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Correlation between Diffusion Tensor Tractography and proton MR spectroscopy in normal controls*

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Abstract— **Tractography is a procedure that can track and demonstrate the 3D neural tracts of the white matter of the brain. The images of the brain are obtained by analyzing the diffusion tensor, identification of which can provide the anatomical connections of the brain. Studying these connections is integral to the understanding of the brain function. Specifically, the uncinate fasciculus and fornix, which are the white matter in the human brain, are said to be related to cognitive function. The tractography is calculated using diffusion tensor imaging (DTI) parameter. Studies have shown that the DTI parameter of dementia patients is lower than that of healthy individuals. It is also suggested that the DTI parameter of healthy individuals decreases with age. In addition, Proton MR Spectroscopy (^{1}H-MRS) is indicative of neuronal damage and has been used for decades as a noninvasive technique for assessing the biochemistry of the human brain. This is reflected by the increasing number of clinical MRS investigations of neurological disorders. Thus, MRS and DTI can provide complementary images on white matter in brain and it is important to investigate the white matter brain changes by simultaneously acquiring DTI and MRS in health control subjects. In this research, we have calculated the correlation coefficient between the DTI parameter of uncinate fasciculus, fornix and ^{1}H-MRS. Our result shows that the correlation coefficient of DTI parameter and ^{1}H-MRS of a left fornix is 0.65 at the maximum. Correlation between DTI measurement and ^{1}H-MRS suggests the relationships between the uncinate fasciculus, fornix and cognitive neuronal function. Our finding matches previous reports on the correlation between DTI parameters and ^{1}H-MRS.**

I. Introduction

The uncinate fasciculus is a major white matter tract connecting the anterior temporal and frontal lobes [1]. It is shaped like a curved dumbbell and links the three anterior temporal convolutions and the amygdala with the gyrus rectus, medial retro orbital cortex, and subcallosal area [2]. The uncinate fasciculus is important for the formation and retrieval of episodic memories [3, 4].

The fornix connects the hippocampal formation to the prefrontal cortex [5]. Recent DWI studies have found that variations in fornix microstructure in young people correlate selectively with recollective memory [6], closely supporting clinical studies of fornix pathology [7, 8].

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Diffusion Tensor Imaging (DTI) measures the molecular motion of water in tissue in six or more directions, and characterizes the magnitude and direction of diffusion in every single voxel. Thus, it is used to reveal the microstructure of white matter [9-11]. The integrated white matter tracts measured by DTI are related to individual differences in performance across a wide range of cognitive functions.

^{1}H magnetic resonance spectroscopy (MRS) has been used for decades as a noninvasive technique for assessing the biochemistry of the human brain. This is reflected by the increasing number of clinical applications of spectroscopy to investigate neurological disorders. ^{1}H-MRS of the brain has also found broad application in the study of MS [12-15].

The purpose of this study is to investigate the correlation of the degree of DTI parameters based on tractography with ^{1}H-MRS.

II. Subjects and Methods

Participants

This study is performed by 10 healthy right-handed individuals (age group: 20-60 years old). The study is approved by the Institutional Review Board of the National Hospital Organization Nara Medical Center, and all subjects have given informed consent prior to the enrollment in the study.

DTI and MRS data acquisition and processing

MR-images are acquired using a 1.5T whole body MR scanner (Toshiba Medical Systems Inc). And then, DTI acquisitions are taken from the subjects. The DTI acquisition consists of axial 2D echo planar imaging (2D EPI) diffusion-weighted sequence with TR/TE = 12000/130 ms, FOV = 24 cm, matrix= 128 × 128, 3-mm contiguous slices without gap, two $\boldsymbol{b}$ values = 0 and 1000 s/mm^2, done in six directions.

