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Time-harmonic magnetic resonance elastography of the normal feline brain

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Abstract

Imaging of the mechanical properties of *in vivo* brain tissue could eventually lead to non-invasive diagnosis of hydrocephalus, Alzheimer's disease and other pathologies known to alter the intracranial environment. The purpose of this work is to (1) use time-harmonic magnetic resonance elastography (MRE) to estimate the mechanical property distribution of cerebral tissue in the normal feline brain and (2) compare the recovered properties of grey and white matter. Various *in vivo* and *ex vivo* brain tissue property measurement strategies have led to the highly variable results that have been reported in the literature. MR elastography is an imaging technique that can estimate mechanical properties of tissue non-invasively and *in vivo*. Data was acquired in 14 felines and elastic parameters were estimated using a global-regional nonlinear image reconstruction algorithm. Results fell within the range of values reported in the literature and showed a mean shear modulus across the subject group of 7–8 kPa with all but one animal falling within 5–15 kPa. White matter was statistically stiffer ($p < 0.01$) than grey matter by about 1 kPa on a per subject basis. To the best of our knowledge, the results reported represent the most extensive set of estimates in the *in vivo* brain which have been based on MRE acquisition of the three-dimensional displacement field coupled to volumetric shear modulus image reconstruction achieved through nonlinear parameter estimation. However, the inter-subject variation in mean shear modulus indicates the need for further study, including the possibility of applying more advanced models to estimate the relevant tissue mechanical properties from the data.

Keywords

Magnetic resonance elastography; brain; grey matter; white matter; finite element method

1. Introduction

Certain pathological processes are characterized by significant changes in tissue mechanical properties, most notably cancer, where property contrast is greater than it is for other common imaging parameters used for diagnosis such as MR relaxation time and X-ray

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absorption (Doyle et al. (2003); Duck (1990); Manduca et al. (2001); Venkatesh et al. (2008)). Manual palpation is a diagnostic technique that exploits this contrast by probing tissue's resistance to deformation, a physical phenomenon which is described by the elastic modulus. Palpation is commonly applied to the liver, breast, and prostate; however, the procedure is only effective if the abnormality is superficial and sufficiently large. Conventional imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) do not directly provide the mechanical property information that is gleaned from palpation. Thus, other methods are needed to study the mechanical characteristics of nonpalpable and/or deep tissue regions such as the brain.

Advanced understanding of brain tissue mechanical properties would aid studies of traumatic brain injury (TBI), brain deformation during neurosurgery, and brain disease processes. Unfortunately, estimates of these properties reported in the literature appear to be highly variable – a consequence of differences in the investigative technique, modeling method, and pathology under evaluation (Kruse et al. (2008)). Because TBI is believed to be caused by large shear strains (Holbourn (1943)), oscillatory shear testing is often applied in studies of *ex vivo* brain tissue (Bilston et al. (2001); Cheng et al. (2008); Hrapko et al. (2006)). Reliability problems arise with this technique at high frequencies as a result of instrument limitations caused by the inertial effects of brain tissue (Arbogast et al. (1997)). Another common measurement method is uniaxial compressive and tensile testing where *ex vivo* tissue is compressed or stretched between two plates or clamps (Cheng et al. (2007); Miller and Chinzei (2002)). These measurements can be technically difficult to perform and rely on a homogeneous, well-prepared sample. A more general problem with most mechanical testing is the reliance on *ex vivo* tissue samples which lack blood circulation and interstitial pressure that result in marked changes in tissue stiffness and do not necessarily correlate quantitatively with *in vivo* experiments.

Elasticity of brain tissue has recently been estimated *in vivo* using magnetic resonance elastography (MRE) (Muthupillai et al. (1995); Muthupillai and Ehman (1996)). MRE is performed on an MR scanner, allowing for comparable spatial resolution to MRI and the ability to measure mechanical properties of small structures that are deeply embedded in soft tissue. In effect, MRE performs non-invasive palpation by gently applying low frequency mechanical waves, measuring the resulting time-harmonic tissue motion with a phase-sensitive MR sequence, and generating a corresponding image of the recovered mechanical parameters, or elastograms. MRE studies have generally assumed tissue to be purely elastic, although recent investigations have employed more advanced models such as viscoelasticity (Green et al. (2008); Kruse et al. (2008); Sack et al. (2008, 2009a)) and poroelasticity (Perrinez et al. (2009)). While current applications of MRE have focused on the breast and liver (Asbach et al. (2008); McKnight et al. (2002); Plewes et al. (2000); Rouviere et al. (2006); Sinkus et al. (2005)) – tissues in which manual palpation has proved to be a successful diagnostic tool – there has been growing interest in studies of MRE as a method for evaluating the prostate, heart, and brain (Green et al. (2008); Kemper et al. (2004); Kruse et al. (2008); Sack et al. (2009b)).

