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Classification of diffusion tensor images for the early detection of Alzheimer's disease

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ABSTRACT

Early detection of Alzheimer's disease (AD) is important since treatments are more efficacious when used at the beginning of the disease. Despite significant advances in diagnostic methods for AD, there is no single diagnostic method for AD with high accuracy. We developed a support vector machine (SVM) model that classifies mild cognitive impairment (MCI) and normal control subjects using probabilistic tractography and tract-based spatial statistics of diffusion tensor imaging (DTI) data. MCI is an intermediate state between normal aging and AD, so finding MCI is important for an early diagnosis of AD. The key features of DTI data we identified through extensive analysis include the fractional anisotropy (FA) values of selected voxels, their average FA value, and the volume of fiber pathways from a pre-defined seed region. In particular, the volume of the fiber pathways to thalamus is the most powerful single feature in classifying MCI and normal subjects regardless of the age of the subjects. The best performance achieved by the SVM model in a 10-fold cross validation and in independent testing was sensitivity of 100%, specificity of 100% and accuracy of 100%.

1. Introduction

In general, Alzheimer's disease (AD) is the main cause of dementia and the diagnosis of AD is important for efficient treatment [1]. Mild cognitive impairment (MCI) is an intermediate disease between normal and AD [2]. Not all MCI patients progress to develop AD – the rate of MCI to AD is much higher than from normal cognition to AD (the rate of MCI progressing to AD is 10–15% per year and that of normal to AD is 1–2% per year) [2]. These facts show that the diagnosis of MCI is very important for the diagnosis of AD and dementia.

Past studies of MCI mostly employed functional magnetic resonance imaging (fMRI) [3,4]. However, studies using fMRI do not account for the damage of nerve fibers according to the progression of disease. Diffusion tensor imaging (DTI) can provide varied information of nerve fibers through analysis of the diffusion of water molecules. Thus, DTI data has gained attention in recent studies [5–7] because of the availability of analysis for nerve fibers and regional connectivity in the human brain. However, it is not easy to align DTI images from multiple subjects and the choice of spatial smoothing extent is somewhat arbitrary. Tract-based spatial statistics (TBSS) resolves the problem by non-linear registration and projection onto a tract representation called the skeleton [8].

The DTI data shows various patterns between individuals, so distinguishing the DTI data of MCI and AD patients from those of normal elderly people is challenging. Thus far, selection of a region of interest, tractography, and registration for individual anisotropy maps have been commonly used in many studies of DTI data [9], but TBSS is becoming a popular method in studies of DTI data. For example, Haller et al. [10] used TBSS to classify MCI subtypes and the classification accuracy is 97%. The results of our previous study [11] showed that the fiber pathways of AD subjects tracked by the FMRIB Software Library (FSL) [12] are distributed over a wider range than those of normal controls (NC). Previous studies by others [13,14] reported that fractional anisotropy (FA) values of Alzheimer's disease (AD) subjects tend to be lower than those of NC subjects in several regions of white matter. These findings suggest the potential to improve the diagnostic accuracy of MCI in addition to AD.

In this study, we developed a support vector machine (SVM) model that classifies MCI and NC using probabilistic tractography and TBSS analysis of DTI data. From the brain region that typically shows significantly different FA values between MCI and NC groups, we randomly selected a fixed number of voxels. The SVM model uses the FA values of the selected voxels, their average FA value, and the volume of fiber pathways to predict MCI. Haller et al. [6] and O'Dwyer et al. [7] also used support vector machines to classify DTI data of MCI and healthy controls. The classification accuracy of Haller's method was 91% and that of O'Dwyer et al. was 93%, both of which are lower than ours.

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2. Materials and methods

2.1. Dataset

We collected a total of 84 DTI data from the LONI Image Data Archive (http://ida.loni.ucla.edu). Forty data (20 MCI, 20 NC) out of the 84 DTI data were used for cross validation and for building a prediction model (Table 1). The average age of 20 MCI subjects is 67.2 years and that of 20 NC subjects is 66.9 years. Thirty eight DTI data (19 MCI, 19 NC) were collected from subjects between 40 and 80 years to test the prediction model on new data of various ages. The remaining 6 DTI data (all NC of age 19) were used to assess using a pre-defined seed region determined from other subjects.

The DTI data of MCI groups were generated from the Alzheimer's Disease Neuroimaging Initiative (ADNI) project of LONI with the following parameters: field strength = 3.0 T; flip angle = 90°; $b = 1000$ s/mm^2; gradient directions = 41; pixel size = 1.36×1.36 mm^2; repetition time (TR) = 9050 ms; echo time (TE) = 62.8 ms; slice thickness = 2.7 mm; matrix = 256×256.

The DTI data of NC groups were generated from the International Consortium for Brain Mapping (ICBM) project of LONI with the following parameters: field strength = 1.5 T; flip angle = 90°; $b = 1000$ s/mm^2; gradient directions = 35; pixel size = 1.25×1.25 mm^2; TR = 6400 ms; TE = 83 ms; slice thickness = 2.5 mm; matrix = 192×192.