The diffusion tensor $\boldsymbol{D}$ is calculated using equation (1),

$$\boldsymbol{S}_b = \boldsymbol{S}_0 \times \exp\left(-\boldsymbol{bD}\right) \quad (1)$$

where each set of diffusion-weighted images is utilized. $\boldsymbol{S}_b$ is the measured MR signal for a given $\boldsymbol{b}$ value, $\boldsymbol{S}_0$ is the MR signal for $\boldsymbol{b}$ = 0, $\boldsymbol{b}$ value is the diffusion gradient factor along each direction (s/mm^2), the diffusion tensor $\boldsymbol{D}$ describes the molecular mobility and correlation towards these directions. The diffusion tensor $\boldsymbol{D}$ can be diagonalized to the eigenvectors and eigenvalues ($\boldsymbol{\lambda}_1, \boldsymbol{\lambda}_2, \boldsymbol{\lambda}_3$). The eigenvectors describe the major diffusion directions and the eigenvalues are related to their diffusivities. The apparent

diffusion coefficient (ADC) can be obtained from the trace of the diagonalized diffusion tensor $(\lambda_1 + \lambda_2 + \lambda_3)/3$. Parametric maps of the ADC and fractional anisotropy (FA) are obtained using these eigenvalues. FA is a scalar value that describes the shape of the diffusion within a given voxel, with a range from 0 to 1.

Automated hybrid point-resolved spectroscopy 2D-CSI measurements with a repetition time (TR) of 132.3 ms and an echo time of 136 ms (SE, double spin echo) were performed. Manual setting volume of interest (VOI) of 3.0 x 1.5 x 1.5 cm^3 for both sides of hippocampus and 1.5 x 2.0 x 1.5 cm^3 for those of temporal stem was acquired. Using standard post processing protocols, the raw data were processed automatically, allowing for operator-independent quantifications such as FWHM of less than 0.2 ppm and water suppression level over 80..

Tractography analysis

DTI Studio software [16] based on the fiber assignment by continuous tracking (FACT) algorithm is used for white matter fiber tracking. Diffusion tensor tractography using multiple regions-of-interest (ROI) are also used to trace the uncinate fasciculus [17] and fornix [18] bilaterally. The tracking method uses fractional anisotropy (FA) threshold of 0.15, and angle threshold of 60 degrees. These thresholds are similar to previous publications [19, 20].

For the uncinate fasciculus, superior and inferior segments traversing the coronal plane is determined as an anatomical landmark as shown in Fig. 1A, ROI. A Boolean "OR" operation on one region combined with an "AND" operation on the other are chosen to construct the uncinate fasciculus on each side.

For the fornix, ROI 1 was on the axial slice where the body of the fornix and both crura were clearly seen (Fig. 1C, upper left). ROI 2 was at the hippocampus (Fig. 1C, upper right). ROI 3 was between first two, where the crus of the fornix was as a single bundle lateral to the splenium of the corpus callosum (Fig. 1C, lower), restricting the fibers passing through one of the first two ROIs.

On the uncinate and fornix fiber tract, its traced volume and corresponding DTI parameters such as FA and ADC are recorded in 3D as shown in Fig. 1D.

MRS analyses

The raw SI data were processed and fitted in the frequency-domain to obtain metabolite peak areas using manufacturer-supplied MRS data processing software. MRS metabolites (NAA, Cho, Cr) were obtained from VOIs. Spearman correlations between FA, ADC and MRS are obtained.

