MR elastography of MPTP-induced Parkinson's disease in the mouse

Ingolf Sack[1], Barbara Steiner[2], Charlotte Klein[2], Elisabeth Hain[2], Kerstin Riek[3], Jing Guo[3], and Jürgen Braun[4]

[1]*Radiology, Charité-Universitätsmedizin Berlin, Berlin, Berlin, Germany,* [2]*Neurology, Charité-Universitätsmedizin Berlin, Berlin, Germany,* [3]*Radiology, Charité-Universitätsmedizin Berlin, Berlin, Germany,* [4]*Medical Informatics, Charité-Universitätsmedizin Berlin, Berlin, Germany*

Target audience: Neurologists and physicists interested and working on Parkinson's disease or MR elastography (MRE).

Background: MR elastography (MRE) [1] is a unique modality for in vivo mechanical imaging of brain tissue and exhibits a high sensitivity to demyelination, inflammation [2,3] and neuronal loss in murine models [4] as well as to multiple sclerosis and Alzheimer's disease in patients [5,6]. All pathophysiological processes studied by cerebral MRE so far exhibited a rather unspecific reduction in either elasticity or viscosity or both. Inversely, no neural alteration has been observed associated with an increase of viscoelastic constants.

Purpose: To study the mechanical response of the brain to dopamine depletion on adult hippocampal neurogenesis as a robust correlate of neuronal plasticity and Parkinson´s disease (PD) in a mouse model of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP).

Methods: A total of 60 eight to ten weeks old female transgenic C57Bl/6 mice expressing green fluorescent protein (GFP) under the nestin promoter were randomly assigned to three groups used for histology (MPTP: n=25, controls [treated with NaCl]: n=25), baseline (untreated mice: n=5) and MRE (MPTP: n = 5, controls: n=5 [out of the group treated with NaCl]). For lesioning mice received three single intraperitoneal injections (i.p.) of MPTP (20 mg/kg body weigh at a time) on three consecutive days. Bromodesoxyuridine (BrdU, Sigma-Aldrich, Steinheim, Germany) was used as mitotic marker to label proliferating cells. Animals received three single i.p. injections of BrdU (50 mg/kg body weight at a time) on three consecutive days started at the final day of MPTP-injections. After the treatment period MRE scans were performed on days 3, 6, 10, 14, and 18 post injection (dpi) on a 7 T scanner (Bruker Pharma Scan, Ettlingen, Germany). A FLASH sequence was customized for MRE by sinusoidal motion encoding gradients (MEG) in through-plane direction and 900 Hz frequency matched to the mechanical vibration induced by air-cooled Lorentz coils (Fig. 1). Further imaging parameters: 128x128 matrix, 25 mm FoV, 14.3 ms TE, 116.2 ms TR, 285 mT/m MEG strength, eight dynamic scans over a vibration period. 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 through a central transversal cerebral slab.

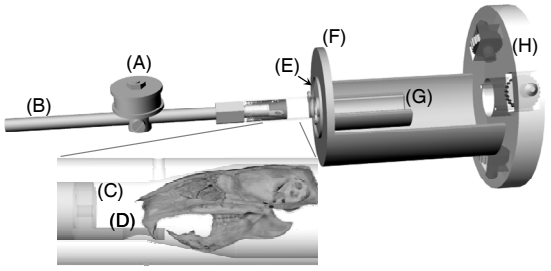

Fig.1: MRE transducer: (A) driving coil; (B) carbon fiber rod; (C) respiratory mask; (D) bite bar; (E) rubber bearing; (F) retaining bracket; (G) mouse bed; (H) plastic disk.

Results: Representative experimental and calculated data are shown in Fig.2. Figure 3 shows results of MRE measurements focussing on the hippocampus, the region that contains a highly neurogenic area which is modulated by dopamine. Mean values (standard error of mean) in the hippocampal region of controls were 4.608 (0.719) kPa, 1.388 (0.125) kPa, 4.816 (0.705) kPa and 0.549 (0.073) for G', G" abs(G*) and φ, respectively. On dpi 6 a marked temporary MPTP-induced increase of G' ($p<0.01$), G" ($p<0.01$) and abs (G*) ($p<0.01$) towards 6971 (1019) kPa, 1767 (103) kPa, 7192 (1011) kPa was found in the hippocampus which was still significant within the whole-brain region. No influence of time was seen in the control group for any of the MRE parameters. As opposed to controls, cell counting for MPTP-treated mice revealed an increased number of Nestin/GFP-expressing neural precursor cells on day 3 ($p<0.001$). Pairwise comparisons showed that MPTP treated mice displayed a larger portion of new neurons ($p<0.05$) regarding the total amount of newly generated cells on dpi 6. On the last day of MRE measurement (dpi 18) MPTP treatment appeared to eventually provoke a reduced neurogenesis indicated by a significant smaller proportion of new neuronal cells.

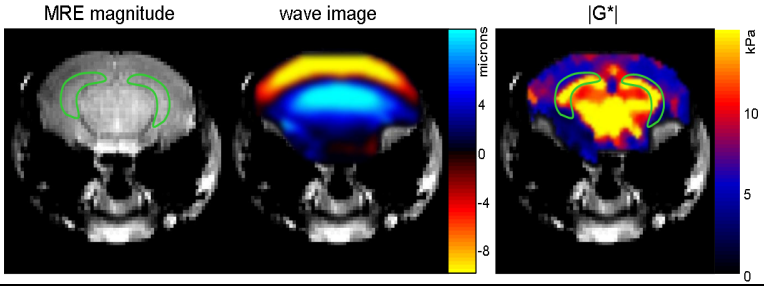

Fig. 2: Magnitude MRE signal, shear waves and the magnitude complex modulus (|G*|) in a mouse. The green line demarcates the chosen region of interest in the hippocampus.

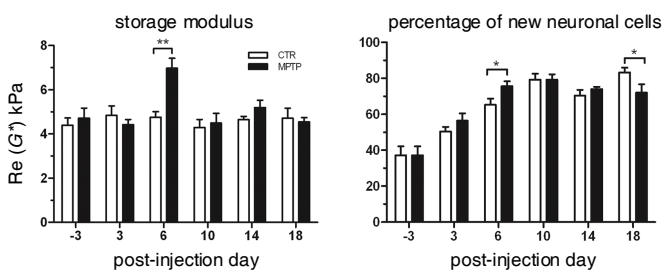

Fig. 3: Storage modulus and percentage of new neuronal cells show a significant increase (**p<0.01, *p<0.05) on post-injection day 6.

Discussion: MPTP acts as neurotoxin and implies depletion of dopamin. It is assumed that this neurotransmitter plays a key role in the regulation of adult neurogenesis and might thus influence viscoelasticity in distinct regions with high cellular turnover, e.g. parts of the hippocampus. The detected increase in stiffness at day 6 post-MPTP injection is in progression with temporary proliferation of Nestin/GFP-expressing neural precursor cells on dpi 3 yielding a significantly elevated proportion of new neurons in response to MPTP intoxication. These findings complement previous studies of MRE in the mouse [2,3] reporting a decrease of G' and G" due to demyelination and inflammation or neuronal loss in a murine stroke model [4]. The results are also in agreement to data obtained by MRE in patients [5,6] and thus highlight altogether the sensitivity of macroscopic shear modulus to the number and type of cells engaged in the mechanical tissue matrix.

Conclusion: The results provide evidence that neurogenesis following neurodegeneration contributes to a stiffening of the mechanical scaffold of the brain and therewith suggests the crucial role of neurons for the constitution of the mechanical tissue matrix of the brain.

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