6225

Diffusion Kurtosis - A sensitive marker for Traumatic Brain Injury (TBI)

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Introduction: The understanding of tissue alterations at an early stage following traumatic brain injury (TBI) is critical for injury management and prevention of more severe secondary damage to the brain. Diffusion Tensor Imaging (DTI) has been a popular imaging modality to measure axonal damage following TBI[1,2]. Diffusion Kurtosis Imaging (DKI)[3] which measures the non-Gaussian behavior of water diffusion has the potential for having even higher sensitivity compared to DTI in characterizing microstructural changes in neural tissues.[4,5] In this study we investigate whether diffusion kurtosis parameters provide information over and beyond that available from DTI parameters regarding tissue damage in various brain regions at acute (2 hours) and sub-acute (7 days) stages post controlled cortical impact (CCI) injury in a rat model.

Methods: TBI model: 12 adult male Sprague-Dawley rats (300-350 gms) were subjected to left parietal CCI injury[6]. A high-speed dental drill was used to perform a left-sided 5 mm craniotomy that was centered 3.5 mm posterior and 4 mm lateral to bregma. A 5 mm round impactor tip was accelerated to 5 m/sec with a vertical deformation depth of 1.5 mm and impact duration of 50 ms. The experimental protocol was approved by the Committee for the Welfare of Laboratory Animals of the University of Maryland.

Imaging: All imaging was performed on 12 isoflurane anesthetized Sprague-Dawley rats on a Bruker Biospec 7T scanner with a 4-channel surface receiver coil. A set of PD and T2-weighted images were acquired for anatomical reference with RARE sequence ($TR/TE_{eff1}/TE_{eff2}$ = 5500/18.9/56.8 ms, FOV = 3.0 × 3.0 cm^2, matrix = 256×256, 24 slices with 1mm slice thickness and no gap). For DKI, diffusion weighted images were acquired with single shot spin-echo EPI sequence. Following 5 images acquired using b = 0 s/mm^2, two separate b-values (1000, 2000 s/mm^2) were acquired for 30 direction (δ/Δ=4/23 ms). Similar slice coverage was obtained as the RARE sequence but with a matrix resolution of 128×128, at a TR/TE of 6000/50 ms respectively. Imaging was performed before the injury and 2 hours after injury for all rats and then 7 days after injury for 7 out of 12 rats.

Histology: At the end of the experiments at 7 day, the rat brains were fixed via perfusion in 4% PFA. Free-floating 35 µm sections were stained for astrocytes using anti-GFAP and developed with the diaminobenzidine reaction. Stained sections were then mounted on gel-coated slides and imaged using light microscopy.

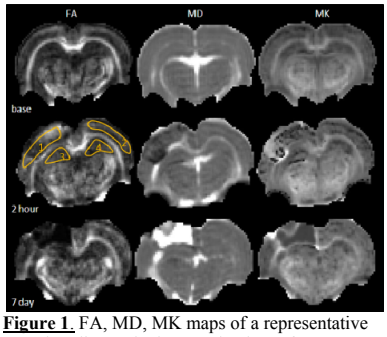

Figure 1. FA, MD, MK maps of a representative rat at baseline and 2 hour and 7 days after TBI. Yellow contour shows ROI placement: cortex at ipsi (1) and contral laterl sides (2), hippocampus at ipsi (3) and contralateral sides (4).

Post processing: Diffusion weighted (DW) images were first motion and eddy-current corrected using the FLIRT algorithm which is part of FSL package (FMRIB Software Library, Oxford, UK). Gaussian smoothing with a FWHM of 0.3mm were then applied to improve the signal-to-noise ratio (SNR). DTI parameters (MD, FA) and the DKI parameter, mean kurtosis (MK) were calculated according to the method described by Jensen et al.[8] Regional measures of ADC, FA and MK were obtained from the cortex and the hippocampus from both the ipsilateral and contralateral to the injury on 3 consecutive slices. Changes in DTI and DKI parameters were compared with the baseline time point using two sample paired t-test.

