Evaluating neuroimaging sensitivities to alterations in structural connectivity following mild traumatic brain injury

Jessica Sevick[1,2], Mikaela Correa[1], Jacob Stubbs[1,2], Wayne Su[2], Allisdair Barr[2,4], Donna Lang[1,2], William Panenka[1,2,3]

(1) Department of Psychiatry, University of British Columbia, Canada, (2) British Columbia Mental Health and Substance Use Services Research Institute, Canada, (3) British Columbia Neuropsychiatry Program, Canada, (4) Department of Anesthesiology, University of British Columbia, Canada

1. Background and Introduction

Mild traumatic brain injury (mTBI), or concussion, affects an estimated 136,000 Canadians per year and is the most common form of brain injury (Gordon and Kuhle, 2018). Despite the high prevalence and impact, mTBI is one of the least understood neurological injuries. The functional and psychological deficits of mTBI are thought to be derived from mild diffuse axonal injury (DAI), which is typically not detectable with clinical imaging tools. Diagnosis and prognosis of mTBI is currently informed by subjective report or relatively coarse observer-based instruments. These validated assessment scales can assist in guiding decisions regarding mTBI, however they are gross scales that lack sensitivity to mTBI and have minimal prognostic value in determining outcome. Therefore it is imperative that new assessment methods be developed to provide a more thorough understanding of mTBI, thereby improving diagnosis and rehabilitation. The need for alternative approaches with greater sensitivity to neuropathology in mTBI has led to the pursuit for biomarkers with the ability to accurately and reliably provide diagnosis and prognosis. Advanced MRI techniques, including diffusion tensor imaging (DTI) and myelin water imaging (MWI), are commonly used to assess the white matter microstructural architecture in the brain, and as such are a promising option for utilization as a potential biomarkers. The purpose of this study was to evaluate the sensitivity of both DTI and MWI to the pathophysiological effects of mTBI on structural connectivity, both acutely and chronically. We hypothesized that (i) DTI would be sensitive to mTBI, specifically the metrics of FA and RD, and (ii) MWI would also be sensitive to alterations in structural connectivity and white matter integrity related to mTBI.

2. Study Population and Methods

Participants were recruited as part of a sub-study to the Canadian Traumatic Brain Injury Project (CanTBI) entitled “A national biobank and database for patients with TBI”. Participants were 51 subjects with mTBI (Table 1), who were recruited from the Emergency Department (ED) of Vancouver General Hospital (VGH), British Columbia, Canada. The mTBI group was separated into two sub-groups: (i) normal day of injury CT scans, and (ii) abnormal day of injury CT scans indicating acute damage (Table 1). A control sample (TC) of 30 subjects was also recruited from the Emergency Department of VGH, and screened to ensure they had no history of head or neck trauma (Table 1). The inclusion of an orthopedic control group, as opposed to healthy controls, was used to eliminate the confounds of body injuries that are not specifically due to brain injury.

Table1

Group	n (Total)	n (Male)	n (Female)	Age (mean)
mTBI	51	27	24	33.7
CT+	8	5	3	34.5
CT-	43	22	21	33.4
TC	30	21	9	32.7

Study population demographics.

In order to capture both the acute and chronic effects of mTBI, data was collected at two timepoints: within two weeks of the injury (acute), and six months post injury (chronic). The general CanTBI protocol included the collection of serum, plasma, and DNA samples as well as social, demographic and clinical data. For the purposes of the sub-study, neuroimaging data was additionally collected. MRI data was acquired on three tesla (3T) Philips scanner at the Djavad Mowafaghian Centre for Brain Health, located at the UBC Hospital.

Image preprocessing was performed using tools within the Functional MRI of the Brain (FMRIB, Oxford University, Oxford, UK) Software Library (FSL). Structural changes in white matter integrity were investigated using FSL’s tract based spatial statistics (TBSS) and Randomise tools. Diffusion weighted images were visually inspected before subject motion and eddy current induced geometric distortion correction.

The DTI and three dimensional anatomical (3DTI) images were registered to standard Montreal Neurologic Institute (MNI) space using FSL. To investigate local changes in WM structure, voxel-wise analysis of the fractional anisotropy (FA) was carried out using TBSS. Individual FA maps were then non-linearly registered via FSL-FNIRT to the John Hopkins University (JHU) International Consortium Brain Mapping (JHU-ICBM) FA template provided by FSL, followed by creation of a mean FA skeleton. Individual FA values were then projected onto the mean skeleton. Mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), and MWI measure of myelin water fraction (MWF). Values were projected onto the skeleton using the previously created FA transformation.