Successful mechanical excitation of cerebral tissue has proven to be challenging because of the damping effects of the cerebral meninges and cerebrospinal fluid (CSF). Recent studies have begun to optimize excitation and acquisition techniques (Gizewski et al. (2005); Mariappan et al. (2009); Uffmann and Ladd (2008)). Similarly to *ex vivo* methods, these investigations have provided estimates of brain tissue properties under a wide range of conditions, as summarized in Table 1.

The purpose of this study was to estimate the shear modulus of healthy feline brain tissue using time-harmonic MRE acquisition coupled to 3D non-linear image reconstruction

methods based on linearly elastic model optimization. Because so much is known about their neurological function, felines are often the species of choice for experimental brain studies. They are commonly used in neurological research to investigate human disorders and ailments including epilepsy (Grossman (1963)) and hydrocephalus (Shapiro et al. (1985)); functional problems related to vision, hearing, and sleep (Somers et al. (1995); Gerken et al. (1991); Swett and Hobson (1968)); diseases such as cancer (Ernestus et al. (1992)) and Parkinson's (Podell et al. (2003)); and genetic disorders and spinal cord injury (Hall et al. (1987); Sullivan et al. (1976)). Grey and white matter is also better distinguished in the feline brain relative to other small animals, appearing more similarly to the human brain. Thus, data on mechanical properties will not only contribute to the wealth of neurological information already available on the feline brain, but it will also inform future studies of these same properties in animal models of human disorders and diseases.

In this study, differences in the mechanical properties of grey and white matter were investigated to serve as a baseline for comparison with values found in later studies of diseased tissue. Grey matter (outer cerebral cortex) and white matter (subcortical axonal tracts) constitute a vast majority of the brain's volume that are affected differently in neuropathological processes. For example, Alzheimer's disease is categorized by a replacement of the fatty myelin sheath in white matter with a stiffer amyloid plaque. Multiple Sclerosis (MS) is another disease in which white matter is primarily affected – here, demyelination occurs along the axonal tracts (Compston and Coles (2002)). Hydrocephalus (HC) is a disease process that is characterized by a steadily increasing pressure on the periventricular tissue, caused by either an obstruction in the transport of CSF in the lateral ventricles (non-communicating HC) or an impairment in the absorption of the CSF through the rest of the venous system (communicating HC). Ventricular enlargement presented on MR and CT is the current diagnostic standard. However, HC can appear similarly to an *ex vacuo* change resulting from periventricular leukomalacia or cerebral atrophy, where there is tissue loss of white matter around the ventricles but no increased ventricular pressure. MRE could allow for detection of a pressure change by locating a marked stiffness change in cerebral white matter (periventricular) due to pre-straining of the tissue. Successful implementation of MRE in studying healthy brain tissue properties would allow for extension of these investigations into specific brain pathologies such as Alzheimer's disease, MS, hydrocephalus, and TBI, among others. While prior MRE studies exist in the human and animal brain, they have relied on 2D analysis and/or shear property estimates based on direct linear or local frequency estimates; none have considered global non-linear inversion of three-dimensional displacement data derived from MRE acquisitions as reported here.

2. Methods

Estimating elasticity using MRE involves (1) actuation of the tissue of interest, (2) phase-sensitive MR detection to infer the resulting tissue displacements and (3) a mechanical model to relate the measured displacement field to the underlying mechanical properties.

