Morphological change of midbrain measured in fractal dimension analysis correlates midbrain atrophy in patients with dementia with Lewy bodies

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Authors: T. Nakatsuka, H. Kudo, R. Kasai, S. Kasuya, M. Odashima, T. Inaoka, H. Terada; Sakura, Chiba/JP
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Aims and objectives

Dementia with Lewy bodies (DLB), the second most common type of degenerative dementia is pathologically characterized by alpha-synuclein inclusions in the brainstem, subcortical nuclei, limbic and neocortical regions [1, 2]. The central feature of DLB is dementia. Core features are visual hallucinations, fluctuating cognitive impairment and parkinsonism [1]. Clinical symptoms and signs of DLB are sometimes non-specific, so various diagnostic imaging studies are performed for aiding in the diagnosis of DLB.

Nuclear medicine studies of the dopaminergic system are the best studies for evaluating pathological states in DLB; especially $^{123}$I-MIBG myocardial scintigraphy has high specificity and sensitivity for the differential diagnosis of DLB from Alzheimer's disease (AD) [3].

MRI, a non-invasive modality without radionuclides or radiation exposure has been used to rule out non-degenerative diseases causing dementia, such as chronic subdural hematoma, cerebral infarction or normal pressure hydrocephalus. Computer-aided voxel-based morphometry based on MRI has recently been applied to detect early atrophy in degenerative diseases, mainly AD because MRI has exquisite spatial and tissue-contrast resolution [4].

Our group obtained a target volume of interest (VOI) for DLB-specific atrophy in midbrain and pons using the voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) compared to bundled normal database [5]. This software was based on statistical parametric mapping 8 plus diffeomorphic anatomic registration through exponentiated Lie algebra (SPM8 plus DARTEL). We also demonstrated that this target VOI was useful for differentiating DLB from AD. Whitwell et al. and Jubault et al. also demonstrated that the atrophy of dorsal midbrain, pons and medulla in the patients with Lewy body disease, respectively [6, 7]. These findings are consistent with pathological findings indicating that Lewy bodies ascend the brainstem into the midbrain and then to the basal areas of the brain before spreading into the cortex [8, 9].

Takahashi et al., however, demonstrated that there was not DLB-specific atrophy in brainstem using SPM8 plus DARTEL [10]. This inconsistency might arise from various differences; the cluster analyses or variability in the clinical cohorts of DLB. Brainstem atrophy in the patients with DLB may be too subtle to be detected constantly with volumetric analysis.

Shape analysis is another useful technique for identifying morphological change including atrophy on neuroimaging [11-13]. Additional information which is not obtained by volumetric analysis may be acquired with this method [14].

Fractal dimension analysis, which is one of the shape analyses and has increasingly been used in recent years, is to characterize the shape complexity based on self-similarity. The
advantage of this technique is that it enables us to detect very complicated structures using relatively plain computational algorithms. Morphological complexity is quantified and assigned a numerical value, which is expressed as the fractal dimension (FD). Fractal dimension analysis is superior to the conventional volumetric methods in terms of less gender effect and smaller variances [15]. This technique has been applied to various diseases; cerebral FDs in patients with AD, schizophrenia, and multiple sclerosis and cerebellar FDs in patients with MSA-C are statistically different from those of controls [15-19]. To the best of our knowledge, however, neither presence of self-similarity in midbrain nor correlation between FD and volume of midbrain has been evaluated using MRI.

The purpose of our study is to determine whether there’s self-similarity in midbrain on reconstructed axial 3D T1-weighted images or not by means of fractal dimension analysis, and to assess the correlation between the FD and the severity score of atrophy (Z score) of midbrain measured with VSRAD in the patients with DLB with mild midbrain atrophy. We evaluate whether the fractal dimension analysis of midbrain can objectively and quantitatively assess midbrain atrophy in the patients with DLB without complicated algorithms in SPM or SPM-based software.
Methods and materials

The ethics committee of Toho University Sakura Medical Center approved this study and all subjects provided informed consent to participate.

We retrospectively reviewed patients with DLB, who had undergone MRI for detailed examination of dementia from 2009 to 2013. All of the patients with DLB had dementia and spontaneous features of parkinsonism. Some of them had fluctuating cognition with pronounced variations in attention and alertness, recurrent visual hallucinations. As a result, they were diagnosed as possible/probable DLB based on the criteria proposed in the consortium on DLB international workshop [1]. All of the patients revealed reduced H/M ratios on delayed phase of $^{123}$I-MIBG myocardial scintigraphy. This examination was performed for aiding in differential diagnosis of DLB and other diseases manifesting dementia. None of them had asymptomatic old cerebral infarction detected by T2-weighted MRI.

