A comparison of gray and white matter density in patients with Parkinson’s disease dementia and dementia with Lewy bodies using voxel-based morphometry

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Department of Medicine
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A comparison of gray and white matter density in patients with Parkinson’s disease dementia and dementia with Lewy bodies using voxel-based morphometry

Directed by Professor Phil Hyu Lee

The Master's Thesis submitted to the Department of Medicine the Graduate School of Yonsei University in partial fulfillment of the requirements for the degree of Master of Medical Science

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December 2010
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Yonsei University
December 2010
ACKNOWLEDGEMENTS

I am very happy to write this letter.

First of all, I appreciate Prof. Phil Hyu Lee for supervising me and helping me to complete this thesis.

And I also thanks to Prof. Young Ho Sohn and my fellows in the department of neurology, especially Sook Keun Song and Ji Eun Lee for their support and help.

Give my love to Ji Hyon and Yungji.

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ABSTRACT

A comparison of gray and white matter density in patients with Parkinson’s disease dementia and dementia with Lewy bodies using voxel-based morphometry

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The Graduate School, Yonsei University

(Directed by Professor Phil Hyu Lee)

Despite clinical and neuropsychological similarities between Parkinson’s disease dementia (PDD) and dementia with Lewy bodies (DLB), recent studies have demonstrated that structural and pathological changes are more severe in DLB than in PDD. We used voxel-based morphometry to compare gray and white matter densities in 20 patients with probable PDD and 18 patients with probable DLB who had similar overall severity of dementia and similar demographic characteristics. The gray matter density was significantly decreased in the left occipital, parietal, and striatal areas in patients with DLB compared to those with PDD. The white matter density was significantly decreased in bilateral occipital and left occipito-parietal areas in patients with DLB compared to those with PDD. The degree of white and gray matter atrophy was similar in patients with DLB; in contrast, there was markedly less atrophy in the white matter than in the gray matter in patients with PDD. In
patients with DLB compared to those with PDD, the area of WM atrophy in the occipital areas was more extensive than that of GM atrophy. Our data demonstrate that gray and white matter atrophy is more severe in patients with DLB, and white matter atrophy relative to gray matter atrophy is less severe in patients with PDD. These data may reflect a difference in the underlying nature of PDD and DLB.

Key words: dementia with Lewy bodies; gray matter density, Parkinson’s disease dementia, voxel-based morphometry, white matter density
A comparison of gray and white matter density in patients with Parkinson’s disease dementia and dementia with Lewy bodies using voxel-based morphometry

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I. INTRODUCTION
Parkinson’s disease with dementia (PDD) and dementia with Lewy bodies (DLB) share many clinical and neurobiological similarities, including similar parkinsonian motor symptoms, neuropsychological profiles, and neurochemical and neuropathological characteristics of α-synuclein.1-4 The clinical distinction between PDD and DLB depends on the onset of cognitive symptoms relative to parkinsonian motor symptoms. However, several lines of evidence suggest that PDD and DLB may represent two distinct subtypes even though they have a similar pathological spectrum. The density of Lewy bodies and the burden of Alzheimer’s disease-like pathology are more severe in DLB than PDD.1, 5-7 In addition, cortical atrophy and metabolic patterns are more severe, and cognitive performance is poorer than in DLB in PDD.8,10

Voxel-based morphometry (VBM) is an unbiased whole-brain MR technique capable of detecting regionally specific differences in brain tissue composition,
including gray matter (GM) and white matter (WM). Previous studies comparing brain structure in patients with PDD and DLB using VBM have focused on GM, and the results have been controversial. In the present study we compared GM and WM densities in patients with PDD and DLB using VBM.
II. MATERIALS AND METHODS

Subjects

Participants were prospectively recruited from a university hospital. We enrolled 20 patients with a clinical diagnosis of probable PDD and 18 patients with probable DLB. The diagnosis of DLB was made according to the consensus criteria for DLB. PD and PDD were diagnosed according to the clinical diagnostic criteria of the UK Parkinson’s Disease Society Brain Bank and clinical diagnosis criteria for PDD, respectively. The onset of PD preceded the development of dementias by at least 12 months in all the patients with PDD.

