 mm and a slice thickness of 1.3 mm. These T1-weighted brain volumes were linearly transformed into stereotaxic space using nine parameters[14] to match the Montreal Neurologic Institute template with a voxel size of 1 × 1 × 1 mm. The volumes also underwent a nonuniformity correction[15] to remove variations in signal intensity related to radiofrequency inhomogeneity. With use of the individual parameters of the linear transformation, the images were transformed into the standardized stereotaxic space. The transformed images were then classified into gray matter, white matter, and CSF using an automatic tissue classification algorithm.[16] Mask images were generated from the individual spatially transformed images to remove the skull and dura.[17] With use of the tissue-classified and mask images, probability images of gray matter were created using an algorithm that estimates the relative amount of gray and white matter, CSF, and background in each voxel.[18] These gray matter probability images were then blurred with an isotropic Gaussian kernel (full width at half-maximum = 8 mm). Statistical analyses were performed on the blurred gray matter probability images.

Statistical analysis. Four voxel-based statistical analyses were performed as follows: 1) group comparison between 31 NCs and 39 ND-PD patients, 2) group comparison between 31 NCs and 19 advanced ND-PD patients (defined as H-Y score of >2), 3) group comparison between 17 advanced ND-PD and 9 D-PD patients, and 4) regression analysis between the RCPM scores and the gray matter probability maps of 38 ND-PD patients. In the third comparison, patients matched to the D-PD patients for age and H-Y score were selected from the advanced ND-PD group. Because these two groups could not be matched for disease duration, this subtraction was also carried out with disease duration as a confounding covariate.

The effect of each comparison was tested, and the result was indicated as a *T* map. Random field theory was used to assign a *p* value to each cluster based on its height and extent.[19] The degrees of freedom for each comparison were set to the number of subject scans used minus 2. Clusters with a height threshold set at *p* < 0.001 and an extent threshold set at corrected *p* < 0.05 were considered significant.

Results. The number, mean age, disease duration, H-Y score, UPDRS motor score, and MMSE score for each group of each comparison are shown in table 1. No significant differences were observed in mean age, H-Y score, or UPDRS motor score in any group comparisons. There was, however, a trend toward longer disease duration in the D-PD group vs the ND-PD group. There were no significant differences in dosages of any antiparkinsonian medication between advanced ND-PD and D-PD groups. The RCPM score ranged from 20 to 36 (mean 30.0 ± 4.4). There was no correlation between the UPDRS motor scores and the RCPM scores in ND-PD patients (correlation coefficient −0.02, *p* = 0.93).

There were no differences in gray matter density between the ND-PD and NC groups. In the advanced ND-PD group vs NCs, there were atrophic changes in the bilateral straight gyrus extending into the subcallosal gyrus, Brodmann area (BA) 11/25, left inferior frontal gyrus (ventrolateral prefrontal cortex, BA 44), and left parahippocampal gyrus (BA 30) (figure 1). In the D-PD group vs matched ND-PD patients, there were atrophic changes in the bilat-
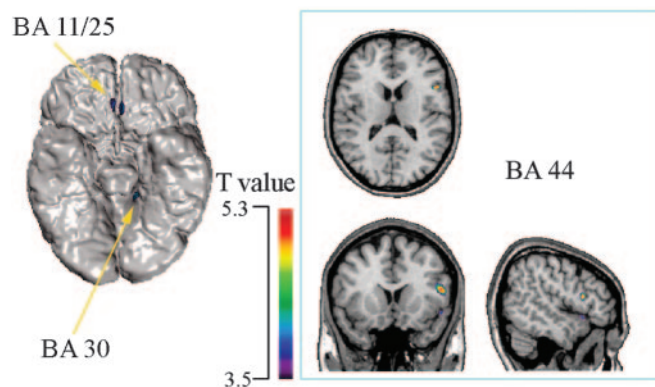

Figure 1. Regions with significant difference between normal control subject and nondemented patient with advanced Parkinson disease. The T *value with 3.5 and above is superimposed on the template MRI. The right side of each axial and coronal figure corresponds with the right side of the brain. BA = Brodmann area.*
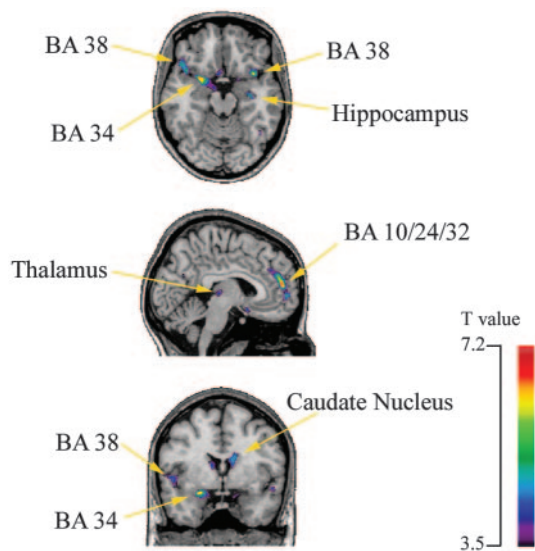
Figure 2. Regions with significant difference between advanced Parkinson disease without dementia and Parkinson disease with dementia. The T value with 3.5 and above is superimposed on the template MRI. The right side of each axial and coronal figure corresponds with the right side of the brain. BA = Brodmann area.