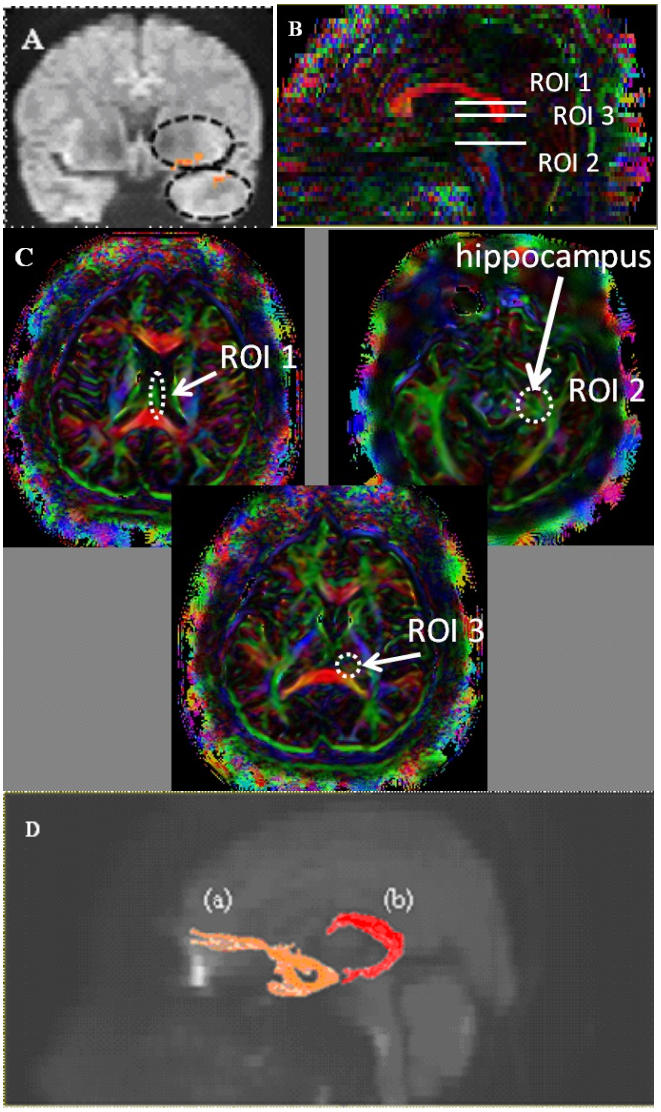

Figure 1. Illustration of the DTI-based fiber tracking of the uncinate fasciculus. (A)The two ROIs for left uncinate. (B)Three ROIs for fornix. (C)Axial slices of three ROIs for the fornix. (D) A 3D saggital view of the (a) left uncinate and (b) fornix.

III. RESULTS

The concentrations of the main metabolites (Cho, Cr and NAA) are shown in Table 1 together with the ADC and FA values, as determined by tractography. The intersubject variations are also presented in Table 1. In tractography of both fornix near gray matter, the values of Cr and ADC were higher, and that of Cho was lower than in both uncinate. Table 2 shows the linear coefficients of correlation (r) between the 4 sets of DTI parameters (FA, ADC) with the corresponding ^{1}H-MRS parameters (Cho, Cr and NAA) in the ten volunteers. The positive correlation of ADC with NAA in the left fornix is strong (r =.65) as shown in Fig. 2 and that of FA with Cr in the right uncinate is also strong (r = 0.64) shown in Fig. 3. The other correlation coefficients in Table 2 are trends only.

TABLE I. DTI AND MRS VALUES

Controls (n=10)	FA MN±SD	ADC MN±SD(×1000)(μm²/ms)
left uncinate	0.378±0.025	840±42.2
right uncinate	0.357±0.029	835±82.9
left fornix	0.357±0.031	1100±187
right fornix	0.372±0.022	1007±104

Controls (n=10)	Cho MN±SD(mM)	Cr MN±SD(mM)	NAA MN±SD(mM)
left temporal stem	3.05±0.388	6.02±0.407	8.53±0.999
right temporal stem	2.66±0.510	5.65±0.905	7.63±1.48
left hippocampus	2.67±0.369	6.09±0.834	8.18±1.06
right hippocampus	2.51±0.314	5.80±0.816	7.72±1.03

TABLE II. LINEAR COEFFICIENTS OF CORRELATION BETWEEN THE DTI AND MRS PARAMETERS FOR 10 CONTROLS

	ROI	Cho	Cr	NAA
FA	Right uncinate	0.516	0.637	0.208
	Left uncinate	-0.178	0.364	-0.267
	Right fornix	0.0642	0.584	0.319
	Left fornix	-0.0111	0.0293	0.210
ADC	Right uncinate	-0.455	-0.625	-0.134
	Left uncinate	0.0930	-0.388	0.0334
	Right fornix	0.351	0.384	-0.0376
	Left fornix	0.061	-0.0176	0.652

