2218

1H MR spectroscopic imaging for identifying diffuse abnormalities in mild traumatic brain injury: initial results from a reproducibility study

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Synopsis

We present initial results from a reproducibility study of 1H MRSI in mild traumatic brain injury. In line with previous investigations in a separate cohort, linear regression analysis revealed white matter differences between patients and controls, which persisted when comparing only non-recovered patients to controls. In contrast to previous findings, however, the differences were not in N-acetyl aspartate (NAA), but in the glial markers creatine (Cr), choline (Cho), and myo-inositol (mi). Correlations were found between metabolites and neuropsychological testing in grey matter (GM), and between metabolites and symptomatology in white matter (WM).

Introduction

Traumatic brain injury (TBI) is a global health concern1, with mild TBI (mTBI) accounting for 75%-90% of cases2–3. TBI sequelae can be histologically explained by axonal varicosities known as diffuse axonal injury4–5, but this pathology is not detectable using conventional CT and MRI. Proton (1H) MRS is a technique sensitive to neurochemical alterations which may enable more precise evaluation of TBI severity and prognostication when macroscopic structural damage is lacking. N-acetyl-aspartate (NAA), glutamate plus glutamine (Glx), creatine (Cr), choline (Cho), and myo-inositol (mi), markers for neuronal integrity, glutamate cycle, cellular energy, membrane turnover, and astroglia, respectively, are altered after TBI. Unfortunately, varying results in regard to which metabolite(s) are most likely to be affected and what brain region(s) should be sampled, contribute to the limited clinical utility of MRS in TBI. 1H MR spectroscopic imaging (1H MRSI) has shed light on the regional distribution of metabolite findings, but a key part of translating the new knowledge to the clinic rests on determining how reproducible are the results of any particular study. We present initial data from a project intending to test the reproducibility of findings from previous studies6–12 with a different mTBI cohort, while keeping the following key parameters constant: MRSI post-processing (global linear regression), patient source (metropolitan ER and concussion clinic), proportion of complicated mTBI (mostly MRI-negative) and time from injury (~20 days post-TBI). Additionally, we are acquiring previously unavailable patient outcome measures, including neuropsychological testing. We hypothesized that, as previously reported10–12, abnormalities would be predominantly (1) diffuse, (2) confined to WM, (3) comprising of low NAA and normal glial markers; and that these findings would (4) correlate with clinical presentation.

Materials & Methods

17 mTBI patients (12 female, 33.2±9.9 years) within about one month after injury and 13 age- and gender-matched healthy controls (7 female, 30.1±8.8 years) were scanned at 3T (Siemens MAGNETOM Prisma) with a 20-channel transmit-receive head coil. Imaging parameters are outlined in Table 1A. 3D MPRIAGE was acquired for anatomical localization, along with FLAIR and SWI for radiological assessment. 1H MRSI was obtained with a whole-brain 3D EPSI sequence, as described previously3. Data were processed using the PRANA module within the Metabolica Imaging and Data Analyses System package, as described previously14,15. Spectra included in the analysis met the following quality criteria: Cramer–Rao lower bound (CRLB) <20% and linewidth 2–12 Hz. Voxels valued >3 standard deviations from the mean were defined as outliers and excluded16,17. Linear regression analysis was performed for eight bilateral atlas-defined lobar brain regions. Left and right hemispheric data were averaged to remove individual differences. The normal distribution of metabolite findings was confirmed using the Shapiro-Wilk test18. The association between metabolite concentrations and BTACT and RPQ. Statistical significance was defined as p<0.05.

Results

Demographics, clinical and neuropsychological testing results are compiled in Table 2A. At the time of scanning, two patients had recovered (GOSE=8). Examples of H MRSI results can be expected to vary within similar study designs. 1H MRSI in mild traumatic brain injury. In line with previous investigations in a separate cohort, linear regression analysis revealed white matter differences between patients and controls, which persisted when comparing only non-recovered patients to controls. In contrast to previous findings, however, the differences were not in N-acetyl aspartate (NAA), but in the glial markers creatine (Cr), choline (Cho), and myo-inositol (mi). Correlations were found between metabolites and neuropsychological testing in grey matter (GM), and between metabolites and symptomatology in white matter (WM).

