Metabolic characterization of gray and white matter in mild traumatic brain injury with 3D proton MR spectroscopy

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INTRODUCTION: Traumatic brain injury (TBI) is a leading cause of neurological disability in all age groups. The vast majority (~85%) of patients are classified with ‘mild’ TBI (mTBI), a diagnosis most often based solely on history and symptomatology. Imaging biomarkers for diagnosis and prognosis are, unfortunately, not available since the clinically used T1-, T2-weighted MRI and CT are usually unremarkable. Quantitative MR metrics detect abnormalities in normal-appearing tissue, but there are conflicting reports on the sites and type of injury. This suggests that in mTBI, any damage is diffuse, heterogeneous and minimal. This scenario calls for a global approach with increased specificity and sensitivity. In this proton MR spectroscopy (1H-MRS) study comprehensive coverage was achieved with a 360 cm3 volume-of-interest (VOI) (~30% of brain) centered on the corpus callosum. For increased specificity and sensitivity, the neuronal health, membrane turnover and glial status of all gray and white matter inside the VOI was assessed via absolute quantification of N-acetylaspartate (NAA), choline (Cho), creatine (Cr) and myo-inositol (mI).

METHODS: 22 subacute (mean time from TBI 19 days, range 3-54), patients (mean age 32, range 18-56, 4 women) were scanned at 3 T. Enrollment is on-going. 4 were on medication and 13 reported at least one post-concussion symptom at time of scanning. Eleven matched controls (mean age 34, 4 women) were also enrolled. The 10 cm × 8 cm × 4.5 cm 1H-MRS VOI was centered on the corpus callosum as shown in Fig. 1, and excited with T2/TR = 35/1800 ms PRESS in 3 sequentially-acquired slabs each with 2nd order Hadamard-encoding in the IS direction (1). The 16 cm × 16 cm × 4.5 cm3 field-of-view (FOV) containing the VOI was partitioned into 1.0 cm × 1.0 cm × 0.75 cm3 voxels with 16 cm × 16 cm 2D chemical-shift imaging matrix, yielding 480 nominal voxels. Their spectra were frequency aligned and relative NAA, Cr and Cho levels were estimated from their peak area using SITools software (2). MP-RAGE MRI was segmented with SPM2 (3) and the resulting GM and WM masks were co-registered with the 1H-MRS using in-house software as shown in Fig. 2. Each 0.75 cm3 voxel was assigned a fractional GM, WM and CSF value (Fig. 2) and an equation: \[ f_{\text{WM}} \times C_{\text{WM}} + f_{\text{GM}} \times C_{\text{GM}} + f_{\text{CSF}} \times C_{\text{CSF}} = Q \], where \( f \) is the WM, GM or cerebro-spinal fluid (CSF) fraction inside the voxel and \( Q \) is the relative level of the specific metabolite (m) inside the voxel. The resulting 480 equations (per metabolite) were solved using least-squares and by assuming no metabolites in the CSF, i.e. \( C_{\text{CSF}} = 0 \). The average relative metabolic levels in GM and WM were converted into absolute concentrations using phantom replacement, incorporating corrections for \( T_1 \) and \( T_2 \) differences between in vivo and in vitro. Two-way analysis of variance (ANOVA) was used to compare patients to controls with respect to each measure, while accounting for the matching of the comparison groups in terms of age and gender. All reported \( p \) values are two sided except for NAA since the metabolite is expected to decrease in almost all pathologies.

RESULTS: Patients’ average GM and WM concentrations of Cho, Cr and mI were not different from controls’ \( p=0.5 \). There was a trend for NAA decrease in the WM of patients’ \( p=0.078 \), but not in the GM \( p=0.6 \) (Fig. 3). We also compared metabolic concentrations between GM and WM within each cohort: only Cr and mI were different in controls, but all metabolites were significantly different in patients. Total brain volume, as well as brain volume inside the VOI, was not different between patients and controls.

CONCLUSION: In the sub-acute stage of mTBI, there is no evidence of brain atrophy, glial or energy abnormalities (normal brain volumes, Cho, mI and Cr), but there is a statistical trend suggesting axonal damage (reduced NAA, \( p=0.078 \)). Based on the model of diffuse axonal injury (4), this may represent neuronal dysfunction or death. Longitudinal follow-up from the acute to chronic stage of TBI and patient stratification based on complaints and recovery are needed to substantiate the current findings.


![Fig. 2 Top: Gray (a) and white (b) matter masks segmented from T1-weighted MRI using SPM software. Bottom: The same masks overlaid with the 1H-MRS VOI, in which each voxel is shaded based on the fraction of GM (e) and WM (d) tissue inside it (brighter red signifying higher fraction).](image)

![Fig. 3: Boxplots of the average concentration of NAA in all of the WM and GM inside the 1H-MRS VOI. Note a trend for WM NAA decrease in the patients.](image)