We applied an extensive neuropsychological battery test using the Seoul Neuropsychological Screening Battery (SNSB) to determine cognitive subsets. The SNSB covers the cognitive subsets of attention (forward and backward digit span and letter cancellation test), language and related functions (reading, writing, comprehension, repetition, confrontational naming using the Korean version of the Boston Naming Test (K-BNT), finger naming, right–left orientation, body part identification, calculation, ideomotor and buccofacial praxis), visuospatial function test (drawing an interlocking pentagon and the Rey Complex Figure Test [RCTF]), verbal memory test (three word registration and recall, and the Seoul Verbal Learning Test), visual memory test (the RCFT; immediate recall, 20 min delayed recall and recognition); frontal executive function test (motor impersistence, contrasting program, go-no-go test, fist-edge-palm, alternating hand movement, alternating square and triangle, luria loop, phonemic and semantic Controlled Oral Word Association Test (COWAT), and the Stroop test). The Exclusion criteria included evidence of focal brain lesions by magnetic resonance imaging (MRI) or the presence of other neurodegenerative diseases that might account for the dementia. Possible medical comorbidities were also excluded by laboratory tests, including a thyroid function test, vitamin B12 and folic acid levels, and a VDRL test.
Healthy age- and sex-matched, elderly volunteers were used as controls for VBM analysis. They were recruited from advertisements about the project, or they were healthy relatives of patients with movement disorders or dementia (n=18, age=71.2 ± 6.5 yr). The controls had no active neurological disorders. They had no cognitive complaints with a minimal score of 28 on the Korean version of Mini-Mental State Examination (K-MMSE). Informed consent was obtained from all patients and control subjects and this study was approved by the Institutional Review Board of our hospital.

**MRI acquisition**

All scans of patients with PDD and DLB were acquired using a Philips 3.0-T scanner (Philips Intera; Philips Medical System, Best, The Netherlands) with SENSE head coil (SENSE factor=2). Head motion was minimized with restraining foam pads provided by the manufacturer. A high-resolution T1-weighted MRI volume data set was obtained from all subjects using 3D T1-TFE sequence configured with the following acquisition parameters: axial acquisition with a 224 × 256 matrix; 256×256 reconstructed matrix with 182 slices; 220 mm field of view; 0.98 × 0.98 × 1.2 mm³ voxels; TE, 4.6 ms; TR, 9.6 ms; flip angle, 8°; slice gap, 0 mm.

**Voxel-Based Morphometry of GM and WM**

VBM was conducted using DARTEL in SPM8 software (Institute of Neurology, University College London, London, England). A group GM and WM template was generated from control groups, to which all individual GM was spatially normalized. Spatially normalized GM maps and WM maps were modulated by the Jacobian determinant of the deformation field to adjust volume changes during nonlinear transformation. These modulated GM and WM maps were smoothed using a 6-mm full-width half-maximum...
isotropic Gaussian kernel. Regional volume differences were determined using t statistics at every voxel in the GM and WM from patients with PDD and DLB and healthy controls. Statistical significance was determined at the uncorrected p<0.001 with the cluster size> 50 mm³.

Statistical analysis
The Mann–Whitney and Fisher’s exact tests were used to compare SNSB subscores between patients groups for categorical and continuous variables, respectively. A two-sided $p < 0.05$ was considered to be statistically significant. Statistical analyses were performed using commercially available software (SPSS, Version 13.0).
III. RESULTS

Demographic characteristics

The demographic characteristics of the patients are shown in Table 1. No significant differences were observed between patients with PDD and DLB in age, gender, years of education, duration of cognitive dysfunction, K-MMSE score, or the sum of Clinical Dementia Rating. The duration of parkinsonism was significantly longer in patients with PDD (74.9 ± 60.3 months) than in those with DLB (16.7 ± 11.6 months, p<0.001). At the time of this neuropsychological test, 19 patients with PDD and 7 patients with DLB took dopaminergic medications. For each patient, the levodopa equivalent dose, calculated as described previously\textsuperscript{18} was significantly higher in patients with PDD (586.4 mg) than in those with DLB (171.7 mg, p<0.001). No significant difference was found in the number of patients taking cholinesterase inhibitors (PDD, 20.0% and DLB, 27.7%). At the time the neuropsychological test was administered, 16 patients with DLB had psychiatric symptoms (4 had delusions and 15 had hallucinations) and 7 patients with PDD had psychiatric symptoms (1 had delusion and 6 had hallucinations). Visual hallucinations were more prevalent in patients with DLB than in those with PDD (p=0.001).
Table 1. Demographic characteristics between patients with PDD and DLB

