Title: Investigation of post-traumatic structural abnormalities in the mouse brain using mean apparent propagator (MAP) MRI to model higher order diffusion.

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Background

Diffusion MRI and diffusion tensor imaging (DTI), are promising approaches to the investigation of brain abnormalities following injury in both humans and animal models of TBI. However, these standard approaches are limited by the underlying models, which assume Gaussian shaped water displacement that may not fully represent the complex and multiscale microstructural environment of brain tissue. Recent advances in non-Gaussian diffusion modeling have made possible the calculation of geometrically complex diffusion processes from diffusion MRI data. In particular, mean apparent propagator (MAP) MRI provides a new set of "stains" that may be helpful for the characterization of DTI abnormalitites or the identification of new markers. In this study, we have applied the MAP-MRI framework to investigate abnormalities in the mouse brain following controlled cortical impact (CCI).

Methods

A total of 19 perfusion-fixed mouse brains were obtained at different time-points following mild CCI (24 hours, 1 week, 4 weeks, 12 weeks and uninjured). Each specimen was imaged using a 3D-EPI pulse sequence on a 7T Bruker microimaging system. Diffusion MRI volumes were acquired with 100-micron isotropic spatial resolution and the following diffusion weighted shells were collected: b(# directions)=1700(32), 3800(32), 6700(56) and 10,000(87) s/mm2 in addition to low diffusion weighted reference images.

Each set of images was first processed using the TORTOISE pipeline for realignment, artifact correction and DTI modeling and to obtain fractional anisotropy (FA) and mean diffusion (MD) maps. Then the diffusion displacement profile was modeled using the MAP-MRI algorithm 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

Both DTI and MAP MRI abnormalities were found in the injured mouse brains and varied by time point and region, the most notable include:

1. In the cortex adjacent to the injury lesion, diffusion was high and anisotropy low at the 24 hour time point, however at all later time points there was a perilesional region of

increased FA that was discernible by eye for all samples and characterized by tissue orientation that was radial to the cavity wall. This region was further characterized by MAP-MRI to have reduced RTOP and increased NG. GFAP histology in this region indicated astrocytosis, but also the presence of additional unknown cell types that are the subject of further investigation.
2. In the frontal cortex, FA was also increased for some brains from the 4-week and 12-week post-CCI time points and the ODF glyphs in this region revealed a change in the tissue orientation profile from heterogeneous to organized in a direction perpendicular to the cortical surface.
3. An unexpected abnormality was detected bilaterally in the frontal cortex of brains from later time points. The shape of this abnormality is elongated and extends between the cortical surface and white matter in a manner similar to that of a penetrating blood vessel, but the size of the abnormality is larger than a blood vessel. The peculiar feature of this abnormality is the low FA and MD, but high RTOP and NG values, suggesting that the signal may arise from restricted water diffusion.
4. Within the white matter, a midline abnormality of reduced FA was found in the corpus callosum for all brains obtained at the 24 hour time point, but none from other time points. The shape and location of this abnormality suggest that it may be related to concentrated shear forces at the midline during impact.

Discussion

Both conventional DTI and the higher order MAP-MRI have identified interesting and potentially informative post-traumatic abnormalities in the microstructure of the mouse brain. Within the perilesional area, we have confirmed the increase of anisotropy noted by others in the field and extended its interpretation based on the non-Gaussian measures, which suggest changes to the microenvironment such as greater restriction and/or the presence of multiple compartments. The more novel observations of this study are the midline white matter abnormality, change in frontal cortex orientation properties and detection of a linear shaped abnormality, where water diffusion is very different from other regions. While work is ongoing to replicate these findings in-vivo and in more samples as well as to explain the basis for the observations using histology from the same brains, this work is an important first step in the characterization of brain structural changes following TBI using high resolution MRI and high order diffusion modeling.