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WHITE MATTER MICROSTRUCTURE ASYMMETRY: EFFECTS OF VOLUME ASYMMETRY ON FRACTIONAL ANISOTROPY ASYMMETRY

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Abstract—Diffusion tensor imaging (DTI) provides information regarding white matter microstructure; however, macroscopic fiber architectures can affect DTI measures. A larger brain (fiber tract) has a 'relatively' smaller voxel size, and the voxels are less likely to contain more than one fiber orientation and more likely to have higher fractional anisotropy (FA). Previous DTI studies report left-to-right differences in the white matter; however, these may reflect true microscopic differences or be caused purely by volume differences. Using tract-based spatial statistics, we investigated left-to-right differences in white matter microstructure across the whole brain. Voxel-wise analysis revealed a large number of white matter volume asymmetries, including leftward asymmetry of the arcuate fasciculus and cingulum. In many white matter regions, FA asymmetry was positively correlated with volume asymmetry. Voxel-wise analysis with adjustment for volume asymmetry revealed many white matter FA asymmetries, including leftward asymmetry of the arcuate fasciculus and cingulum. The voxel-wise analysis showed a reduced number of regions with significant FA asymmetry compared with analysis performed without adjustment for volume asymmetry; however, the overall trend of the results was unchanged. The results of the present study suggest that these FA asymmetries are not caused by volume differences and reflect microscopic differences in the white matter.

Key words: arcuate fasciculus, diffusion tensor imaging, fractional anisotropy, integrity, laterality.

INTRODUCTION

The hemispheres of the human brain are asymmetric in structure and function. Language is the most notable and strongly lateralized function in the human brain, and is usually lateralized to the left hemisphere of the brain. Leftward asymmetry of the planum temporale is one of the most consistent structural asymmetries (Geschwind and Levitsky, 1968; Toga and Thompson, 2003). The planum temporale is a triangular-shaped region lying caudal to Heschl's gyrus on the superior temporal plane, and forms part of the classical Wernicke's area (Griffiths and Warren, 2002), which is responsible for language comprehension.

Several studies have investigated left-to-right differences in white matter volume (or density) using T_1-weighted images and voxel-based morphometry (Good et al., 2001; Herve et al., 2006; Shibata, 2007). Voxel-based morphometry is widely used to assess gray matter differences, but may not be optimal for white matter morphometry. A problem concerning white matter morphometry based on T_1-weighted imaging is that T_1 signal intensities are not well correlated with white matter microstructure. In contrast to T_1-weighted imaging, diffusion imaging provides subtle information regarding the composition of white matter tissue.

Diffusion tensor imaging (DTI) is one of the most widely used magnetic resonance (MR)-imaging techniques for assessing brain tissue integrity, and white matter in particular. Diffusion imaging is sensitive to the random thermal motions of water and is one of the few non-invasive methods for probing white matter microstructure and connectivity *in vivo*. DTI measures the direction and extent of microscopic water diffusion, which is affected by microstructure and is greatest in the direction of least restriction. Fractional anisotropy (FA), which is the most widely used diffusion tensor parameter, characterizes the degree to which the diffusion ellipsoid is anisotropic. Subtle white matter changes can be detected by measuring anisotropy, even if the brain tissue appears normal on T_1-weighted and T_2-weighted images (Rovaris et al., 2002). FA is used as a measure of white matter microstructure.

DTI has been used to study white matter asymmetry in healthy adults (Cao et al., 2003; Buchel et al., 2004; Gong et al., 2005b; Catani et al., 2007; Westerhausen et al., 2007; Glasser and Rilling, 2008; Huster et al., 2009; Jahanshad et al., 2010; Takao et al., 2011a,d; Thiebaut de Schotten et al., 2011b), in the developing human brain (Snook et al., 2005; Bonekamp et al., 2007; Dubois et al., 2009; Lebel and Beaulieu, 2009; Verhoeven et al., 2010; Qiu et al., 2011), and in a variety of neuropsychological disorders (Kubicki et al., 2002, 2003, 2011; Park et al., 2004; Wang et al., 2004; Fletcher et al., 2010; Takao et al., 2010a). Leftward

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Abbreviations: DTI, diffusion tensor imaging; FA, fractional anisotropy; FAT, frontal aslant tract; FDT, FMRIB's Diffusion Toolbox; FPUT, fronto-parietal U-shaped tracts; FSL, FMRIB Software Library; FWE, family-wise error; MR, magnetic resonance; SMA, supplementary motor area; TBSS, tract-based spatial statistics.

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asymmetry of the arcuate fasciculus is one of the most consistent white matter asymmetries. The arcuate fasciculus connects Wernicke's area in the temporal lobe with Broca's area in the frontal lobe, and is involved in human language.