<table>
<thead>
<tr>
<th></th>
<th>PDD (n=20)</th>
<th>DLB (n=18)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>71.9 (5.9)</td>
<td>73.2 (7.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (number of men)</td>
<td>9</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Education durations (yrs)</td>
<td>6.1 (6.1)</td>
<td>7.0 (4.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Parkinsonism duration</td>
<td>74.9 (60.3)</td>
<td>16.6 (11.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cognitive impairment duration (months)</td>
<td>27.5 (35.2)</td>
<td>26.4 (18.6)</td>
<td>NS</td>
</tr>
<tr>
<td>K-MMSE</td>
<td>16.7 (4.8)</td>
<td>15.6 (4.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Orientation</td>
<td>6.1 (2.6)</td>
<td>5.1 (3.1)</td>
<td>NS</td>
</tr>
<tr>
<td>SOB</td>
<td>7.0 (3.4)</td>
<td>8.9 (4.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Psychiatric symptoms, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Delusions</td>
<td>1 (5.0%)</td>
<td>4 (22.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>6 (30.0%)</td>
<td>15 (83.3%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Both</td>
<td>0 (0%)</td>
<td>3 (16.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Levodopa equivalent dose (mg)</td>
<td>586.4 (377.3)</td>
<td>171.6 (228.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Use of cholinesterase inhibitors, n (%)</td>
<td>4 (20.0%)</td>
<td>5 (27.7%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

PDD: Parkinson’s disease with dementia, DLB: dementia with Lewy bodies, K-MMSE: the Korean version of the Mini-Mental State Examination, SOB: the sum of box score of the Clinical Dementia Scale.

Values are expressed as mean (standard deviation), NS; not significant.

**GM analysis**
GM density was significantly decreased in the bilateral dorsolateral prefrontal, temporal, occipital, posterior cingular, and right parietal cortical areas in patients with PDD compared to controls (Fig. 1A). The pattern of decreased GM density in patients with DLB was similar to that in patients with PDD; however, GM atrophy in the patients with DLB was more pronounced, especially in the occipital cortex, and included the bilateral orbitofrontal and left parietal cortices as well as bilateral lentiform nucleus (Fig. 1B). In a comparison between patients with PDD and DLB, GM density was significantly decreased in left occipital, parietal, and striatal areas in DLB than in PDD (Table 2, Fig. 1C). No area was observed where the density of GM was more severely decreased in PDD than in DLB.

Figure 1. Areas of decreased gray matter density in patients with Parkinson’s disease with dementia (A) and dementia with Lewy Bodies (B), compared with healthy subjects, and areas of decreased gray matter density in patients with dementia with Lewy bodies compared with Parkinson’s disease dementia (C). Significant changes were indicated by an uncorrected p<0.001.
Table 2. Anatomic location of areas of reduced gray matter in dementia with Lewy bodies compared with Parkinson disease with dementia

<table>
<thead>
<tr>
<th>Talairach Coordinates</th>
<th>Anatomical location</th>
<th>Voxel-level</th>
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<tr>
<td>x</td>
<td>y</td>
<td>z</td>
</tr>
<tr>
<td>-34</td>
<td>-88</td>
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<td>-24</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>-48</td>
<td>-36</td>
<td>26</td>
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</table>

WM analysis

In patients with PDD, the decrease in WM density was localized in the left posterior temporal, occipital, and prefrontal areas compared to controls (Fig. 2A). In contrast, the patients with DLB exhibited decreased WM density throughout the bilateral temporal, occipital, parietal, and frontal regions compared to controls (Fig. 2B). Thus, the decrease in WM density relative to GM density was more pronounced in patients with DLB. In a comparison between patients with PDD and DLB, WM density was significantly decreased in the bilateral occipital and left occipito-parietal areas in DLB than in PDD (Fig. 2C). No area was observed where the density of WM was more severely decreased in PDD than in DLB.