All the patients underwent MRI examinations on a 1.5T Gyroscan (Philips, Best, the Netherlands). One hundred eighty 3D sections of a T1-weighted, magnetization-prepared rapid acquisition of gradient-echo (MPRAGE) sequence were obtained in a sagittal orientation as 1-mm thick gapless sections (FOV 240 mm, TR 9.7 ms, TE 4.6 ms, flip angle 10°, and TI 525 ms).

Using a free software program, VSRAD based on SPM8 plus DARTEL [4], we classified MRIs of all patients into gray matter (GM), white matter (WM), or cerebrospinal fluid images using a unified tissue-segmentation procedure after image-intensity nonuniformity correction, anatomically standardized to a customized template of WM, and then smoothed using an 8-mm full width at half maximum isotropic Gaussian kernel. VSRAD provided statistical Z score images for WM atrophy in each of the patients compared to that of the " normal " database of WM. The Z score was defined as: ((control mean) # [individual value])/(control SD). The " normal " database bundled with VSRAD comprised 80 healthy volunteers (37 men and 43 women), aged 54 to 86 years who underwent 3D T1-weighted MPRAGE sequence using a 1.5T Siemens Vision Plus scanner (Siemens, Erlangen, Germany). Their performance was within normal limits both on the Wechsler Memory Scale - Revised and Wechsler Adult Intelligence Scale - Revised [4]. Their mini-mental state examination (MMSE) scores ranged from 26 to 30; 29.1±1.2. We obtained the averaged positive Z score in midbrain with MRIcroN (http://www.mccauslandcenter.sc.edu/mricro/mricron/).

We excluded the patients without proper segmentation of 3D T1-weighted MPRAGE sequence on VSRAD, without undergoing MMSE or with average Z score of midbrain higher than 1.5 because we only focused on the patients with mild atrophy of midbrain in this study. Thirty-eight patients (male: female; 20:18, age; 76.8±5.7, MMSE score;
21.2±3.9, average Z score of midbrain; 0.69±0.30) were included and proceeded the next analysis.

We reconstructed 3D T1-weighted MPRAGE images as 1mm-isotrophic axial images of midbrain parallel to the anterior commissure - posterior commissure line (AC-PC line) using a free software; ImageJ (http://rsbweb.nih.gov/ij/) (Fig. 1a, 1b, 1c). Then we converted these images to binary images and extracted the midbrain on each axial slice (Fig. 1d, 1e). If aqueduct of the midbrain was depicted, it's filled with brainstem signal intensity (Fig. 1f).

If each axial slice of midbrain was completely divided from surrounding structures, e.g. medial-temporal lobes, we calculated the FD by means of fractal dimension analysis with ImageJ. We selected a box-counting algorithm for fractal dimension analysis (box size; 2, 3, 4, 5, 6, 7, 8, 9, 10) because of the simplicity of implementation (Fig. 2) [16]. The algorithm counted the number of boxes needed to cover the midbrain a given box scale. The scale was changed, and the process was repeated. The FD of midbrain was computed as the ratio of the change in the log of the box count to the change in the log of the box size (see Eq. 1)

\[
D = - \frac{\log \text{box count}}{\log \text{box size}} \quad (1)
\]

If it's impossible to divide midbrain from surrounding structures, the axial slice was excluded from fractal dimension analysis. If it's impossible to divide midbrain from surrounding structures on the image 4mm behind AC-PC line, the case was excluded from fractal dimension analysis.

We performed correlated analyses between each of the FD of axial images (4mm, 5mm and 6mm behind AC-PC lines, maximum and minimum FD in each cases) and the averaged positive Z score in all analyzable patients. To assess self-similarity, the coefficient of determination ($R^2$) of linear regression analyses in box-counting algorithm was calculated. These statistical analyses were performed using Microsoft Excel 2010 software (Microsoft Corp, Redmond, WA, USA).
Images for this section:

Fig. 1: Reconstituent and analytical procedure of MRI in a patient with DLB: a axial 3D T1-weighted image including right mammillary body, b sagittal image of 3D T1-weighted image including right mammillary body, c axial 3D T1-weighted image focusing on midbrain, d binary image focusing on midbrain, e binary image of midbrain (surrounding structures removed), f binary image of midbrain with aqueduct of the midbrain filled with brainstem signal intensity

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**Fig. 2:** A graph of fractal dimension analysis (box-counting method) and a table of fractal dimension analysis with box size and box count.

<table>
<thead>
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<th>3</th>
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</tbody>
</table>

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Results

Thirty patients with DLB (male: female; 15:15, age; 76.4±6.1, MMSE score; 21.0±3.8, average Z score of midbrain; 0.71±0.28) out of 38 patients were eligible for these analyses. Eight patients were eliminated because it’s impossible to divide the midbrain from surrounding structures on the images 4mm behind AC-PC line. The coefficient of determination ($R^2$) of analyzed axial images was 0.997±0.002.

