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Diffusional kurtosis imaging of cingulate fibers in Parkinson disease: Comparison with conventional diffusion tensor imaging

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ABSTRACT

Objective: The pathological changes in Parkinson disease begin in the brainstem; reach the limbic system and ultimately spread to the cerebral cortex. In Parkinson disease (PD) patients, we evaluated the alteration of cingulate fibers, which comprise part of the limbic system, by using diffusional kurtosis imaging (DKI).

Methods: Seventeen patients with PD and 15 age-matched healthy controls underwent DKI with a 3-T MR imager. Diffusion tensor tractography images of the anterior and posterior cingulum were generated. The mean kurtosis (MK) and conventional diffusion tensor parameters measured along the images in the anterior and posterior cingulum were compared between the groups. Receiver operating characteristic (ROC) analysis was also performed to compare the diagnostic abilities of the MK and conventional diffusion tensor parameters.

Results: The MK and fractional anisotropy (FA) in the anterior cingulum were significantly lower in PD patients than in healthy controls. The area under the ROC curve was 0.912 for MK and 0.747 for FA in the anterior cingulum. MK in the anterior cingulum had the best diagnostic performance (mean cutoff, 0.967; sensitivity, 0.87; specificity, 0.94).

Conclusions: DKI can detect alterations of the anterior cingulum in PD patients more sensitively than can conventional diffusion tensor imaging. Use of DKI can be expected to improve the ability to diagnose PD.

1. Introduction

Parkinson disease (PD)—the most common human neurodegenerative disorder after Alzheimer disease [1]—is classically characterized by resting tremor, slowness of initial movement, rigidity, and general postural instability. PD has a prevalence of approximately 1% of the population older than 60 years. The primary pathologic changes involve loss of midbrain dopaminergic neurons in association with the presence of α-synuclein-immunoreactive inclusions in the cytoplasm of neurons (Lewy bodies) and within neuronal processes (Lewy neurites) elsewhere [2–5]. The presence of Lewy-related aggregations is required for neuropathologic confirmation of the clinical diagnosis. These intracerebral neuropathological changes begin in the dorsal motor nucleus of the vagal nerve and anterior olfactory nucleus; spread to the limbic system and forebrain; and finally reach the neocortex [2–5].

Thus far, conventional magnetic resonance imaging (MRI) has been unsuccessful in evaluating these pathophysiologic changes in PD, even in cases of long disease duration. In contrast, advanced MRI techniques such as diffusion tensor imaging (DTI) have enabled the assessment of changes in PD at the microstructural level in vivo [6–11]. Specifically, DTI has enabled researchers to assess white matter integrity and thus demonstrate disruption of neural tracts. In a recent study, Vaillancour et al. reported that PD patients could be completely distinguished from controls on the basis of reduced fractional anisotropy (FA) values in the caudal part of the substantia nigra [10]. In another study, DTI using region-of-interest (ROI) analyses revealed changes in FA in the cingulate fibers in PD patients relative to controls [12]. Karagulle et al., by using statistical parametric mapping analysis in conjunction with DTI, observed decreased FA bilaterally in the frontal lobes, including the supplementary and presupplementary motor areas as well as the cingulate fibers, in PD patients relative to controls [8]. Similarly, Kamagata et al. found reduced FA in the cingulate fiber tracts in PD patients relative to controls [6]. However, in a recent study using tract-based

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spatial statistics, Hattori et al. reported that FA values were not significantly altered in the cerebral white matter in PD patients without dementia relative to control subjects [11,13]. Wiltshire et al. used DTI to investigate the cingulum and corpus callosum in Parkinson disease patients, Parkinson disease patients with mild dementia, and healthy controls [14]. However, they found no changes in the cingulum or corpus callosum. The findings from DTI studies of PD are thus controversial.

In conventional DTI, water is assumed to undergo Gaussian diffusion. However, water in biological tissues is restricted by its interactions with other molecules and cell membranes; consequently, the assumption of Gaussian water diffusion may be inadequate to describe the actual diffusion process in biological tissues. Diffusional kurtosis imaging (DKI) is a new and promising diffusion imaging technique [15,16] that extends DTI to the quantification of non-Gaussian water diffusion. In addition to conventional DTI parameters such as mean diffusivity (MD) and FA, an additional parameter related to the non-Gaussian diffusion profile, called the mean kurtosis (MK), is obtained in DKI, whereby a higher MK value indicates a more restricted diffusion environment. Recent studies have reported that, relative to conventional DTI, DKI improves the sensitivity in detecting developmental and pathological neural changes for conditions such as age-related degeneration, cerebral infarctions, PD, attention-deficit hyperactivity disorder, gliomas, multiple sclerosis, and spondylotic myelopathy [15,17–26]. Wang et al. reported increased mean kurtosis (MK) values in the basal ganglia and substantia nigra [22]. They found that the mean kurtosis for the ipsilateral substantia nigra had the best diagnostic performance relative to the conventional diffusion tensor parameter (sensitivity, 0.92; specificity, 0.87).

