Computational Prediction of Contusion and White Matter Injury in an Animal Model of Traumatic Brain Injury

Mazdak Ghajari, Cornelius K. Donat, Maria Y. Lopez, Nicoleta Baxan, Magdalena Sastre, David J. Sharp

I. INTRODUCTION

Traumatic brain injury (TBI) is the leading cause of death and disability in under 40s in developing countries. Mechanical loading of the head in road traffic and sporting collisions, falls and assaults causes TBI. Finite element (FE) models of TBI, which incorporate detailed anatomy of brain tissues and high-fidelity material models and properties, allow us to predict the mechanical response of brain tissues to the head loading. A key question is what level of mechanical strain or stress can produce damage in different brain tissues. Previous studies have used accident reconstructions and animal modelling to address this question. Here we present a new approach in which high-fidelity FE modelling and high-field MRI are used in an animal model of TBI to better understand the relationship between mechanical strain, grey matter contusion and white matter damage.

II. METHODS

The animal model of TBI. Controlled cortical impacts (CCI) were performed on male Sprague Dawley rats. The experiments were designed in compliance with a Home Office license [1]. Surgeries were performed under anaesthesia. A 6 mm rectangular craniotomy was performed, 0.5 mm posterior and 3.5 mm lateral to Bregma. Injury was performed with a 5 mm diameter electromagnetic impactor launched at an average speed of 4 m/s. Three groups of animals were investigated: sham (no impact – n = 3); mild injury (1 mm indentation – n = 10); and moderate injury (2 mm indentation – n = 11).

Neuroimaging. MRI scans were acquired before injury (baseline) and two weeks post-injury in a 9.4T Bruker scanner. T1 and T2 high-resolution structural images and multi-shell diffusion scans were acquired. Baseline T1/T2 images were used to create a template space. The Waxholm Space atlas was registered to the template using neuroimage processing tools of the packages FMRIB FSL [2] and ANTs [3]. The T2 images of the injured animals were semi-automatically segmented to delineate the focal lesions. The diffusion images were analysed to extract standard diffusion tensor imaging (DTI) metrics, including fractional anisotropy (FA). The coronal section of the corpus callosum located at the impact centre was chosen as the region of interest for white matter injury analysis. Five segments with equal length were generated over the ipsi and contralateral corpus callosum (S1 to S5 in Fig. 1A) and the mean value of FA was evaluated in each segment.

Fig. 1. A: corpus callosum segments. B: the FE model of the controlled cortical impact in rats, showing the
**Finite element modelling.** The Waxholm atlas was used to develop a FE model for the rat. The atlas was re-sampled to a 0.15x0.15x0.15 mm³ resolution, an in-house code was used to generate hexahedral elements at the location of voxels and the outer surface of the model was smoothed with a mesh-smoothing algorithm [4]. The model included skull, dura, CSF, grey and white matter and ventricles (Fig. 1B). A visco-hyperelastic material model, used in our previous study on human [2], was used to model the brain. Since there were no data available on relaxation modulus of rat brain at very short response time relevant to our CCI experiments, the relaxation modulus of the human brain was used and it was scaled to match the long-term shear modulus of rat brain [5]. The material properties are provided in table 1. The craniotomy was modelled by removing a rectangular patch from the skull and the impactor was modelled as a rigid cylinder. The impactor was launched towards the brain with 1 mm and 2 mm indentation depths. Simulations were performed for 4 ms, when the strain was almost settled across the brain. We determined the maximum value of 1st principal Green-Lagrange strain in each element and determined the mean strain in each corpus callosum segment.

Table 1. Material properties used to model rat brain tissue.