Coefficients of correlation of FD$_4$ (4mm behind AC-PC line), FD$_5$ (5mm behind AC-PC line), FD$_6$ (6mm behind AC-PC line), FD$_{max}$ (maximum FD in each case) and FD$_{min}$ (minimum FD in each case) were -0.36, 0.12, -0.20, -0.62 and -0.02 respectively in these 30 patients (Fig. 3a, 3b, 3c, 3d, 3e). The coefficient of correlation of FD$_{max}$ was the largest among these FDs and statistically significant (p<0.001). Percent standard deviations over mean (%SD) of FD$_{max}$ and Z score were 0.9% and 39.4%, respectively.

The presence of significant brainstem atrophy in the patients with Lewy body disease was variable because this atrophy might be too subtle to be detected constantly with volumetric analysis speculating from the inconsistency of results among previous reports [5-7, 10]. We only enrolled the patients with DLB with mild midbrain atrophy (average Z score of midbrain less than 1.5) in this study to assess whether fractal dimension analysis was an adjunct or in substitution for volumetric analysis or not because pathological background seemed not to be profoundly different among these patients.

The present study demonstrated for the first time that reconstructed axial 3D T1-weighted MPRAGE images of midbrain had self-similarity statistically because the coefficient of determination ($R^2$) was very high in fractal dimension analysis. The presence of self-similarity in definite box size indicates that the fractal dimension analysis of midbrain is effective as previous reports of cerebral fractal dimension analysis showed its usefulness [15, 18, 19].

We also demonstrated that the FDs in designated position (FD$_4$, FD$_5$ and FD$_6$) were not correlated with midbrain atrophy by means of VSRAD because shape of midbrain was influenced by several factors, e.g. age, sex, head position in scanning and so on. On the other hand, the FD$_{max}$ was well correlated with midbrain atrophy and relatively insulated from these factors.

%SD of the FD was smaller than that of Z score in our study, which was consistent to the result of the previous report; FD had smaller variance [15]. These results showed fractal dimension analysis is more stable than volumetric analysis.

Type of disease varied correlations between the FDs and brain atrophy or disease stage on previous reports referring to GM analyses because pathological background
of atrophy and methods to extract GM might strongly influence these results. This inconsistency resulted from a degenerative process, i.e. cortical thinning and widening of sulci (decreased folding area) would have counteracting effects on the measured FD [16]. On the other hand, two reports analyzing WM in the patients with multiple sclerosis and with MSA-C and our research analyzing WM and GM showed the FDs were well negatively correlated with midbrain atrophy. This consistency suggests the hypothesis; morphological change of damaged cerebral, cerebellar WM and midbrain in fractal dimension analysis does not have counteracting effects and proceeds in only one direction regardless of pathological background.

These analyses focused on surface of midbrain on axial images, so other images including CT and T2-weighted MRI would be applied to fractal dimension analysis. Morphological change of midbrain in fractal dimension analysis is influenced by both GM and WM atrophy; we can assess GM and WM atrophy of midbrain directly without segmentation. Axial images of CT and MRI acquired long before would be available for fractal dimension analysis. We can longitudinally assess images acquired more than twice, which is effective for evaluating time-dependent change of disease even if acquired images are conventional, inappropriate for volumetric analysis.

Our study has several limitations. First, the shape of midbrain is influenced by several factors; static magnetic field, spatial resolution, sequences of MRI and software for analysis. We can assess FD change objectively as we acquired 3D T1-weighted images in defined circumstance (the same machine and parameters). To assess variability is necessary to apply it in various conditions. Second, it's impossible to separate midbrain from brain structures around it in more than 20 percent cases (8/38 cases). This value is too large to ignore. To avoid this separation error, we have to try to develop new methods, e.g. performing fractal dimension analysis only for separable surface. Third, we performed MRI routinely without focusing on midbrain in field-of-view, so acquired images of midbrain was small. This indicates the number of voxels covering midbrain was so small that we could not assess the FDs of midbrain in detail. But the number of voxels was proper for fractal dimension analysis, because self-similarity in midbrain was maintained in our study. We will apply this method to healthy controls and other diseases causing dementia in future work.
**Fig. 3:** Correlation between Z score and FD with coefficient of correlation: a FD4, b FD5, c FD6, d FDmax, e FDmin

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Conclusion

Morphological change of midbrain measured in fractal dimension analysis correlates mild midbrain atrophy in patients with dementia with Lewy bodies.
References


