The Relation between Free-Water, Atrophy and Microstructural Pathologies in Retired NFL Players – A Combined Diffusion MRI and MRS study

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TARGET AUDIENCE Scientists and clinicians developing or applying diffusion MRI methods. Scientists or clinicians studying neurodegenerative disorders, and in particular brain injuries, sports related concussions and chronic traumatic encephalopathy.

PURPOSE Many recent diffusion models include a compartment of free-water that accounts for water molecules that are in the extra-cellular space and are not bound by tissue membranes. Accounting for the contribution of free-water is important in order to eliminate partial volume effects, such as cerebrospinal fluid (CSF) contamination[1], making the remaining signal more specific to changes that occur within the tissue. In addition, changes in the extracellular space might have clinical correlates, and could be surrogate markers for neurodegenerative processes such as atrophy and neuroinflammation[2]. While complex diffusion models with a free-water compartment (e.g., CHARMED, NODDI, DBSI) typically require sophisticated acquisition methods, the free-water compartment can also be estimated from a conventional DTI data, using the free-water imaging method[3]. In order to better characterize the possible association of the free-water compartment with underlying pathology, we acquired diffusion MRI and MRS on a cohort of retired National Football League (NFL) players who are at high risk for having chronic traumatic encephalopathy (CTE)[4], and controls. We identified metabolite changes that can explain differences in free-water volume between the groups, or that correlate with the free-water imaging measure.

METHODS Forty-nine retired NFL players at high risk for CTE resulting from multiple subconcussive blows to the head, and 14 controls (retired non-contact sport athletes) received multimodal MRI scans. Short-echo single-voxel MRS (PRESS, TE=35ms, TR=2s, 128 avgs) was acquired from 2X2X2 cm^3 regions of interest (ROI) defined in the parietal white matter (PWM) and in a predominantly gray matter area in the post-cingulate gyrus (PCG). Free-water maps (FW) and free-water-corrected maps of radial diffusivity (RDt) were computed from the diffusion MRI[3] (64 directions; b=900s/mm^2). The MRS ROIs were mapped onto the diffusion MRI space via nonlinear registration of the b0 image with a T2-weighted image, and a linear registration of the T2-weighted image with a T1-weighted image on which the MRS ROIs were defined. Gray matter, white matter, and CSF volumes were extracted from the T1-weighted image and used in addition to unsuppressed water signal from the same ROI to calculate concentrations of individual brain metabolites, using a linear combination model analysis. CSF voxels were excluded from the ROIs (Fig. 1). Group comparisons were carried out using a t-test. Correlation tests over the NFL players, between the average free-water measures within each ROI and the metabolite concentrations, were carried out using Pearson correlation.

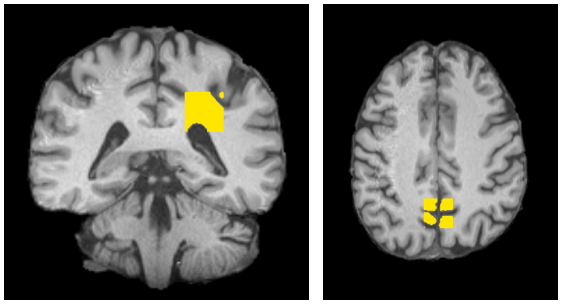

Fig.1: MRS regions of interest on the parietal white matter (PWM; left) and the posterior cingulate gyrus (PCG; right) were defined. CSF voxels were excluded. Free-water imaging measures were averaged within each ROI and correlated with metabolite counts.

RESULTS The FW measure was significantly lower in the PCG of the NFL players compared to controls (p=0.0012). There were no significant FW or RDt group differences in the PWM. N-acetylaspartate (NAA) was negatively correlated with the FW measure both in the PCG (R=-0.48; p=0.0008) and in the PWM (R=-0.42; p=0.0055). NAA also correlated with RDt in the PWM (R=-0.47; p=0.0014). Using the NAA measure as a covariate showed, in the PWM, that FW was correlated with Glutamate (Glu; R=0.42; p=0.0053), and RDt was correlated with myo-inositol (Ins; R=0.42; p=0.0061). In the PCG, covarying for NAA showed that FW was negatively correlated with Ins (R = -0.33; p = 0.027) and with Creatine (R = -0.41, p = 0.0054)

DISCUSSION The NAA metabolite is a putative marker of neuronal density[5]. Thus, the correlation between FW and NAA suggests that FW is primarily associated with atrophy, and reflects a neurodegenerative process of neuronal loss and excessive extracellular space. At the same time, this correlation shows that NAA is sensitive to partial volume in the MRS ROI. Moreover, the correlation between RDt and NAA suggests that changes in white matter density also affect the microstructural domain, increasing the overall diffusivity. We note that similar correlations with NAA were recently reported for another diffusion model[6]. Secondary correlations were revealed by controlling for NAA, demonstrating the sensitivity of the FW measure to additional pathologies. For example, the correlation of FW with Glu suggests sensitivity to excitotoxicity, which in turn changes the volume of the extracellular space. Neuroinflammation is a by-product of excitotoxicity through the activation of microglia via proinflammatory cytokines[7]. This relation is further supported by the correlation of RDt with Ins, which is indicative of gliosis, i.e., microglia and astrocyte activation and proliferation. Comparisons between the two groups demonstrate changes in the NFL cohort in gray matter but not in white matter. This is consistent with a previous study of chronic traumatic brain injury subjects that demonstrated changes in the gray matter, consistent with gliosis[8]. Since the ROIs used here are limited to two specific brain areas, it is certainly possible that changes occur outside of these areas.

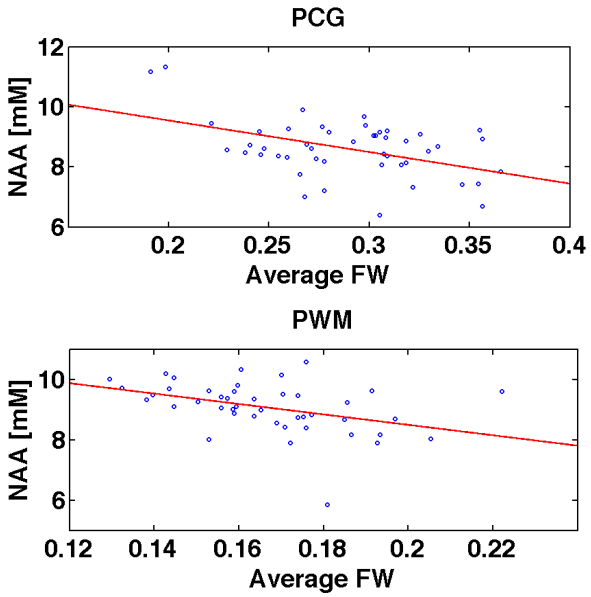

Fig.2: The free-water volume was primarily correlated with N-acetylaspartate (NAA) in the PCG and PWM. Covarying for NAA revealed secondary correlations with glutamate, myo-inositol, and creatine.

CONCLUSIONS Combining the information from MRS and DTI provides a technique to identify subtle, secondary sensitivities in addition to atrophy. We are currently working on generalizing the comparison to take advantage of the higher resolution of the diffusion space. Taken together, this work demonstrates that the free-water compartment can be utilized to identify pathologies, in addition to eliminating partial volume effects.

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