Diffusion Tensor Spectroscopy (DTS) of the Human Brain

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Introduction – Diffusion Tensor Imaging (DTI) of water can provide a measure of the metabolic status (i.e. cytotoxic edema) and microstructural integrity of the brain. However, changes in water diffusion are not localized to a specific compartment of the brain whereas brain metabolites, such as N-acetyl aspartate (NAA), are known to be located primarily in the intra-cellular space of neurons and axons. Investigation of the diffusion properties of the brain metabolites using diffusion-weighted spectroscopy (DWS) may yield insights into changes in the underlying intracellular environment with disease. Four published studies have reported diffusion parameters of metabolites in the human brain. The apparent diffusion coefficients (ADC) of N-acetyl aspartate (NAA), creatine and phosphocreatine (tCr), and choline (Cho) were measured along one diffusion direction in the periventricular white matter (1,2). In order to eliminate directional bias, the rotationally invariant trace/3 ADC of those same metabolites was reported in two distinct regions, one primarily gray matter and the other primarily white matter (3). A recent study that measured diffusion in two directions demonstrated a 2-3 fold greater ADC for NAA diffusion parallel to the axonal direction, relative to perpendicular, of the splenium of the corpus callosum in 2 volunteers (4). Although this study demonstrated anisotropy of NAA diffusion, the full diffusion tensor has not been evaluated for any metabolite in human brain. The purpose of this study was to measure the diffusion tensor of NAA, tCr, and Cho in the healthy human brain in two distinct regions and to calculate the Fractional Anisotropy (FA), Trace/3 ADC, and principal eigenvalues (i.e. directional ADCs) of those metabolites.

Methods – Five healthy volunteers (ages 23-30) were scanned on an SMIS 3T MRI equipped with a maximum gradient strength of 20mT/m. An in-house single-voxel, diffusion-weighted STEAM (STimulated Echo Acquisition Mode) sequence was used to measure the diffusion of the metabolites NAA, tCr, and Cho. The diffusion sequence parameters were: δ=15ms, Δ=208.3ms, TM=170ms, TE=76.6ms, TR=3s. Two regions were studied consisting of either a 2 x 2 x 3 cm^3 voxel surrounding the splenium of the corpus callosum (Figure 1A), or a 2.5 x 2.5 x 2.5 cm^3 voxel located in the occipital gray matter along the midline (Figure 1B). Phantom studies were done using a 125 mL sphere containing a solution of NAA (30mM), tCr (30mM), and Cho (10mM). The gradients were calibrated with this phantom to the tCr ADC at 20°C (0.80 x 10^{-3} mm^2/s) (5). Twelve spectra were acquired (6 spectra at low b, 654 s/mm^2, and 6 spectra at high b, 1890 s/mm^2) for each region in six different directions [(-1,-1,0), (-1,0,-1), (0,-1,-1), (1,-1,0), (1,0,-1),(0,1,-1)], where (G_x, G_y, G_z) signifies the diffusion sensitizing gradient direction. Sixty-four single average spectra were acquired for the metabolite spectra, and were individually phased (zero and first order, zero on the NAA peak) prior to summing the spectra, which was required to correct for motion induced phase errors between individual spectra.