eral anterior cingulate gyrus extending to the medial frontal gyrus (BA 10/24/32), bilateral parahippocampal gyrus (BA 34), bilateral anterior part of the superior temporal gyrus, corresponding to the temporal operculum, extending to the temporal polar region (BA 22/38), right hippocampus, right middle frontal gyrus (dorsolateral prefrontal cortex, BA 46), bilateral caudate nuclei, and left thalamus (figure 2). These results were essentially unaffected when disease duration was covaried out (table 2). In ND-PD patients, the RCPM score was positively correlated with the gray matter density in the right parahippocampal/fusiform gyrus (BA 37), left parahippocampal gyrus (BA 19/28), left superior frontal gyrus (BA 10), and right middle frontal gyrus (dorsolateral prefrontal cortex, BA 9) (figure 3). Table 2 lists the peaks of the most significant differences in these results.

Discussion. *NCs vs ND-PD patients.* In the ND-PD group as a whole, no loss of gray matter was observed vs NC, and this result is consistent with previous MRI studies.[20,21] In contrast, the advanced ND-PD patients showed gray matter loss in three areas vs NCs: straight gyrus, inferior frontal gyrus, and parahippocampal gyrus. The straight gyrus, which is considered to be an extension of the anterior cingulate into the frontal lobe,[22] belongs to the paralimbic system, as does the parahippocampal gyrus. This finding is consistent with pathologic studies showing that the components of the limbic system are particularly vulnerable to degeneration in PD.[23] Mild pathologic change has also been observed in frontal association areas in PD,[23] and the atrophic change in the lateral prefrontal cortex observed in

Table 2 *List of peaks of most significant differences in comparisons*

Comparison	Region	Cluster				Coordinate		
		Voxels	p Corrected	Peak T value	Peak T value*	x	y	z
NC vs PD advanced	L rectal gyrus (BA 11/25)	1,143	<0.001	4.59		0	28	−26
	R inferior frontal gyrus (BA 44)	635	0.001	5.31		52	13	15
	L parahippocampal gyrus (BA 30)	380	0.026	4.3		−13	−40	−6
PD vs D-PD	L medial frontal gyrus (BA 10/24/32)	4,316	<0.001	7.21	6.82	−5	50	13
	L superior temporal gyrus (BA 38/22)	2,761	<0.001	5.34	5.11	−47	20	−18
	L parahippocampal gyrus (BA 34)	1,286	<0.001	6.75	5.84	−24	2	−16
	R caudate nucleus (body/head)	1,211	<0.001	4.82	4.72	12	1	18
	R superior temporal gyrus (BA 38/22)	1,034	<0.001	6.16	5.55	36	9	−17
	L thalamus	705	0.001	4.87	3.45	−7	−27	2
	R hippocampus	524	0.004	5.27	4.57	32	−17	−17
	L caudate nucleus (body/head)	464	0.007	4.39	4.33	−11	0	14
	R middle frontal gyrus (BA 46)	365	0.024	4.39	4.18	42	47	15
PD and RCPM	R parahippocampal/fusiform gyrus (BA 37)	678	0.001	5.01		27	−40	−14
	L superior frontal gyrus (BA 10)	611	0.002	6.07		−25	55	13
	L parahippocampal gyrus (BA 19)	511	0.005	4.63		−30	−56	−2
	R insula	509	0.005	4.74		38	11	2
	R middle frontal gyrus (BA 9)	441	0.011	5.39		45	8	37
	L parahippocampal gyrus (BA 28)	418	0.015	4.02		−22	−13	−14

* Peak *T* value with disease duration covaried out.