DTI provides information regarding white matter microstructure; however, macroscopic fiber architectures can affect DTI measures. To date *in vivo* human DTI usually has a pixel resolution of 2–3 mm. The degree of partial volume averaging, which is more complex in DTI than in other neuroimaging techniques (Alexander et al., 2001), depends on the voxel size. Larger voxels are more likely to contain more than one fiber tract (crossing fibers). The term 'crossing fibers' has been loosely used to represent a whole range of fiber architectural paradigms within a voxel including, but not limited to, fibers crossing, kissing, splaying – and even single-fiber bundles that bend, curve or twist within a voxel (Jones, 2008). Behrens et al. estimated that over one third of voxels in the brain exhibit marked departures from the Gaussian diffusion behavior characterized by the tensor model (Behrens et al., 2007). A recent study by Takao et al. revealed that FA was positively correlated with head size (overall brain size) in a number of white matter regions (Takao et al., 2011b). Another study by Vos et al. showed that the estimated bundle-specific DTI measures were modulated by fiber bundle thickness, orientation, and curvature (Vos et al., 2011). A larger brain (fiber tract) has a 'relatively' smaller voxel size, and the voxels are less likely to contain 'crossing fibers' and more likely to have higher FA. As mentioned above, the arcuate fasciculus is usually larger in the left than in the right hemisphere. FA of the arcuate fasciculus is also commonly reported to be higher in the left than in the right hemisphere; however, this may or may not be caused purely by hemispheric differences in the volume of the arcuate fasciculus.

The purpose of the present study was to examine whether or not left-to-right differences in white matter FA are caused by volume differences and to find out true microscopic differences. To this end, we investigated left-to-right differences in white matter FA across the whole brain, controlling for volume differences, using tract-based spatial statistics (TBSS) and DTI data obtained from 857 normal subjects. To control for left-to-right differences in regional brain volumes, we used Jacobian determinant maps of the deformation fields derived from spatial normalization of subjects' FA data on a symmetric FA template as a volume index. To the best of our knowledge, no previous study has investigated left-to-right differences in white matter FA across the whole brain, controlling for volume differences.

TBSS is an unbiased and automated whole-brain analysis technique that compares diffusion tensor properties among multiple subjects (Smith et al., 2006, 2007), and is currently widely used in clinical studies for investigating white matter integrity. Unlike conventional voxel-based analyses, TBSS does not require perfect brain alignment or smoothing; instead, brains are projected onto an FA skeleton prior to comparison. TBSS combines the respective strengths of voxel-based and tractography-based analyses (Smith et al., 2006). By projecting FA values onto a subject-mean FA tract skeleton, cross-subject FA becomes more Gaussian and of lower variability; hence, analyses become more robust and more sensitive. Thus, we used TBSS in the present study. In addition to FA data, we projected Jacobian determinant maps onto a mean FA tract skeleton, for use as a volume index.

EXPERIMENTAL PROCEDURES

Subjects

A total of 857 normal subjects (310 females, 547 males; mean age, 56.1 ± 9.9 years; age range, 24.9–84.8 years) were included in this study. All subjects were volunteers who underwent private health screening. None of the subjects had a history of neuropsychiatric disorders including serious head trauma, psychiatric disorders, or alcohol/substance abuse or dependence. The mean Mini-Mental State Examination (MMSE) score was 29.2 ± 0.9 (range, 27–30). A board-certified radiologist reviewed all scans (including T_2-weighted images) and found no gross abnormalities such as infarct, hemorrhage, or brain tumor in any subject. The Fazekas score (range, 0–3) was 0 (absence) or 1 (caps, pencil-thin lining and/or punctuate foci) (Fazekas et al., 1987). The ethics committee of the University of Tokyo Hospital approved of this study. After a complete explanation of the study to each subject, written-informed consent was obtained.

Acquisition of imaging data

MR data were obtained on two 3.0-T Signa HDx scanners (GE Medical Systems, Milwaukee, WI, USA) of the same model with an 8-channel brain-phased array coil. Diffusion tensor images were acquired using a single-shot spin-echo echo-planar sequence in 50 axial slices (repetition time = 13,200 ms; echo time = 62 ms; field of view = 288 mm; slice thickness = 3 mm with no gap; acquisition matrix = 96 × 96; number of excitations = 1; image matrix = 256 × 256). Diffusion weighting was applied along 13 non-collinear directions with a *b*-value of 1000 s/mm^2, and a single volume was collected with no diffusion gradients applied (b_0). Parallel imaging (Array Spatial Sensitivity Encoding Technique, ASSET) was used with an acceleration factor of 2.0.

Image processing

Image analysis was performed using TBSS 1.2 (Smith et al., 2006, 2007), which is part of FSL (FMRIB Software Library 4.1, http://www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004). The raw diffusion data were first corrected for eddy current distortion and head motion using FMRIB's Diffusion Toolbox (FDT) 2.0 (Smith et al., 2004), and were corrected for spatial distortion due to gradient non-linearity using grad_unwarp (Jovicich et al., 2006). Following brain extraction using Brain Extraction Tool (BET) 2.1 (Smith, 2002), FA maps were created by fitting a tensor model to the diffusion data using FDT. All of the subjects' FA data were then aligned into Montreal Neurological Institute (MNI) 152 space using FMRIB's nonlinear registration tool (FNIRT) 1.0 (Smith et al., 2004), which uses a b-spline representation of the registration warp field. The symmetric FMRIB58_FA standard-space image (generated by flipping and