Diffusion Tensor Spectroscopy of Myo-Inositol in Human Brain

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Introduction - Diffusion Tensor Imaging (DTI) of water has become important for brain studies; however, interpretation is complex since tissue water is known to include contributions from exchanging intra- and extracellular water. Examining a single compartment might provide a more accurate assessment of the underlying cellular environment. Purely intracellular metabolites such as N-acetyl aspartate (NAA) and myo-inositol (mI), may be useful in differentiating between different compartments in brain. mI is known to be located primarily in the glial cells such as astrocytes (1), whereas NAA is thought to be located primarily in the neurons and axons (2). While Diffusion Tensor Spectroscopy (DTS) of the metabolites NAA (3-5), creatine/phosphocreatine (tCr) and choline (Cho) (3) have been performed previously in human brain; DTS of mI has not been measured and poses a greater challenge given its lower concentration. The purpose of this study was to use DTS to measure the diffusion characteristics of mI in the gray and white matter of human brain.

Methods - All experiments were performed on a SMIS 3T MRI equipped with a maximum gradient strength of 20 mT/m. An in-house single voxel, diffusion weighted PRESS sequence, which was optimized for the detection of mI based on previous non diffusion spectroscopy simulations and experiments (6), was used with a TE_1 of 36 ms, and a TE_2 of 160 ms to measure the diffusion of NAA, tCr, Cho, and mI. In-vivo DTS spectra were obtained from two regions in the human brain of 5 volunteers (ages 22-36 years). Both regions were investigated using a 2.7 x 2.7 x 2.7 cm^3 voxel located in either the occipital gray matter (OGM, Figure 1A), or the subcortical white matter (SWM, Figure 1B). ADCs were calculated in six different directions: [(1,1,0), (1,0,1), (0,1,1), (-1,1,0), (-1,0,1), and (0,1,-1)] , where (Gx, Gy, Gz) signifies the diffusion sensitizing gradient direction. Two b-values of 347 and 5018 s/mm^2 (δ = 36 ms and Δ = 87 ms) were used per direction. We acquired sixty-four single average spectra for a total measurement time of ~43 min for the set of 12 metabolite spectra. Zero order phase correction was performed on the residual water peak in the 64 single average metabolite spectra prior to summation and quantification. The upper b value is much higher than earlier DTS studies which used b~2000 s/mm^2 and was chosen to yield more accurate two point measurements of the low metabolite ADCs (7).

Results and Discussion – Table 1 lists the Eigenvalues, Trace/3 ADC, and FA for the SWM and the OGM regions in the human brain. Trace/3 ADCs of the four metabolites do not differ between the white and gray matter regions, in agreement with the similar Trace/3 ADCs between the same two regions in adult human brain (8). The Trace/3 ADC of mI was found to be significantly smaller in SWM and OGM region when compared to NAA (note that NAA and mI have similar ADCs in aqueous solution). The smaller Trace/3 ADC of mI seems to indicate a greater environmental restriction than seen with NAA, which is confirmed by the significantly smaller λ_1 eigenvalue of mI. A significant increase in the FA of all four metabolites was found in the white matter region when compared with the gray matter region. This significant FA difference was not seen previously between the gray and white matter regions when lower b values of 1900 s/mm^2 were used for DTS (3). The mI FA value was also increased in the white matter, which was unexpected since mI is thought to be mainly located in glial cells, presumably isotropic structures. Judging by the FA of mI in the SWM it is debatable whether mI is actually in an isotropic compartment in the SWM region, or perhaps the glial cells are quite elongated within the white matter tracts. The FA of 0.54 ± 0.12 for mI is similar to that of NAA (0.47 ± 0.13) in the SWM. The mI data presented in the SWM could be artefactually high, however, due to the much lower SNR for mI (6.7 ± 1.0, at low b-value) when compared to NAA (43.0 ± 6.3), tCr (17.5 ± 2.7), and Cho (18.5 ± 4.1). However, the FA of mI is low in the cortical gray matter which also has a low SNR of 11.5 +/- 1.9. Although the veracity of these results need to be confirmed, they are the first reported measurements of the diffusion properties of mI in human brain.

References – 1) Brand et al. Dev Neurosci, 1993, 15:289-298. 2) Bhakoo et al. J Neurochem, 1996, 66:1254-63. 3) Ellegood et al. MRM, 2006, 55:1-8. 4) Upadhyay et al. MRM, 2007, 58:1045-1053. 5) Upadhay et al. Neuroimage, 2007 (published online). 6) Kim et al. MRM, 2005, 53:760-769. 7) Bedet et al. Chemical Physics Letters, 2005, 408:237-240. 8) Ellegood et al. MRM, 2005, 53:1025-1032.

Table 1 – Eigenvalues, Trace/3 ADC, and FA of two regions in the Human Brain.
* indicates a significant difference ($p<0.05$) when compared to the OGM region.

Metab.	ADC (x 10^{-3} mm^2/s)				Fractional Anisotropy
	λ_1	λ_2	λ_3	Trace/3	
Subcortical White Matter Region (N=5)					
NAA	0.33 ± 0.08*	0.19 ± 0.03	0.12 ± 0.02	0.21 ± 0.02	0.47 ± 0.13*
tCr	0.32 ± 0.07*	0.19 ± 0.02	0.09 ± 0.02	0.20 ± 0.02	0.51 ± 0.13*
Cho	0.26 ± 0.06	0.15 ± 0.05	0.08 ± 0.01	0.16 ± 0.02	0.51 ± 0.14*
mI	0.25 ± 0.06	0.14 ± 0.02	0.06 ± 0.02*	0.15 ± 0.02	0.54 ± 0.12*
Occipital Gray Matter Region (N=5)					
NAA	0.23 ± 0.03	0.18 ± 0.03	0.14 ± 0.03	0.18 ± 0.02	0.25 ± 0.10
tCr	0.24 ± 0.03	0.19 ± 0.02	0.13 ± 0.03	0.19 ± 0.02	0.30 ± 0.07
Cho	0.21 ± 0.03	0.17 ± 0.02	0.12 ± 0.03	0.17 ± 0.03	0.28 ± 0.06
mI	0.18 ± 0.03	0.15 ± 0.03	0.11 ± 0.03	0.15 ± 0.03	0.25 ± 0.08

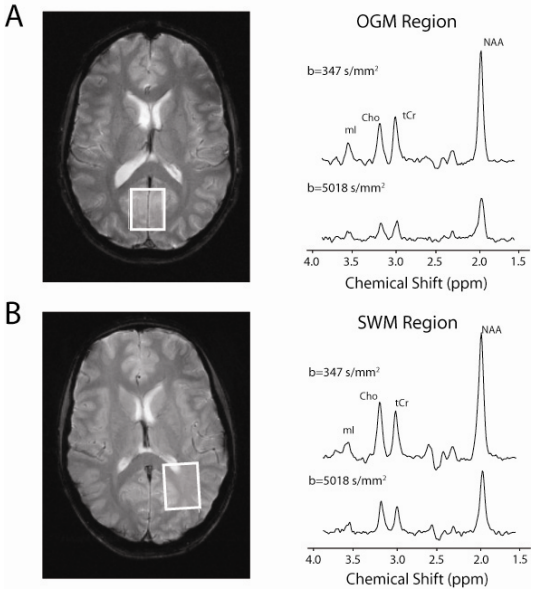

Figure 1 – The four metabolites peaks are clearly visible at both low and high b-value for both (A) occipital gray matter (OGM) and (B) subcortical white matter (SWM). Notice the considerably lower SNR of the mI peak.