2.1. Actuation

Achieving sufficient wave propagation through brain tissue has been challenging because of the brain's natural motion damping properties (Green et al. (2008); Kruse et al. (2008)). A bite-bar has been used in many cases involving human and animal studies, but can result in bulk brain movement instead of shearing motion (Green et al. (2008); Kruse et al. (2008); Xu et al. (2007)). In this study, a pneumatic actuator was used (shown in Figure 1) which proved to be an effective motion driver for the size of the feline brain. The unit, consisting of a small (70 mm-diameter) pneumatic surface, was attached to the MR table as illustrated in Figure 1. The anesthetized feline was laid prone with its lower jaw placed directly on the

actuator to provide mechanical coupling. The pneumatic actuator was connected to two subwoofer drivers via 40 mm-diameter reinforced tubing. The mechanical excitation frequency was set at 85 Hz.

A measure of shear strain energy was used to quantify the elasticity information present within the overall motion field. An example of the shear and normal strains calculated in the feline brain is shown in Figure 2 which indicates that the shear strain is 1–2 orders of magnitude greater than the normal strain. A typical example of the overall motion measured in the feline brain during the study is shown in Figure 3.

2.2. Acquisition

Two 10 cm-diameter RF coils were placed perpendicularly to the MR table. Experiments were performed on a 3.0 T Philips MR scanner (Philips Electronics N.V., Netherlands) using a phase-contrast spin-echo sequence. Motion-encoding gradients (MEGs) were synchronized with the externally-applied mechanical waves. Eight phase shifts between the MEGs and mechanical waves, ranging from 0 to 2π , were acquired to capture an accurate representation of the harmonic tissue motion. Motion data was encoded in three orthogonal directions. The MRE sequence included a 64×64 reconstruction matrix with a field-of-view (FOV) of 80×80 mm, a voxel size of $2 \text{ mm} \times 2 \text{ mm} \times 1.8 \text{ mm}$ (with a slice gap of 0.2 mm), and a repetition time (TR) of 900 ms and echo time (TE) of 50 ms. A corresponding turbo spin echo (TSE) T2-weighted MR sequence was recorded using the same FOV but acquired with a 256×256 matrix and a TR of 4000 ms and TE of 96.0 ms. Twelve coronal slices were captured during each MRE and MRI sequence.

2.3. Phantom studies

Once the displacement data was recorded, the material properties of interest were obtained from a reconstruction algorithm based on Navier's equations of motion for a linearly elastic continuum discussed in detail in previous publications (Van Houten et al. (1999, 2001)). Single-inclusion gelatin molds were constructed to test the repeatability and accuracy of the technique. Further information on phantom construction, independent material testing techniques, and mechanical property results can be found in the online supplementary material.

2.4. Animal studies

A series of 14 adult female domestic felines, each weighing between 2.0–3.5 kg, underwent MRI/MRE imaging. General anesthesia was induced using 100 mg of subcutaneous ketamine HCl (100mg/ml IVX Animal Health, St Joseph, MO) followed by $2.0 \pm 0.5\%$ of inhaled isoflurane in 100% oxygen. IACUC approval was obtained for this study.

Brain tissue was segmented and the MRE displacement data was interpolated onto a linear tetrahedral finite element mesh. The elastogram was generated using the subzone-based inversion algorithm, and values of the recovered shear modulus were determined at each pixel in the coregistered high resolution anatomical scans through the finite element basis function expansion.

Manual segmentation of grey and white matter was performed on the high resolution T2-weighted images to generate the most accurate differentiation of these tissues. Segmentation occurred over a series of 5 slices (10 mm total thickness) in approximately the same region of the brain for each subject. The fourth ventricle was located and considered to be the mid-slice in the coronal direction. The center of the brain image volume was selected to reduce the appearance of anatomical features such as the falx and tentorium, which are known to be very stiff and may bias the mean shear modulus estimates. Example contours in a single

coronal T2-weighted MR slice are shown in Figure 4. Because the estimation algorithm encodes the recovered shear modulus in terms of a continuously varying linear basis function expansion involving the MRE data sampling locations, no partial volume effects occur in the usual sense of relating two image volumes (i.e. the grey-white segmentation volume and the MRE data volume) with different acquisition resolutions.

3. Results

Of the 14 felines undergoing MRE examination in the study, only 10 had data suitable for estimating normal feline brain mechanical properties. Two subjects suffered from ventriculomegaly (dilated ventricles) and were removed from the analysis as abnormal. While these animals offered the opportunity to observe mechanical property changes under abnormal conditions, the origins of the presumed pathology (i.e. enlarged ventricles in MR) were unknown and only two subjects were available for study which would render any findings both anecdotal and difficult to substantiate. Shear strain-based SNR was calculated as a ratio of the average shear strain energy of each dataset to the strain energy measured with no actuation. Two datasets with SNR less than 5 were discarded.