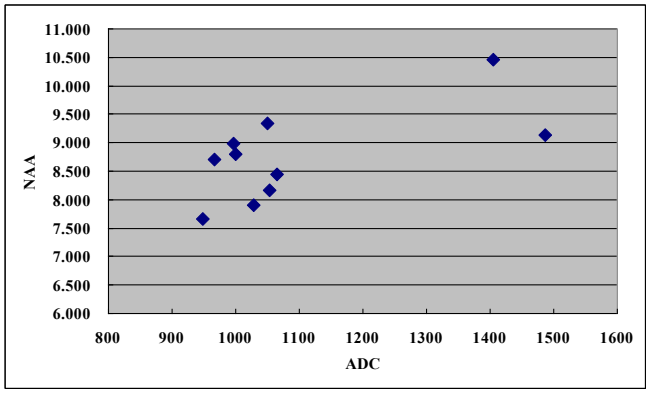

Figure 2. Correlations between ADC in the left fornix and NAA in the left hippocampus.

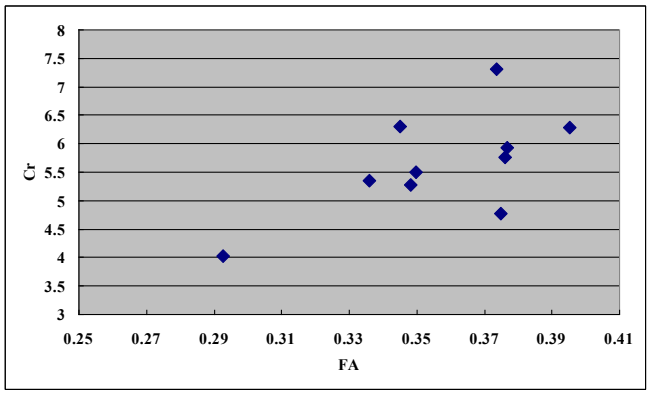

Figure 3. Correlations between FA in the right uncinate fasciculus and Cr in the right temporal stem.

IV. DISCUSSION

In this work, tractography were directly compared with ^{1}H-MRS using the same volunteers in the near regions. The results show a strong correlation of neuron structure as indicated by ADC with neuronal content indicated by NAA (lower right of Table 2). There is similar evidence that the extent of neuron structure within a tractography is related to the level of NAA, a compound in neurons.

With less neuron structure in tractography, the ADC is higher with less restriction of water molecules and the NAA level is lower except right hippocampus. Cho also showed significance to both ADC and FA in the right uncinate suggests a constructive role of Cho in the preservation of neuron structures [21]. Cr level of around 6 mM is very close to the report by Michaelis et al. [22] in 1993, and, it is often used as an internal reference level. In both temporal stem where VOI containing gray matter, the level of Cr was higher and those of Cho and NAA lower than in both hippocampus, agreed with previously published data [23].

A similar study by Steel et. al. [24] found no significant correlations in NAA or FA. There is a reason for those findings. Single voxel MRS is subjective to partial volume contamination. They only surveyed the frontal and occipital lobe which was not the same location where significant differences were found for both NAA and FA. Irwan et. al. [25] using DTI and MRS acquired in a supraventricular region found similar significance in control subjects. Although they have not specifically looked at tractography, significant correlations between NAA and FA as well as between NAA with ADC were reported.

Limitation of our study is without coregistration of the tractography ROIs with the MRS ROIs. It is necessary to accurately coregister the tractography to the MRS slices using conventional image matching techniques. In this study, we only have used anatomy knowledge of ROI. Other limitations are the different slice thickness between DTI and MRS. The DTI was 3 mm thick whereas the MRS were 15 mm.

Combining these two different imaging modalities before the diagnosis of disease would prospect defective NAA following reduced FA. Differences in the DTI and MRS results may clarify the nature of the white matter defects and

their independent importance. This finding will enhance further understanding of human cognitive function in terms of both anatomically and physiologically.

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