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Correlation of fractional anisotropy and metabolite concentrations measured using ^{1}H-MRS of cerebral white matter in healthy adults

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Abstract. Fractional anisotropy (FA) is currently an ideal index capable of reflecting the white matter structure. ^{1}H magnetic resonance spectroscopy (^{1}H-MRS) is often used as a noninvasive concentration measurement of important neurochemicals in vivo. This study was conducted to investigate the relationship between FA and metabolite concentrations by comparing ^{1}H-MRS of bilateral medium corona radiata in healthy adults. The data of diffusion tensor imaging (DTI) and ^{1}H-MRS were acquired from 31 healthy adults using a 3.0 T MR system. All subjects were divided into three groups: the total group (mean age=42 years), the junior group (mean age=29 years) and the senior group (mean age=56 years). There was a negative correlation between FA and age in three groups (r=-0.146, r=-0.204, r=-0.162, $p<0.05$). The positive correlation of FA with corresponding concentrations of N-acetylaspartate (NAA) was significant in three groups (r=0.339, r=0.213, r=0.430, respectively, $p<0.05$). The positive correlation of FA with the corresponding NAA/Cr was only significant difference between the total 353 samples and the junior group (r=0.166, r=0.305, respectively, $p<0.05$). Combining ^{1}H-MRS with DTI reveals the relationship between structure and metabolic characteristics of white matter.

Keywords: Diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), white matter

1. Introduction

There were many research conducted in the past to explore the structure and function of the brain [1,2]. Fractional anisotropy (FA) in cerebral white matter, which derived from diffusion tensor imaging (DTI), describes the directional selectivity of the random movement of water molecules. FA values were considered to be related to white matter structure and often used as imaging indices of the local microstructure [3,4].^{1}H magnetic resonance spectroscopy (^{1}H-MRS) in cerebral white matter is

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often used as a noninvasive way to measure neurochemicals in vivo. The three most frequently measured metabolites are N-acetylaspartate (NAA), choline (Cho) and creatine (Cr). It has been reported in the past that, the combination of DTI and ^{1}H-MRS measurements had been used in hypertension and presumed cerebral small vessel disease [5], Multiple Sclerosis [6] and Alzheimer's disease [7]. In this study the correlation of microstructure and metabolic concentrations was analyzed and measured by DTI and ^{1}H-MRS respectively, in bilateral medium corona radiata region of healthy adults. The result may provide a reference for combination of the two techniques in diseases.

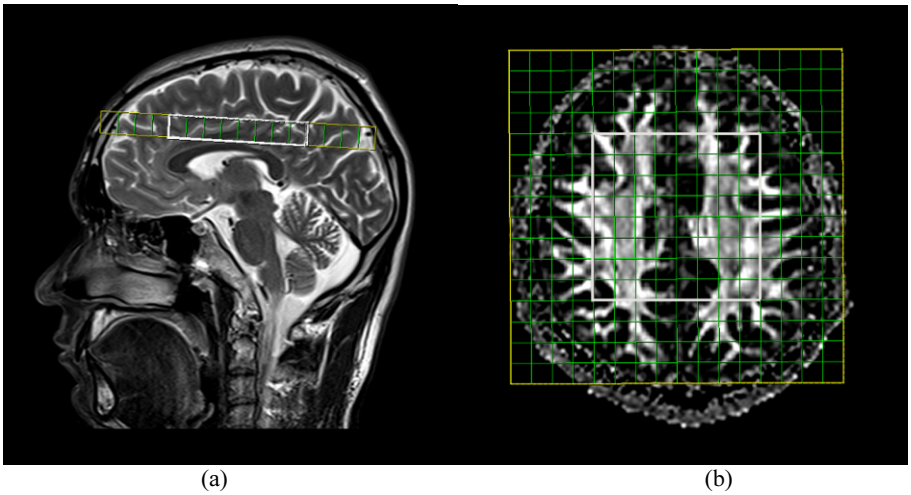
2. Materials and methods

2.1. Participants

This study was permitted by the institutional ethics committee. All subjects had been given informed consent before the enrollment. Studies were performed in 31 (15 men and 16 women) healthy volunteers, aged from 18 to 66 (mean age=42). All participants were right-handed without MRI contraindications. Exclusion criteria included: the presence of white matter hyper-intensities, history of substance abuse, stroke or other major psychiatric or neurological illnesses.

2.2. MRI acquisition

All participants underwent DTI and ^{1}H-MRS using 3.0T MR system (Siemens, Skyra, Germany), equipped with sixteen-channel phased array head coil. On the mid-sagittal structural images, scan line was positioned on the upper section of corpus callosum parallel to the anterior-posterior commissure (AC-PC) line.



