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Mean kurtosis alterations of cerebral white matter in patients with schizophrenia revealed by diffusion kurtosis imaging

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ABSTRACT

Introduction: Diffusion kurtosis imaging can provide a better understanding of microstructural white matter (WM) changes where crossing fibers exist, compared with conventional diffusion tensor imaging. Here, we aimed to examine the differences of mean kurtosis (MK) and fractional anisotropy (FA) values between patients with schizophrenia and control subjects using voxel-based analysis (VBA). Additionally, we examined the correlation between these values and severity of clinical symptoms in patients with schizophrenia.
Methods: MK and FA values were acquired with a 3.0 T scanner from 31 patients with schizophrenia and 31 age-, handedness-, and sex-matched healthy controls. VBA was used to compare the MK and FA maps of the patients with schizophrenia and healthy controls. We also performed a correlation analysis between the MK and FA values of the regions with significant differences and the positive and negative syndrome scale scores in patients with schizophrenia.
Results: Compared to FA values, voxels with MK decrease were more widespread across bilateral cerebral the WM of patients with schizophrenia. The MK values of left superior longitudinal fasciculus were significantly negatively correlated with the severity of positive symptoms ($r = -0.451$, $P = 0.011$). There was no significant correlation between MK and FA values and other clinical variables.
Conclusion: The diffusion kurtosis indices are suitable for evaluating altered WM structures in the human brain as they may detect white matter alterations of crossing fibers alterations of WM in schizophrenia and assess the clinical state of patients.

1. Introduction

Schizophrenia is a common and severe psychiatric disorder classically characterized by delusion and hallucinatory behavior, with a prevalence of approximately 0.30–0.66% (van Os and Kapur, 2009). Neural disconnectivity between frontal and temporal areas (Friston and Frith, 1995) has been proposed as the neural basis of the disease, and white matter (WM) abnormalities in schizophrenia have been intensively investigated using different imaging methodologies.

Diffusion tensor imaging (DTI) is a non-invasive MRI technique to detect minute WM alterations (Pierpaoli et al., 1996). Several DTI studies have reported WM abnormalities in schizophrenia (Ellison-Wright and Bullmore, 2009; Frodl and Amico, 2014; Fujino et al., 2014). According to these reports, WM abnormalities are observed throughout the whole WM (Lim et al., 1999), in the frontal lobe (Hoptman et al., 2002; Wolkin et al., 2003), uncinate fasciculus (Kubicki et al., 2002; Wang et al., 2004), corpus callosum (Agartz et al., 2001; Foong et al., 2000), and middle cerebellar peduncle (Okugawa et al., 2004); these WM abnormalities are correlated with positive symptoms (Rotarska-Jagiela et al., 2009).

DTI measures water diffusion based on the assumption of the displacement distribution of water molecules in Gaussian distribution (Basser and Jones, 2002). Among several DTI indices, fractional anisotropy (FA) is most commonly used to assess WM integrity (Moseley, 2002). However, several researchers have argued that DTI is not suitable for assessment of WM microstructure because the assumption of Gaussianity of water diffusion is not always true in biological tissues due to the presence of cell membranes and organelles (Alexander et al., 2001; Jbabdi et al., 2010; Jensen and Helpern, 2010; Tuch et al.,

Abbreviations: AK, axial kurtosis; DKI, diffusion kurtosis imaging; DTI, diffusion tensor imaging; FA, fractional anisotropy; JART-25, the Japanese Version of the National Adult Reading Test; MK, mean kurtosis; PANSS, the positive and negative syndrome scale; RK, radial kurtosis; ROI, region of interest; SLF, superior longitudinal fasciculus; VBA, voxel based analysis; WM, white matter.

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2003). DTI fails to describe the directional information in regions with complex fiber configurations (Jbabdi et al., 2010). The FA values could be lower in the areas where fibers cross because of the lower diffusional directionality on a voxel scale (Jbabdi et al., 2010). Consequently, the FA value of a voxel containing intact crossing fibers could be similar to that of a voxel containing degenerated fibers (Jbabdi et al., 2010). Several methods, such as diffusion spectrum imaging and Q-space imaging (Assaf et al., 2002), have been proposed to characterize non-Gaussian distribution of diffusion (Wedeen et al., 2005). Although there have been recent technical improvements that shorten scan time (e.g., multi-band accelerated EPI), scan time is still lengthy for incorporation in routine clinical imaging protocol, the application of these techniques as clinical protocols is limited by their long scan time and higher hardware demands.

Diffusion kurtosis imaging (DKI) is a diffusion imaging technique that quantifies the deviation of water molecule diffusion without assuming any specific diffusion model. DKI provides kurtosis indices (e.g., mean kurtosis (MK), axial kurtosis (AK), and radial kurtosis (RK)), which represent excess kurtosis of displacement distribution of water molecules (Jensen and Helpern, 2010). DKI is independent of the assumption of Gaussian distribution, so that characterization of microstructural WM changes by DKI indices can be more appropriate than FA and the other DTI indices (Cheung et al., 2009; Hui et al., 2008; Jensen and Helpern, 2010; Tabesh et al., 2011; Van Cauter et al., 2012). In fact, several studies using DKI in patients with glioma (Raab et al., 2010; Van Cauter et al., 2012), Parkinson's disease (Ito et al., 2015; Kamagata et al., 2013), and Alzheimer's disease (Falangola et al., 2013) have shown better sensitivity and specificity in detection of developmental and pathological changes of neural tissues compared with conventional DTI.