Results and Discussion – Phantom Study: The eigenvalues, FA, and Trace/3 ADC of NAA, tCr, and Cho are listed in Table 1A. The trace/3 ADC values agree with the previous literature values of 0.6-0.9x$10^{-3}$$mm^2/s$, 0.8x$10^{-3}$$mm^2/s$ and 0.9-1.3x$10^{-3}$$mm^2/s$ for NAA, tCr and Cho, respectively (5). The low FA values of 0.11-0.13 indicate isotropic diffusion, although the observed differences in the three eigenvalues are due to sorting bias of noisy data. In Vivo Study: The Trace/3 ADC values in the occipital gray matter (GM) (Table 1B,C) agree with previously reported trace/3 ADC values obtained with only 3 diffusion gradient directions (3). The FA value in the splenium of the corpus callosum was significantly larger than the FA in the occipital gray matter region for NAA (p=0.018) and Cho (p=0.005); however, this difference was not seen for tCr (p=0.78). The reported water FA values are 0.22 and 0.75 in the cortical gray matter and the splenium of the corpus callosum, respectively (6), and therefore, the higher FA of NAA in the corpus callosum was expected due to the highly ordered nature of the axons. The parallel diffusivity (λ_1) and trace/3 ADC values in the corpus callosum region were significantly greater for NAA than in the occipital GM region ($p<0.001$ and $p=0.002$, respectively). The parallel diffusivity in the splenium of the corpus callosum (0.33 x 10^{-3} mm^2/s) in our study demonstrates an ~3 fold increase, relative to the perpendicular [(λ_2+ λ_3) / 2, 0.13 x 10^{-3} mm^2/s] which is consistent with two direction diffusion measurements from that same region (4). The FA in the occipital GM region for all three metabolites is higher than was expected based on the water FA in cortical gray matter of 0.22 (6); however, this may be due to partial volume inclusion of white matter due to the large voxel size. The FA values for tCr and Cho appear to be greater than for NAA in both regions, and although the origin of this is unclear, it may reflect their lower SNR. In summary, this study provides the first report of tensor-derived fractional anisotropy of intra-cellular metabolites in the human brain, which could be useful in examining micro-structural changes associated with disease.

References: (1) Posse et al. *Radiology*, 1993; 188:719-725. (2) Harada et al. *NMR Biomed*, 2002; 15:69-74. (3) Ellegood et al. Proc. ISMRM, Kyoto, 2004, p.1417. (4) Kroenke et al. *MRM*, 2004; 52:1052-1059. (5) Nicolay et al. *NMR Biomed*, 1995; 8:365-374. (6) Bhagat et al. *JMRI*, 2004, 20:216-227.

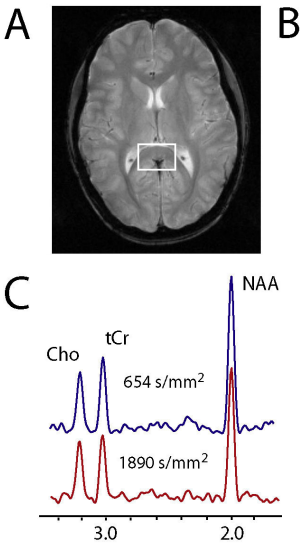

Figure 1 – **A**) Voxel location for the corpus callosum region. **B**) Voxel location in the occipital gray matter. **C**) Example spectra at low and high b-values from the occipital gray matter region (B).

Table 1 – Diffusion Tensor values for NAA, tCr, and Cho in an in-vitro phantom, and two regions in the human brain.

Metabolite	Eigenvalues (x$10^{-3}$$mm^2/s$)			FA	Trace/3 ADC (x$10^{-3}$$mm^2/s$)
	λ1	λ2	λ3		
A) Phantom (n=8)					
NAA	0.68±0.05	0.61±0.02	0.55±0.02	**0.11±0.04**	0.62±0.02
tCr	0.91±0.05	0.79±0.02	0.73±0.02	**0.11±0.03**	0.81±0.02
Cho	1.08±0.06	0.93±0.03	0.84±0.02	**0.13±0.03**	0.95±0.03
B) Occipital Gray Matter (n=5)					
NAA	0.20±0.03	0.12±0.01	0.09±0.02	**0.40±0.08**	0.14±0.01
tCr	0.35±0.06	0.21±0.05	0.06±0.03	**0.62±0.06**	0.21±0.04
Cho	0.32±0.06	0.23±0.07	0.06±0.02	**0.57±0.04**	0.20±0.04
C) Corpus Callosum (n=5)					
NAA	0.33±0.04	0.18±0.05	0.08±0.05	**0.58±0.11**	0.20±0.03
tCr	0.52±0.09	0.33±0.08	0.09±0.06	**0.60±0.08**	0.32±0.06
Cho	0.42±0.09	0.27±0.04	0.03±0.02	**0.68±0.05**	0.24±0.04