(a) (b)

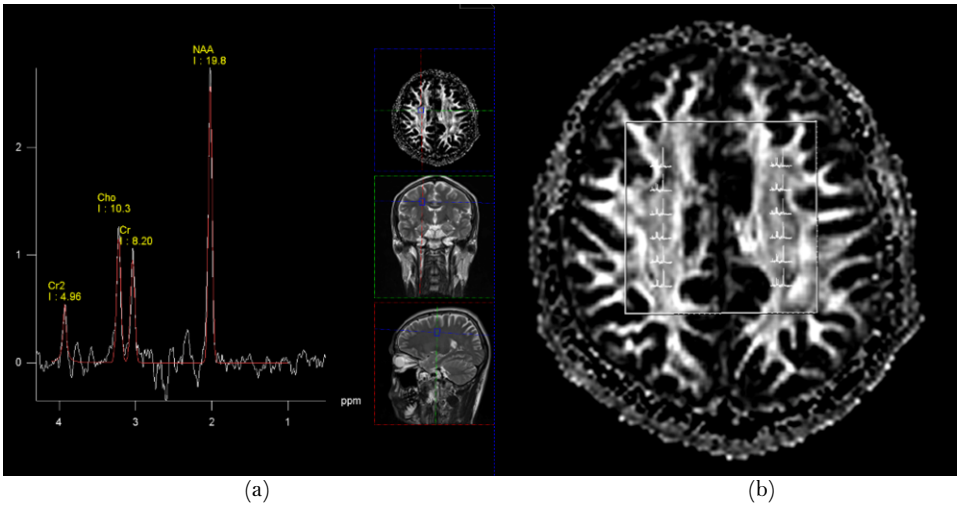
Fig. 1. ^{1}H-MRS VOI was positioned on the upper section of corpus callosum from mid-sagittal T2WI image (a) and axial FA maps (b) paralleling to the anterior-posterior commissure (AC-PC) line.

For DTI, a single-shot, echo-planar, single-refocusing spin-echo sequence is used with a spatial resolution of 1.8×1.8×3.0 mm. The GRAPPA method with parallel imaging factor set to 2 was employed in order to reduce distortions. The sequence parameters were as TE/TR=91/8500 ms, FOV=230 mm, slice thickness=3 mm, 46 slices with no gaps, 30 isotropically distributed diffusion-weighted directions, b-value =0 and 1000 s/mm^2. When b-value was 0 and 1000 the images were acquired eight times and twice respectively.

^{1}H-MRS: Multi-voxel ^{1}H-MRS was performed in each subject with point-resolved spectroscopy (PRESS) pulse sequence. The sequence parameters were as TE/TR=1700/135 ms, volume of voxel =10×10×13 mm, volume of interest (VOI) =80×80×13 mm, automated shimming resulted in water peak line widths 8-17 Hz. Figure 1 shows that sagittal and coronal T2WI and axial FA maps were used for positioning the spectroscopic volume of interest (VOI). VOI was located in the bilateral medium corona radiata, where provided good ^{1}H-MRS signal to easily shim and replicate from one individual to another. The VOI was placed by the same investigator in a uniform manner.

2.3. Data processing

The raw data were sent to a computer workstation (Multimodality Workplace Syngo MR). ^{1}H-MRS data were processed by spectroscopy software as shown in Figure 2(a). The post processing of spectroscopy including water reference processing, filter, zero-filling, Fourier transformation, frequency shift correlation, baseline correction, phase correction and curving fitting. Figure 2(b). shows 4~6 voxels were selected from each side and the inclusion criteria included: (1) Voxel was covered with pure white matter and without gray matter; (2) Voxel was not contaminated by cerebrospinal fluid; (3) Voxel was located in the center of the VOI. The area under the peaks was calculated by the software as a measure of the metabolite concentration. The concentrations of N-acetylaspartate (NAA, 2.01 ppm), choline (Cho, 3.2 ppm), creatine (Cr, 3.01 ppm) and the ratio of NAA/Cr were measured in each selected voxel. The voxels that selected from ^{1}H-MRS were



(a) (b)

Fig. 2. (a) Area under the curve, derived from a single spectroscopic voxel of a 24-year-old volunteer, demonstrates the corresponding metabolic concentrations. (b) 12 voxels were selected from bilateral medium corona radiata on FA maps.

positioned on FA maps based on the absolute coordinates in order to ensure that the size (10×10 mm) of the cross section of a region of interest (ROI) on FA maps was equal to the size of the cross section of corresponding spectroscopic voxel. The ROIs were manually drawn on the FA map of each individual subjects in Syngo viewing software and then calculated the mean of FA value among all voxels in each ROI.

