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Magnetic resonance elastography of the brain in a mouse model of Alzheimer's disease: initial results

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Abstract

The increasing prevalence of Alzheimer's disease (AD) has provided motivation for developing novel methods for assessing the disease and the effects of potential treatments. Magnetic resonance elastography (MRE) is an MRI-based method for quantitatively imaging the shear tissue stiffness in vivo. The objective of this research was to determine whether this new imaging biomarker has potential for characterizing neurodegenerative disease. Methods were developed and tested for applying MRE to evaluate the mouse brain, using a conventional large bore 3.0T MRI system. The technique was then applied to study APP-PS1 mice, a well-characterized model of AD. Five APP-PS1 mice and 8 age-matched wild-type mice were imaged immediately following sacrifice. Brain shear stiffness measurements in APP-PS1 mice averaged 22.5% lower than those for wild-type mice ($P = .0031$). The results indicate that mouse brain MRE is feasible at 3.0T, and brain shear stiffness has merit for further investigation as a potential new biomarker for Alzheimer's disease.

Keywords

Alzheimer's disease; MR elastography; Brain; Stiffness; APP-PS1

1. Introduction

Alzheimer's disease (AD) is clinically characterized by the progressive loss of memory and impairment of specific cognitive functions including language, motor skills and perception. Pathologically, the disease is characterized by amyloid plaques, neurofibrillary tangles and neurodegeneration [1]. An estimated 4.5 million people in the United States suffer from AD, and that number is expected to grow to 13.2 million by 2050 due to demographic changes [2]. New techniques for detection, prevention and treatment are needed to mitigate this expected increase.

The progression of AD is also reflected by the sequential progression of several biological processes related to the *amyloid cascade hypothesis* [3]. Some of these effects can be measured and used in combination to determine an individual's disease stage. These measures include amyloid load (measured by CSF A β 42 or PET amyloid imaging), tau-mediated neuronal injury (measured by CSF tau), synaptic dysfunction (measured by FDG PET), and brain atrophy (measured by anatomical MRI) [4]. Another implication of amyloid

deposition may be a change in brain tissue stiffness. Early deposition of amyloid may increase brain stiffness since amyloid fibrils are significantly stiffer than the neuropil which contains neurons and glia [5,6]. Alternatively, synaptic loss and neurodegeneration could result in a weakening of the brain parenchyma and result in a stiffness decrease.

In this work, changes in brain tissue stiffness due to AD were investigated using a well-studied mouse model. It is a double mutant with mutations in APP and presenilin-1 (APP-PS1). These mutations are linked to familial AD and cause an increase in amyloid plaques by altering the way APP is processed to produce more A β 42 relative to A β 40 [7,8]. The mutations also have a behavioral phenotype in mice, with APP-PS1 mice showing impaired alternation in a Y maze test [7].

Magnetic resonance elastography (MRE) is a new technique to noninvasively measure tissue stiffness [9]. In this technique, shear waves are first introduced into the tissue of interest with a mechanical driver. A phase-contrast MRI sequence with motion-encoding gradients synchronized to the external motion is used to image the shear waves as they propagate through the tissue of interest. These wave images are then mathematically inverted to calculate tissue stiffness. Several groups have begun investigating the potential for using MRE to diagnose brain diseases [10–20].

The purpose of this pilot study was a) to determine if MRE of the mouse brain is feasible in a 3.0T human scanner, and b) to measure the brain stiffness in APP-PS1 mice to determine if the mouse model of AD causes a significant change in brain stiffness compared to a group of WT mice.

2. Methods

MRE was performed on eight wild-type (WT) mice ($5 \times 17.5 \pm 0.5$ months and 3×23 months) and five APP-PS1 transgenic (AD) mice (20.5 ± 0.5 months). Brain MRE was performed on anatomically intact animals immediately following sacrifice. The mice were sacrificed in accordance with our institutional animal care and use committee (IACUC) with an intraperitoneal injection of a lethal dose of sodium pentobarbital and immediately setup for imaging.