NC = normal control; PD = Parkinson disease; D-PD = demented Parkinson disease; RCPM = Raven Colored Progression Matrices; BA = Brodmann area.
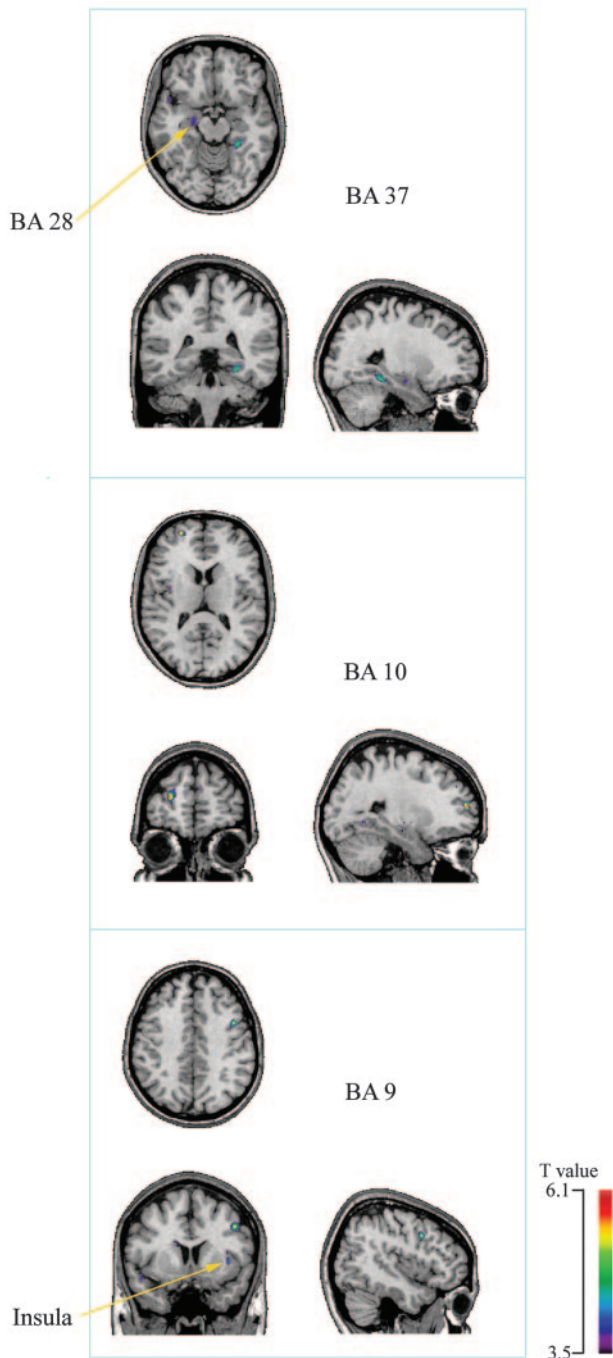
Figure 3. Region with significantly positive correlation to the Raven Colored Progressive Matrices score. The T *value with 3.5 and above is superimposed on the template MRI. The right side of each axial and coronal figure corresponds with the right side of the brain. BA = Brodmann area.*

our study in advanced PD patients likely reflects intrinsic frontal lobe degeneration.

ND-PD vs D-PD patients. When we compared D-PD patients with a group of ND-PD patients matched for motor disability, we observed widespread atrophic changes in the limbic/paralimbic system. We selected D-PD patients according to the DSM-IV criteria, which require memory impairment. Thus, our finding of atrophy involving the Papez cir-

cuit, which is strongly implicated in memory, likely accounts for the memory impairment in our group of D-PD patients. Pathologic studies have implicated the medial temporal lobe in dementia in PD. Demented patients have higher densities of parahippocampal Lewy bodies on pathologic examination,[24] and there have been reports of correlations between clinical dementia severity and the number of Lewy bodies in the entorhinal cortex[25] and the density of Lewy neurites in the CA2 field of the hippocampus.[26] Moreover, previous MRI studies indicated that hippocampal atrophy is related to impaired memory in ND-PD patients.[10,27] We conclude that atrophy of the hippocampus and parahippocampal gyrus may be an important determinant of dementia in PD.

Within the limbic/paralimbic system, the strongest difference in gray matter between the ND-PD and D-PD patients was observed in the anterior cingulate gyrus extending into the medial frontal gyrus. The anterior cingulate cortex is one of the cortical areas showing the greatest concentration of Lewy bodies in PD,[23,24,28] and a significant correlation has been reported between Clinical Dementia Rating Scale score and Lewy body density in this region.[25] Neuroimaging studies have implicated the anterior cingulate gyrus in attention[29] and in a variety of tasks that require high-level cognitive processing.[30] Thus, the loss of gray matter in the anterior cingulate gyrus may be related to the impairment in the ability to spontaneously generate efficient cognitive strategies in patients with PD.[31]

In a previous PET study, we described a decrease in the 6-[^{18}F] fluoro-L-dopa influx rate constant in the anterior cingulate in D-PD vs ND-PD.[32] It is possible that the loss of gray matter in the anterior cingulate described in the current study includes the loss of mesolimbic dopaminergic projections to the area. However, anterior cingulate atrophy would likely also cause partial volume effects that could have accounted for our previous result.

