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Automated detection of pathologic white matter alterations in Alzheimer's disease using combined diffusivity and kurtosis method

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ABSTRACT

Diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI) are important diffusion MRI techniques for detecting microstructure abnormities in diseases such as Alzheimer's. The advantages of DKI over DTI have been reported generally; however, the indistinct relationship between diffusivity and kurtosis has not been clearly revealed in clinical settings. In this study, we hypothesize that the combination of diffusivity and kurtosis in DKI improves the capacity of DKI to detect Alzheimer's disease compared with diffusivity or kurtosis alone. Specifically, a support vector machine-based approach was applied to combine diffusivity and kurtosis and to compare different indices datasets. Strict assessments were conducted to ensure the reliability of all classifiers. Then, data from the optimized classifiers were used to detect abnormalities. With the combination, high accuracy performances of 96.23% were obtained in 53 subjects, including 27 Alzheimer's patients. More highly scored abnormal regions were selected by the combination than alone. The results revealed that more precise diffusivity and complementary kurtosis mainly contributed to the high performance of the combination in DKI. This study provides further understanding of DKI and the relationship between diffusivity and kurtosis in pathologic white matter alterations in Alzheimer's disease.

1. Introduction

Structural changes in brains affected by Alzheimer's disease (AD) are important contributors for identifying cognitive decline and pathological developments, including the abnormal diffusion properties of tissues caused by axonal myelin sheath degradation, changed membrane permeability and cerebral atrophy (Chopra et al., 2011; Hahn et al., 2013). Diffusion tensor imaging (DTI) is a conventional technique to measure the microstructure of brain tissue and has been widely used in the clinic. However, as only one principle orientation is confirmed in every voxel because of DTI's Gaussian diffusion assumption, diffusion kurtosis imaging (DKI) (Hui et al., 2008; Jensen et al., 2005) has been put forward and developed as one of the new diffusion MRI techniques beyond DTI. DKI is also a comprehensible extension of DTI when kurtosis measurements are additionally introduced as non-Gaussian quantifications for the deviations from Gaussian diffusion. DKI is proposed as being highly sensitive to micro-changes in tissues and has the potential for early diagnosis of diseases such as Alzheimer's (Cheung et al., 2009; Hui et al., 2008; Struyfs et al., 2015).

DKI is increasing in popularity, and clinical research using DKI has been conducted for conditions such as AD (Gong et al., 2014; Yuan et al., 2016), multiple sclerosis (Yoshida et al., 2013), stroke (Weber et al., 2015), prostate cancer (Roethke et al., 2015), Parkinson's disease (Giannelli et al., 2012) and traumatic brain injury (Zhuo et al., 2012). Those studies generally support the hypothesis that DKI has greater potential in abnormality detection than DTI with non-Gaussian measurement (Lazar et al., 2008; Lu et al., 2006; Wu and Cheung, 2010). DKI provides kurtosis tensor and diffusion tensor simultaneously, and the kurtosis tensor is assumed to supplement the diffusion tensor in describing the microstructure (Roethke et al., 2015; Weber et al., 2015; Yoshida et al., 2013; Yuan et al., 2016). Nonetheless, the advantages of DKI, including measuring kurtosis and diffusivity, have not been directly clarified. Most research in DKI has performed analyses or comparisons of the diffusivity and kurtosis indices separately. Although a complementary relationship between diffusivity and kurtosis information has been proposed, no direct evidence has demonstrated it clearly and properly. Considering the complementarity, we think that the combination or fusion of these two types of measurements would

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markedly promote and uncover the potential advantages of DKI from a novel viewpoint.

Machine Learning (ML)-based approaches have been widely used in the detection of AD based on neuroimaging data. ML can capture and uncover the multivariate relationships or patterns among high-dimensional features. ML is also a powerful tool for computational automatic diagnosis (CAD) that can improve prediction accuracy by complementing the neuropsychological assessments performed by expert clinicians (Alves et al., 2015; Blockx et al., 2012; Nakaaki et al., 2013). Furthermore, ML is particularly sensitive to the distribution of disease-specific changes hidden within image data, which are difficult to identify using conventional single index statistics (Blockx et al., 2012). Thus, an ML-based approach can be used to combine diffusivity and kurtosis in pathologic detection. Additionally, to our knowledge, there is no DKI research underway using an ML-based approach in the diagnosis of any nervous system disease.

The following hypothesis is addressed in this paper: the fusion or combination of diffusivity and kurtosis information in DKI improves the sensitivity and specificity of detecting AD compared with diffusivity or kurtosis alone. There were 53 subjects (27 Alzheimer's patients and 26 normal healthy controls) and 23 manually defined regions of interest (ROIs) involved in this study. To investigate how multiple indices of diffusivity or kurtosis can be used in conjunction, a Support Vector Machine (SVM)-based ML approach was adopted for the classification of control and AD subjects. Several aspects of the classifier were considered to access reliability and pathological relevance, including classification accuracies, permutation tests, receiver operator characteristic curves and regression analyses. We first compared the performance of diffusivity indices derived from DTI and DKI. Second, we analyzed the difference in pathological detection between diffusivity and kurtosis alone. Third, we expected that the combination of diffusivity and kurtosis with an SVM-based approach would reach a dramatic performance in pathological detection.

