

# IMPROVED MICROSTRUCTURAL CHARACTERISATION OF T2-HYPERINTENSE LESIONS BY COMBINING MULTI-SHELL DIFFUSION MRI AND MYELIN WATER IMAGING

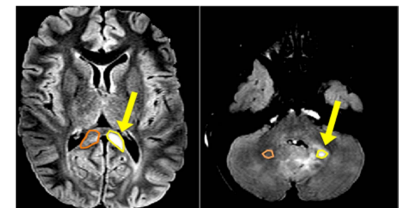
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**Target audience:** Basic scientists and clinicians with an interest in T2-FLAIR signal hyperintensities, diffusion MRI, neuroscience and microstructural imaging .

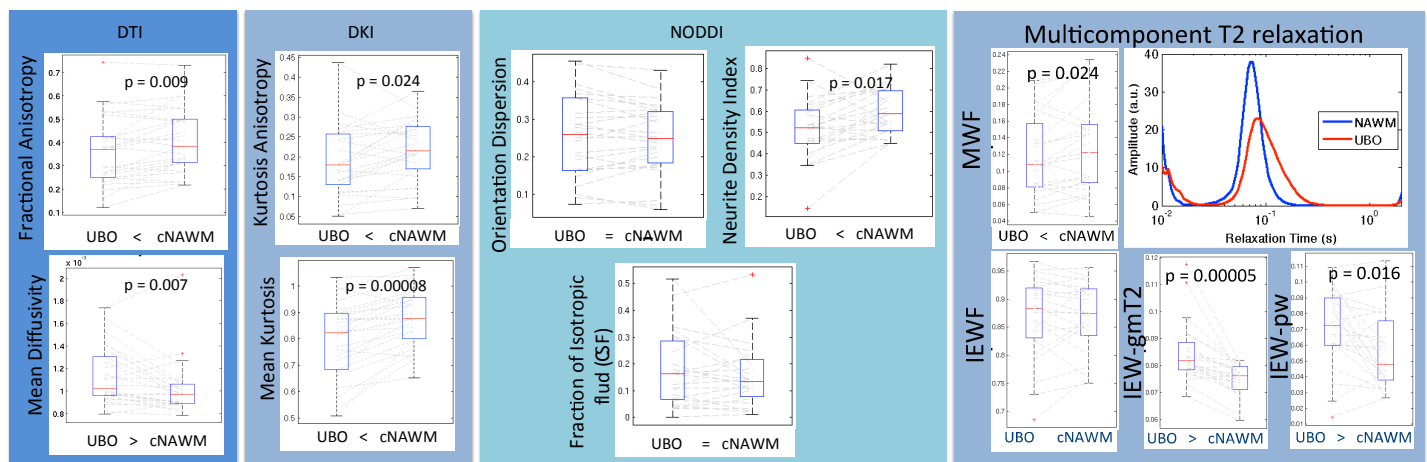
**Introduction:** Neurofibromatosis type 1 (NF1) is a genetic disorder associated with hyperintensities visible on T2-weighted MR images: “unidentified bright objects” (UBOs, Fig.1). Some of these lesions may regress and disappear over time, making histopathological analysis challenging [1]. The underlying microstructure associated with UBOs is therefore unknown. Limited evidence suggests vacuolization of the myelin sheath and neuropil [2]. The present in vivo study aims to characterise microstructural differences in UBOs compared to normal appearing white matter (NAWM) by combining diffusion imaging (dMRI) with myelin water imaging (MWI).

