Viscoelastic Properties of the brain in High Field MR Elastography - In-Vivo Application to an Alzheimer's Mouse Model

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Introduction:

Beta (β)-Amyloid precursor protein (APP) is widely expressed in the brain. Abnormal up-regulation can lead to the accumulation of β-Amyloid (Aβ) [1, 2]. Aβ is a major component of senile plaques and is one of the pathologic hallmarks of Alzheimer's disease (AD) [3]. Nowadays, the only definite way to diagnose AD is to find out whether there are plaques and tangles in brain tissue. This requires histopathlogical examination of brain tissue, generally with autopsy. Since there are no specific diagnostic tests for AD, reliable in vivo non-invasive diagnostic markers of disease and of disease progression will be a valuable tool for diagnosis. Magnetic Resonance Elastography (MRE) is a non-invasive imaging technique to measure the mechanical properties of tissue [4, 5]. This study aims to test the hypothesis that Alzheimer's disease (AD) might affect the viscoelastic properties in the hippocampus as well as in the cortex. The complex shear modulus G* is measured via 3D MRE [5].

Materials and methods:

Transgenic mice expressing mutant human PS1 – Leu235Pro and APPswe were established at the National Institute of Environmental Health Science, NC3. Seven 16- to 18-month-old male (25–40g) APP/PS1 (n=3) and wild-type (WT) mice (n=4) were studied in vivo to determine the viscoelastic properties of the brain. MRI is performed on a 7T Bruker MRI Pharmascan. Mechanical oscillations of the head are produced by a piezoelectric bending element (D220-A4-503YB, Piezo Systems, Inc.). Different components of the mechanical waves are measured using a modified spin-echo pulse sequence. Data acquisition parameters for MRE are: TR 2000ms, TE 18ms, acquisition matrix 64x64, FOV 19.2mm, and slice thickness 0.3mm.This yields an isotropic voxel size of 300μm. Seven adjacent slices are acquired with total acquisition time of about 76min. The frequency of mechanical oscillations is fixed at 1000Hz in order to provide sufficiently small wavelength within the mouse brain, whose diameter is about 5mm. Curved regions of interest (ROIs) are drawn on the hippocampus and cortex area to extract mean values for the real and imaginary part of G*. Immunohistological images of Congo Red are obtained with standard method.

Results:

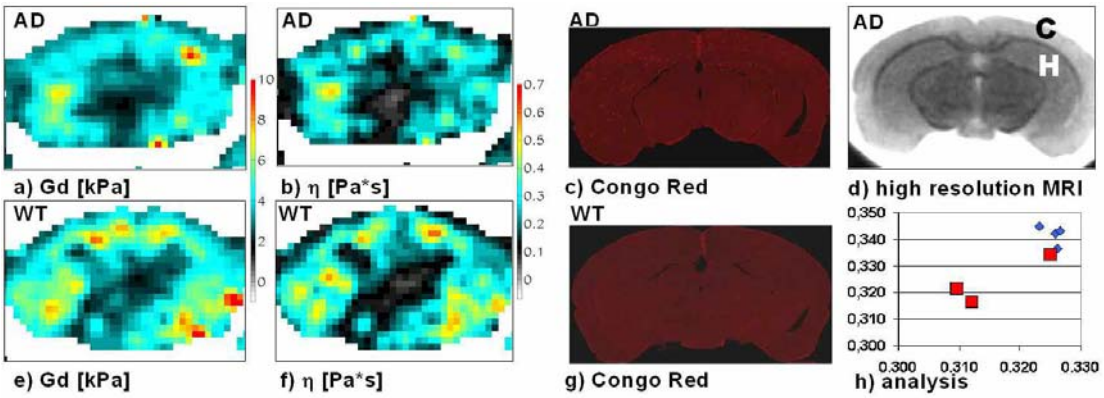

Figure a) and b) show the real (Gd) and the imaginary part (η=Gl/ω) of the complex shear modulus for an AD mouse. The corresponding high resolution anatomical image is presented in Figure d). The different anatomical structures (C=cortex, H=Hippocampus) are vaguely differentiated. The differentiation becomes much more obvious in case of a healthy WT mouse (Figure e and f). There, the hippocampus if well delineated from the cortex and shows enhanced values for real and imaginary part. Figure h) shows the ratio y=2/π*atan(Gl/Gd) of imaginary part over real part interpreted in terms of the exponent of a frequency power-law for the complex shear modulus. On the x-axis we show this ratio obtained as an average value within the entire region of cortex and hippocampus and on the y-axis the average value of y only within the hippocampus. It is obvious that y is systematically lower for the AD mice (red squares) when compared to the WT mice (blue diamonds). A drop in the ratio y indicates that the material is less viscous and behaves more like a classical solid material at low frequencies. Immunohistological analysis using Congo Red (Figure c and g) showed the large and dense deposition of plaques in hippocampus and cortex area in AD mice but not in WT mice.

Discussion:

Although the senile plaque deposits appear to have different constitution comparing with the brain tissues from which they are derived, there has been no report of their mechanical properties in the literature. As far as we know, this work represents the first report of the viscoelastic properties of the brain in AD and wild-type mice models. The amyloid plaques have been found to contain iron [6], copper [7] and zinc [8]. The more mature plaques tend to have higher iron concentration [9] which could conceivably reduce the local elasticity and viscosity. The MRE data correlated well with the increase of senile plaque formation in the same localities. We may therefore conclude that MRE is potentially useful as a non-invasive technique for *in vivo* amyloid plaque detection and early AD diagnosis.

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