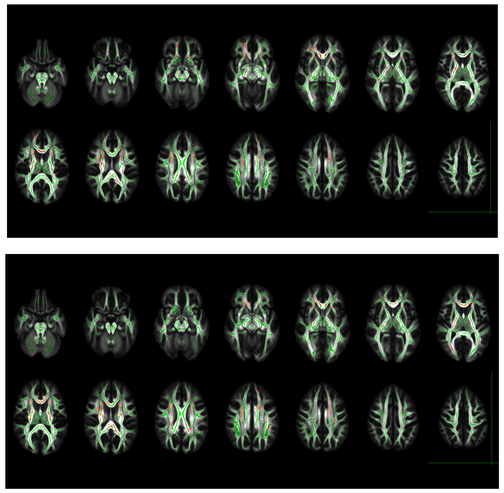
Voxel-based comparisons of FA, MD, AD and RD were performed on the TBSS skeleton using Randomise with the number of permutations set at 5000 and threshold-free cluster enhancement (TFCE) with correction for family wise error rate employed. The p<.05 T-contrast maps were projected on the mean FA images. To identify which specific anatomical areas were implicated, the mean FA skeleton and contrast map were overlaid with the JHU-ICBM white matter (WM) label atlas. Between group statistical analysis of the data using FSL’s Randomise tool was conducted to measure voxel-wise differences in DTI measures of FA, AD, MD, and RD as MWF. Comparisons were made between the mTBI group and TC, at both timepoints, as well as longitudinally within the groups. The CT- and CT+ sub-groups were also compared against the TC, as well as each other, at both timepoints and longitudinally. Age, sex and education were used as covariates.

3. Results

DTI

TBSS comparisons between the mTBI group and TC revealed multiple areas of significant differences in FA and RD, at both the chronic and acute timepoints. At the acute timepoint there was a widespread decrease in FA at the acute timepoint (p=0.028 to 0.042) including the areas of the corpus callosum, cerebral peduncle, internal capsule and corona radiata. RD was significantly increased (p=0.014 to 0.043) in the areas including the corpus callosum, uncinate fasciculus, inferior fronto-occipital fasciculus and corona radiata. TBSS comparisons between the mTBI group and TC group at 6 months revealed the differences in FA and RD were persistent. A decrease in FA (p=0.011 to 0.038) and an increase in RD (p=0.024 to 0.037) were observed in similar areas as the 2 week timepoint. For the mTBI sub-groups, there were no significant differences observed between the CT+ and CT- groups. However both groups differed from TC in the metrics of FA and RD at both timepoints, in similar areas an the whole mTBI group. There were no changes in AD or MD for any of the comparisons. There were no changes observed longitudinally for any of the metrics, for any of the comparisons.

Figure 1



Results of TBSS and Randomise Analyses of FA in the mTBI group versus TC at (i) 2 weeks and (ii) 6 months.

MWI

There were no statistical results or trends observed for differences in the MWF for any of the group comparisons at any of the timepoints (p = 0.32 to 0.59)

4. Discussion and Implications

TBSS revealed there were significant differences in FA and RD, at both the acute and chronic timepoints, between the mTBI subjects and TC. The mTBI subjects demonstrated reduced values of FA when compared to trauma controls at both two weeks and six months post-injury. The impact of the reduced FA was widespread, affecting the integrity of many integral WM areas of the brain including the corpus callosum, uncinate fasciculus, the internal capsule and the corona radiata. Reduced FA values are thought to represent a decrease in WM organization, axonal density and myelination due to the deviation or disruption of fibers, inflammation, or axonal degradation (Kumar et al., 2013) . The persistence in the differences between the groups from the acute to the chronic time point indicates that there may be lag in FA recovery in subjects with mTBI. The mTBI subjects demonstrated augmented RD values compared to the trauma controls at both the two weeks and six months post-injury). These coincide with decreases in FA, as RD and FA are interrelated mathematical derivations of each other. Increases in RD have been related to structural WM degradation, and were observed in the study subjects in a variety of WM structures including the corpus callosum, uncinate fasciculus, corticospinal tracts, corona radiata, and internal capsule. Similar to the FA values, the RD differences did not recover from the two week to the six month timepoints, suggesting a lag in the reestablishment of myelination in subjects with mTBI.

TBSS revealed non-significant findings in MWF. MWF is supposed to be a direct marker of myelin content in the brain (Wright et al., 2016), and there were no significant differences observed between the mTBI subjects and the trauma controls the two week and six month timepoints, longitudinally or between the sub-groups. This suggests that MWI is not as sensitive to mTBI as previously reported.

Our findings suggest that pathologic processes and changes in WM microstructure related to mTBI may persist beyond the initial injury. They also suggest that DTI metrics are imaging biomarkers that are sensitive to the subtle changes in WM structure incurred after mTBI, such as neuroinflammation, diffuse axonal injury and demyelination, while MWI is not. Therefore, MWI require further investigation and validation in order to be used as a diagnostic imaging tool for mTBI.

Limitations

Given the relatively small sample size of this study, further studies are warranted to validate the findings outlined above

References

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1 Department of Psychiatry, University of British Columbia, Canada
2 British Columbia Mental Health and Substance Use Services Research Institute, Canada
3 British Columbia Neuropsychiatry Program, Canada