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Automated Measurement of Cerebral Cortical Thickness Based on Fuzzy Membership Map Derived from MR images for Evaluation of Alzheimer's Disease

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Abstract— **We have proposed an automated method for three-dimensional (3D) measurement of cerebral cortical thicknesses based on fuzzy membership maps derived from magnetic resonance (MR) images for evaluation of Alzheimer's disease (AD). The cerebral cortical thickness was three-dimensionally measured on each cortical surface voxel by using a localized gradient vector trajectory in a fuzzy membership map. The proposed method could be useful for the 3D measurement of the cerebral cortical thickness on individual cortical surface voxels as an atrophy feature in AD.**

I. Introduction

Alzheimer's disease (AD) is not a normal part of aging, but can seriously affect parts of cerebral cortex that can control thought, memory, and language. The atrophy of the cerebral cortex occurring in early stages of AD is localized to specific regions such as the hippocampus, amygdala, entorhinal area, and medial-temporal cortex [1,2]. Querbes et al [3] reported that patients with AD in early stages can be diagnosed using a normalized thickness index-based criterion. Therefore, radiologists attempt to subjectively estimate the degree of atrophy by analyzing atrophic morphological changes on magnetic resonance (MR) images such as the cerebral cortical thickness, but the subjective diagnosis based on such analysis is not quantitative or reproducible.

Previous methods [4-7] for measuring cortical thickness depended on the accuracy of determination of the boundary between the cerebral cortex and white matter regions. It could be very difficult to determine the boundary in the case of diffuse neuronal cell death, since the edges of white matter regions may be blurred or voxels of the cortex and white matter in the boundary may be mixed, making them appear fuzzy. In addition, past studies have not considered the voxel value information in MR images, which could include the atrophy information in the cerebral cortex. To overcome these issues, we employed fuzzy c-means (FCM) clustering [8-11]. We assumed that the 3D fuzzy membership map in the FCM clustering can express the fuzzy boundary between the cerebral cortex and white matter regions, and the fuzzy framework can incorporate voxel value information related to the AD atrophy.

We have proposed an automated method for measuring the 3D cerebral cortical thicknesses in AD patients based on 3D fuzzy membership maps derived from T1-weighted images, which includes atrophy information in the cerebral cortical regions. In the proposed method, the boundary between the cortical and white matter regions is determined on each cortical surface voxel by using membership profiles on trajectories of local gradient vectors in a fuzzy membership map, so that the white matter regions do not have to be segmented.

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II. Methods and Materials

Figure 1 shows the overall scheme for measurement of the 3D cerebral cortical thickness.

Figure 1. Overall scheme for measurement of the 3D cerebral cortical thickness.

A. Extraction of brain parenchyma

First, the background (BG) and cerebrospinal fluid (CSF) regions were removed from an original T1-weighted image using several threshold values obtained based on a histogram analysis. Next, the brain parenchymal region was extracted based on a brain model matching. The brain parenchymal model image was manually created from a T1-weighted image of a cognitively normal (CN) subject, whose brain seemed to be of average size and shape.

B. Fuzzy membership map for the brain parenchymal region based on a fuzzy c-means clustering

The 3D cerebral cortical thicknesses were measured in a fuzzy membership map space for the brain parenchymal

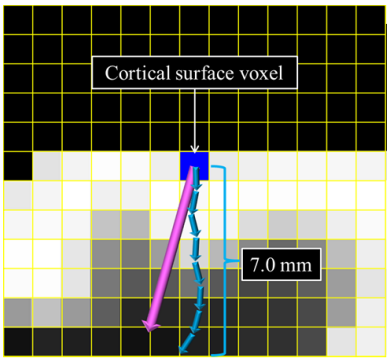

Figure 2. An illustration of a trajectory of local gradient vectors.

region based on the FCM clustering, because the fuzzy membership can represent the phenomenon in which the cerebral cortical voxel value (gray color in T1-weighted MR image) gradually increases from the cortical surface to the white matter surface due to AD. The FCM clustering method assigns a class membership value to each voxel, depending on the similarity of the pixel to a particular class relative to all other classes. In this study, all voxels were assigned two class membership values, i.e., cerebral cortical regions and white matter regions.

C. *Cerebral cortical thickness using a localized gradient vector trajectory in a fuzzy membership map*

We adopted the basic idea of Jones et al [5], in which the cerebral cortical thicknesses were measured by the trajectories of gradient vectors in a virtual electromagnetic field that was constructed to resemble the neuronal sublayers between the cerebral cortical surface and white matter surface. In this study, we employed a fuzzy membership map of the brain parenchyma obtained from the T1-weighted MR image instead of the virtual electromagnetic field. Furthermore, the local gradient vector was calculated by the first-order polynomial within a volume of interest (VOI) for reducing the impact of image noise on the local gradient. The local gradient vectors were almost orthogonal to the isosurface in the fuzzy membership map. The 3D cerebral cortical thickness was measured based on a membership profile using a local gradient vector trajectory in a fuzzy membership map.

