

MR Elastography of the Brain in a Mouse Model of Alzheimer's Disease

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Introduction

Magnetic resonance elastography (MRE) is a technique that uses MRI to noninvasively measure tissues stiffness [1]. Shear waves are introduced via a mechanical actuator, imaged using a phase-contrast MRI sequence, and then mathematically inverted to calculate tissue stiffness. Recently MRE has been investigated in the brain for its potential to detect diffuse diseases that are currently difficult to diagnose with current imaging techniques [2-7]. The purpose of this work was to determine if a difference in stiffness could be detected in a mouse model of Alzheimer's disease (AD) compared with age-matched wild-type (WT) mice. The transgenic model is a double mutant with mutations in amyloid precursor protein and presenilin-1 (APP-PS1). These mutations have been linked to familial cases of AD and cause an increase in amyloid plaques [8, 9].

Methods

MRE of the brain was conducted on 5 wild-type (17.5 months old +/- 0.5 months) and 5 AD (20.5 months old +/- 0.5 months) mice. Mice were sacrificed with an overdose of sodium pentobarbital and immediately set up for imaging. All images were collected on a 3.0 T GE MR imager with each mouse prone in a 6-cm quadrature transmit/receive birdcage coil. The scalp of each animal was cut to expose the skull, and shear waves at 1500 Hz were generated in the brain using an electromechanical driver that was attached by a pin to the skull of the mouse at bregma. Wave images were collected in an axial imaging plane centered on the widest portion of the cerebrum using a modified spin echo pulse sequence with the following imaging parameters: FOV = 3cm, 64x64 imaging matrix reconstructed to 256x256, 3mm slice thickness, right-left frequency encoding direction, TR/TE = 1000/80ms, 50 through-plane motion-encoding gradients on each side of the refocusing pulse with an amplitude of 2.73 G/cm, and 4 phase offsets over one period of motion. Background phase was removed from the wave images through highpass filtering, and the wave images were 2D directionally filtered in 16 directions to minimize the effects of wave convergence [10]. The data were then inverted with a local frequency estimation (LFE) algorithm [11], and the mean stiffness was reported for each mouse as the average stiffness over the entire brain with 4 voxels from the edge excluded. The null hypothesis that the wild-type and AD mice had the same brain stiffness was tested with a two-sample T-test.

Results

The magnitude image, real and imaginary parts of the temporal first harmonic of the wave data and an LFE inversion from a wild-type and an AD mouse are shown in Figure 1. The mean stiffness for each of the ten mice is plotted in Figure 2. The average wild-type stiffness was 26.0 kPa while the average AD stiffness was 22.0 kPa. The stiffness of the two groups was significantly different with a p-value of less than 0.01.

Discussion

These results show that MRE is capable of detecting mechanical changes in brain tissue resulting from deposition of extracellular human-like amyloid plaques. The decrease in stiffness likely reflects changes in the mechanical properties of the extracellular matrix that occur as a result of deposition of hydrophobic fibrillar amyloid protein. These data demonstrate the merit in further mouse studies to determine how early in disease progression mechanical changes can be detected and whether investigating MRE in humans might aid in the detection of AD.

References

[1] Muthupillai et al. *Science* 1995. 269 (5232): 1854. [2] Kruse et al. *Neuroimage* 2008. 39 (1): 231. [3] Sack et al. *NMR Biomed* 2008. 21: 265. [4] Wuerfel et al. *Neuroimage* 2009. [5] McCracken et al. *Magn Reson Med* 2005. 53 (3): 628. [6] Green et al. *NMR Biomed* 2008. 21: 755. [7] Xu et al. *Acta Radiol* 2007. 48 (1): 112. [8] Holcomb et al. *Nat Med* 1998. 4 (1): 97 [9] Wengenack et al. *Neuroscience* 2000. 101 (4): 939. [10] Manduca et al. *Med Imag Anal* 2003. 7: 465. [11] Manduca et al. *Med Imag Anal* 2001. 5: 237.

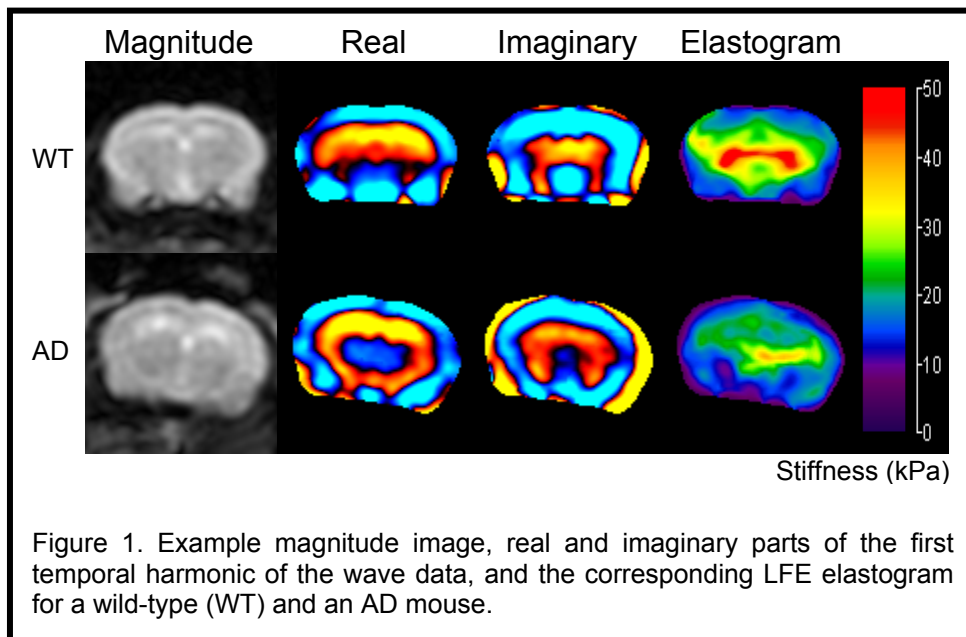


Figure 1. Example magnitude image, real and imaginary parts of the first temporal harmonic of the wave data, and the corresponding LFE elastogram for a wild-type (WT) and an AD mouse.

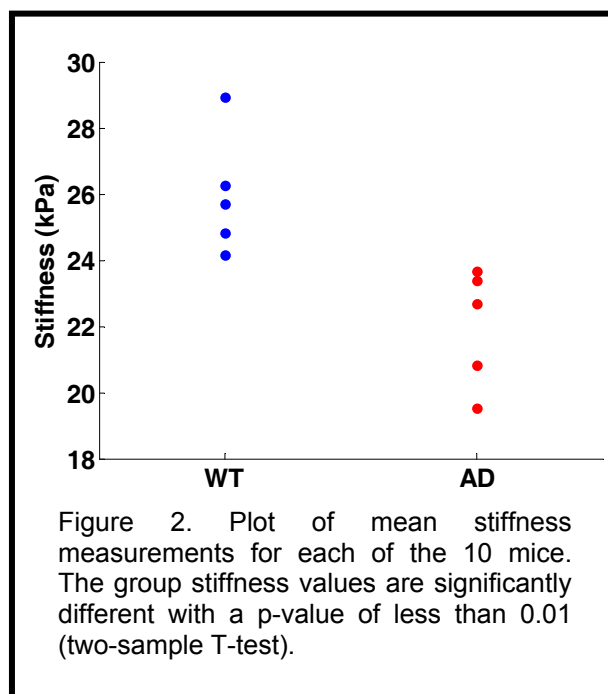


Figure 2. Plot of mean stiffness measurements for each of the 10 mice. The group stiffness values are significantly different with a p-value of less than 0.01 (two-sample T-test).