2.4. Statistical analysis

Statistical analysis of DTI and ^{1}H-MRS results of total 353 samples were performed by Statistical Product and Service Solutions (SPSS) software (version 20.0). All data were divided into three groups: total group (n=31, number of samples=353, 18~66 years old, mean age=42 years), junior group (n=16, number of samples=181, 18~42 years old, mean age=29 years), senior group (n=15, number of samples=172, 48~66 years old, mean age=56 years). FA values were enlarged by 1000 times. The correlations between FA and age were analyzed by Pearson's correlation coefficients. The correlations between FA and metabolite concentrations were estimated using partial correlation test controlling for the age related bias. Values were significant difference at $p<0.05$.

3. Results

Means for FA values, ^{1}H-MRS parameters (NAA, Cho, Cr, NAA/Cr) were shown in Table 1. The FA and the corresponding age were showed as a significant negative relationship among total 353 subjects, junior and senior group (r=-0.146, r=-0.204, r=-0.162, respectively, $p<0.05$). It is demonstrated in Figure 3 that the positive correlation of FA with the corresponding NAA was the strongest in all three groups (r=0.339, r=0.213, r=0.430, respectively, $p<0.05$). The partial correlation coefficient of FA with Cho or Cr was trend only in three groups. The positive correlation of FA with the corresponding NAA/Cr wasstrongin the total 353 samples and the junior group (r=0.166, r=0.305, respectively, $p<0.05$) but was not significant in the senior group (r=0.114, p=0.139).

4. Discussion

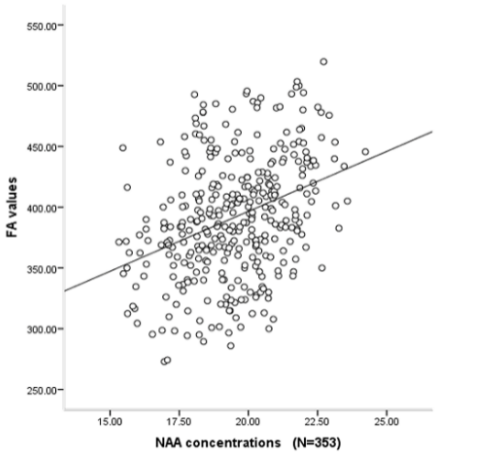
4.1. FA and white matter microstructure

Most white matter structures in healthy and mature human brain consist of myelinated fibers which

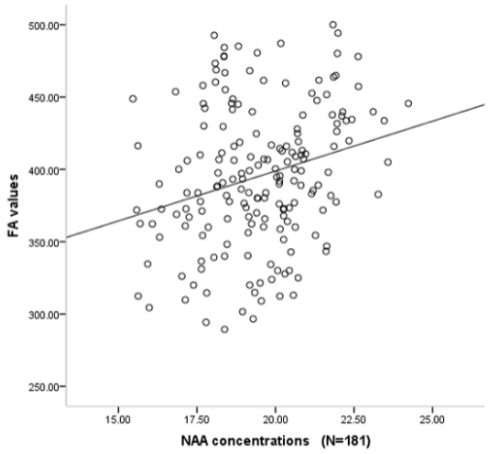
Table 1

Diffusion and metabolic measures in three groups ($\bar{x}$ ±s)

Group (number of samples)	FA ($\times10^{-3}$)	NAA	Cho	Cr	NAA/Cr
Total group (353)	391.790±49.673	19.513±1.770	11.137±1.923	9.580±1.672	2.080±0.322
Junior group (181)	395.330±48.420	19.487±1.802	10.729±1.793	9.001±1.345	2.195±0.283
Senior group(172)	388.064±50.832	19.541±1.740	11.566±1.965	10.184±1.770	1.959±0.316



(a)



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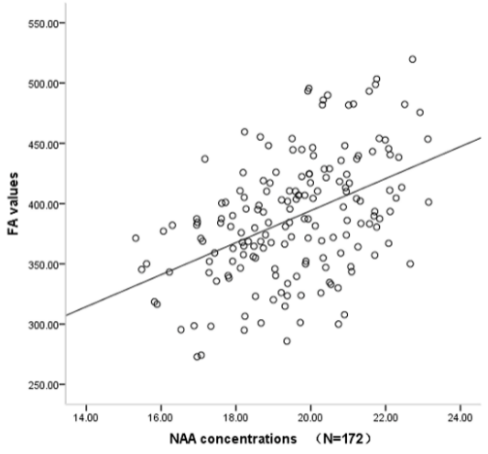

