

Species differences in white matter markers of traumatic brain injury: high-resolution T2-weighted and diffusion MRI of fixed tissue specimens from mouse, ferret and human.

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TARGET AUDIENCE: Clinical and basic researchers of TBI, diffusion imaging scientists.

PURPOSE: In recent years, there has been a surge in the efforts to understand and treat traumatic brain injury (TBI). At the forefront of this field are: 1) the development of animal models to study the mechanisms of injury and regeneration following TBI and 2) the application of conventional and advanced MRI modalities to identify clinically relevant markers of brain tissue changes. Furthermore, increasing numbers of MRI studies in animal TBI models are being undertaken. The objective of this study was to image fixed brain tissue from mouse, ferret and human to determine the presence of human-like MRI and diffusion tensor MRI (DTI) markers of abnormalities across two animal models – mouse and ferret controlled cortical impact (CCI).

METHODS: Formalin fixed brain specimens were obtained from three species - mouse (n=10, various times post-CCI), ferret (n=4, 1week post-CCI and 1 control) and human (n=1, 6 months post-TBI). Following rehydration, the specimens were imaged using a spin-echo or fast spin-echo sequence for T2W imaging and a 3D-EPI pulse sequence for diffusion tensor imaging data (reference images and b=1700 and 3800 s/mm², 32 directions each shell). The spatial resolution of the scans was isotropic with voxel sizes of: mouse-100um³, ferret-200 um³ and human-1mm³. DTI alignment, corrections and tensor fitting were accomplished using the TORTOISE package¹.

RESULTS & DISCUSSION:

White matter abnormalities were found in the human brain images and investigated in the animal models. Proximal to lesioned tissue, very distinct regions of white matter T2 hyperintensity (Fig. 1) and diffusion abnormalities (Fig. 2) were observed for both human and ferret. However, in mouse brains, T2 differences in WM were only evident at 24 hours post-injury and diffusion abnormalities were present only in brains where the corpus callosum was directly damaged. Furthermore, decreased FA in these brains was not accompanied by increased diffusion.

Another white matter abnormality investigated was midline corpus callosum damage as it has been described in existing work and is seen clinically to follow some brain injury². Although subtle abnormalities in the human and ferret brain maps may be present in the specimens investigated, this determination requires validation with histopathology, which is ongoing. However, in the mouse brain, a clear midline lesion was found in 2/2 specimens taken at 24 hours following CCI (Fig. 3) indicating the sensitivity of DTI in the mouse model to detect indirect midline lesions due to TBI.

CONCLUSION: Non-invasive imaging is a promising approach to the investigation of TBI using animal models. We have demonstrated species differences between mice and ferrets in the relevance of three MRI and DTI markers to human white matter pathology. The suitability of the mouse may be greatest for midline abnormalities as the subcortical white matter tracts are very small relative to the imaging resolution and partial volume artifacts may be a concern. The ferret offers advantages of similar cerebral geometry and white matter complexity to humans that likely contributes to the analogous imaging markers demonstrated by this work.

REFERENCES: 1. Pierpaoli et al., ISMRM 2010;#15972013 2. Liu et al., AJNR Am J Neuroradiol, 20 (1999)

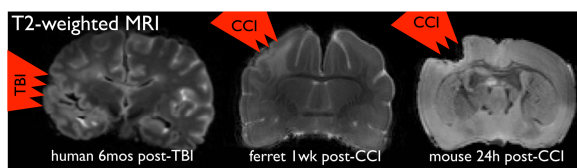


Fig. 1. T2 hyperintensity can be seen in the white matter of the human, ferret and mouse brain near to the site of injury.

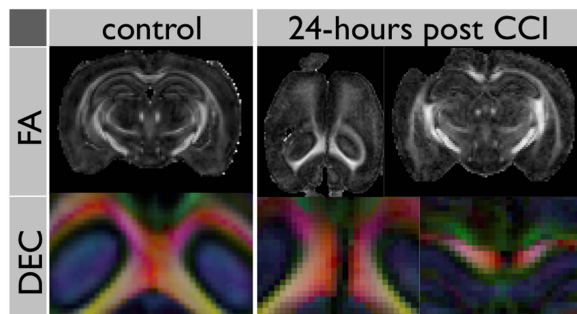


Fig. 3. Midline diffusion abnormality in the corpus callosum is shown for the mouse brain

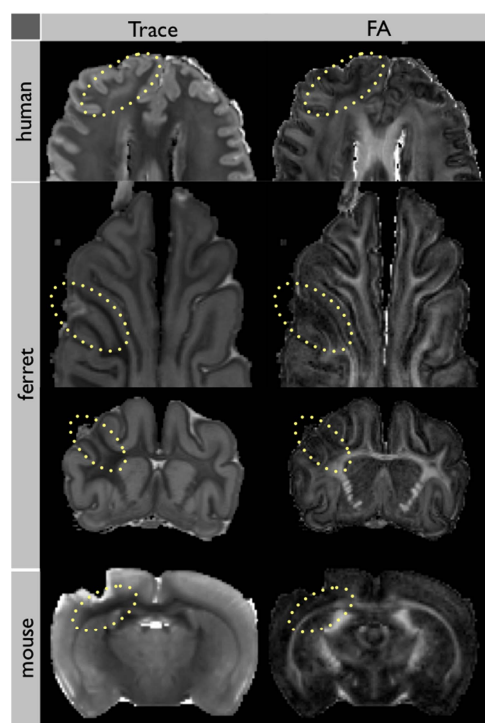


Fig. 2. DTI maps for each species are shown with vulnerable white matter indicated by dotted circles.