The DTI data were generated from two different projects, and had different dimensions for the two groups (256×256 for MCI, 192×192 for NC). To make their sizes comparable, we mapped the DTI data to the standard space using FMRIB's non-linear image registration tool (FNIRT) [15]. After the non-linear registration, the DTI data of the two groups have the same size. Brains are so variable in shape and size that a point-to-point correspondence across any two brains does not exist even in the same brain over time [16]. Registration of brain images to one another or to a template enables one to determine correspondence across brains [16]. Many image registration methods have been developed so far, and FMRIB's non-linear image registration tool (FNIRT) used in our study is known to be within the top three rankings in permutation test ranking and indifference-zone ranking of registration methods [16].

Table 1
Summary of 84 DTI data. The data are represented as mean ± SD (standard deviation).

	Cross validation		Prediction		EX2 and EX3
	MCI (20)	NC (20)	MCI (19)	NC (19)	NC (6)
Age (years)	67.2 ± 5.9	66.9 ± 6.3	76.8 ± 4.0	49.5 ± 6.6	19 ± 0
Gender (F/M)	7/13	18/2	10/9	8/11	4/2
DTI matrix	256×256	192×192	256×256	192×192	192×192

2.2. DTI processing

Fig. 1 shows the process of tract-based spatial statistics (right column) and probabilistic tractography. For this study, we used the FSL developed by Oxford Center for Functional MRI of the Brain (FMRIB Center). First, we removed distortions of eddy currents and head motion in DTI data. From the corrected image, a standalone 3D image with no diffusion was extracted for use as a reference image. From the reference 3D image, we removed the skull part using the Brain Extraction Tool (BET) [17] to obtain a pure brain and then generated an FA map from a tensor-model fit in FSL. We detected crossing-fiber voxels by the Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques (BEDPOSTX) [18].

2.3. Probabilistic tractography with tract-based spatial statistics

To perform probabilistic tractography, we identified a seed region using TBSS. Different subjects have different brain sizes, so their brain images should be transformed into one coordinate system for comparison. For image registration, we used the standard 1 mm isotropic FA image (FMRIB58_FA) provided by FLS and warped all data to the standard space. After the image registration, transformed brain images have the same size but have different shapes of white matters. Thus, we averaged the aligned FA images to create a mean FA image, and then thinned them to create the mean FA skeleton (Fig. 2). The skeleton consists of the voxels with the highest FA value, representing the common white matter tracts to all subjects. The aligned FA images of all subjects were projected onto the mean FA skeleton.

Since all FA images are mapped to a skeleton, it is possible to perform voxel-wise statistical analysis. To identify significant regions of voxels, we used a one-tail t-test in TBSS. After the t-test in each voxel, two contrast-images (AD > NC and NC > AD

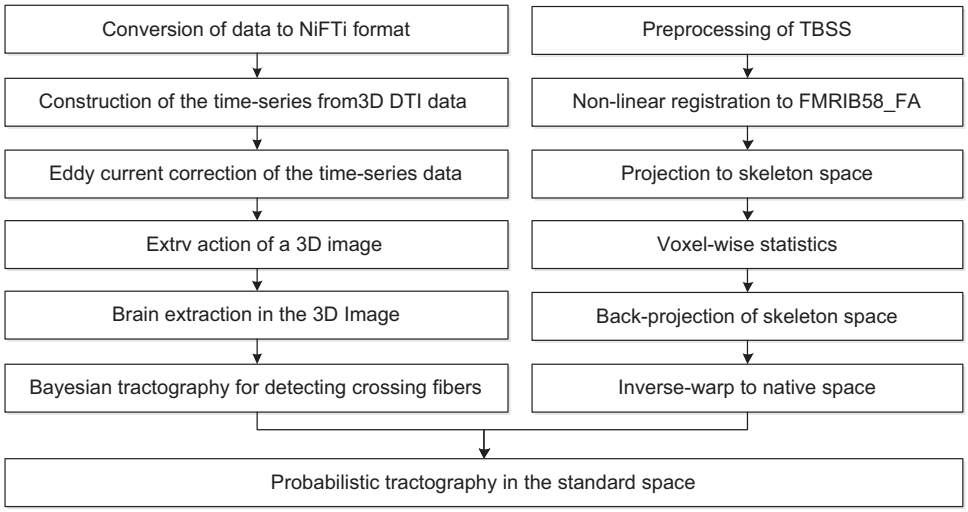

Fig. 1. The process of obtaining fiber pathways from DTI data. After the initial DTI data is converted and corrected, we obtain a pure brain image, FA map and a multi-fiber diffusion model (steps in the left column). We then identify a seed region using TBSS (steps in the right column), which was used to track fiber pathways in probabilistic tractography.