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Quantifying degeneration of white matter in normal aging using fractal dimension

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Abstract

Although degeneration of brain white matter (WM) in aging is a well-recognized problem, its quantification has mainly relied on volumetric measurements, which lack detail in describing the degenerative adaptation. In this study, WM structural complexity was evaluated in healthy old and young adults by analyzing the three-dimensional fractal dimension (FD) of WM segmented from magnetic resonance images of brain. FDs detected in the old were significantly smaller than in the young subjects. Specifically, WM interior structure complexity degenerated in the left hemisphere in old men but in the right hemisphere in old women. Men showed more complex WM patterns than women. An asymmetrical (right-greater-than-left-hemisphere) complexity pattern was observed in the interior and general structures of WM, yet the surface complexity was symmetrical across WM structures of the two hemispheres. WM volumes were also measured, but no significant decline was found with aging. These results suggest that the deterioration of WM complexity is not uniformly distributed between the genders and across brain hemispheres.

Keywords: Box-counting dimension; Fractal dimension (FD); Gray matter; Magnetic resonance imaging; Skeleton; White matter structure asymmetry

1. Introduction

Aging is accompanied by anatomical and functional degenerative adaptations in the nervous system [1]. Among these, age-related brain white matter (WM) degeneration has long been recognized because it interferes with normal communications within the nervous system and disrupts regulatory functions of the nervous system toward various body systems. It has been suggested that age-related WM changes could potentially act as disease-prediction parameters, such as motor function impairments [3,6], cognitive deficits [13,22], depression [25,39], or dementia [27]. Despite the importance of WM structural integrity in maintaining normal body function and its adaptive information in predicting/diagnosing various disorders, reports of accurate assessments of multi-feature brain WM structure in vivo are scarce. This is largely due to the lack of appropriate methods for quantifying different aspects of WM structure.

Brain WM structure has most frequently been studied by magnetic resonance imaging (MRI) using various methods, among which volumetric analysis has most often been

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performed. Volumetric analysis is an appropriate assessment for brain atrophy, but it might not be sensitive enough in characterizing WM structural features and their adaptations. So far, there have been no consistent conclusions regarding whether age or neurological disorders induce brain WM volume reduction. Although some investigators have reported a significant decrease in WM volume with normal aging [17,24,26], others did not see this degenerative change [19,45]. Moreover, the volume measurement only captures one of multiple features of WM structural characterization and reveals very little about adaptations of the features because of limitations of volumetric evaluation in describing nonlinear structures, such as complexity and variability of WM structural organization.

Shape analysis of brain structures has been suggested to provide new information that is not accessible by conventional volumetric measurements [18]. Structural fractal analysis [36] provides one such shape descriptor and is a prominent method in quantifying morphometric complexity and variability of nonlinear structures. (A brief introduction of the fractal concept is provided in Section 2.) Although a relatively large number of fractal studies on brain gray matter (GM) have been reported [5,28,30,32,34,44,48], few such studies have investigated brain WM [9,10,16,33], and these only examined surface (or contour) features of the structure. None has performed three-dimensional (3D) volumetric fractal analysis. Furthermore, there has been no report of fractal analysis of WM structural changes in normal aging.

Recently, we have developed a method that performs simultaneous 3D fractal analysis of three features of brain WM structures (interior structure, surface [interface between GM and WM], and general structure [whole WM voxel set]) with high accuracy and sensitivity [51]. The combination of the three shape representations provides a more comprehensive characterization of WM structures in detecting age- or disease-related human brain WM degenerative adaptations. The purpose of this study was to evaluate complexity and variability alterations of WM in normal aging using the 3D and multi-feature fractal analysis methods. Brain WM volumes were also compared between old and young participants using conventional volumetric techniques.

2. Materials and methods

2.1. Theory of fractal methodology

The fractal concept, first introduced by Mandelbrot [36], provides a useful tool to quantify the inherent irregularity of phenomena. A fractal is any rough and irregular object made of parts that are in some way similar to the whole (self-similarity). It is mathematically defined as any set for which the dimension (fractal dimension [FD]), a continuous function, exceeds the discrete topological dimension. Compared with the topological dimension of conventional geometry, the dimension of fractal geometry is fractional. It serves as an index of morphometric variability and complexity of an object.

The box-counting method [36] is a desirable approach in estimating FD because it can be applied to fractal patterns with or without self-similarity, such as the brain (brain is self-similar only in a certain range of scales and thus not strictly self-similar). Box-counting works by repeatedly covering the fractal image with different-sized boxes (r) and then evaluating the number of boxes (N) needed to cover the fractal completely (Fig. 1A and B). In Fig. 1, two meshes with different-sized boxes (5-pixel and 15-pixel) have been overlaid on a two-dimensional (2D) WM slice (binary image). For the two meshes, a total of 681 boxes (blue boxes in Fig. 1A) and 112 boxes (blue boxes in Fig. 1B) covered the WM pixels completely. The FD is defined in the power-law relationship (Eq. (1)):

$$Nkr^{\mathrm{FD}} \tag{1}$$

where k is a constant. The FD was obtained by a linearly fitting equation (Eq. (2)):

$$\ln N\mathrm{FD} \ln\left(\frac{1}{r}\right) \ln k \tag{2}$$

The range of box sizes is important in the box-counting method since the fractal images we studied are not pure fractals. When the size of an overlaid box is too small, no fractal but only a mosaic from black-and-white voxels can be seen. On the other hand, when the box size is too large, the fractal disappears into the background [38]. The distortion is shown in the linear regression analysis as disturbance of linearity (arrow in Fig. 2). Accurate determination of FD requires the linear part of the function (Eq. (2)). As shown in Fig. 2, the final FD was not the slope of the regression line (2.20) based on data of all the box sizes (dashed line in Fig. 2), but the slope of the regression line (2.39) based on chosen box sizes (solid line in Fig. 2). This regression line (solid line in Fig. 2) represented the linear portion of the function (Eq. (2)), and its slope is FD.

2.2. Shape representation

In shape analysis, appropriate shape representations are extracted using shape descriptors before the shape characterization (e.g., FD) [11]. The criterion of an appropriate shape representation of biological object is that the representation is biologically meaningful and adequately characterizes shape variation. Three shape representations of WM were adopted in the present study—general, surface, and interior (skeleton) structures. General structure, the first representation of the WM shape in the study, was the whole set of WM voxels in the segmented images. The surface was the set of boundary voxels in the WM images. The skeleton represents the interior shape and is the essential structure of the WM. It provides a representation that is as thin as possible and that lies near the middle of the many portions of a shape [11].