First, the global gradient vector was obtained prior to calculation of the local gradient vector by using the following equation:

$$f(x, y, z) = ax + by + cz + d, \quad (1)$$

where $f(x, y, z)$ is the approximated membership value at a location of (x, y, z) in a VOI (9×9×9), and a, b, c and d are constants. The vector (a, b, c) consisting of coefficients in (1) is almost orthogonal to the isosurface of the fuzzy membership map. Therefore, the 3D gradient vector Gg from the surface of a cerebral cortical region to a white matter region is expressed by

$$Gg = (a, b, c). \quad (2)$$

Although the local gradient vector should proceed toward the white matter, the local gradient vectors may proceed in wrong directions away from the white matter due to image noise. Therefore, the global gradient vector was obtained prior to calculation of the local gradient vector, whose direction should be within a 2π solid angle with respect to the global gradient vector. A local gradient vector was calculated based on the first-order polynomial within a VOI (5×5×5) by using the same as (1).

The 3D cerebral cortical thicknesses were measured by using membership profiles on trajectories of local gradient vectors in a fuzzy membership map. A trajectory of the local gradient vector was tracked until the sum of 0.1-mm-long local gradient vectors was 7.0 mm, as shown in Figure 2. A membership profile was constructed as a trajectory of the local gradient vector by connecting the membership value at each terminal point of the local gradient vector from the cortical surface to the white matter regions. The membership value at the terminal point of 0.1-mm-long local gradient vector was calculated by using a linear interpolation method. The membership profile was normalized by setting the membership value at the cortical surface voxel and the minimum value of the profile as 1.0 and 0.0, respectively. Finally, the 3D cerebral cortical thickness at each cortical surface voxel was estimated at a normalized membership value of 0.75 as the boundary between the cerebral cortical and white matter regions. The membership value of 0.75 was empirically determined so that the cerebral cortex could be segmented as accurately as possible for a spherical model with a cortical thickness of 3 mm. This spherical model will be described in a later section.

D. *Segmentation of ten lobar regions*

In order to investigate the regional atrophy at the lobe level, the cerebral cortical thicknesses were separately evaluated in ten lobar regions. For this purpose, ten lobar regions were segmented by registering the lobar model image to each brain parenchymal image by using the affine transform and the free-form deformation (FFD) [12]. The lobar model image was selected from a probabilistic reference model for the human brain at the International Consortium for Brain Mapping (ICBM) website of the Laboratory of Neuro Imaging (LONI) [13].

E. *Spherical brain models for the validation test*

Spherical brain models of known cortical thicknesses were used to evaluate the proposed method. The spherical brain models were of various noise levels and isotropic voxel sizes (resolutions), so that the ability of the proposed method, which would accurately determine cortical thicknesses under a variety of conditions, could be analyzed.

A sphere of a brain model with an inner and outer radii of 37 mm and 40 mm, respectively, in which the cortical thickness was 3 mm, was generated in a fine grid space (1100×1100×1100) with an isotropic voxel size of 0.1 mm^3. The pixel value spatial distribution of the cortical region in the inward direction to the center of the model was modeled by using the following error function:

$$erf(x) = \frac{2}{\sqrt{\pi}} \int_0^x e^{-t^2} dt, \quad (3)$$

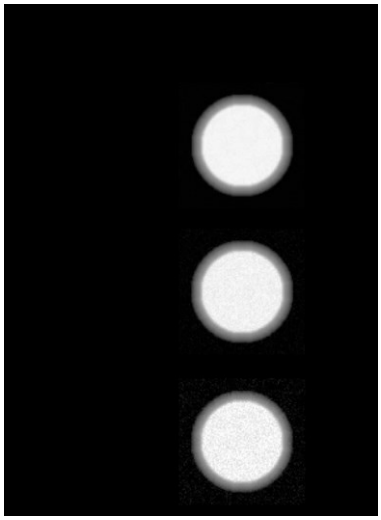

Figure 3. Spherical brain models with three noise levels of 2%, 5%, and 10% used for measurement of the cerebral cortical thicknesses, where the true thickness was 3 mm.

where x is the position in the inward direction. This function increases with the inward direction. Furthermore, brain models with three noise levels were produced by adding the Gaussian random noise to the brain models so that the percentage of standard deviation of Gaussian noise to the mean voxel value in the whole original image can be 2%, 5%, and 10%. The Gaussian noise was generated by converting uniform random numbers with a Box-Muller transform. To evaluate the robustness of the method to the noise, we prepared spherical brain models with three noise levels of 2%, 5%, and 10%. Figure 3 shows the spherical brain models with three noise levels of 2%, 5%, and 10% used for measurement of the cerebral cortical thicknesses, where the true thickness was 3 mm. In addition to the three noise level models, we made two resolution models with voxel sizes of 0.5 mm and 1.0 mm by averaging a certain cubic VOI in order to investigate the impact of the partial volume effect on the proposed method.

