MR elastography of mice in experimental autoimmune encephalitis

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Background: In multiple sclerosis (MS), diffuse brain parenchymal damage exceeding focal inflammation is increasingly recognized to be present from the very onset of the disease and may present a major cause of clinical disability. Experimental Autoimmune Encephalitis (EAE) is a animal model of MS that enables researchers to study neuronal tissue degradation caused by a chronic inflammatory autoimmune attack.
Problem: Conventional MRI parameters correlate only modestly with the clinical course of MS [1]. Consequently, new imaging modalities are needed to provide accurate in vivo measurements of pathologic tissue alterations during disease.
Objective: A direct determination of the micro-structural constitution of tissue may be based on the macroscopic viscoelasticity of brain parenchyma. Cerebral MR elastography (MRE) [2] can assess the viscoelastic properties of brain tissue in vivo and has been demonstrated to be sensitive to MS-related diffuse tissue damage in patients [3]. Since in MS patients a correlation of MRE data with histological alteration is unfeasible, cerebral MRE of mice is used to study the relationship between viscoelasticity and degree of tissue degradation during EAE.

Methods: Measurements were performed on a 7 T scanner (Bruker Pharma Scan, Ettlingen, Germany). A FLASH sequence was customized for MRE by sinusoidal motion sensitizing gradients in through-plane direction and 900 Hz frequency matched to the mechanical vibration. Further imaging parameters: 128x128 matrix, 25 mm FoV, 14.3 ms TE, 116.2 ms TR, eight dynamic scans over a vibration period. The setup of the vibration unit is shown in Fig. 1. The complex modulus G* with real part G' (storage modulus) and imaginary part G" (loss modulus) was calculated by direct Helmholtz inversion of complex wave images (*U*) at 900Hz and averaged over the entire brain parenchyma visible in one transversal image slice through a central cerebral slab.

Mouse model: To assess potential correlation between viscoelasticity and EAE severity and tissue damage, we induced EAE in six eight-week old female SJL mice by immunisation with a peptide of the myelin proteolipidprotein (PLP). Four additional non-immunized mice were used as controls. From the immunized mice, three mice developed clear EAE (score 1 to 2) while three mice showed no disease signs. Control and EAE mice were scanned 7 days before immunisation and at days 7, 14, 21 and 28 post-immunisation.

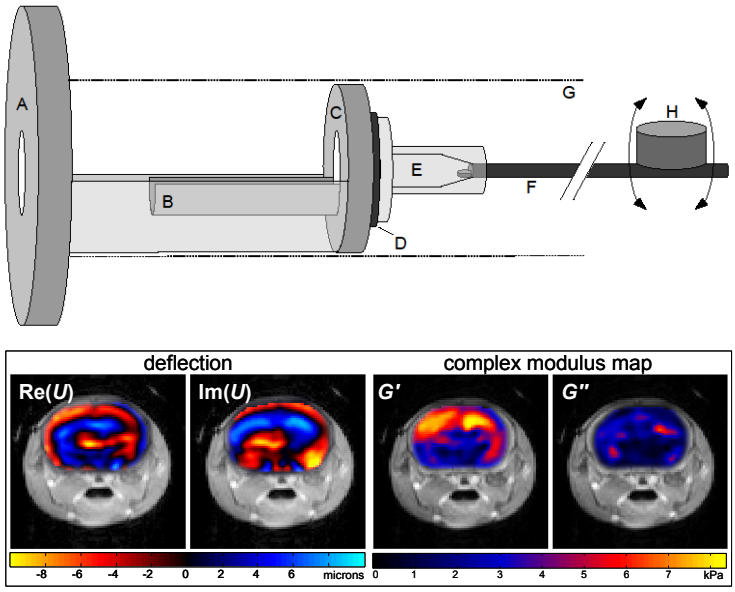

Fig.1 top row: setup of the mouse MRE vibration unit; A: centre plate attached to the magnet bore; B: tempered mouse bed; C: retaining bracket; D: rubber bearing; E: respiratory mask with bite-bar transducer; F: carbon fiber piston; G: magnet bore; H: driving coil; **bottom row:** wave images and complex modulus maps (color coded) superimposed to gray-scale T2w-magnitude images of a mouse head. Shown are both real and imaginary parts of complex wave images after Fourier transform (900-Hz component) and of the corresponding complex shear modulus. For data processing G'- and G"-values were averaged over the color-coded region.

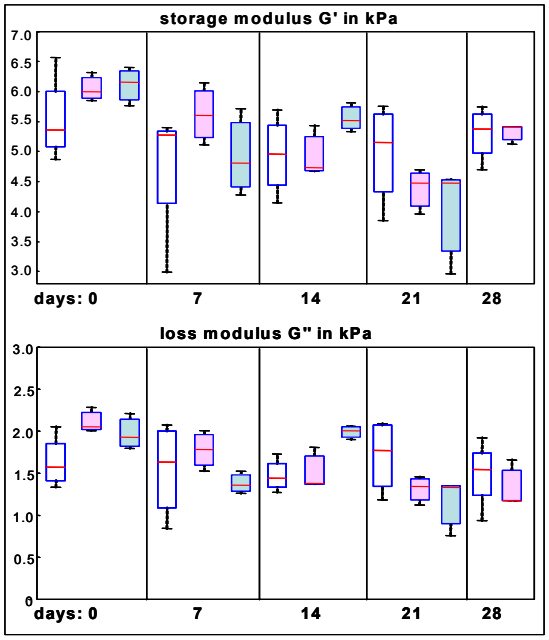

Fig.2: Storage and loss modulus in healthy control mice (white), symptomatic EAE (red) and asymptomatic EAE (blue).

Results: Principal findings are illustrated in Fig. 2. There was no correlation between examination time and complex modulus G* in healthy controls (R=-0.047[-0.05] P=0.84[0.83] for G'[G"]). In contrast, symptomatic EAE mice presented with a decrease in both storage modulus (R=-0.597, P = 0.019) and loss modulus (R=-0.811, P < 0.001) with the tendency of leveling after day 21. Asymptomatic EAE mice showed a significant decrease in G' with age (R=-0.688, P=0.013) while there was only a trend of decreasing G" (R=-0.515, P=0.086). The high interindividual variability of G* hindered a comparison of groups.

Discussion: EAE was used as mouse model of MS. EAE mice develop focal inflammation predominantly in cerebellum and spinal cord. Beside these focal effects, diffuse cerebral demyelination occurs. This may present the cause of the decrease in storage and loss modulus observed in brains of EAE-affected mice. This interpretation is supported by the assumption that the mechanical matrix of the brain is established by soft-elastic neuronal fibers embedded in even softer glial cells [3].Our data suggest that the rigidity of neurons is further decreased through demyelization. Most interestingly, the measured EAE-effect on the cerebral viscoelasticity is not correlated to clinical signs. Although results are very preliminary due to the reduced number of investigated animals, the observed G*-decrease corroborates so far results from human MRE [3]. We are currently performing additional experiments to confirm our preliminary data.

Literature: [1] Barkhof et al. Curr Opin Neurol 2002;15(3):239-245. [2] Kruse et al. Neuroimage 2008;39(1):231-237. [3] Wuerfel et al. Neuroimage 2010;49(3):2520-2525. [4] Lu et. al. Proc Natl Acad Sci USA 2006;103(47):17759-17764.