All images were collected on a 3.0T MR imager (SIGNA Excite, GE Healthcare, Waukesha, WI) with a custom 6-cm quadrature birdcage transmit/receive coil. Shear waves were generated in the brain at 1500 Hz using an electromechanical driver suspended above the coil and attached to the exposed mouse skull via a pin. A picture of the coil and driver is shown in Fig. 1. The electromechanical driver was attached to a flexible platform and due to the lever action of the driver, most of the displacement occurred in the rostral-caudal direction (through-plane with respect to the coronal images acquired). Wave images were collected with a modified spin-echo pulse sequence with the following parameters: field of view (FOV) = 3 cm, 64×64 imaging matrix reconstructed to 256×256 , one 3-mm slice, TR/TE = 1000/80 ms, 50 through-plane motion-encoding gradient pairs (totaling 33.3 ms) on each side of the refocusing pulse with amplitude 2.73 G/cm, and 4 phase offsets over one period of motion (acquisition time approximately 8.5 minutes). Motion encoding was applied in both the positive and negative through-plane direction. The difference of these phase images was taken to obtain a set of 4 wave images.

The wave images were first unwrapped to remove the effects of phase aliasing. Subsequent processing was performed on the first temporal harmonic of the unwrapped phase data (to isolate motion occurring at the frequency of interest) and included the use of four 2D directional filters composed of a radial 4th-order Butterworth bandpass filter with cutoff frequencies of 2 and 128 waves/FOV (0.67 and 42.67 cm^{-1}) [21]. Directional filters were

used to minimize the effects of interfering waves. The lower cutoff was used to remove the effects of bulk motion, longitudinal wave motion, and other low-frequency wave artifacts, while the higher cutoff only removes the corners of k -space. The resulting images were then inverted with a 2D direct-inversion algorithm using a circular window with a diameter of 11 voxels [22]. The wave field within each window was fit with 2nd- and 4th-order polynomials to estimate the displacement and Laplacian, and an F test was used to determine which fit was best for each window. The differential equation of motion was then solved with an orthogonal least-squares fit to account for noise in both the displacement and Laplacian with an additional constant term to account for background phase. The median stiffness for the portion of the brain above the 3rd ventricle and excluding 5 voxels around the edge was reported for each mouse. This region of interest was chosen since most plaques are found in the neocortex and hippocampus. The null hypothesis that WT and AD mice had the same brain stiffness was tested with a Wilcoxon rank sum test.

The phase/wave data signal-to-noise ratio (SNR) was calculated as the product of the amplitude of the first temporal harmonic (after background phase removal) and the magnitude SNR. The magnitude SNR was calculated as the mean signal within the window (averaged over the 4 phase offsets and smoothed with a 3×3 mean filter) divided by the standard deviation of a magnitude difference image over the entire brain.

A five-slice acquisition was performed on a separate WT mouse to verify that results obtained from single-slice and multislice data using this setup and acquisition strategy are equivalent. The multislice acquisition was performed with the following parameters: FOV = 3 cm, 64×64 imaging matrix reconstructed to 256×256 , five 0.5-mm slices, TR/TE = 3000/51 ms, 25 through-plane motion-encoding gradient pairs (totaling 16.7 ms) on each side of the refocusing pulse with amplitude 2.73 G/cm, and 4 phase offsets over one period of motion (acquisition time approximately 25.5 minutes). Background phase was removed from the wave images using the above algorithm.

After background phase removal, the slope of the phase of the first temporal harmonic of the multislice data was calculated in a $5 \times 5 \times 5$ window in the x, y and z directions (m_x , m_y and m_z). The shear stiffness is equal to the tissue density times the shear wave speed squared. The shear wave speed is proportional to the shear wavelength, which for a single plane wave is directly proportional to the quantity, $(m_x^2 + m_y^2 + m_z^2)^{-1}$. Ignoring the phase/wave variations in the z direction, the stiffness would be proportional to the quantity, $(m_x^2 + m_y^2)^{-1}$. Therefore, the quantity, $((m_x^2 + m_y^2)^{-1} / (m_x^2 + m_y^2 + m_z^2)^{-1} - 1) * 100$, provides a measure of the percent error in the 2D model of the wave data due to not sampling the wave field in the z direction.

