Magnetization transfer ratio detects myelin loss in thalamocortical pathways more consistently than DTI after a traumatic brain injury in rat

Lauri Juhani Lehto[1], Alejandra Sierra[1], Asla Pitkänen[1,2], and Olli Gröhn[1]

[1]*Neurobiology, University of Eastern Finland, Kuopio, Eastern Finland, Finland,* [2]*Neurology, Kuopio University Hospital, Kuopio, Eastern Finland, Finland*

Target audience MRI scientists interested in MT and DTI contrasts after brain injury and in animal models of brain diseases.

Purpose Traumatic brain injury (TBI) is a worldwide major cause of disability and death. Recently, our fMRI study assessing a response to somatosensory stimulus showed that post-TBI functional recovery is related to the loss of myelinated, presumably thalamocortical fibers in the deep layers of the cortex[1]. Here, our aim was to compare MT and DTI in the thalamocortical pathways, and to characterize the underlying changes with histology.

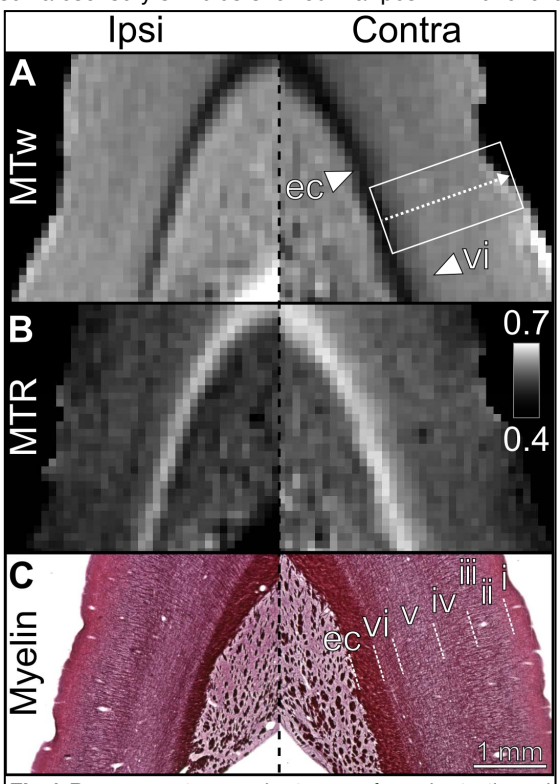

Fig 1 Representative *ex vivo* images from the ipsilateral and contralateral cortex after TBI. (A) MT weighted images, (B) MTR maps, and (C) myelin stained sections. The external capsule (ec) and layer 6 (vi) are thinner and have less intense contrast on the ipsilateral side in MRI. Myelin staining indicated demyelination. Also other cortical layers were affected as seen in the MTR map. The placement of profile analysis is shown in Fig. 2A.

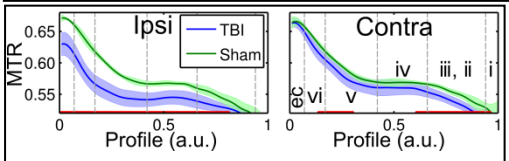

Fig 2 Cortical profile analysis using MTR. The red dots represent statistically significant difference (TBI vs. sham, $p < 0.05$, Mann-Whitney U-test). MT is abnormal ipsilaterally in all cortical layers, and contralaterally in layers v, iii, and ii.

