Inflammation, axonal loss and trans-synaptic degeneration affect the visual system in multiple sclerosis – a preliminary 7 Tesla MRI and optical coherence tomography study.

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Introduction: Axonal loss is common in multiple sclerosis (MS)[1,2] and detectable from the earliest clinical stages.[3,4] However, the underlying neurodegenerative pathomechanisms in MS have not been fully understood, a factor that impedes the development of neuroprotective drugs. Today, the optic radiation - a structure highly susceptible to MS related damage[5] – can be visualized with near microscopic resolution *in vivo* by ultrahigh field MRI at 7 Tesla (7T). We studied the extent of focal inflammatory damage within the optic radiation in clinically isolated syndrome (CIS) and MS patients. Our findings were correlated with atrophy of the optic radiation, retinal nerve fiber layer thinning measured by optical coherence tomography (OCT), visual evoked potentials (VEP), and functional acuity contrast testing (FACT).

Methods: We investigated 31 patients (13 women, mean±SD age 36±8 years, including 8 CIS and 23 MS patients) and 10 matched healthy controls (HC) using 7T MRI (Siemens Magnetom, Erlangen, Germany), OCT and FACT. Our MRI protocol included T2*-weighted FLASH as well as T2-weighted TIRM sequences. Transmission and reception was performed using a 1TX/24RX brain coil (Nova Medical, Andover, USA). We quantified the lesion volume affecting the optic radiation (ORV), and the optic radiation thickness (ORT). A subset of 17 patients additionally underwent VEP examination.

Results: High spatial resolution 7T MRI revealed neuroinflammatory lesions affecting the optic radiation in 25 of 31 patients (figure 1). Statistical analysis revealed a strong association between focal damage of the optic radiation as indicated by ORV and thinning of the optic radiation as indicated by ORT (figure 2; $p<0.001$). Furthermore, ORV correlated inversely with the retinal nerve fiber layer thickness ($p<0.001$), and we observed a dependency between ORV and delayed VEP latency ($p=0.029$). Regarding visual disability, we observed an association between ORV and impaired visual perception as indicated by FACT under photopic ($p=0.016$) and mesopic ($p=0.012$) conditions as well as visual acuity ($p=0.005$).

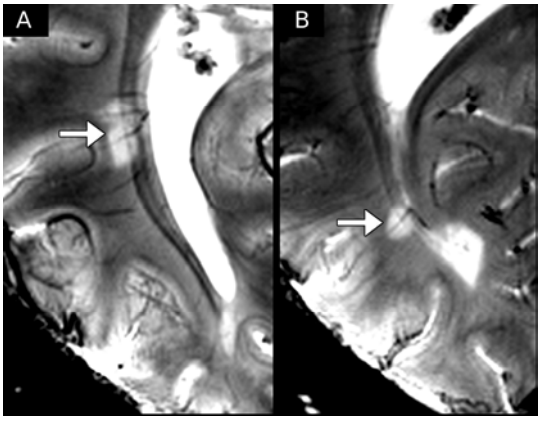

Figure 1. *MS Plaques (white arrows) affecting the optic radiation.* Due to its periventricular pathway, the occurrence of focal neuroinflammatory lesions within the optic radiation is common in MS (A, B).

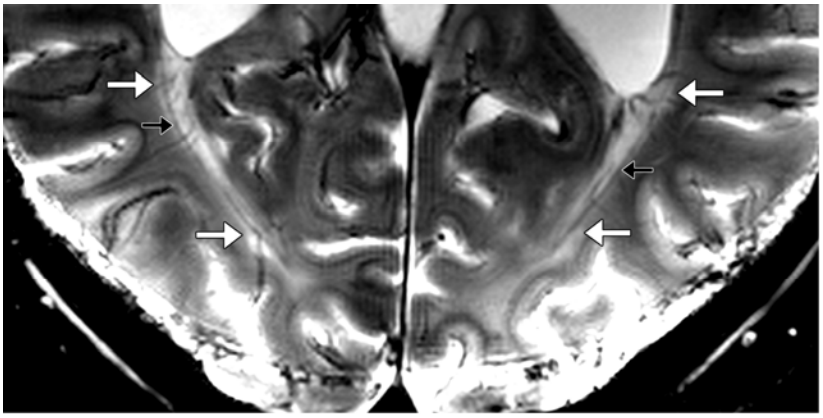

Figure 2. *Example of severe damage within the optic radiation in an MS patient* (male, 42 years old, EDSS 4.5). 7T T2*-weighted FLASH imaging revealed extensive bilateral damage (white arrows) and pronounced thinning of the optic radiation (black arrows).

Conclusion: Damage of the optic radiation is a frequent finding in MS often causing visual disturbances. The high incidence might be partially explained by the anatomical congruency of the optic radiation passing through a predominantly affected area of MS related demyelination, namely the periventricular white matter.
In alignment with recent reports,[6-9] the significant correlation between focal damage of the optic radiation and retinal nerve fiber layer thinning in MS suggests retrograde trans-synaptic degeneration. Furthermore, acute inflammatory lesions within the optic radiation should be considered as a differential diagnosis of acute optic neuritis in patients with bilateral visual disturbances.

References: 1 Bermel et al. Lancet Neurol 2006. 2. Trapp et al. Brain 1997. 3 Filippi et al. Brain 2003. 4 Miller et al. Lancet Neurol 2012. 5 Reich et al. Arch Neurol 2009. 6 Cowey et al. Brain 2011. 7 Jindahra et al. Brain 2009. 8 Jindahra et al. Brain 2012. 9 Sriram et al. Invest Ophthalmol Vis Sci 2012.