

## Detecting histological changes in traumatic brain injury with magnetization transfer imaging

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**Introduction:** The pathologic mechanisms of traumatic brain injury (TBI) are still poorly understood. However, detailed radiologic and morphologic description of specific lesions can considerably improve diagnosis and clinical processing [1]. As changes due to secondary axonal demyelination (Wallerian Degeneration) after a blunt impact against the head can be visible on a microstructural level, histological confirmation should be used to validate changes in quantitative MR imaging associated with neuronal and axonal damage [2]. The aim of this study was to investigate if magnetization transfer (MT) imaging can be used to reflect traumatic alterations in white matter by comparing a group of deceased subjects after brain trauma to a group of non-traumatic controls. Additionally, the MRI results were correlated with histological findings including axonal density and thickness of myelin sheaths.

**Materials & Methods:** 10 deceased subjects without trauma or known neurological deficits (median/range: age 63/48-81 years, body temperature 14.5-24°C, postmortem interval (PMI) 32/12-64 hours) and 4 deceased subjects (age 55/37-79y, body temperature 16.6-22°C, PMI 37/18-53h) with blunt head trauma obtained MRI within 64 hours after death at 3T (TimTrio, Siemens Healthcare, Erlangen, Germany) using a head coil array with 12 receiving elements. For calculation of the MT ratio (MTR) from balanced steady-state free precession (MTR\_bSSFP) [3], two bSSFP sequences (FA 30°, TR/TRF 2.8 and 8.2, resolution 1.3x1.3x1.3 mm<sup>3</sup>) were performed (saturated and non-saturated). For conventional MTR (MTR\_sat) a 3D spoiled FLASH sequence (TR/TE 40/7.38 ms, FA 15°, resolution 1x1x4 mm<sup>3</sup>) was performed with and without a Gaussian shaped saturation pre-pulse. MTRs were calculated by normalizing the signal intensities of MT saturation to the reference MT scan. MTR were evaluated in 3 subunits of the body of corpus callosum (CC), frontal white matter (FWM), temporal WM (TWM) and occipital WM (OWM) (Fig. 1) of both hemispheres. A Student's t-test was used to test for differences in MTR\_sat and MTR\_bSSFP between TBI cases and controls. Autopsy was done within 14 hours after the scan. The entire brains were removed and fixed in 4% neutral buffered formalin for at least 30 days. Tissue samples from transversal brain slices were dissected from CC, FWM, TWM, and OWM and embedded in paraffin. Axonal density and thickness of myelin sheaths were evaluated using Luxol fast blue staining. The study was approved by the local ethics' committee and informed consent of near relatives was obtained.

**Results:** Mean values for MTR\_sat and MTR\_bSSFP of both groups for the different white matter regions are presented in Fig. 2. For MTR\_sat significant differences ( $p<0.0005$ ) between the two groups were found in all examined regions, with clearly higher values for the trauma group. Equally, MTR\_bSSFP was significantly increased in the subjects with head injury in all regions except the corpus callosum (FWM  $p<0.01$ , TWM  $p<0.05$ , OWM  $p<0.0001$ ). At microscopy a thinning of myelin sheaths was observed in all white matter regions of the trauma cases when compared to the non-traumatic cases. Axonal density did not differ between the two groups.

Fig. 3 shows an example of a subject which died after a traffic accident compared to a control case. The sample of the corpus callosum of the subject after trauma exhibits bulking caused by edema and thinner myelin sheaths (stained in blue). The axons represented by the cellular nuclei, however, do not seem to be diminished. No visible differences of axonal density and thickness of myelin sheaths were observed within each group.

**Discussion & Conclusions:** In-vivo, decreased MTR is believed to indicate demyelination processes occurring after forceful impact and deceleration of the head [2]. Surprisingly, the presented postmortem study shows increased MTR for both methods applied. This might possibly be attributed to age-dependent MTR decrease [4], as median age of the non-trauma group was 63 years opposed to 55 years for the trauma group. Median body temperature and time between death and scanning should not have a big impact on these differences as for both groups they were in the same range. Microstructural thinning of axonal myelin sheaths in all investigated white matter regions was present in the trauma cases at histopathologic examination. The potential of detecting microstructural changes following TBI by means of MT imaging could significantly improve injury assessment both in a clinical and forensic context.

