Regional Outlier Analysis of Longitudinal MAP-MRI Changes following Mild Traumatic Brain Injury

Mihika Gangolli[1,2,3,4], Priyanka Nadar[1,5], Luca Marinelli[6], Peter J. Basser[1,2], and Alexandru Avram[1,2]
[1]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, United States, [2]Military Traumatic Brain Injury Initiative (MTBI2), Bethesda, MD, United States, [3]Uniformed Services University of the Health Sciences, Bethesda, MD, United States, [4]The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD, United States, [5]Division of Internal Medicine, The University of Colorado Anschutz Medical Campus, Aurora, CO, United States, [6]GE HealthCare Technology & Innovation Center, Niskayuna, NY, United States

Synopsis

Keywords: Traumatic Brain Injury, biomarkers, longitudinal imaging

Motivation: Cross sectional radiological assessments of mild traumatic brain injury (mTBI) often produce conflicting findings with poor correlation to clinical outcomes.

Goal(s): Mean apparent propagator MRI (MAP-MRI) in a pilot longitudinal study is proposed to probe complex alterations in tissue microstructure following mTBI.

Approach: Quantitative region of interest analysis of MAP-MRI and DTI-derived metrics was performed in a pilot cohort of mTBI patients at four timepoints up to 90 days following injury.

Results: Several MAP-MRI derived parameters had increased intersession variability in white matter tracts and deep gray matter nuclei relative to healthy controls during the 90-day period of observation.

Impact: Longitudinal monitoring of changes in MAP-MRI metrics may provide a more comprehensive means to study pathological alterations that evolve at multiple timepoints in mTBI, where current image-based biomarkers lack the sensitivity and specificity to predict outcome.

Introduction

Mild traumatic brain injury (mTBI) is a signature injury in civilian and military populations, which is characterized by heterogenous etiology and associated with multiple alterations in tissue microstructure, including edema, gliosis, and axonal injury[1-3]. Diffusion tensor imaging (DTI) has been used to explore these alterations with conflicting imaging findings that have limited correlation with clinical outcomes[4]. This inconsistency may arise from the limitations of the Gaussian diffusion model, which does not adequately represent the complexity of brain tissue made up of neurons, crossing fibers, and glial processes, and the use of cross-sectional study designs, which can obscure individual changes over time[5]. Longitudinal studies could provide valuable insights into the progression of both clinical and radiological outcomes[6]. Mean apparent propagator (MAP) MRI[7] is a clinically feasible imaging approach[8] that explicitly and comprehensively quantifies the 3D net displacement distribution of water molecules. We aim to establish and optimize a MAP-MRI analysis pipeline to aid in characterizing the spatiotemporal evolution of tissue microstructure changes following mTBI.

Methods

Image Acquisition and Processing: A pilot dataset was selected from MR images (3T GE Signa MR750, 32 channel RF coil, Nova Medical) that were previously acquired[9] from 2014-2015 in 18 mTBI patients (aged 15-50; Glasgow Coma Scale ≥ 13) and 13 neurologically healthy controls. Patients were scanned at a maximum of four encounters (E_1 - <72 hours; E_2 – 5-10 days; E_3 - 15-29 days; E_4 - 83-97 days) post-trauma. 2D axial diffusion weighted MRI data (single spin echo, matrix: 96x96x21, FOV= 24cm, slice thickness = 2.5mm, α= 90°, TR/TE = 2,600ms/~77ms three shells-25,40,75 directions per shell with b-values 800,1200,2800 s/mm^2, 7 interspersed b=0 s/mm^2 weighted volumes, scan time = 6:56 min) was corrected for motion/eddy current distortion and skull-stripped[10]. The sagittal 3D T1-weighted MP-RAGE (matrix: 284x284x180, FOV = 25.6cm, slice thickness = 0.9mm, α= 8° TR/TE/TI = 8.1ms/3.3ms/1100ms, scan time = 4:33 min) was used to generate segmentation maps[11] and registered to the diffusion image space.
Statistical Assessment: Eleven regions of interest (ROIs) were defined based on segmentation maps: corpus callosum, caudate, putamen, hippocampus, pallidum, thalamus, amygdala, left and right cortical gray matter, and left and right cortical white matter. The coefficient of variation (CoV) across controls was computed for each ROI to assess intersubject variability. Test-retest variability was assessed using Bland-Altman plots (with bias and limits of agreement (LOA) computed as the mean and 99.9% confidence intervals of the percent difference between scans) for DTI and MAP-MRI metrics in each ROI for five control subjects who returned for two visits. In mTBI subjects, the means and percent differences of ROI-values for each metric were computed between encounters (E_1vE_2, E_2vE_3, E_3vE_4) and compared to the LOAs from the control cohort to identify outliers.

Results

The intersubject CoVs of MAP-MRI and DTI metrics (Figure 1), were less than 15% across all ROIs apart from the return-to-origin probability (RTOP) in the corpus callosum (56% CoV). Qualitative examination of the DTI and MAP-MRI images showed localized perivascular hyperintensities in the RTOP of seven mTBI subjects that did not all resolve over time(Figure 2). Outlier analysis identified ROIs and timepoints where longitudinal changes in MAP-MRI metrics were beyond the LOA of controls (Figure 3). Examination of Bland-Altman plots in these ROIs (Figure 4) showed elevated percentages of outliers in the corpus callosum (non-Gaussianity (NG) – 44% of subjects at E_3vE_4), caudate (RTOP – 50% of subjects), thalamus (propagator anisotropy (PA) – 28% of subjects), and pallidum (PA – 50% at E_1vE_2).