F. Clinical cases

This study was approved by an institutional review board of our university. High-resolution T1-weighted MR images of whole brains acquired from 10 clinically diagnosed AD cases (age range: 63-84 years; median: 78.0 years) and 10 CN (67-86 years; 74.5 years) were randomly selected from among outpatients who visited our memory clinic from 2007 to 2008. Seven healthy volunteers were recruited, taking into account age matching with the AD patients, and they gave informed consent to undergo MR examination and for use of the data for research purposes. There was no statistical significant difference ($p = 0.35$) between the AD and CN groups in terms of age. The MMSE scores for AD patients and CN subjects ranged over 11-23 (median: 21) and 27-30 (median: 29), respectively. The 10 AD cases were determined by neuropsychiatrists based on the diagnostic and statistical manual of mental disorders (DSM)-IV criteria for the diagnosis of dementia of the Alzheimer's type. These data were obtained with a 3.0-T MRI scanner (Intera Achieva 3.0 T Quasar Dual R2.1; Philips Electronics, Best, Netherlands) at our university hospital by using T1-weighted 3D turbo field echo (TFE) sequences (time of repetition (TR): 8.3 ms; time of echo (TE): 3.8 ms; time of inversion (TI): 240 ms; flip angle: 8 degrees; sensitivity encoding (SENSE) factor: 2; number of samples averaged (NSA): 1; field of view (FOV): 240 mm x 240 mm). The images were obtained in sagittal planes, and were reconstructed into 150 consecutive transverse slice images with a 1-mm-slice thickness and a matrix size of 240 x 240 pixels. All images were normalized from 0 to 1,023 for voxel value, and preprocessed by a median filter for reduction of noise.

III. Results

A. Spherical brain models

The cortical thicknesses with a voxel size of 0.5×0.5×0.5 mm^3 for spherical brain models with three noise levels of 2%, 5%, and 10% were 3.041±0.212, 3.041±0.210, and 3.040±0.204 mm, respectively. Cortical thicknesses with a voxel size of 1.0×1.0×1.0 mm^3 for the three noise levels were 2.953±0.342, 2.953±0.342, and 2.952±0.343 mm, respectively.

B. Clinical cases

The average cortical thicknesses in the right and left temporal lobes, and the left insula in AD cases were 3.32±0.21, 3.16±0.26, and 2.66±0.23 mm, respectively. The cortical thicknesses for AD cases were significantly thinner than those in the corresponding regions in CN subjects, whose cortical thicknesses were 3.64±0.40, 3.47±0.32 and 3.00±0.41 mm, respectively ($p < 0.05$). Figures 4 and 5 show color-coded maps of cerebral cortical thickness for an AD case and a CN subject produced by the proposed method. The AD case (Figure 4) appears to have a thinner cerebral cortex in the temporal or frontal lobes, compared with the CN subject (Figure 5).

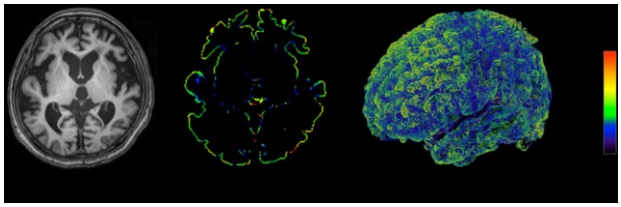

Figure 4. Color-coded map of cerebral cortical thickness for an AD case produced by the proposed method: (a) an original MR image, (b) an axial image, (c) a 3D image.

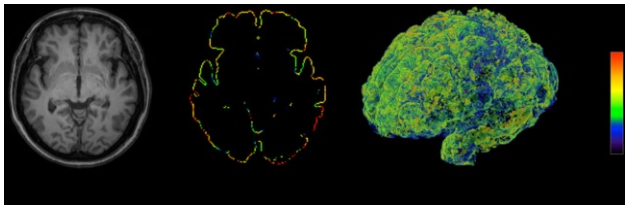

Figure 5. Color-coded map of cerebral cortical thickness for a CN case produced by the proposed method: (a) an original MR image, (b) an axial image, (c) a 3D image.

IV. CONCLUSION

We have developed an automated method for measuring the 3D cerebral cortical thicknesses in Alzheimer's patients using 3D fuzzy membership maps derived from T1-weighted images. The proposed method could be robust against the image random noise, because the 3D cerebral cortical thicknesses were measured by using membership profiles on trajectories of local gradient vectors in a fuzzy membership map. Our results showed that our proposed method was able to provide quantitative and useful information of the AD atrophy. The proposed method could assist radiologists in classification of AD patients by visually showing three-dimensional cortical thicknesses in cerebral lobes separately.

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