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 (^{1}H-MRS) study comprehensive coverage was achieved with a 360 cm^3 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 (*m*I).

METHODS: 22 sub-acute (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 $10_{AP}\times8_{LR}\times4.5_{IS}$ = 360 cm^3 ^{1}H-MRS VOI was centered on the corpus callosum as shown in **Fig. 1**, and excited with *TE*/*TR* = 35/1800 ms PRESS in 3 sequentially-acquired slabs each with 2nd order Hadamard-encoding in the IS direction (1). The $16_{AP}\times16_{LR}\times 4.5_{IS}$ cm^3 field-of-view (FOV) containing the VOI was partitioned into $1.0_{AP}\times1.0_{LR}\times 0.75_{IS}$ = 0.75 cm^3 voxels with $16_{AP}\times16_{LR}$ 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 ^{1}H-MRS using in-house software as shown in **Fig. 2**. Each 0.75 cm^3 voxel was assigned a fractional GM, WM and CSF value (**Fig. 2**) and an equation: $f^{WM}\times C^{WM} + f^{GM}\times C^{GM} + f^{CSF}\times C^{CSF} = Q^m$, 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.* $C^{CSF} = 0$. 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.

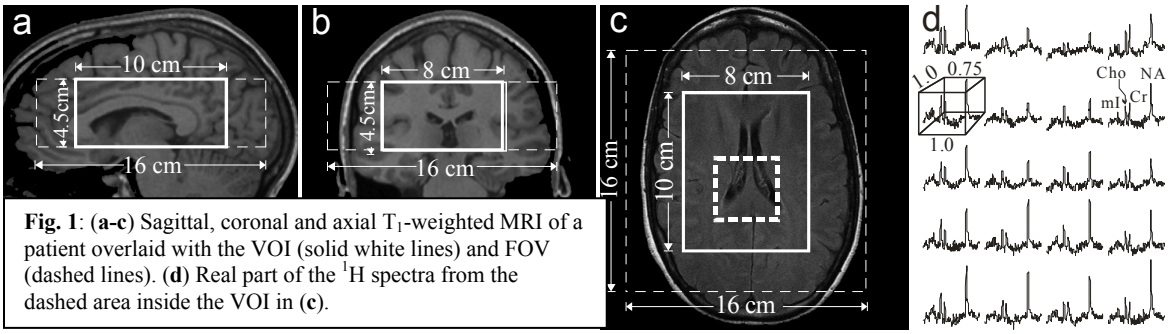

Fig. 1: (**a-c**) Sagittal, coronal and axial T_1-weighted MRI of a patient overlaid with the VOI (solid white lines) and FOV (dashed lines). (**d**) Real part of the ^{1}H spectra from the dashed area inside the VOI in (**c**).

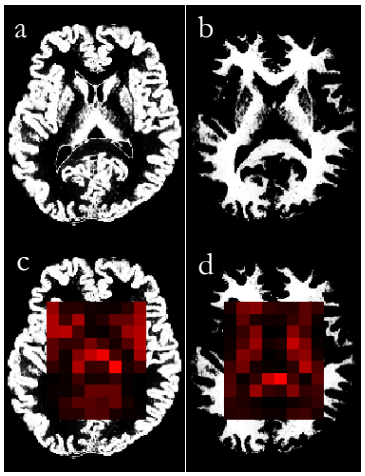

Fig. 2 Top: Gray (**a**) and white (**b**) matter masks segmented from T_1-weighted MRI using SPM software. Bottom: The same masks overlaid with the ^{1}H-MRS VOI, in which each voxel is shaded based on the fraction of GM (**c**) and WM (**d**) tissue inside it (brighter red signifying higher fraction).

RESULTS: Patients' average GM and WM concentrations of Cho, Cr and *m*I 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 *m*I 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, *m*I 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.

REFERENCES: (1) Gonen, MRM 1998
(2) Soher, MRM 1998 (3) Ashburner, Neuroimage 1997
(4) Smith, J Head Trauma Rehabil. 2003

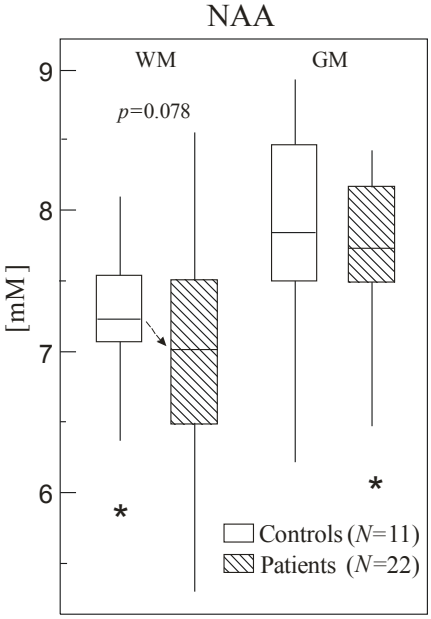

Fig. 3: Boxplots of the average concentration of NAA in all of the WM and GM inside the ^{1}H-MRS VOI. Note a trend for WM NAA decrease in the patients.