Early neonatal brain development: Correlation between DTI and MRS

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INTRODUCTION: Cellular-level changes in the developing brain, such as changes related to myelination, can be indirectly tracked using non-invasive MR techniques including diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS). While DTI measures the motion of water molecules reflecting cellular microstructure, MRS measures brain metabolite concentrations. Each technique represents independent measures related to brain development, and combining the two techniques can provide complementary information regarding brain changes. Previous work that combined the two techniques evaluated various disease states[1,2], but no studies have combined these two modalities to examine the rapidly developing neonatal brain. Therefore, we aim to evaluate the relationships between MRS and DTI measures during normal early brain development.

METHODS: Thirty healthy, full-term infants (birth age: 39.2 ± 1.5 weeks post-conception) were scanned 1-3 times between the ages of 4 days (first visit) and 3 months (third visit; post-conceptional age: 42.6 ± 3.6 weeks). Mothers who reported prenatal drug use, other than nicotine or light alcohol use (<3 drinks/month), were excluded. Localized ^{1}H MRS was performed using a 3 Tesla Siemens Trio MR scanner in five brain regions: medial frontal gray matter (FGM), right frontal white matter (FWM), right basal ganglia (BG) , medial thalamus (TLM) , and left corticospinal tract (CST). In each region, the concentrations of total Creatine (tCr), total Choline (CHO), Myo-Inositol (MI), N-Acetyl-Aspartate (NA), and Glutamine+Glutamate (GLX) were measured using a standard PRESS acquisition sequence (TR/TE=3000/30ms, 48 averages) with absolute quantitation[3,4]. Additionlly, all infants were imaged using a 12 direction echo-planar DTI sequence (128x128 resolution, 3mm slices, b = (0,1000)s/mm^2). Infants were scanned during unsedated sleep. The mean values of fractional anisotropy (FA) and average diffusion coefficient (ADC) across the MRS voxels were calculated using a custom Matlab program that registered MRS voxel coordinates into the DTI image space.

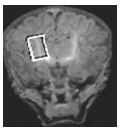

Table 1: Age-dependent changes in MRS and DTI measures (correlation with post conceptional age and MRS or DTI values by region).

	BG	FGM	FWM	CST	TLM
NA	R=0.50 P=0.01	R=0.81 P=< 0.0001	R=0.80 P=< 0.0001	R=0.67 P=< 0.0001	R=0.42 P=0.02
tCr	NS	R=0.57 P=0.006	R=0.50 P=0.02	NS	NS
MI	NS	NS	NS	R=-0.62 P=0.0004	R=-0.56 P=0.002
CHO	NS	NS	NS	R=-0.40 P=0.03	R=-0.48 P=0.009
GLX	NS	R=0.51 P=0.003	R=0.52 P=0.004	R=0.43 P=0.02	NS
FA	R=0.50 P=0.01	NS	R=0.61 P=0.002	R=0.42 P=0.02	R=0.33 P=0.08
ADC	R=-0.48 P=0.02	NS	R=-0.74 P=< 0.0001	R=-0.70 P=< 0.0001	R=-0.36 P=0.06

RESULTS: Diffusion and metabolite measures independently showed expected developmental changes. FA values increased and ADC values decreased with age in all regions except in the FGM (**Table 1**). NA increased with age across all regions, tCr increased only in FGM and FWM, and GLX increased in FGM, FWM, and in the CST. In contrast, MI and CHO decreased with age in the CST and TLM. These measures also showed developmental changes when correlated. The NA increase in FWM was closely associated with an increase in FA but a decrease in ADC (**Figure 1, left**). Similarly increases in both NA and GLX in the CST were associated with decreased ADC (**Figure 1, middle, right, Table 2**). Decreased MI in the CST was associated with increased FA and decreased ADC and increasing tCr and decreasing CHO in FGM were associated with decreasing ADC.

Table 2: Correlations of DTI and MRS by region and metabolite.

	BG		FGM		FWM		CST		TLM	
	FA	ADC	FA	ADC	FA	ADC	FA	ADC	FA	ADC
NA	NS	NS	NS	NS	R=0.61 P=0.003	R=-0.83 P=< 0.0001	NS	R=-0.65 P=0.0002	NS	R=-0.34 P=0.07
tCr	NS	NS	NS	R=-0.50 P=0.01	R=0.30 P=0.19	R=-0.53 P=0.01	NS	NS	NS	NS
MI	R=-0.31 P=0.12	NS	R=0.37 P=0.10	NS	NS	NS	R=-0.61 P=0.0006	R=0.51 P=0.005	NS	R=0.34 P=0.07
CHO	R=-0.30 P=0.16	NS	R=-0.30 P=0.18	R=-0.45 P=0.04	NS	NS	NS	R=0.28 P=0.15	NS	NS
GLX	NS	NS	NS	R=-0.34 P=0.12	NS	R=-0.34 P=0.08	R=0.34 P=0.07	R=-0.52 P=0.004	NS	NS

DISCUSSION: Correlating DTI and MRS measurements provides some specific information about the developing brain that cannot necessarily be inferred from either measure alone. Consistent with ongoing early brain development, age-related increases in FA and decreased ADC in the frontal WM reflect more coherent fiber organization occurring while the increased NA indicate axonal growth. Similar results were also seen in the rapidly developing corticospinal tract with the addition of decreased MI which suggests myelination or reductions in radial glia. Changes in tCr and CHO in the frontal gray matter combined with a decrease in ADC suggest cellular pruning. Future analyses will further explore these relationships to determine what drives brain development.

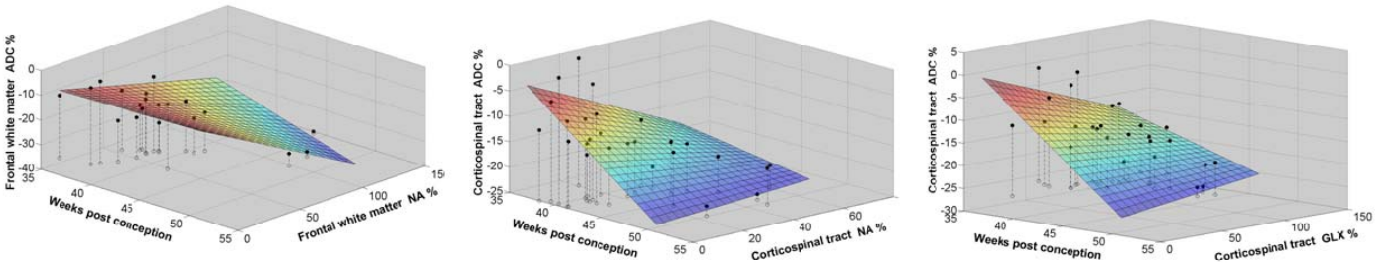

Figure 1: Percent ADC and metabolite represent the percent change with post-conceptional age relative to the highest ADC value or lowest metabolite value of a first-visit subject. ADC decreases with age and indendently with NA in the FWM (left) as well as in the CST (middle). Similarly, CST ADC decreases with age and as GLX increases (right).

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