2. Materials and methods

2.1. Participants

A total of 56 participants, 29 patients with Alzheimer's disease (AD) and 27 age-matched normal controls (NCs), were recruited. The approval to carry out the study was obtained from the ethics committee of Tianjin First Central Hospital, China. All participants provided written informed consent in accordance with the Human Research Committee guidelines, and all AD patients were informed and provided their consent with the help of their families or guardians. The examination of every participant included an informative interview, medical history, structural MRI and neuropsychological assessment test, consisting of the cognitive behavioral assessment scale of the Mini-Mental State Examination (MMSE, Chinese version, education corrected), Montreal Cognitive (MOCA) and Clinical Dementia Rating (CDR). The cognitive profiles of the AD patients were assessed using a battery of validated neuropsychological tests. The inclusion criteria for the AD group were as follows: (i) the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for AD; and (ii) cognitive assessment scales with MMSE $\leq$ 23, MOCA < 26, 1 $\leq$ CDR $\leq$ 2. The inclusion criteria for the normal control group were as follows: (i) no evidence of dementia or MCI; and (ii) MMSE $\geq$26, MOCA $\geq$ 26, CDR = 0. All the participants were additionally examined for the absence of vascular and mixed dementia, depression and anxiety using the Hachinski Ischemic Score (HIS) < 4, Hamilton Depression Scale < 7 and Hamilton Anxiety Scale < 6. Two AD patients were excluded because of incompatibility with the inclusion criteria. One of the normal controls was removed because of subject head motion. Finally, 27 AD and 26 normal control cases were included. The demographic and neuropsychological information of the AD and NC groups in this paper is shown in Table 1.

Table 1
Participant characteristics.

	AD (n = 27)	NC (n = 26)	*p*-value
Gender (m/f)	13/14	11/15	0.427[a]
Age (year)	66.5 ± 7.7	66.0 ± 8.1	0.843[b]
Education (year)	10.9 ± 2.6	10.7 ± 2.4	0.821[b]
MMSE	19.5 ± 2.8	28.5 ± 0.9	0.000[b]
CDR	1.4 ± 0.4	0	–

[a] Chi-squared test
[b] Two-sample *T*-test

2.2. Data acquisition

A 3.0 T MRI scanner (Siemens, Trio) was used for diffusion weighted imaging (DWI) acquisition with pulsed gradient spin-echo planar imaging sequences with TR/TE = 10800 ms/103 ms. Images were acquired for a 128 × 128 matrix per slice with a resolution of $1.8 \times 1.8 \times 1.8$ mm^3. Seventy-three transverse slices with no gaps were acquired for complete brain coverage. Diffusion weighted gradients were applied in 30 non-collinear directions for each of the two diffusion weighted *b*-values 1000 s/mm^2 and 2000 s/mm^2. The b = 0 s/mm^2 image without diffusion weighting was also acquired. For co-registration and structure information, 3D T1-weighted anatomical images were obtained using a magnetization-prepared rapid-acquisition gradient echo (MP-RAGE) sequence with the parameters: TR/TE = 1900 ms/2.5 ms, TI = 100 ms, flip angle = 9°, FOV = 256 × 256 mm^2, matrix = 256 × 256 mm^2, ensuring = 1 × 1 × 1 mm^3.

2.3. Diffusivity and kurtosis mapping

For strict control of the image quality, several examinations were conducted. First, a visual quality assurance (QA) check (2 years of experience) on all data was conducted to check for gross image artifacts, such as "Venetian blinds" and severe slice dropouts covering more than half of a slice. After the visual check, an automated QA was also performed by running a slice-wise correlation check within the software DTIPrep (Oguz et al., 2014). This test detects intensity abnormalities and/or motion between different gradients and interleaved parts within one gradient image volume (Oguz et al., 2014). One normal control sample was rejected in this automated QA procedure. Subsequently, eddy current and motion correction were performed using FSL-eddy (FMRIB Software Library v5.0, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl/) (Andersson and Sotiropoulos, 2015; Jenkinson et al., 2012). The quality of the eddy-current and motion-corrected images was considered satisfactory if the residual motion was below 2 mm for translation and 0.5 degrees for rotation between consecutive DWIs (Liu et al., 2010). In the eddy procedure of FSL, the b-matrix was reoriented after motion correction to match the affine registration for more accurate tensor estimations (Leemans and Jones, 2009). Then, DKE (diffusion kurtosis estimation, http://academicdepartments.musc.edu/cbi/dki/dke.html) software was used for DKI indices calculation. As reported in Van Hecke et al. (2010), the Gaussian kernel-smoothing filter can maintain specificity. All images were smoothed with an FWHM of 2.25 mm (1.25 times the voxel size).

According to previous methods (Cheung et al., 2009; Hui et al., 2008), DKI-derived kurtosis parameters (mean kurtosis, MK; axial kurtosis, AK; and radial kurtosis, RK) and diffusion parameters (mean diffusivity, MD; axial diffusivity, AxD; radial diffusivity, RD; and fractional anisotropy, FA) (Fig. 1) were calculated (Cheung et al., 2009; Hui et al., 2008) with the 61 volumes in the DKE software (diffusion kurtosis estimation, http://academicdepartments.musc.edu/cbi/dki/dke.html) using the CLLS-QP (constrained linear least squares-convex quadratic programming) algorithm (Lazar et al., 2008). Addi-