**References:** [1] Haacke EM et al. JMRI 2010;32:516; [2] Mamere AE et al. AJNR 2009;30:947; [3] Bieri O, Scheffler K. MRM 2007;58:511; [4] Ropele S. et al. AJNR 2010;31:1297.

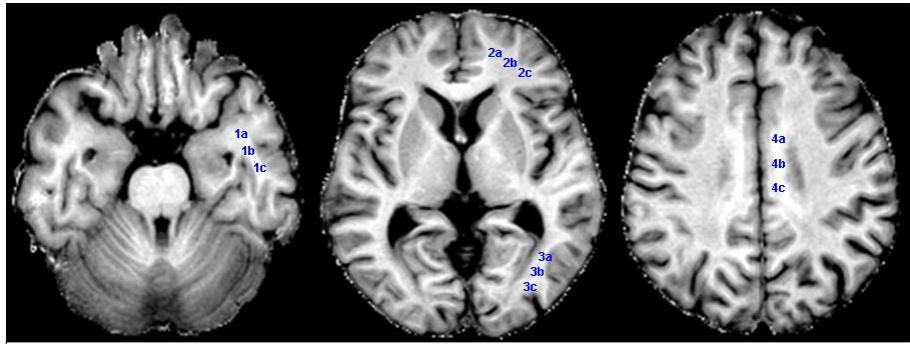


Fig. 1 TWM (1), FWM (2), OWM (3) and CC (4) with subunits (a-c) for MTR calculation in images acquired with a 3D spoiled FLASH sequence

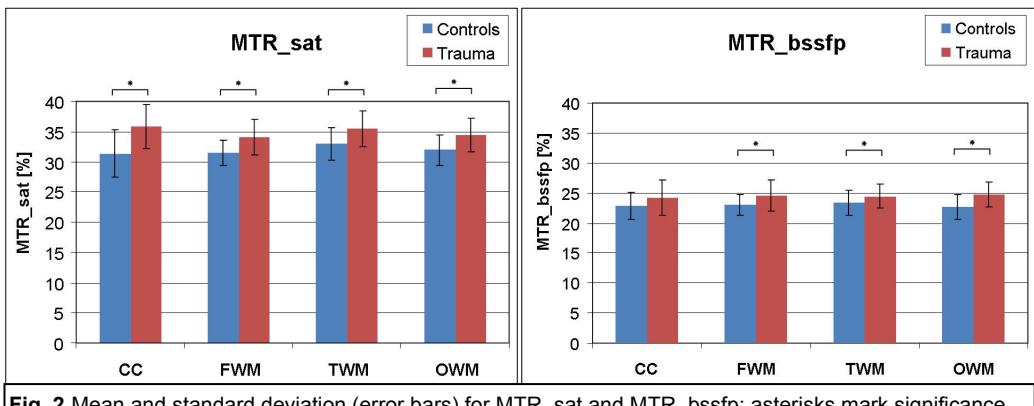


Fig. 2 Mean and standard deviation (error bars) for MTR<sub>sat</sub> and MTR<sub>bSSFP</sub>; asterisks mark significance

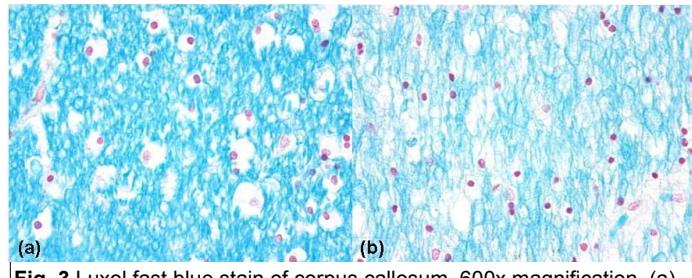


Fig. 3 Luxol fast blue stain of corpus callosum, 600x magnification, (a) control case and (b) subject with a traffic accident 4 days prior to death