Viscoelasticity of the mouse hippocampus and the influence of enriched environment

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Target audience: Physicians and biologists interested in the relationship between functional ability and the mechanical properties of the mouse brain.

Purpose: Hippocampus is a critical brain region for learning and memory. It is one of the first affected areas in neurodegenerative diseases such as Alzheimer's disease (AD). Magnetic resonance elastography (MRE) [1] is capable of measuring in vivo the mechanical properties of the mouse brain [2,3]. Recent findings demonstrated that tissue mechanical properties can reveal information about neurogenesis [4]. In this study, we used MRE to investigate the effect of enriched environment (EE) to the intrinsic viscoelastic properties of the mouse hippocampus.

Methods: 30 C57/ B6 mice were firstly separated into two groups with different environment conditions (15 mice per group): standard cage (standard environment, SE) and cage with complex interior design (enriched environment, EE) which is known as robust stimulus for adult neurogenesis in the dentate gyrus. These two groups were then investigated by MRE in 6 weeks, 3 months and 6 months (n = 5 per age group). MRE was performed on a 7 T scanner (Bruker Pharma Scan, Ettlingen, Germany). 900 Hz external mechanical vibration was induced by air-cooled Lorentz coils [3] and recorded by FLASH sequence equipped with motion sensitizing gradients (MSG). Four axial slices with slice thickness of 1mm were acquired. Further imaging parameters were: 128x128 matrix, 25 mm FoV, 14.3 ms TE, 116.2 ms TR, 285 mT/m MSG strength, 8 time steps over a vibration period. A 2D-Helmholtz inversion [3] was performed, yielding the complex shear modulus G^*; the real part of G^*, $G' = \mathrm{Re}(G^*)$, which reflects tissue elasticity, and the imaginary part $G'' = \mathrm{Im}(G^*)$, which relates to viscosity.

Results: T2, MRE magnitude, wave image and elastograms were selectively shown in **Fig.1**. ROI of hippocampus was drawn based on both T2 and MRE magnitude images. Longitudinal comparison revealed that in both SE and EE groups, MRE parameters of hippocampus and rest of the brain were not significantly altered from 6 weeks to 6 months (**Fig.2a**). Based on the observed age independence, we pooled data from three age groups and analyzed the MRE parameters in different regions under various environment conditions (**Fig.2b**). Regarding regional difference between hippocampus (h) and the rest of the brain (rb), mean values of both G' and G'' are significantly different in case of SE (G'_h = 7.6±0.8 kPa vs. G'_rb=6.4±0.9 kPa, $P < 0.001$ [t-test]; G''_h = 1.3±0.3 kPa vs. G''_rb=1.7±0.2 kPa, $P = 0.005$ [t-test]), however, in EE, the difference was only observed in G' (G'_h = 7.5±0.9 kPa vs. G'_rb=6.0±1.0 kPa, $P < 0.001$ [t-test]; When comparing different environment conditions, G' of hippocampus is significantly higher in EE. (EE: 1.7±0.3 kPa vs. SE: 1.3±0.3 kPa, P = 0.002[t-test])

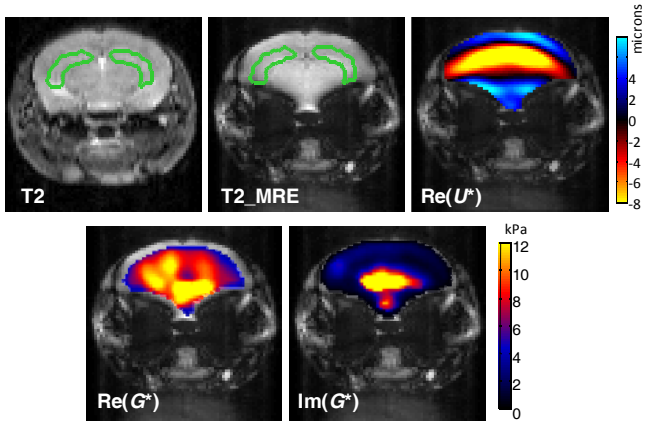

Fig.1: T2, MRE magnitude, real part of the complex wave image and elastograms. ROI are outlined on the T2 images.

Discussion: Firstly, our results obtained in SE mice revealed that hippocampus is intrinsically different compared to the rest of the brain, in terms of both elasticity and viscosity. This likely reflects underlying anatomical differences and different cell types in these regions. Since the hippocampus plays a key role in many neurodegenerative diseases, reference viscoelastic constants are important for future MRE studies in mouse models. Secondly, comparing results from SE and EE, we found that exposure to enriched environment altered hippocampal viscosity. Enhanced neurogenesis due to enriched environment was reported in the literature [5,6]. Considering the increased viscosity while unaltered elasticity, we hypothesized that new neurons preliminary affect the attenuation properties of the tissue due to their incomplete integration into the viscoelastic lattice of brain tissue. This tentative interpretation clearly needs further validation by histological and biomolecular examinations. In our preliminary behavioral test, mice from EE group performed better in motor coordination and orientation, an evidence of cell proliferation.

Conclusion: We observed that the hippocampus in the mouse is more elastic and less viscous compared to the rest of the brain. By examining mice under two environment conditions, we found that MRE is sensitive in detecting neurogenesis.

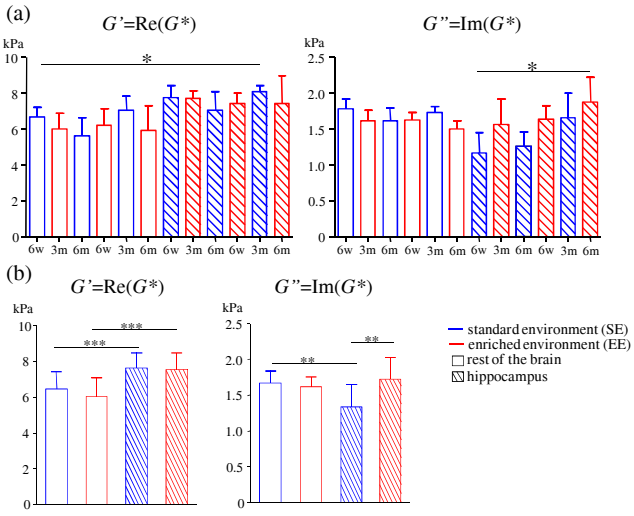

Fig.2: Longitudinal(a) and pooled(b) comparison of tissue viscoelasticity in mice from standard environment (SE) and enriched environment (EE).

Literature: [1] Muthupillai R, Ehman RL. Magnetic resonance elastography. Nature Med 1996;2(5):601-603. [2] Clayton et al. *Phys Med Biol*. 2011;56; 2391-406. [3] Riek et al. Wide-range dynamic magnetic resonance elastography. J Biomech 2011;44(7):1380-1386. [4] Klein et al. Enhanced adult neurogenesis increases brain stiffness: in vivo magnetic resonance elastography in a mouse model of dopamine depletion. PLoS One 2014;9(3):e92582. [5] Kempermann G1, Kuhn HG, Gage FH. More hippocampal neurons in adult mice living in an enriched environment. Nature. 1997 Apr 3;386(6624):493-5.[6] van Praag H, Kempermann G, Gage FH. Neural consequences of environmental enrichment.Nat Rev Neurosci. 2000 Dec;1(3):191-8.