Proton MR spectroscopy correlates diffuse axonal injury with post-concussive symptoms in mild traumatic brain injury

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TARGET AUDIENCE: MR application scientists/neurologists/radiologists interested in imaging markers for traumatic brain injury.

PURPOSE: There are no established biomarkers for mild traumatic brain injury (mTBI), in part because post-concussive symptoms (PCS) are subjective and conventional imaging is typically unremarkable. To test whether diffuse axonal injury (DAI) quantified with three-dimensional (3D) proton magnetic resonance spectroscopic imaging (^{1}H-MRSI) correlated with patients' PCS we studied 26 mTBI patients (mean Glasgow Coma Scale score (GCS) of 14.7) and 13 controls.

METHODS: The previously described 26 patient cohort[1] was recruited serially based on history of closed head trauma, GCS score of 13-15, loss of consciousness of 30 minutes or less and post-traumatic amnesia under 24 hours. 13 age- and gender-matched healthy controls were also enrolled. Based on a review of 11 original research articles, a 2004 report by the World Health Organization Collaborating Center Task Force on mTBI classified the following as the most common acute self-reported mTBI symptoms: headache, dizziness, sleep disturbance, memory problems and blurred vision[2]. On scan day, patients completed a 'yes' or 'no' questionnaire whether they were experiencing any of these five symptoms, which they attributed to the trauma. Patients reporting at least one symptom were grouped as "PCS-positive", whereas the rest were defined as "PCS-negative".

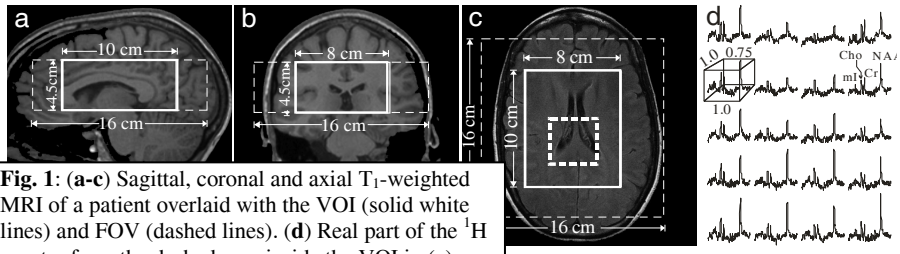

Fig. 1: (**a-c**) Sagittal, coronal and axial T_1-weighted MRI of a patient overlaid with the VOI (solid white lines) and FOV (dashed lines). (**d**) Real part of the ^{1}H spectra from the dashed area inside the VOI in (**c**).

All measurements and post-processing have been previously described[1]. In short, the 10×8×4.5=360 cm^3 ^{1}H-MRSI volume of interest (VOI) (6 slices, 80 voxels per slice, each 0.75 cm^3) was image-guided over the corpus callosum, as shown in **Fig. 1** and two averages were obtained. After segmentation of the MP-RAGE images, the resultant cerebro-spinal fluid (CSF), gray matter (GM) and white matter (WM) masks were co-registered with the ^{1}H-MRSI grid using in-house software, yielding their volume in every voxel in each subject. Absolute metabolite amounts of *N*-acetylasparte (NAA), creatine (Cr), choline (Cho) and *myo*-inositol (*m*I) were obtained using phantom replacement with correction for differences in T_1 and T_2 relaxation time. Global GM and WM concentrations were calculated for each metabolite using linear regression[3]. Two-way analysis of variance was used to compare each patient group to the cohort of controls matched to them in terms of each metabolite within GM and WM. The indicator variable identifying subjects that were matched to each other was included as a blocking factor. The error variance was allowed to differ across comparison groups. The Cohen's *d* statistic was calculated as a measure of effect size for the difference between each patient group and the cohort of controls matched to them in terms of each metabolite within GM and WM.

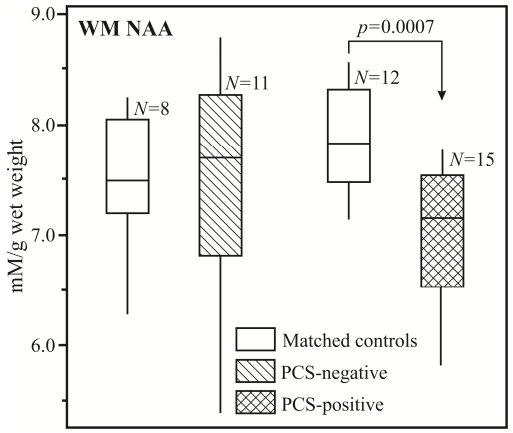

Fig. 2 Box plots displaying 25%, median and 75% (box) and 95% (whiskers) of the NAA concentrations distributions in the WM of post-concussive symptom (PCS)-negative and PCS-positive mTBI patients compared with their age- and gender-matched controls. Note that a highly significant ($p<10^{-3}$) NAA deficit is observed only in the PCS-positive cohort.

RESULTS: There were no statistical differences in the GCS score or time from injury between the PCS-positive (n=15) and the PCS-negative (n=11) groups. None of the concentrations of any metabolite either in GM or WM were different between the PCS-negative patients and their age- and gender-matched controls (n=8). PCS-positive patients had normal GM NAA, Cr, Cho and *m*I, as well as normal WM Cr, Cho and *m*I, but significantly lower WM NAA than their age- and gender-matched controls (n=12): 7.0±0.6 *versus* 7.9±0.5 mM, p=0.0007, as shown in **Fig. 2**. Based on its Cohen's *d* value of 1.65, the effect size of this difference is defined as 'large'.

DISCUSSION: DAI is the hallmark TBI injury, thought to occur across the entire clinical TBI spectrum, including patients with GCS=15 and normal neuroimaging. To be able to detect it in this population we previously used two ^{1}H-MRSI post-processing approaches developed specifically for increased sensitivity to diffuse disease[3, 4]. We found decreased global WM NAA, but no other metabolic abnormalities either in WM or GM, and these results were interpreted as DAI without glial involvement or cell body injury.[1] Here we report that the WM NAA decrease can be entirely ascribed to those patients who reported at least one PCS at the time of scanning. The association was robust statistically (Cohen's *d* = 1.65), even despite the relatively small sample sizes.

CONCLUSION: In cohorts representative of patients for whom there are no established radiological or clinical measures of outcome, global WM NAA levels were lower in PCS-positive patients, but were normal in the PCS-negative group. This indicates that global WM NAA is sensitive to the DAI sequelae underlying common subacute mTBI symptoms.

REFERENCES:

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