Discussion

Our initial data (40% of the planned final sample size) provide preliminary evidence in support of three of the four hypotheses. Linear regression analysis yielded statistically significant results only in WM, supporting previous findings of global WM, but not global GM injury10 (hypotheses 1 and 2). In contrast to hypothesis 3, however, the findings were among the glial markers Cho, Cr and mi, not NAA. Correlations with clinical presentations (hypothesis 4) were not seen for all abnormalities, and RPQ and BTACT correlated with metabolites which did not differ between patients and controls. BTACT correlated only with metabolites in GM, while RPQ correlated only with metabolites in WM. Given the connection between cognition (measured by the BTACT) and GM, and somatic symptoms (assessed by the RPQ) and WM, these preliminary results are noteworthy. We also noted that in the lobes where WM Cr and Cho did not show statistically significant differences, the effect sizes were unidirectional (Table 2A), suggesting lack of statistical power1,2, rather than lobe-specific injuries. Completing our enrollment and data analysis will test this hypothesis and reveal the extent to which 1H MRSI results can be expected to vary within similar study designs.

Acknowledgements

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References


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<tr>
<th>Parameter</th>
<th>mTBI patients (n=17)</th>
<th>Controls (n=12)</th>
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</thead>
<tbody>
<tr>
<td>Median (IQR)</td>
<td>(9.0 (7.5), 15.0 (9.0))</td>
<td>(7.0 (5.0), 11.0 (8.0))</td>
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<td>Range</td>
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<td>Age (years)</td>
<td>20.2 (18.1 - 25.2)</td>
<td>24.4 (18.1 - 25.2)</td>
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<tr>
<td>Sex (male)</td>
<td>13 (76.5%)</td>
<td>9 (75.0%)</td>
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<tr>
<td>Employment status</td>
<td>8 (47.1%)</td>
<td>3 (25.0%)</td>
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<tr>
<td>Time since injury (months)</td>
<td>2 (1 - 5)</td>
<td>3 (1 - 10)</td>
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### Table 1: Imaging parameters (A) and demographics and clinical characteristics of study population (B). Median value, range or percentage of population are presented in parentheses. The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) measures symptom severity and is summarized in the RPQ total score. The Brief Test of Adult Cognition by Telephone (BTACT) provided sub-scores in memory, executive function, and reasoning, which are summarized in a composite z-score of cognitive function.

### Table 2: Group differences between controls (CTL, n=13) and (A) mTBI patients (n=17) and (B) non-recovered patients only (n=15); and (C) Spearman correlations. Statistically significant results are in bold. Note all statistically significant comparisons in (A) are maintained in (B). For (C), r and p values are shown for the association of each metabolite with scores from the Brief Test of Adult Cognition by Telephone (BTACT) and Rivermead Post-Concussion Symptoms Questionnaire (RPQ), without (direct) and with (partial) adjustment for the elapsed time from injury to imaging.
Figure 1: Representative spectroscopic map images for a single control subject. Presented is every fifth slice from the volumetric data for (A) creatine (Cr), (B) choline (Cho), (C) myo-inositol (mI), (D) glutamate plus glutamine (Glx), (E) N-acetyl aspartate (NAA), (F) grey and (G) white matter segmentation (GM, WM), (H) lobar parcellation, and (I) water (used as quantification reference) at the spectroscopic image spatial resolution.

Figure 2: Representative occipital lobe white matter spectra for (A) a single mTBI patient and (B) a single control subject. Shown on the right of each spectra is the corresponding T1-weighted MPRAGE image, slice, and voxel from which the spectra were obtained.

Figure 3: Boxplots of lobar metabolite distributions within mTBI and control (CTL) cohorts. Occipital WM Cho and Cr, parietal WM Cr, and frontal WM mI are higher in mTBI patients compared to controls (MW, ♦: p < 0.05). Note that in all lobes WM Cr and Cho medians are higher in mTBI patients compared to controls. Cho: choline, Cr: creatine, mI: myo-inositol, Glx: glutamine plus glutamate; NAA: N-acetyl aspartate; WM: white matter.