Multiparametric MRI characterization of mild traumatic brain injury in mice

Yichu Liu[1,2], Lora Watts[1], Qiang Shen[1], Hemanth Manga[1,2], and Timothy Duong[1]

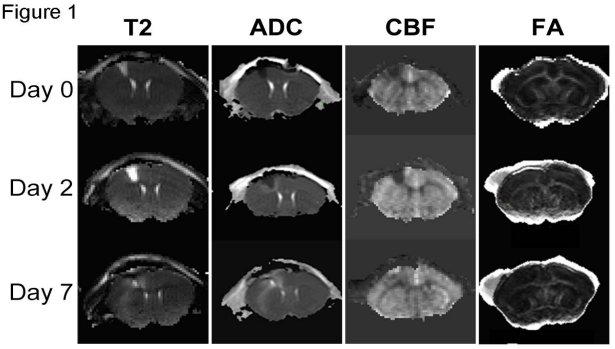
[1]*Research Imaging Center, University of Texas Health Science Center, San Antonio, Texas, United States,* [2]*Biomedical Engineering, UT San Antonio, San Antonio, Texas, United States*

Target Audience Researchers in traumatic brain injury

Purpose The goal of this study was to use multiparametric MRI (T_2, CBF, ADC, and FA) to longitudinally characterize the spatiotemporal dynamics during hyperacute and subacute mild traumatic brain injury (TBI) in mice. The impact was targeted to the left primary forelimb somatosensory cortex. Comparisons were made with functional assessment measured by the forelimb asymmetry test. Moreover, comparisons were also made with published rat mild TBI data under essentially identical conditions [1].

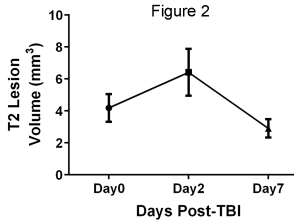
Methods Male mice (25-35g, n=4) were studied under 1.2-1.5% isoflurane. A 2mm craniotomy was created over the left forelimb somatosensory cortex, exposing the dura matter. The intact dura matter was impacted with a 1mm tip (3.5m/s, 250μs dwell time, 1.0 mm depth). The cranial opening was gently sealed with bone wax following the impact. Behavioral assessment (forelimb asymmetry test) was made pre-TBI and again 2 and 7 days post TBI in the same animal. MRI was performed at 3 hrs, and 2 and 7 days after TBI. MRI was performed on an 11.7T under 1.5% isoflurane. Multislice conventional T_2, DTI, CBF were obtained for seven 1-mm thick coronal slices, FOV=1.28x1.28cm, matrix=64x64. Images were co-registered. Lesion volumes were determined. T_2, ADC and fractional anisotropy (FA) were tabulated for the S1 cortices and the corpus callosum (CC). Error bars are SDs.

Figure 1



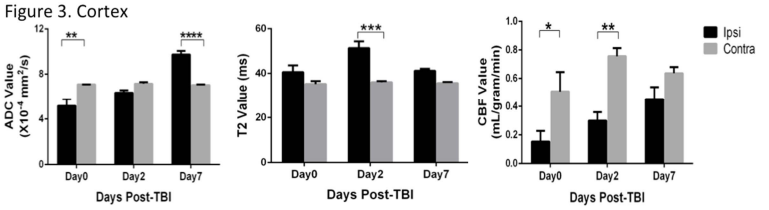
Results Figure 1 shows representative images of multiparametric MRI at 3 different time points. 3 hrs after injury, T_2 increased, ADC decreased, and CBF decreased, while FA did not change. The damage was localized to the injured site. On day 2, T_2 further increased, ADC remained reduced with an enlarged ring of ADC increase, CBF remained decreased and there was no hyperperfusion. FA did not change. On day 7, T_2 mostly renormalized with some diffused enhancement, ADC showed diffused enhancement including the corpus callosum (CC), CBF showed slight heterogeneous increase and decrease, and FA decreased. T_2 lesion volume peaked on day 2 and was reduced on day 7 (**Figure 2**).

Figure 2



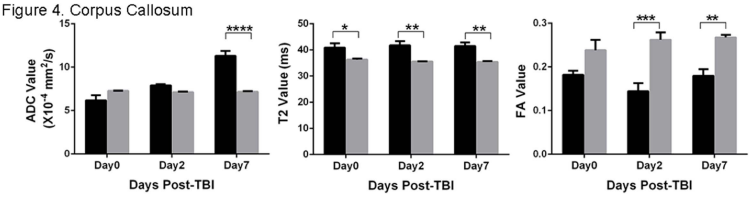
Quantitative T2, ADC, FA and CBF were analyzed for the S1 and CC. The contralesional T2, ADC, CBF and FA in the S1 and CC were all within normal ranges and did not change with time. In the ipsilesional S1 (Figure 3), ADC was reduced on day 0, pseudo-normalized on day 2 and increased on day 7. T_2 increased slightly on day 0, further increased on day 2, and returned toward normal on day 7. CBF was reduced on day 0, and trended toward recovery on days 2 and 7, but did not reached normal value. FA did not change significantly until day 7 (data not shown).

Figure 3. Cortex



In the ipsilesional CC (**Figure 4**), ADC was only significantly abnormal on day 7, T_2 was slightly elevated at all time points, and FA decreased on day 0, further decreased on day 2, and returned toward normal on day 7 but did not reached normal values.

Figure 4. Corpus Callosum



Forelimb asymmetry scores were worst on day 2 post-TBI, indicating increased utilization of the unaffected forelimb. The asymmetry score returned toward pre-TBI values on day 7.

Discussion & Conclusions Compared to rat TBI model (using identical preparation except for impact velocity) previously reported by our group [1], there are similarities and differences. The similarities are: i) T_2 lesion volume and behavioral deficit peaks on day 2 in both models, ii) T_2 increases and CBF decreases in the impact area, and iii) both models exhibit some behavioral recovery by day 7 but substantial lesion remains. The differences are that: i) in rat TBI ADC increases while in mouse TBI ADC decreases at 3 hrs, ii) hyperperfusion in the impact core and hypoperfusion in the surrounding tissue was observed in rat TBI, whereas no significant hyperperfusion or hypoperfusion was detected in the surrounding tissue in mouse TBI on day 2, iii) ADC increases were detected only on day 7 in mouse TBI. While it is possible slight differences in experimental parameters could contribute to differences in MRI characteristics, the dramatic spatiotemporal differences among multiple MRI parameters also suggest species differences, underscoring the importance of accounting for species differences in evaluating treatment efficacy. In conclusion, this study established a mild TBI model in mice, which opens additional avenues to study TBI in transgenic animals targeting molecular mechanisms of injury. MRI provides rich and multi-parametric information about TBI.

References: [1] Long, J Neurotrauma 2014