3. Results

Example images from one of the WT mice are shown in Fig. 2. Fig. 2a is the magnitude image from the MRE acquisition, showing the anatomical location of the MRE data. Fig. 2b is the calculated stiffness map and Figs. 2c and 2d show the real and imaginary parts of the first temporal harmonic of the wave data. Note that the wave amplitude is high throughout the entire brain. Fig. 3 shows phase SNR maps of the brain in all 13 mice. The mean and median phase SNR for the entire slice was at least 30 for all the mice. No mouse had more than 8% of the voxels within the ROI with an SNR less than 15. Also, there was no significant difference in median SNR within the ROI between the WT and AD groups ($P = .94$, Wilcoxon rank sum test).

The WT mice were pooled after no significant difference was found between the 17 and 23 month old groups ($P = 1$, Wilcoxon rank sum test). The stiffness maps for each of the

thirteen mice are displayed in Fig. 4. The median stiffness of the WT mice was 25.0 kPa with a range of 6.4 kPa ($n = 8$) while the median stiffness of the AD mice was 19.3 kPa with a range of 3.3 kPa ($n = 5$). The 22.5% decrease in stiffness was significant with a p value of 0.0031 (Wilcoxon rank sum test). The median stiffness of the two groups is plotted in Fig. 5 along with the median stiffness for each mouse.

Fig. 6 shows the results of the single-slice stiffness error estimate analysis calculated from the volumetric wave data (5 slices with 0.5 mm thickness). Images of the stiffness error produced by neglecting each of the x , y and z directions of phase change in a model of the wave propagation are shown in Fig. 6. The error due to ignoring the phase variations in the z direction is small throughout the brain. These results indicate that the shear waves measured in this study were propagating almost entirely in-plane and thus a 2D acquisition and inversion are sufficient for the measurement of stiffness.

4. Discussion

This study has demonstrated that MRE of the mouse brain is feasible at 3.0T with high phase SNR by using a custom RF coil and a 2D acquisition with one direction of motion encoding. The wave images shown in Fig. 2 demonstrate strong shear wave penetration throughout the brain. The phase SNR maps (Fig. 3) verify that the wave images are more than adequate for a reliable inversion. In addition, the results in Figs. 4 and 5 showed a significant decrease in stiffness associated with the extracellular deposition of fibrillar amyloid protein present in this animal model.

While this work reports a median stiffness of 25.0 kPa at 1500 Hz in the WT mice, previous work by Atay et al. reported an average shear stiffness of 13.8 kPa at 1200 Hz for cortical gray matter at a middle slice location [23]. Shear stiffness is expected to increase with increasing frequency of excitation due to the dispersive nature of brain tissue. More recently, Clayton et al. have used MRE to investigate the mechanical properties of mouse brain tissue at a wider range of frequencies from 600 to 1800 Hz [24]. The power-law fit of their data indicates a complex shear modulus of approximately $5.6 + 2.4i$ kPa at 1500 Hz, which would equate to a shear stiffness of 6.35 kPa [25]. While there are differences in these three results, the discrepancy in calculated stiffness could be due to several factors, including the method of vibration, slice location, preprocessing of the wave images, inversion algorithm characteristics, and the ROI chosen for measuring stiffness.

While the APP-PS1 mouse model is primarily a model of amyloidosis, which may be the cause of the observed stiffness changes, there is also some neurodegeneration that could explain the change of stiffness reported in this work. This neurodegeneration is evidenced by a mild behavioral phenotype [7], the presence of atrophic neurons around gray matter plaques [26], and the loss of CA1 pyramidal neurons in APP-PS1 mice [27]. Another potential confounding factor is the variation in background strain between the WT and AD mice.