Results: Figure 1 shows FA, MD and MK maps of a representative rat before and after injury with the ROIs indicating the location of the regional measures. Figure 2 shows average MD, FA and MK values from the 4 ROIs shown in Figure 1 at 2 hour and 7 days after injury. **At 2 hour after injury**, MD was significantly decreased in all four regions. A significant increase in FA was observed in all regions except in the contralateral cortex. MK was significantly increased in the ipsilateral cortex and had a similar trend for the ipsilateral hippocampus. The signal abnormality was worse for regions closer to the direct impact site compared to more remote areas (e.g., Cor_ips > hip_ips > hip_con > cor_con). **At 7 days post injury**, MD recovered for all regions back to baseline level except for a reduced trend in contralateral hippocampus and an increased trend in ipsilateral cortex. FA also normalized to baseline level except for a significant decrease in ipsilateral cortex compared to baseline. On the other hand, MK was significantly increased compared to baseline at 7 days in both the ipsilateral cortex and hippocampus. Although not significant, this trend was also observed in the contralateral cortex and hippocampus. Histology revealed significant astrocytic immunoreactivity indicative of astrocyte activation both in the hippocampus and the cortex. Figure 3 shows histology on a representative rat at 7 day post injury for both the ipsi- and contra- lateral cortex. Compared to baseline, significantly increased astrocyte activity was observed on both sides, with the ipsilateral side showing significantly higher activity. The pair-wise scattered plot of MD, FA and MK in the contralateral cortex region for the same rat also indicates a clear increase of MK compare to baseline, while the normal DTI parameters (FA & MD) do not have the sensitivity to capture this increased astrocytic immunoreactivity. Similar results were obtained for the hippocampus.

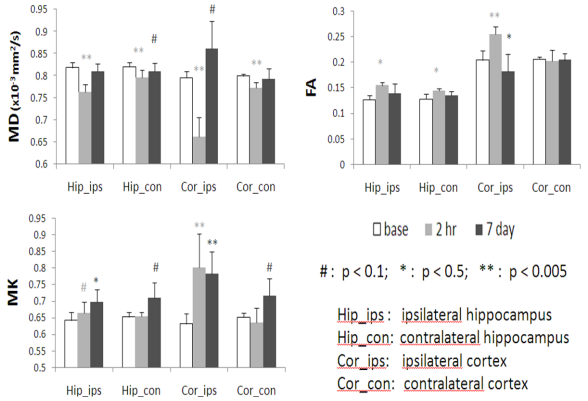

Figure 2. Regional FA, MD, MK values for baseline and post injury.

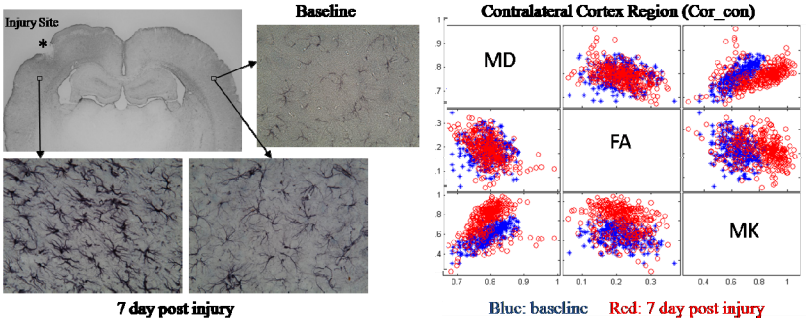

Figure 3. Histology shows increased astrocyte activity in ipsi- and contra- lateral side cortex compare to baseline (left). A pair-wise scattered plot of diffusion and kurtosis parameters for voxels within the contralaterl cortex region for the same rat was also shown (right).

Discussion: This study showed a decreased MD and increased FA at the acute injury stage which is consistent with previous studies, indicating cytotoxic edema[1,2]. At sub-acute stage, MK was significantly increased even when the DTI parameters were indicating normalization to baseline. Elevated MK at the 7 day period appears to be indicative of water diffusion heterogeneity resulting from increased astrocyte immunoreactivity indicative of astrocyte activity that is not easily captured by the standard DTI parameters. The fact that changes in mean kurtosis were detected on the contralateral side at 7 days following injury which correlated with histology suggests that MK may serve as a sensitive marker for cellular inflammatory reactions in response to TBI.

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