<table>
<thead>
<tr>
<th>Density [kg/m³]</th>
<th>µ₁ [Pa]</th>
<th>α₁</th>
<th>µ₂ [Pa]</th>
<th>α₂</th>
<th>Bulk modulus [MPa]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1040</td>
<td>29.5</td>
<td>10.1</td>
<td>-66.0</td>
<td>-12.9</td>
<td>50</td>
</tr>
<tr>
<td>τ₁ [ms]</td>
<td>τ₁=0.001</td>
<td>τ₂=0.01</td>
<td>τ₃=0.1</td>
<td>τ₄=1</td>
<td>τ₅=10</td>
</tr>
<tr>
<td>Gᵢ [kPa]</td>
<td>G₁=175.5</td>
<td>G₂=42.8</td>
<td>G₃=3.4</td>
<td>G₄=4.4</td>
<td>G₅=0.05 G₆=1.6</td>
</tr>
</tbody>
</table>

III. INITIAL FINDINGS

We found good agreement between the predicted strain and strain rate contours and the lesion map (Fig. 2A). We determined the contusion volume and the volume of the brain exceeding strain values of 0.25, 0.3, 0.35, 0.4 and 0.45 and strain rate values of 0.5, 1.0, 1.5, 2.0 and 2.5 /ms. The root mean square error of FE prediction of the contusion volume fraction vs mean value of experimental results showed that a strain threshold of 0.3 and a strain rate threshold of 2.5 /ms better predict the contusion volume.

Fig. 2. A: the lesion maps from imaging and strain/strain rate contours from FE modelling. B: change in FA vs. strain for 1 mm (blue) and 2 mm (red) impacts in all corpus callosum segments. C: an example showing FA vs. strain in the corpus callosum segments of a 1 mm and a 2 mm injury.

Diffusion MRI provided evidence for white matter damage focused in the regions of the corpus callosum located under the impactor. In mild injuries, there was a significant reduction in FA in S4 [t(45.00)=4.005, p=0.0011] and FA reductions in S2 and S3 were of borderline significance [t(45.00)=2.584, p=0.0637 and t(45.00)=2.680, p=0.0502, respectively]. In moderate injuries, the FA reduction was significant in S3 and S4 [t(50.00)=4.215, p=0.0005 and t(50.00)=4.825, p<0.0001].

To investigate the relationship between FA and strain, we constructed a linear mixed effects model. The dependent variable was the change in FA in ipsilateral segments compared to contralateral segments. The fixed
effect was strain and the random effect was animal. Our results showed that increasing strain was associated with a reduction in FA (Fig. 2B-C). The marginal R-squared was 0.27, which indicates that strain can explain 27% of the variation in FA. We also determined the predictive R-squared, which was nearly the same as the marginal R-squared, indicating that the model makes similar predictions for new data, thus no risk of overfitting.

IV. DISCUSSION

This study validated, for the first time, the predictions of a high-fidelity FE model of traumatic brain injury (TBI) against high-field MRI data in an animal model of TBI. This approach allowed us to link the mechanical strain within the short duration of the impacts to the post-traumatic translational measurements of grey and white matter damage. We found a clear relationship between mechanical strain at the time of injury and reduction in FA two weeks post-injury. This shows that high-fidelity FE modeling of TBI can predict neuropathology after TBI.

We found good correlation between distribution of mechanical strain in corpus callosum and patterns of white matter damage, with areas undergoing larger strains showing more abnormalities. Previous work has shown that strain is a key factor in producing brain pathology [6-7]. We determined, for the first time, the spectrum of white matter damage vs. strain in a major white matter tract, the corpus callosum. White matter damage and degeneration is often seen in TBI patients [8-9], and our results show that strain distribution produced by head loading is a major factor in predicting white matter injury.

One limitation of this work is that we investigated one time point only. This limits our ability to understand the link between the initial mechanical loading and progression of white matter injury. Future studies should include more time points to address this issue.

In summary, we combined high-fidelity FE modeling with high-field MRI to determine a strain threshold for contusion and a spectrum of change in white matter integrity vs. strain. Our results can be used together with high-fidelity FE models of TBI in human, e.g. [2], to understand the effects of different head loadings on producing neuropathology. This modelling approach can be used to evaluate the protection effects of TBI prevention systems, such as helmets and airbags, and guide their design for maximum protection.

V. ACKNOWLEDGEMENTS

This study was funded through Wellcome Trust Networks of Excellence and the Royal British Legion Centre for Blast Injury Studies, Imperial College London.

VI. REFERENCES