The change of WM density relative to that of GM density in patients with DLB compared to those with PDD is schematically illustrated in Fig. 3. In patients with DLB compared to those with PDD, the area of WM atrophy (red color) in the occipital areas was more extensive than that of GM atrophy (blue color).
Figure 2. Areas of decreased white matter density in patients with Parkinson’s disease with dementia (A) and dementia with Lewy Bodies (B), compared with healthy subjects, and areas of decreased gray matter density in patients with dementia with Lewy bodies compared with Parkinson’s disease dementia (C). Significant changes were indicated by an uncorrected p<0.001. L; left, R; right

Figure 3. Schematic illustration showing the change of WM density relative to that of GM density in patients with DLB compared to those with PDD. In patients with DLB compared to those with PDD, the area of WM atrophy (light gray color) in the occipital areas was more extensive than that of GM atrophy (dark gray color).
IV. DISCUSSION

Our study demonstrated that patients with DLB had more severe GM and WM atrophy in the occipito-parietal areas than did patients with PDD. In addition, the change of WM density relative to GM density was more pronounced in patients with DLB. Since there was no significant difference in the overall severity of dementia or demographic characteristics between groups, the different patterns of GM and WM density seen in our study may reflect a difference in the underlying nature of these two diseases.

In a recent VBM study, Beyer et al.\(^8\) reported that patients with DLB had more pronounced cortical atrophy in the temporal, occipital, and parietal areas relative to patients with PDD. Our findings are in agreement with those of Beyer and colleagues with the exception that the area of atrophy in our study was not as wide. However, our results are in contradiction with those of Burton et al.\(^11\) who, in a VBM study found no difference in the degree of cortical atrophy between PDD and DLB. Differences in demographic data such as age, duration of dementia, duration of disease onset, or treatment may account for discrepancies between our findings and those of previous VBM studies. In the Beyer et al. study,\(^8\) the patients with PDD had parkinsonism longer (~12 yrs) before developing dementia than did the patients in the Burton et al. study (~7 yrs)\(^11\) and the duration of dementia was significantly shorter in patients with PDD than in those with DLB, which may lead to a less pronounced cortical atrophy in patients with PDD relative to those with DLB because patients with PDD having a shorter duration of parkinsonism prior to dementia are associated with more severe pathological changes.\(^19\) In the present study, no difference was found in the duration of dementia between the PDD and groups, and the duration of parkinsonism in patients with PDD was shorter than Beyer et al. group. This may explain why the area of atrophy in DLB relative to PDD in our
study was not so pronounced compared to Beyer and colleague’s study.

Controversy still exists as to whether PDD and DLB are indeed the same disease entities.

The few neuropsychological studies to directly compare the cognitive profiles of patients with PDD and those with DLB demonstrated that those with DLB had a trend for poorer performance in executive functions, attention or visual recognition memory, whereas other studies reported no difference of cognitive profiles. More severe atrophy in occipito-parietal areas and the lentiform nucleus in our patients with DLB relative to those with PDD may explain why patients with DLB had poorer performance in visual-related cognitive subsets or executive functions. In addition, our finding that visual hallucinations are more prevalent in patients with DLB than in those with PDD may be in line with more severe atrophy in occipital GM and WM in patients with DLB because recent neuropathological studies have suggested that functional or pathological alterations in the temporo-occipital area may underlie visual hallucination. Yamamoto et al. suggested that severe LB pathology in the secondary visual pathway and the inferior temporal cortex in DLB patients may be the cause of visual stimulus-related cognition and visual misidentification. In addition, Harding et al. showed that DLB patients had higher LB densities in the inferior temporal cortex than did PDD patients, and well-formed visual hallucinations are highly correlated with temporal lobe LB.

Another interesting finding in our study is that the degree of atrophy in WM relative to GM differs between patients with PDD and DLB. The degree of WM and GM atrophy was similar in patients with DLB, but patients with PDD exhibited less WM atrophy than GM atrophy. Additionally, the area of WM atrophy relative to that of GM in patients with DLB compared to those with
PDD was extensive in the occipital areas. WM analysis using VBM has a lower sensitivity to detect WM abnormalities because the correlation between WM T1 signal intensities and WM integrity is poor. However, simultaneous application of the same VBM technique using 3T MR in our patients suggests that differences in the degree of WM atrophy relative to GM density in patients with PDD and DLB may reflect the difference in underlying pathomechanism between the two diseases rather than technical problems. Regarding the WM pathology in patients with DLB, Higuchi et al. reported that WM spongiform pathology and gliosis occurred predominantly in the occipital area, and these WM pathologies are an important pathological substrate for decreased glucose metabolism in patients with DLB. Furthermore, in a study using diffusion tensor imaging, Bozzali et al. showed WM abnormalities in frontal, parietal, and occipital areas in patients with DLB. Therefore, it is possible that an unknown factor, which may determine PDD and DLB distinctively, may contribute to difference in the degree of WM pathology in PDD and DLB.