Methods Adult rats with lateral fluid-percussion induced TBI[2] ($n_{TBI} = 6$, $n_{control} = 5$) were imaged at 9.4 T six months post-TBI. MT weighted images were acquired using SWIFT[3] *ex vivo* and *in vivo* (not shown), DTI was conducted only *ex vivo*. SWIFT parameters were: TR = 8.1 ms, α = 5°, prep every 16 acquisitions, MT prep = 2*20 ms HS4 (R = 20) at ±1500 Hz off-resonance and ω_1 = 500 Hz. Reference image was taken with the MT prep replaced by a delay. 3D SE DTI parameters were: TR = 1 s, TE = 30 ms, nt = 2, b = 1000 s/mm^2 and six directions. The primary somatosensory cortex (S1BF) was analyzed with a profile averaged over 1 mm distance parallel to the cortex and over 2-3 horizontal slices. The profiles were normalized in length and averaged. Region of interest (ROI) analysis was conducted on white matter (WM) and the thalamus of the pathway horizontally over 3-6 slices. In the end, brains were perfusion-fixed and histologically stained for thionin, myelin and iron.

Results A clear loss of myelinated fibers was seen in the ipsilateral cortex and external capsule (ec, Fig 1). This was verified by the profile analysis which indicated reduced MTR in the ipsilateral cortex (Fig 2). MTR was also decreased in all analyzed ipsilateral WM and thalamic ROIs. FA was more variable, although showing significant increases in selected areas (Fig 3).

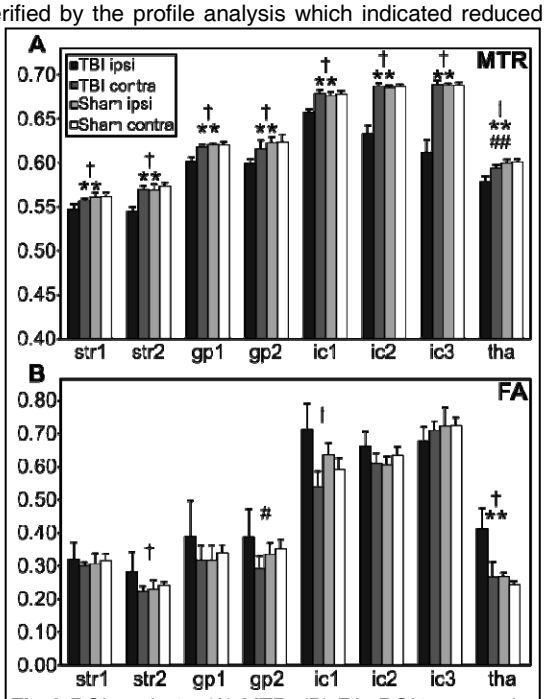

Fig 3 ROI analysis. (A) MTR, (B) FA. ROI1 covers the rostral and ROI2 the caudal half of the particular WM structure on horizontal plane, ic3 is on the most caudal portion of the ic2 ROI. MTR shows the highest change in ic3, whereas FA was unchanged. ic3 is the most damaged area based on histology. † $p < 0.05$ TBI_{ipsi} vs TBI_{contra}, Wilcoxon; */** $p < 0.05/0.01$ TBI_{ipsi} vs $Sham_{ipsi}$, #/## $p < 0.05/0.01$ TBI_{contra} vs $Sham_{contra}$, Mann-Whitney U-test. str = striatum, gp = globus pallidus, ic = internal capsule, tha = thalamus.

Discussion and Conclusion MTR has been shown to decrease with increasing demyelination, for example, in multiple sclerosis[4]. Very few studies have applied MTR to assess demyelination in experimental or human TBI. Our results show that MTR can be a valuable tool for assessing demyelination after TBI. It is sensitive for detection of demyelination even in the deep cortical layers with low density of myelinated fibers. FA has also been related to demyelination[5]. According to our results MTR could be more robust in some cases such as in the internal capsule, containing crossing fibers, where MTR follows increasing demyelination, but FA does not.

Acknowledgements The study was funded by the Emil Aaltonen Foundation, Academy of Finland and EU/FP7 EPITARGET. **References** 1. Niskanen et al. J Neurotraum 2013 2. Kharatishvili et al. Neuroscience 2006 3. Idiyatullin et al. JMR 2006, 4. Schmierer et al. Ann Neurol 2004, 5. Schmierer et al. NeuroImage 2009.