In conclusion, these data show that the brain stiffness of AD mice is significantly lower than in WT mice. This change is likely due to alterations to the extracellular matrix, synaptic loss, neurodegeneration or some combination of these processes. These results suggest that MRE may provide an opportunity to aid in the detection or grading of AD as an additional biomarker to improve the specificity and sensitivity of current techniques and merits further investigation.

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References

1. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984; 34:939–44. [PubMed: 6610841]
2. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer Disease in the US Population. *Arch Neurol*. 2003; 60:1119–22. [PubMed: 12925369]
3. Hardy J, Selkoe DJ. The Amyloid Hypothesis of Alzheimer's Disease: Progress and Problems on the Road to Therapeutics. *Science*. 2002; 297:353–6. [PubMed: 12130773]
4. Jack CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010; 9:119–28. [PubMed: 20083042]
5. Lu YB, Franze K, Seifert G, Steinhäuser C, Kirchhoff F, Guck HWJ, et al. Viscoelastic properties of individual glial cells and neurons in the CNS. *Proc Natl Acad Sci U S A*. 2006; 103:17759–64. [PubMed: 17093050]
6. Smith JF, Knowles TP, Dobson CM, MacPhee CE, Welland ME. Characterization of the nanoscale properties of individual amyloid fibrils. *Proc Natl Acad Sci U S A*. 2006; 103:15806–11. [PubMed: 17038504]
7. Holcomb L, Gordon MN, McGowan E, Yu X, Benkovic S, Jantzen P, et al. Accelerated Alzheimer-type phenotype in transgenic mice carrying both mutant *amyloid precursor protein* and *presenilin 1* transgenes. *Nat Med*. 1998; 4:97–100. [PubMed: 9427614]
8. Wengenack TM, Whelan S, Curran GL, Duff KE, Poduslo JF. Quantitative Histological Analysis of Amyloid Deposition in Alzheimer's Double Transgenic Mouse Brain. *Neuroscience*. 2000; 101:939–44. [PubMed: 11113343]
9. Muthupillai R, Lomas DJ, Rossman PJ, Greenleaf JF, Manduca A, Ehman RL. Magnetic resonance elastography by direct visualization of propagating acoustic shear waves. *Science*. 1995; 269:1854–7. [PubMed: 7569924]
10. Green MA, Bilston LE, Sinkus R. In vivo brain viscoelastic properties measured by magnetic resonance elastography. *NMR Biomed*. 2008; 21:755–64. [PubMed: 18457350]
11. Hamhaber U, Sack I, Papazoglou S, Rump J, Klatt D, Braun J. Three-dimensional analysis of shear wave propagation observed by in vivo magnetic resonance elastography of the brain. *Acta Biomater*. 2007; 3:127–37. [PubMed: 17067861]
12. Klatt D, Hamhaber U, Asbach P, Braun J, Sack I. Noninvasive assessment of the rheological behavior of human organs using multifrequency MR elastography: a study of brain and liver viscoelasticity. *Phys Med Biol*. 2007; 52:7281–94. [PubMed: 18065839]
13. Kruse SA, Rose GH, Glaser KJ, Manduca A, Felmlee JP, Jack CR, et al. Magnetic Resonance Elastography of the Brain. *Neuroimage*. 2008; 39:231–7. [PubMed: 17913514]
14. McCracken PJ, Manduca A, Felmlee JP, Ehman RL. Mechanical transient-based magnetic resonance elastography. *Magn Reson Med*. 2005; 53:628–39. [PubMed: 15723406]
15. Sack I, Beierbach B, Hamhaber U, Klatt D, Braun J. Non-invasive measurement of brain viscoelasticity using magnetic resonance elastography. *NMR Biomed*. 2008; 21:265–71. [PubMed: 17614101]
16. Sack I, Beierbach B, Wuerfel J, Klatt D, Hamhaber U, Papazoglou S, et al. The impact of aging and gender on brain viscoelasticity. *Neuroimage*. 2009; 46:652–7. [PubMed: 19281851]
17. Tikkakoski T. Magnetic Resonance Elastography of Brain Tumors. *Acta Radiol*. 2007; 48:249. [PubMed: 17453488]
18. Wuerfel J, Paul F, Beierbach B, Hamhaber U, Klatt D, Papazoglou S, et al. MR-elastography reveals degradation of tissue integrity in multiple sclerosis. *Neuroimage*. 2010; 49:2520–5. [PubMed: 19539039]
19. Xu L, Lin Y, Xi ZN, Shen H, Gao PY. Magnetic Resonance Elastography of the Human Brain: A Preliminary Study. *Acta radiol*. 2007; 48:112–5. [PubMed: 17325935]
20. Xu L, Lin Y, Han JC, Xi JN, Shen H, Gao PY. Magnetic Resonance Elastography of Brain Tumors: Preliminary Results. *Acta radiol*. 2007; 48:327–30. [PubMed: 17453505]