Nevertheless, the pathoanatomical mechanisms underlying the different patterns of GM and WM atrophy in DLB and PDD remain a matter of speculation. According to previous reports, together with more widespread burden of LB densities in DLB patients, more severe β-amyloid burden may lead to the more severe pathological changes in DLB. In particular, in vivo data have demonstrated that the cortical amyloid burden is higher in patients with DLB than in those with PDD. However, the cortical amyloid burden in those studies was not region-specific; therefore it is difficult to explain why the more severe GM and WM pathology exhibited by our patients with DLB was restricted to the posterior cortical GM and WM areas in addition to the lentiform nucleus. In this regard, it is possible that in DLB patients, the interaction of LB showing more severe densities in temporo-occipital areas and
lentiform nucleus\textsuperscript{35} and the $\beta$-amyloid burden may lead to accelerate microstructural alterations in these areas, as suggested by Masliah’s group that $\beta$-amyloid promotes $\alpha$-synuclein aggregation and toxicity in vivo through the stabilization in the formation of hybrid nanopores that lead to neuronal death.\textsuperscript{36, 37}

Some limitations in our study need to be addressed. First, the diagnosis of PDD and DLB was based on clinical consensus criteria rather than on histopathological confirmation. This raises the possibility of misdiagnosis, especially for DLB. However, it is generally agreed that that the specificity of the clinical diagnosis of DLB is high when consensus diagnostic criteria for DLB are used.\textsuperscript{2} We used the clinical diagnostic criteria for PDD suggested by the Movement Disorders Society rather than DSM-IV criteria for the PDD diagnosis. Second, even though the demographic characteristics and overall severity of dementia severity were similar between groups, the sample size was small, and large intragroup variability may have limited the detection of group differences.
V. CONCLUSION

A VBM analysis comparing patients with PDD and DLB demonstrated that GM and WM atrophy were more severe in patients with DLB and that WM atrophy relative to GM atrophy was less severe in patients with PDD. These data may reflect a difference in the underlying nature of PDD and DLB.
REFERENCES


복셀 기준 형태계측법을 이용한 파킨슨병 치매와 루이소체 치매 환자의 회질과 백질 밀도의 비교

<지도교수 이필휴>

연세대학교 대학원 의학과

박보석

파킨슨병 치매와 루이소체 치매 사이에 임상적과 신경정신학적으로 유사함에도 불구하고, 최근의 연구들은 구조적으로나 병리학적인 변화가 루이소체 치매가 파킨슨병 치매보다 더 심하다는 것을 보여주었다. 우리는 복셀 기준 형태계측법을 이용하여 치매의 전반적인 심각도와 인구학적으로 유사한 20명의 파킨슨병 치매 환자와 18명의 루이소체 치매환자들의 회질과 백질의 밀도를 비교하였다. 회질의 밀도는 파킨슨병 치매환자보다 루이소체 치매 환자의 왼쪽 후두엽, 두정엽, 그리고 선조체 부위에서 유의하게 떨어졌다. 백질의 밀도는 파킨슨병 치매환자보다 루이소체 치매 환자의 양쪽 후두엽과 왼쪽 후두-두정엽 부위에서 떨어졌다. 루이소체 치매 환자에서 백질과 회질의 위축 정도는 비슷하였으나 파킨슨병 치매 환자에서는 회질의 위축보다 백질의 위축이 덜 현저하게 나타났다. 파킨슨병 치매환자와 비교하여 루이소체 치매환자에서는 후두엽의 백질의 위축은 회질의 위축보다 더 광범위하였다. 우리의
자료는 파킨슨병 치매환자보다 루이소체 치매환자에서 회질과 백질의 위축이 더 심하다는 것을 보였고 상대적으로 백질은 회질보다 위축의 정도가 덜 심하다는 것을 보여주었다. 이는 파킨슨병 치매와 루이소체 치매사이에 근본적으로 다른 본질이 있다는 것을 반영한다.

핵심되는 말 : 루이소체 치매, 회질 밀도, 파킨슨병 치매, 복셀 기준 형태계측법, 백질 밀도