Computer-aided diagnosis scheme for detection of Alzheimer's disease in routine CT scan

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Aims and objectives

Introduction

The rapid increase in Alzheimer's disease (AD) patients has become a critical issue worldwide. The World Health Organization estimates there are 35.6 million people in dementia worldwide and the number of people with dementia is expected to double by 2030 and triple by 2050 [1]. AD is the most frequent cause of dementia and has become a major public health concern. Early diagnosis of AD is widely considered to be important as one of the principal goals for AD care.

Recently, neuroimaging examinations, such as amyloid or fluorodeoxyglucose positron emission tomography scanning, or magnetic resonance (MR) imaging have reliably contributed to early diagnosis of AD. However, these examinations remain very expensive for detecting AD. Computed tomography (CT) scan, which is better in its cost and availability than MR imaging, could be suitable for detecting AD, if CT scan was more reliable for diagnosis of AD.

In AD patients, the decrease of the medial temporal lobe (MTL) that includes hippocampalus, parahippocampal gyrus, and entorhinal cortex is usually recognized. The MTL atrophy causes the enlargement of the temporal horn of the lateral ventricle (THLV) adjacent to the MTL. Enlargement of the THLV on CT or MRI images has been reported as an accurate diagnostic marker of AD [2-5].

In this study, we present a z-score-based semi-quantitative analysis of the volume of the THLV so as to detect AD on CT images. We have developed the z-score method based on a voxel-by-voxel analysis for CT images [6, 7]. We examined the accuracy of this method for evaluating the volume of the THLV, and evaluate the performance of this method for detecting AD on CT images.
Methods and materials

Data selection

The study protocol was approved by our institutional review board and patient informed consent was not required.

Thirty-eight AD patients (female:men = 27:11; mean age, 76.8 years; age range, 60 - 88 years) and 33 controls (female:men = 23:10; mean age, 73.7 years; age range, 62 - 82 years) were selected from CT files of Sendai city hospital in Japan for this study. We selected the 38 patients with a clinical diagnosis of AD according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV). The MMSE scores and the Neurobehavioural Cognitive Status Examination scores for the AD patients were 11 - 23 (mean, 18.2) and 34 - 87 (mean, 66.3), respectively. The 33 controls were excluded by using the DSM-IV. These controls had headache (n=21), depression (n=9), delirium (n=1), delusional disorder (n=1), and personality change (n=1).

All images were acquired with a two-section multidetector CT scanner (Spirit; Siemens Medical Solutions, Forchheim, Germany). All images were reformatted in contiguous sections of 5 mm thickness. CT images from an additional normal 40 subjects [10] were used to create a normal reference database for the z-score mapping. The mean age of the normal subjects was 41.6 years (age range, 30-60 years).

Semi-quantitative analysis method for THLV volume using the z-score mapping

The semi-quantitative analysis method consists of four steps, i.e., anatomic standardization, construction of a normal reference database, calculation of a z score, and calculation of the mean z score in a VOI (regional mean z score). The regional mean z score was used as an index of THLV volume. Figure 1 shows a flowchart of the z-score-based semi-quantitative analysis of the volume of the THLV.

First, for anatomical standardization, all CT data were transformed into a standard brain atlas by use of Statistical Parametric Mapping 2 (SPM2) software (The Welcome Department of Cognitive Neurology, London, United Kingdom) (Fig. 2). Second, a normal reference database was constructed (Fig. 3). Third, z score was calculated at each voxel (Fig. 4). In the fourth step, two VOIs that covered the regions of the right and left
THLV were created at the normalized coordinate. Figure 5 shows parts of the two VOIs superimposed on normalized averaged images of the 40 normal controls. Finally, the two VOI masks were automatically applied to the z-score dataset obtained from the z-score mapping. Within each VOI, all z-score values higher than or equal to 0 were extracted and the regional mean z score was calculated in the VOI.

The accuracy of the proposed method for evaluating the volume of the THLV was examined using the relation between the regional mean z score and the reference THLV volume. CT scans from 50 subjects with THLVs of varying size were retrospectively evaluated for this study. The volume (the number of voxels) of the THLV was also manually determined by two neuroradiologists (reference volume). As a result, the quadratic polynomial regression equation demonstrated a statistically significant correlation between the regional mean z score and the reference volume of the THLV ($R^2 = 0.94; P < 0.0001$; Fig. 6). The proposed method was found to have the potential to quantitatively evaluate the volume of the THLV.

