

## Mean apparent propagator MRI to determine the spatio-temporal trajectory of cortical microstructure abnormalities following controlled cortical impact in the mouse.

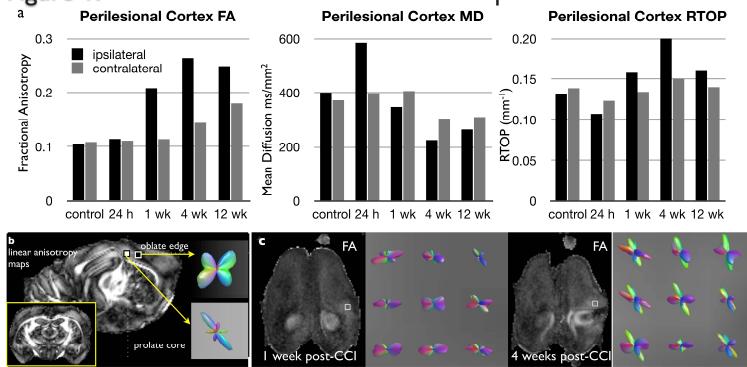
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**TARGET AUDIENCE:** neuroscientists, clinical researchers and diffusion imaging scientists.

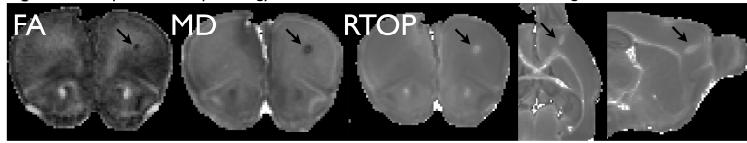
**PURPOSE:** Measures based on the diffusion propagator, or probability density function of water displacement, reach beyond standard diffusion imaging techniques by characterizing non-Gaussian diffusion to interrogate restricted compartments of brain tissue. Because microstructural changes in these compartments are hypothesized to follow brain injury, it is expected that the new “MRI stains” offered by mean apparent propagator (MAP)-MRI<sup>1</sup> will be useful for more specific characterization of the complex sequelae that follow traumatic brain injury (TBI). The primary objective of this work was to characterize DTI and MAP-MRI biomarkers at multiple time points following controlled cortical impact (CCI) in the mouse brain.

**METHODS:** A total of 12 perfusion-fixed mouse brains were obtained at different time-points following CCI (24 hours, 1 week, 4 weeks, 12 weeks and uninjured) and imaged using a 7T Bruker microimaging system. For each specimen, 426 image volumes were acquired using 3D-EPI with 100-micron isotropic resolution and ~8 minute imaging time per volume. In addition to reference images, the following DW shells were collected:  $b=1700, 3800, 6700$  and  $10,000\text{ s/mm}^2$ .

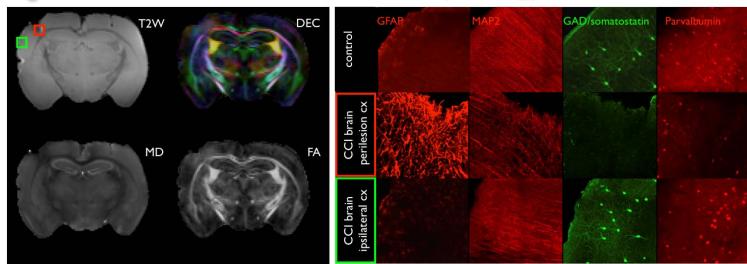
**Figure 1: DTI and MAP abnormalities of the perilesional cortex**



**Figure 2: Example of linear pathology in the cortex with low FA and MD, but high RTOP**



**Figure 3: Correlation of DTI maps and histopathology in the same brain**



Initial histological investigation of these imaging abnormalities suggest a differential pattern of underlying mechanisms with strong GFAP staining in the perilesional region and increased neuronal processes in the more remote cortical regions (Fig. 3).

**CONCLUSION:** The combination of high-resolution, fast, 3D imaging and the MAP-MRI framework has enabled improved microstructural characterization of cortical changes following CCI. While ongoing histological validation of DTI and MAP-MRI indices will undoubtedly improve our understanding of the underlying mechanisms, this work is an important first step in translating recent advances in higher-order diffusion modeling to identification of new markers in experimental models of brain injury.

**REFERENCES:** 1 Ozarslan et al., Neuroimage, 2013; 2. Pierpaoli et al., ISMRM 2010;#1597 3. Peled et al., Brain Res. 1998

Each set of images was processed using the TORTOISE pipeline for realignment, artifact correction and DTI modeling<sup>2</sup>. The diffusion displacement profile was modeled using the MAP-MRI algorithm<sup>1</sup> implemented in IDL and quantitative maps for return to the origin, axis and plane probabilities (RTOP, RTAP and RTPP, respectively), non-Gaussianity (NG), and propagator anisotropy (PA) were computed. ROI analysis of cortical regions and visualization of orientation distribution function (ODF) glyphs were performed.

**RESULTS and DISCUSSION:** Three main abnormalities were identified in the cortex:

1) Adjacent to the lesion cavity, diffusion was increased at 24 hours. At later time points a distinct pattern was seen of high anisotropy, characterized by prolate (cigar-shaped) diffusion in the core and oblate (pancake-shaped) diffusion at the edges of the abnormality as seen in linear anisotropy maps<sup>3</sup>, which report diffusion “prolateness”.

RTOP, RTAP and RTPP in this region were all increased, and the ODF profile showed differences between 1 and 4 week post-CCI timepoints and between prolate and oblate diffusion domains.

2) Increased anisotropy was found at later time points in cortical regions distant from the injury that were ipsilateral to the side of injury at 1 and 4 weeks and bilateral by 12 weeks.

3) For brains from the 4 and 12 week time points, small linear abnormalities of high restriction (low diffusion and anisotropy, but high RTOP, RTAP and RTPP) were found bilaterally in the frontal cortex (Fig. 2). This indicates that the source of this abnormality is from non-Gaussian contributions, likely dominated by restricted water.