Discussion

In this pilot study, we report promising albeit anecdotal findings regarding the conspicuity of mTBI-induced changes using MAP-MRI derived quantitative imaging biomarkers. In a subset of mTBI patients, focal hyperintensities were visible on the MAP-derived RTOP but not on corresponding DTI metrics. Bland-Altman analysis identified regions including the caudate, thalamus, pallidum and corpus callosum where up to 50% of mTBI subjects had increased variability in PA, NG and RTOP relative to controls.

Conclusions

This work illustrates the potential value of performing longitudinal studies to follow mTBI, not only because of the concomitant pathophysiological responses that develop following injury but also because of the heterogeneity of mTBI when considering injury severity and mechanism. Future directions of this work include expansion of our pilot cohort to include more mTBI and control subjects, which will improve the quality of our statistical analysis to test the correspondence, if any, between the evolution of MAP-MRI metrics and clinical outcomes.

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Disclaimer

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Figures

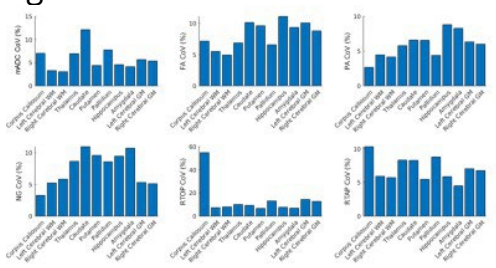

Figure 1. Assessment of intersubject variability of DTI and MAP-MRI metrics in healthy controls. The coefficient of variation for each metric and each ROI was computed across healthy controls who were scanned at one encounter (n = 13). Abbreviations: mADC- mean apparent diffusion coefficient; FA – fractional anisotropy; PA – propagator anisotropy; NG – non-Gaussianity; RTOP – return-to-origin probability; RTAP – return-to-axis probability.

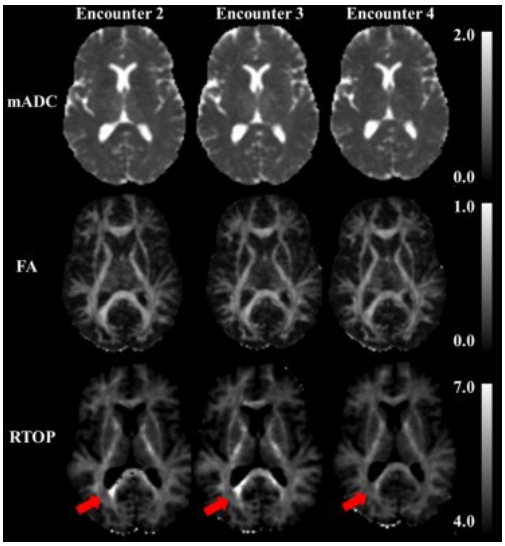

Figure 2. Regional hyperintensities are visible in MAP-MRI metrics but not DTI metrics in mTBI subjects. Hyperintensities that did not always resolve over encounters in MAP-MRI RTOP were visible in periventricular regions (red arrows) in a subset of mTBI subjects (n = 7 of 18). These regions had normal values in the corresponding DTI images. Abbreviations: mADC – mean apparent diffusion coefficient; fractional anisotropy (FA); return-to-origin probability (RTOP).

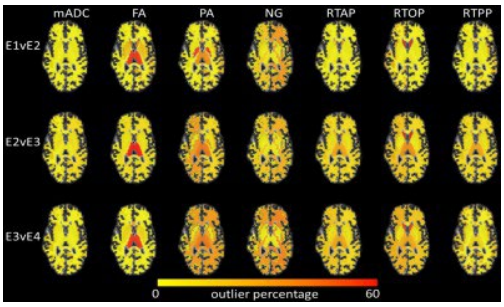

Figure 3. Intersession alterations of diffusion metrics in mTBI subjects relative to controls. The percentage of mTBI subjects that had intersession differences exceeding the 99.9% confidence intervals of test-retest variability of control subjects was computed for each diffusion metric and each ROI. Abbreviations: mADC- mean apparent diffusion coefficient; FA – fractional anisotropy; PA – propagator anisotropy; NG – non-Gaussianity; RTOP – return-to-origin probability; RTAP – return-to-axis probability; RTPP – return-to-plane probability.

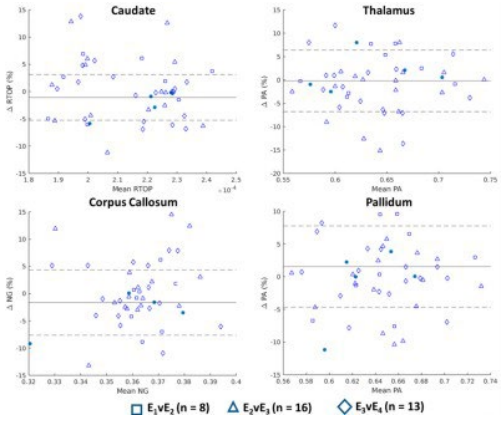

Figure 4. Bland-Altman plots of diffusion metrics in gray and white matter. The test-retest variability between visits was determined for controls (n = 5; filled circles) along with the bias (mean difference between encounters, solid line) and limits of agreement (99.9% confidence intervals of differences between encounters, dashed line). Intersession differences of DTI and MAP-MRI metrics in each ROI were measured between each encounter for mTBI subjects (open symbols). Abbreviations: PA – propagator anisotropy; NG – non-Gaussianity; RTOP – return-to-origin probability.