(c)

Fig. 3. Scatterplots with fit lines indicating the relationship between FA and NAA in the three groups: the total 353 samples (a), junior (b) and senior (c).

act as a natural passageway for water molecules. The diffusion of water molecules is limited in the direction perpendicular to the longitudinal axis of the fiber tract. DTI was taken advantages of the preferential diffusion of water molecules. Diffusion gradients were applied in a multiplicity of directions. FA was derived from the standard deviation of 3 eigenvalues. White matter FA probably reflects the demyelination, reduction in the density of oligodendrocytes and replacement of axonal fibers with other cells [8–11]. The brain white matter is composed of liaison fibers, associative fibers, projective fibers and each fiber has different structural and metabolic characters. It is important to definite the type of fibers.

This study demonstrated that FA was negatively correlated with normal aging in projective fibers of bilateral medium corona radiata. This result is similar to previous studies [3,12]. The development and degradation of white matter may be the reason. During childhood, white matter undergoes myelination, increases in fiber density and alterations of size and shape [13]. Through the aging process, reductions in size are obvious [14]. As a result, FA increases during childhood, peaks at the age of 21-44 years, and then decreases at a slightly slower rate [12].

This correlation may be more significant in dense, longer and fewer crossing fibers. In this study, investigators found that FA was higher in the region of corpus callosum than the upper region even in the same bundle of continuous fibers. The result may be interpreted that the weaker correlation between FA and normally aging in bilateral medium corona radiata than the corpus callosum.

4.2. FA and important cerebral metabolites

The result demonstrated a positive correlation between FA and concentrations of NAA, which is mainly related to neuron and glia. NAA is mainly concentrated in neuron. It serves as an acetyl donor, an initiator of protein synthesis or a carbon transfer source across the mitochondrial membrane [15]. The NAA signal that derived from pure cerebral white matter was considered a marker of the neuron health. Terry [16] found that the prominent changes are the shrinkage of large neurons and the increasing numbers of small neurons and glia during the aging process. In this study, the magnitude of the correlation coefficient between FA and NAA was larger in senior group (r=0.403) than junior group (r=0.213), which agrees with Wijtenburg's report [17]. The correlation of FA with NAA/Cr (r=0.166) was weaker than with NAA (0.339). Batouli [18] considered that strong environmental influence on Cr level suggests that it cannot be the best internal reference. So metabolite concentrations were considered to be a better reference when making a correlation research between microscopic white matter structure and metabolic characteristics.

4.3. The clinical significant of combination of ^{1}H-MRS and DTI

Pathological changes in the brain often lead to diffusion and metabolites concentration changes of water molecules. Therefore, the combination of the two techniques contributes for understanding pathology mechanism in various diseases. Nitkunan [5] used ^{1}H-MRS to determine the pathological changes which were abnormal on DTI in a range of patients with cerebral small vessel disease. The strength of the correlations between FA and NAA increased with severity of their disease. The authors considered that axonal loss was the salient process causing the DTI changes. The patients with multiple sclerosis (MS), correlations between FA and NAA revealed no significant difference except for the progressive forms of MS (secondary progressive and primary progressive). These findings revealed the specificity of NAA to reflect chronic lesions and the underlying axonal loss [6]. Ding [7] pointed out that partial correlation analysis showed a positive correlation ($r=0.524$, $p<0.05$) between

myoinositol (mI)/Cr and left-side FA in patients with mild AD. It was probably associated with gliosis or membrane dysfunction in early AD.

A limitation of this study is that the volumes of DTI group and ^{1}H-MRS group are different, and further study is required to combine these two technologies for a better result. Another limitation is that there were no clinical disease cases. In future, further evaluation using DTI and ^{1}H-MRS for larger samples may be taken for better result.

5. Conclusion

There is a significant relationship between FA and NAA concentration, which is closely related to the structure and metabolic characteristics of neurons and glia. The combination of DTI and ^{1}H-MRS is capable to provide a better understanding of relationships between changes in white matter structure and metabolic characteristics.