**Materials & methods:** **Subjects:** 18 NF1 patients (8 girls (age 13±3), 10 boys (age 12±3)) with known UBO expressions. **Imaging:** DWIs were acquired (3T Philips Achieva) with b-values 700, 1000 and 2800 s/mm<sup>2</sup> along 25, 40 and 75 directions, respectively. Multicomponent T2-relaxation data were acquired using a modified GraSE sequence [3][4]. **Measures:** fractional anisotropy (FA), mean diffusivity (MD) kurtosis anisotropy (KA) and mean kurtosis (MK) were estimated using ExploreDTI [5]. The fraction of isotropic fluid (FISO), the neurite density index (NDI) and the orientation dispersion index (ODI) were calculated using the NODDI toolbox [6]. Relaxometry data yielded the myelin water fraction (MWF), and parameters describing the intra- and extracellular water peak in the T2 distribution: its fraction (IEWF), geometric mean T2 (IEW-gmT2) and peak width (IEW-pw) [7]. Regions of interest around 26 white matter UBO sites and contralateral NAWM (cNAWM) were drawn on T2-weighted FLAIR images (Fig. 1) coregistered to each subjects native dMRI and MWI images. **Statistical analysis:** Average parameter values were obtained in UBO and cNAWM. A Wilcoxon signed ranks test was then applied on all pairs to test for statistically significant differences:  $p > 0.05$ .



**Fig. 1** UBO (yellow) and contralateral NAWM (orange) on T2-weighted image

**Results:** Figure 2 illustrates the results. UBOs showed significantly decreased FA ( $p=0.009$ ) and increased MD ( $p=0.007$ ) compared to cNAWM. Furthermore both KA ( $p=0.024$ ) and MK ( $p=0.00008$ ) were lower in UBOs. In the NODDI model the NDI ( $p=0.017$ ) was lower in UBOs. Myelin water imaging revealed a decreased MWF ( $p=0.024$ ) in UBOs compared to cNAWM. IEWF was unchanged, while the IEWF peak on average, was shifted towards longer T2 values ( $p=0.00005$ ) and an increased range (peak width) of T2 values ( $p=0.016$ ) compared to cNAWM.



**Figure 2** Boxplots of diffusion and multicomponent T2 relaxation metrics in UBOs and cNAWM. The T2 distribution of a UBO and cNAWM of a representative subject is shown in the right panel.

**Discussion:** The DTI findings are in agreement with previous reports [8]. MK is reduced in UBO, meaning that there is reduced non-gaussian contribution to the overall signals. With NODDI, this is interpreted as a reduction in the intra-neurite water fraction which is the primary source of non-gaussian diffusion.

The decreased NDI reveals a disparity between the fractions of intra- and extracellular compartments in UBOs. Since no loss in combined intra- and extracellular water (IEWF) is seen, the NDI decrease and increased IEWF-gmT2 in UBOs suggests that intracellular water “behaves” more like extracellular water. This may result from increased exchange or, as hypothesised, vacuolization. In the context of intramyelinic vacuolization, the decreased MWF in UBOs could be caused by shortened T2 times rather than strict demyelination.

**Conclusion:** This study suggests that UBOs in NF-1, which arise from an increase in T2 relaxation times of intra- and extracellular water, are mediated in part by abnormalities in the myelin sheath. Furthermore, the combination of multi-shell diffusion MRI models and T2 relaxometry aids in disentangling contributions from intra- and extracellular compartments.

## References:

[1] Kraut M. et al, Am. J. Med. Gen. 129A:113-119 (2004) [2] DiPaolo, P. et al, *Neuroradiology* 195:721-724 (1995) [3] Madler, B., S. A. Drabycz, et al. *Magnetic resonance imaging* 26(7): 874-888 (2008), [4] Prasloski, T., A. Rauscher, et al. *Neuroimage* 63(1): 533-539 (2012), [5] Leemans, A. *Proc. Intl. Soc. Mag. Reson. Med.* (2009), [6] Zhang H. et al, *NeuroImage* 61:1000-1016 (2012), [7] MacKay, A., C. Laule, et al. *Magnetic resonance imaging* 24(4): 515-525 (2006), [8] Ferraz-Filho J. R. et al, *Eur. J. Paediatr. Neuro.* 16:42-47 (2012)