**Performance evaluation**

We applied the z-score-based semi-quantitative analysis method to the 38 AD patients and the 33 controls, resulting in 71 averaged z scores (38 AD and 33 controls).

The difference in the averaged z scores between the AD group and the control group was compared by using nonparametric Mann-Whitney $U$-test. Receiver operating characteristic (ROC) analysis was applied to evaluate the performance of the z-score-based semi-quantitative analysis method for detecting AD.
Fig. 1: Flowchart of the z-score-based semi-quantitative analysis of the volume of the THLV.

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**Statistical Parametric Mapping 2 (SPM2) software**
(The Welcome Department of Cognitive Neurology, London, UK)

1. Spatially normalize a CT data set to a standard atlas.
2. Smooth the normalized CT data set.

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**Fig. 2:** Anatomical standardization using statistical parametric mapping.

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**Fig. 3:** Normal reference database for z-score mapping. Normal 40 subjects were used to create a normal reference database for the z-score mapping. The mean age of the normal subjects was 41.6 years (age range, 30-60 years).

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**Fig. 4:** Calculation of z score for input CT data.

\[ z_{score(x,y,z)} = \frac{Mean_{(x,y,z)} - Input_{(x,y,z)}}{SD_{(x,y,z)}} \]

- **Mean**: a mean of a normal controls
- **Input**: a value of normalized patient data
- **SD**: a standard deviation of a normal controls
**Fig. 5:** Determination of VOI. The two VOIs superimposed on the normalized averaged images of the 40 normal controls. Black curves indicate the contour of the VOIs.

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Fig. 6: Relation between the mean z score and the reference volume of the THLV.

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Results

Figure 7 shows a box-and-whisker plot in the distribution of the averaged \( z \) scores for the 38 AD patients and the 33 controls. The median values of the averaged \( z \) scores for the AD patients and the controls were 1.67 and 1.04, respectively, indicating a significant difference (\( P < .0001 \)).

Figure 8 shows the ROC curve for distinction between the 38 AD patients and the 33 controls. The AUC value was 0.846.

Examples for the proposed method for the volume of the THLV applied to the AD patients are given in Fig. 9.
**Fig. 7**: Distribution of the averaged z scores for the 38 AD patients and the 33 controls. Box-and-whisker plot shows the distribution of averaged z score between the AD patients and the controls. The horizontal line in each box represents median value of the averaged z score. A circle indicates the outlier. A half of whole data lie in side of two boxes, and a total of 99% of the data lie in side of the ranges of the whiskers.

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Fig. 8: The ROC curve for distinction between the 38 AD patients and the 33 controls.

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**Fig. 9:** Example images from patients with AD. The top row shows that original CT images present parts of THLVs. The bottom row shows that z-score maps present high z scores in areas corresponding to the THLVs within registered VOIs (areas surrounded by white lines). A) A 74-year-old-man (z score, 0.99; MMSE score, 19). B) A 81-year-old-man (z score, 2.06; MMSE score, 23). C) A 60-year-old-man (z score, 2.13; MMSE score, 20). D) A 82-year-old-man (z score, 2.52; MMSE score, 23).

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Conclusion

We presented the z-score-based semi-quantitative analysis method to assess enlargement of the THLV for the diagnosis of AD. Our results indicates that this method has the potential to discriminate AD patients form control.

The structures of the MTL are affected in the early stage of AD [8, 9]. The atrophy of the MTL, which contains the hippocampus, the parahippocampal gyrus and the entorhinal cortex, are recognized in patients with mild cognitive impairment (MCI) and AD on MR images [10-15]. Thus, volumetric MR imaging measurements of these regions can identify patients with MCI and AD [10-15]. The degree of atrophy of the MTL has been found to be nearly identical to that of enlargement of the THLV [16]. Therefore, the z score of our computerized method for THLV volume would indirectly represents the degree of the MTL atrophy on CT images.

The enlargement of the THLV is presented in not only AD but also other dementias (e.g., dementia with Lewy bodies and frontotemporal lobar degeneration). Although the z-score-based method can distinguish AD patients from normal subjects, this method may not differentiate patients with between AD and the other dementias. In clinical use, physicians should essentially diagnose dementia based on a patient's clinical manifestation, additionally using the result of the z-score-based method applied to the patient to increase their confidence for the diagnosis as a reference.

In conclusion, the results obtained from this study showed that the z-score-based semi-quantitative analysis of the volume of the THLV has the potential to detect AD in routine CT scan.
References