There has been only one original report in which DKI was used to investigate WM abnormality in schizophrenia (Zhu et al., 2015). In this study, the authors compared MK, AK, and RK values between patients with schizophrenia and healthy subjects using tract-based spatial statistics (Smith et al., 2006), and reported the sensitivity of the kurtosis indices in detecting WM abnormalities in the regions with complicated fiber arrangements, such as the juxtacortical WM. However, to the best of our knowledge, no study has examined the correlations between the DKI indices and clinical symptoms in schizophrenia.

The aims of the present study were to examine the differences of MK and FA values between the patients with schizophrenia and healthy control subjects using voxel-based analysis, and to examine the correlation between these values and the severity of clinical symptoms, especially positive symptoms, in schizophrenia. Our hypothesis was that DKI has added value to DTI in depicting the microstructural WM changes of schizophrenia patients.

2. Materials and methods

The protocol of this cross-sectional study was approved by the institutional Ethical Review Board of Hokkaido University hospital. Written informed consent was obtained from all subjects in this study before enrollment.

2.1. Subjects

All patients with schizophrenia were recruited from April 2013 to May 2015 at the Department of Psychiatry, Hokkaido University Hospital. All patients were aged between 20 and 60 years, and schizophrenia was diagnosed by a research psychiatrist (H.N. 8 years of experience in psychiatry) based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I). Exclusion criteria were any absolute contraindication to MRI, comorbidity of axis I or II disorders, history of diseases that might affect WM integrity (i.e., prior head injury, cerebrovascular disorder, or degenerative disease), existence of past substance abuse or dependency, pregnancy, or a high risk of suicide. Subjects' age, sex, age of onset, duration of illness, and daily dose of antipsychotics were investigated through individual interviews at enrollment. Of the 33 patients who fulfilled the inclusion criteria, two patients were excluded due to visible artifacts on image quality control.

To obtain normal control data, 31 sex-, handedness- and age-matched normal subjects were also studied. Exclusion criteria were any contraindication to MRI, history of axis I or II disorders, history of diseases that might affect WM integrity, and no family history of psychiatric diseases in first-degree relatives.

2.2. Assessment of psychiatric symptoms

The clinical symptoms of patients with schizophrenia were evaluated using the positive and negative syndrome scale (PANSS) (Kay et al., 1987). We adopted the original three subcategories (positive symptoms, negative symptoms, and general psychopathological symptoms) in this study. All the PANSS assessments were performed by the research psychiatrist (H.N.) The Edinburgh inventory was used to determine handedness (Oldfield, 1971). Premorbid IQ was estimated using the Japanese Version of the National Adult Reading Test (JART-25) (Matsuoka et al., 2006).

2.3. MRI acquisition

In all subjects, MRI was acquired using a 3.0 Tesla scanner (Achieva TX; Philips Medical Solutions, Best, the Netherlands) and a 32-channel head coil. MRI was performed within 2 weeks of the symptom assessment. We used padding and fixation device to minimize head motion during acquisitions.

DKI data and three-dimensional magnetization-prepared rapid gradient echo T1-weighted images (3D-T1WI) were obtained to evaluate WM alterations. The sequence indices for DKI were as follows: image orientation, axial; repetition time (TR)/echo time (TE) = 5032/85 ms, b values = 0, 1000, and 2000 s/mm^2, flip angle = 90°, field of view = 224 × 224 mm^2, matrix size = 76 × 72, slice thickness = 3 mm, inter-slice gap = 0 mm, number of diffusion gradient directions = 32, number of slices = 43, number of excitations = 1, and scan time of 7:54 min. The voxel size, b-values, and the number of diffusion gradient directions were almost identical to previous work (Jensen and Helpern, 2010).

The scan indices for the 3D-T1WI were TR/TE = 6.8/3.1 ms, flip angle = 8°, inversion time (TI) = 1100 ms, matrix size = 256 × 256, voxel size = 1 × 1 × 1.2, slice thickness = 1.2 mm, slice orientation sagittal, number of slices = 170, and number of echoes = 1.

Several conventional structural images, such as axial fast spin echo T2-weighted images (TR/TE = 4137/90 ms, and effective echo train length = 15) and fluid-attenuated inversion recovery (FLAIR) images (TR/TE = 10,000/100 ms, and TI = 2700 ms), were additionally obtained to evaluate WM hyper-intensities. Visual review of DKI and 3D-T1WI was performed to ensure no gross motion and other artifacts (K.K.T., 15 years of experience in neuroimaging). Images with visible artifacts were excluded from further analysis.

2.4. Image processing

Voxel-based analysis was chosen to identify the microstructural WM abnormalities in patients with schizophrenia. This method has been regarded as well-suited if the area of involvement is not known, or when a hypothesis about the location of abnormalities is not made.

Registration between the echo-planar images (EPIs) with no diffusion weighting and the DKI data, and correction for eddy current distortion were performed at the MRI operator console. The DKI data were processed using Diffusional Kurtosis Estimator (DKE) version 2.6.0 (http://nitrc.org/projects/dke), which generates parametric maps of diffusion and kurtosis indices. Images with b values = 0 and 1000 s/mm^2