According to Braak et al. [27], pathological characteristics are divided into six subgroups depending on the locations of the deposition of Lewy bodies. In Braak staging, ~~the~~ deposition of Lewy bodies in the anterior cingulum is classified as Stage 5—a relatively early stage for the neocortex. Furthermore diffusion abnormalities in cingulate fibers have been reported in some DTI study [6,8,12]. Therefore, we used DKI—a non-Gaussian diffusion model—to quantify microstructural changes in the cingulate fibers and to compare these data with conventional DTI parameters. The purpose of this study was to examine the usefulness of DKI in the diagnosis of PD.

2. Materials and methods

2.1. Subjects

The study was approved by an institutional review board, and informed consent was obtained from all participants before evaluation. The demographic characteristics of the subjects are shown in Table 1. In all PD patients the disease had been diagnosed by neurologists and fulfilled the UK Parkinson's Disease Society Brain Bank criteria. PD was staged according to the Hoehn and Yahr scale. All PD patients were taking levodopa at the time of the MR imaging and clinical examination. Eighteen months or more after scanning, all patients remained free of atypical parkinsonism and continued responding satisfactorily to antiparkinsonian therapy. Fifteen healthy subjects were recruited from the general population as control subjects and carefully matched in age to the patients. Individuals with any history of hypertension, diabetes mellitus, cardiovascular disease, stroke, brain tumor, epilepsy, PD, dementia, depression, drug abuse, or head trauma were excluded as controls.

Table 1
Demographic characteristics of subjects.

	CN ($n = 15$)	PD ($n = 17$)	P value
Sex, male:female	10:5	9:8	NS (0.430)
Age in years, mean (SD)	64.0 (12.7)	65.0 (9.3)	NS (0.80)
Disease duration in years, mean (SD)	NA	6.7 (4.6)	NA
Hoehn-Yahr stage (SD)	0	2.7 (0.7)	NA
Levodopa dosage mg/day, median (SD)	0	464.2 (175.0)	NA

Note: CN indicates normal controls; PD, Parkinson disease; NA, not applicable; NS, not significant ($P > 0.05$); SD, standard deviation.

2.2. MR Imaging

The brains of all patients were examined with a 3-T Magnetic resonance imaging unit (Achieva; Philips Healthcare, Best, the Netherlands) and an 8-channel- array (receiving) head coil for sensitivity-encoding parallel imaging. Regular structural images such as T1-weighted spin-echo images, T2-weighted turbo spin-echo images, and fluid-attenuated inversion recovery images were obtained before acquisition of diffusion tensor images.

DKI data were acquired with a spin-echo EPI sequence with 20 isotropic diffusion gradient directions. For each diffusion gradient direction, DKI images were acquired with 3 values of b (0, 1000, and 2000 s/mm^2). The sequence parameters were: image orientation, axial; TR, 7041 ms; TE, 70 ms; diffusion gradient pulse duration (δ), 13.3 ms; diffusion gradient separation (Δ), 45.3 ms; NEX, 1; field of view, 240 mm; matrix, 80 × 80; thickness, 3 mm; number of slices, 50; and imaging time, 6 min 26 s.

Diffusion tensor and kurtosis analyses were performed by using the free software dTV II FZRx and Volume-One 1.81 (http://www.volume-one.org), developed by Masutani et al. (University of Tokyo; diffusion tensor visualizer available at http://www.ut-radiology.umin.jp/people/masutani/dTV.htm) [6,28,29], on an independent Windows PC. First, FA and MD maps based on the conventional mono-exponential model were calculated. Because the kurtosis image data included those for multiple values of b, the FA and apparent diffusion coefficient (ADC) could be calculated by using part of the diffusion kurtosis data. Next, mean DK maps were obtained (Fig. 1). Details of their calculation procedure were as previously described [16,19,30]. Moreover, as described in previous papers [16,30], the DK for a single direction can be determined by acquiring data at three or more b values (including b = 0) and fitting them to Eq. (1):

$$\ln[S(b)] = \ln[S(0)] - b \cdot Dapp + 1/6 \cdot b2 \times D2app \times Kapp \quad (1)$$

where Dapp is the apparent diffusion coefficient for the given direction and Kapp is the apparent kurtosis coefficient, which is dimensionless.

2.3. DTI image processing using tract-specific analysis (TSA)

We created color-coded maps by using 21 sets of images (20 sets of images with $b = 1000$ s/mm^2, 1 set of images with $b = 0$ s/mm^2). On the color maps, red, green, and blue were assigned to the left-right, anteroposterior, and craniocaudal directions, respectively [31]. Fiber tracts were based on fiber assignments made by using the continuous tracking approach [32] to obtain a 3D tract reconstruction. Identification of fiber tracts was initiated by placing a "seed" and a "target" area in anatomic regions through which the particular fibers were expected to course [33]. We performed diffusion tensor tractography of the anterior and posterior cingulum. The FA threshold for tracking was set at 0.18, and the stop length was set at 160 steps, in accordance with a previous report by Yasmin et al. [34]. The bending angle of the tract was not allowed to exceed 45°. Tract measurements were performed by 2 of the authors (K.S., K.K.), who were blinded to the disease status of the subjects. Tractography of the anterior cingulum was performed from the seed ROI in the anterior part of the cingulum to the target ROI in the middle of the