21. Manduca A, Lake DS, Kruse SA, Ehman RL. Spatio-temporal directional filtering for improved inversion of MR elastography images. *Med Image Anal.* 2003; 7:465–73. [PubMed: 14561551]
22. Oliphant TE, Manduca A, Ehman RL, Greenleaf JF. Complex-Valued Stiffness Reconstruction for Magnetic Resonance Elastography by Algebraic Inversion of the Differential Equation. *Magn Reson Med.* 2001; 45:299–310. [PubMed: 11180438]
23. Atay SM, Kroenke CD, Sabet A, Bayly PV. Measurement of the Dynamic Shear Modulus of Mouse Brain Tissue *In Vivo* by Magnetic Resonance Elastography. *J Biomech Eng.* 2008; 130:021013. [PubMed: 18412500]
24. Clayton EH, Garbow JR, Bayly PV. Frequency-dependent viscoelastic parameters of mouse brain tissue estimated by MR elastography. *Phys Med Biol.* 2011; 56:2391–406. [PubMed: 21427486]
25. Manduca A, Oliphant TE, Dresner MA, Mahowald JL, Kruse SA, Amromin E, et al. Magnetic resonance elastography: Non-invasive mapping of tissue elasticity. *Med Image Anal.* 2001; 5:237–54. [PubMed: 11731304]
26. Kurt MA, Davies DC, Kidd M, Duff K, Rolph SC, Jennings KH, et al. Neurodegenerative Changes Associated with beta-Amyloid Deposition in the Brains of Mice Carrying Mutant Amyloid Precursor Protein and Mutant Presenilin-1 Transgenes. *Exp Neurol.* 2001; 171:59–71. [PubMed: 11520121]
27. Sadowski M, Pankiewicz J, Scholtzova H, Ji Y, Quartermain D, Jensen CH, et al. Amyloid-beta Deposition Is Associated with Decreased Hippocampal Glucose Metabolism and Spatial Memory Impairment in APP/PS1 Mice. *J Neuropathol Exp Neurol.* 2004; 63:418–28. [PubMed: 15198121]

Fig. 1.
Picture of the custom 6-cm quadrature transmit/receive birdcage coil and integrated electromechanical driver.

Fig. 2. Example images from a WT mouse. (a) Magnitude image showing the anatomical location of the MRE data. (b) Stiffness map calculated from the wave images. (c,d) Real and imaginary parts of the wave images following phase unwrapping and background phase removal.

Fig. 3. Phase SNR maps for all thirteen mice demonstrating high phase SNR throughout the brain for all mice.

Fig. 4. Elastograms for each of the 13 mice overlaid on the magnitude images. Note that the WT mice have higher brain stiffness compared to the AD mice.

Fig. 5. Summary of the WT and AD mouse brain stiffnesses. Lines represent the median stiffness for each group while the circles represent the median stiffness for each individual mouse.

Fig. 6.

Error maps calculated from multislice data. Each error map represents the % error in the stiffness that would be present if that direction of wave propagation was ignored. Since the error due to ignoring the z direction is small, particularly when compared to the x and y directions, a 2D acquisition and inversion is sufficient.