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References

[1] R. Irwan, P.E. Sijens, J.H. Potze and M. Oudkerk, Correlation of proton MR spectroscopy and diffusion tensor imaging, Magn. Reson. Imaging **23** (2005), 851–858.
[2] A. Bieza amd G. Krumina, Magnetic resonance study on fractional anisotropy and neuronal metabolite ratios in peritumoral area of cerebral gliomas, Medicina (Kaunas) **48** (2012), 497–506.
[3] P. Kochunov, P.M. Thompson, J.L. Lancaster, G. Bartzokis, S. Smith, T. Coyle, D.R. Royall, A. Laird and P.T. Fox, Relationship between white matter fractional anisotropy and other indices of cerebral health in normal aging: Tract-based spatial statistics study of aging, Neuroimage **35** (2007), 478–487.
[4] K. Kamagata, Y. Motoi, O. Abe, K. Shimoji, M. Hori, A. Nakanishi, T. Sano, R. Kuwatsuru, S. Aoki and N. Hattori, White matter alteration of the cingulum in Parkinson disease with and without dementia: Evaluation by diffusion tensor tract-specific analysis, Am. J. Neuroradiol. **33** (2012), 890–895.
[5] A. Nitkunan, R.A. Charlton, D.J. McIntyre, T.R. Barrick, F.A. Howe and H.S. Markus, Diffusion tensor imaging and MR spectroscopy in hypertension and presumed cerebral small vessel disease, MagnReson. Med. **59** (2008), 528–534.
[6] S. Hannoun, M. Bagory, F. Durand-Dubief, D. Ibarrola, J.C. Comte, C. Confavreux, F. Cotton and D. Sappey-Marinier, Correlation of diffusion and metabolic alterations in different clinical forms of multiple sclerosis, PLoS One **7** (2012), e32525.
[7] B. Ding, K.M. Chen, H.W. Ling, H. Zhang, W.M. Chai, X. Li and T. Wang, Diffusion tensor imaging correlates with proton magnetic resonance spectroscopy in posterior cingulate region of patients with Alzheimer's disease, Dement. Geriatr. Cogn. Disord. **25** (2008), 218–225.
[8] M.A. Horsfield and D.K. Jones, Applications of diffusion-weighted and diffusion tensor MRI to white matter diseases-A review, NMR Biomed. **15** (2002), 570–577.
[9] S.M. Smith, M. Jenkinson, H. Johansen-Berg, D. Rueckert, T.E. Nichols, C.E. Mackay, K.E. Watkins, O. Ciccarelli, M.Z. Cader, P.M. Matthews and T.E. Behrens, Tract-based spatial statistics: Voxel wise analysis of multi-subject diffusion data, Neuroimage **31** (2006), 1487–1505.
[10] S.K. Song, S.W. Sun, W.K. Ju, S.J. Lin, A.H. Cross and A.H. Neufeld, Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia, Neuroimage **20** (2003), 1714–1722.

[11] S.K. Song, J. Yoshino, T.Q. Le, S.J. Lin, S.W. Sun, A.H. Cross and R.C. Armstrong, Demyelination increases radial diffusivity in corpus callosum of mouse brain, Neuroimage **26** (2005), 132–140.
[12] C. Lebel, S. Caverhill-Godkewitsch and C. Beaulieu, Age-related regional variations of the corpus callosum identified by diffusion tensor tractography, Neuroimage **52** (2010), 20–31.
[13] F. Aboitiz, E. Rodríguez, R. Olivares and E. Zaidel, Age-related changes in fibre composition of the human corpus callosum: Sex differences, Neuroreport **7** (1996), 1761–1764.
[14] L.S. Allen, M.F. Richey, Y.M. Chai and R.A. Gorski, Sex differences in the corpus callosum of the living human being, J. Neurosci. **11** (1991), 933–942.
[15] G. Tsai and J.T. Coyle, N-acetylaspartate in neuropsychiatric disorders, ProgNeurobiol. **46** (1995), 531–540.
[16] R.D. Terry, R. DeTeresa and L.A. Hansen, Neocortical cell counts in normal human adult aging, Ann. Neurol. **21** (1987), 530–539.
[17] S.A. Wijtenburg, S.A. McGuire, L.M. Rowland, P.M. Sherman, J.L. Lancaster, D.F. Tate, L.J. Hardies, B. Patel, D.C. Glahn, L.E. Hong, P.T. Fox and P. Kochunov, Relationship between fractional anisotropy of cerebral white matter and metabolite concentrations measured using 1H magnetic resonance spectroscopy in healthy adults, Neuroimage **66** (2013), 161–168.
[18] S.A. Batouli, P.S. Sachdev, W. Wen, M.J. Wright, C. Suo, D. Ames and J.N. Trollor, The heritability of brain metabolites on proton magnetic resonance spectroscopy in older individuals, Neuroimage **62** (2012), 281–289.