Reduced gray matter density was also observed in the thalamus and caudate in D-PD patients. These subcortical atrophic changes are consistent with a previous pathologic study in D-PD patients[33] and two recent VBM studies.[11,34] Another MRI study reported no caudate atrophy in D-PD patients vs controls[35]; however, the measure used was whole caudate volume rather than gray matter density.

In a recent VBM study, D-PD patients were found to have a pattern of gray matter loss similar to dementia with Lewy bodies but different from Alzheimer disease (AD).[11] D-PD patients and patients with dementia with Lewy bodies both had widespread cortical (temporal, occipital, lateral prefrontal) and subcortical (caudate, putamen, thalamus) atrophy, with relative sparing of the medial temporal structures compared with control subjects and patients with AD. These results are at odds with those presented here. We found atrophy of the medial temporal lobe structures in the D-PD patients, consistent with previous reports in PD and similar to what has been

reported in AD.[27,36] A possible explanation is that our use of the DSM-IV criteria likely weighted our D-PD sample more toward memory impairment. Thus, the pattern of cerebral atrophy in D-PD most likely depends on the clinical characteristics of the patients studied.

There were no significant differences in medication dosages and clinical features, except MMSE scores, between the D-PD and ND-PD groups. However, the disease duration of D-PD tended to be longer than in ND-PD patients, consistent with a previous observation that longer disease duration is a risk factor for dementia in PD.[1,2] Thus, we cannot say whether atrophy of caudate and limbic/paralimbic and prefrontal areas is merely a result of disease progression or a feature specific to the subgroup of PD patients who develop dementia. Nonetheless, our results allow us to identify gray matter loss in these areas as the anatomic substrate of dementia in PD, a notion that is supported by the fact that co-varying out disease duration did not significantly affect the statistical map and also by the regression analysis in ND patients (see below). Finally, it should be noted that in our study, all D-PD patients had experienced visual hallucinations; therefore, our results may not generalize to PD patients with dementia and no hallucinations.

Regression analysis using RCPM score. Performance on the RCPM can be considered to involve both executive and visuospatial function in PD patients.[7] Previous PET activation studies with the Raven Progressive Matrices task (a variation of RCPM) in young healthy subjects showed a task-related increase of regional cerebral blood flow in areas involved in executive (prefrontal cortex) and visuospatial (occipital, parietal, and hippocampal/parahippocampal regions) function.[37] Therefore, our finding of a positive correlation between the RCPM score and gray matter density in the dorsolateral prefrontal cortex provides an explanation for executive dysfunction in PD. Although dopamine loss in the striatum may affect frontal lobe function by disrupting activity within basal ganglia–thalamocortical circuits,[38,39] our finding suggests that intrinsic frontal lobe degeneration may also play a role. We also observed a positive correlation between the RCPM score and gray matter density in the fusiform and parahippocampal gyri. This parahippocampal gyrus peak, which is more posterior than the parahippocampal gyrus peak in the D-PD vs ND-PD comparison, is in an area thought to be involved in the processing of spatial information.[40,41] Thus, atrophic change in the posterior part of the parahippocampal gyrus may lead to impairment of the visuospatial component of the RCPM.

PET activation with a delayed visual discrimination task that shares cognitive features with the RCPM has been reported.[42] In young subjects, the neutral network involved in this task was shown to include the prefrontal cortex (BA 10), fusiform gyrus, parahippocampal gyrus, posterior cingulate (precu-

neus), and inferior parietal gyrus. On the contrary, in the older subjects, the network included more anterior areas, namely, the caudate nucleus, dorsolateral prefrontal cortex (BA 9/46), and anterior cingulate gyrus (BA 32). Thus, in older subjects, the caudate nucleus is likely important in the RCPM task. However, in PD patients, because of the impairment of nigrostriatal dopaminergic projection, the network for the "young" (prefrontal cortex and fusiform/parahippocampal gyrus) may be recruited. Recruitment of the hippocampus during performance of a task that normally activates the caudate nucleus has previously been described in PD.[38] If such a recruitment is compensatory, damage to prefrontal and medial temporal structures would likely impair performance on the task. Indeed, we observed a significant correlation between the amounts of the gray matter and the RCPM performance in these two regions in our patients with PD.

RCPM performance did not correlate significantly with severity of PD motor symptoms in this current study, as also reported previously.[7] There is controversy regarding the effectiveness of dopamine replacement on cognitive impairment in PD.[43,44] In PD, the combined impairment of the basal ganglia–thalamocortical circuits due to dopamine deficiency and of the prefrontal cortex and parahippocampal gyrus due to gray matter atrophy may account for the lack of effect of dopamine repletion on cognition.

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