Elastic reconstructions show that white matter is consistently stiffer in a feline brain than corresponding grey matter. Figure 6 illustrates these differences, showing the mean shear modulus value of white matter to be higher than grey matter in the same feline in all cases except one. Over the entire series of felines, the average white matter was 8.32 ± 3.67 kPa and the average grey matter was 7.09 ± 2.78 kPa. The average difference between grey and white matter (1237.09 Pa) per feline subject was statistically significant ($p < 0.01$) as shown in Table 2.

4. Discussion

Quantitative values of shear stiffness recovered in single-inclusion gelatin phantoms using MRE (background = 3.27 ± 1.29 kPa, inclusion = 8.93 ± 1.55 kPa) had a strong correlation with those obtained during independent mechanical testing (background = 3.30 ± 0.805 kPa, inclusion = 8.80 ± 0.883 kPa). Reproducibility studies showed that the variability in the mechanical actuation, measurement, and image reconstruction techniques was small (<5%). Thus, the 3D reconstructions generated in phantoms (see further details in the online supplementary material) proved to give quantitatively accurate estimates of the mechanical properties of an elastic medium that were reproducible, consistent with previously reported results (Doyley et al. (2003, 2004); Weaver et al. (2005)).

Furthermore, the shear stiffness property distribution of *in vivo* normal feline brain was successfully estimated using MRE. Mean values for grey and white matter were found to be in the range reported in the literature (Green et al. (2008); Hamhaber et al. (2007); Kruse et al. (2008); Sack et al. (2008); Uffmann et al. (2004)). Specifically, our values spanned 5–15 kPa depending on the animal, which were similar to the range observed in humans by Kruse *et al.*, but consistently higher than the Green *et al.* and Sack *et al.* findings. Our data also showed that the difference between grey and white matter per feline subject was small but statistically significant, where white matter was stiffer than grey. Although some disagreement on the relative stiffness of white versus grey matter has appeared in the literature, our results are consistent with the conclusions reached in the majority of studies (Green et al. (2008); Mehdizadeh et al. (2008); Miller et al. (2000); Miller and Chinzei (2002); Shuck and Advani (1972); Soza et al. (2005)). Here, we did not observe the sizable differences between white and grey matter reported by Kruse *et al.* but found much smaller differences similarly to Green *et al.*

While the pioneering work of Green et al. (2008) reported the first 3D MRE results in the *in vivo* brain, substantial differences exist between the methods deployed in Green *et al.* and those used in this work, especially in terms of image reconstruction. Specifically, the reconstruction method used by Green *et al.* developed an elasticity estimate based on locally evaluated spatial derivatives of motion data that is numerically processed (and smoothed); whereas, the reconstruction method used in this study estimates a global material property distribution through an overlapping regional nonlinear parameter optimization based on the unprocessed and unmodified motion data. The method used here also supports a continuously varying (and inhomogeneous) mechanical property distribution represented in terms of a linear basis function expansion of estimated mechanical property coefficients whereas the description used by Green *et al.* assumes local mechanical property homogeneity, even at tissue boundaries. While the work of Green *et al.* was the first important and valuable reference on *in vivo* brain mechanical property estimates from 3D MRE, an accepted gold standard for the elastic properties of brain tissue is apparently not yet recognized (as seen by the large range of brain tissue estimates in Fig. 1 of Kruse et al. (2008)). The results reported here contribute to the effort to establish agreement between multiple assessment methods as independent forms of validation.

The highest stiffness areas were found closer to interior brain structures (located in the periventricular tissue, see Figure 5), with softer tissue in the cerebral cortex. Interestingly, anatomical features were evident in the elastogram image as well. While the feline ventricles are extremely narrow in coronal view, lower stiffness corresponding to these locations was observed presumably due to the inability of cerebrospinal fluid to withstand a shear stress (marked as 2 in Figure 5). Additionally, a thin band of higher stiffness occurred in the top center region of the brain, corresponding with the falx (marked as 1 in Figure 5), a strong fold of dura mater that runs along the fissure between brain hemispheres.

One drawback in the study was the variability in mechanical properties observed between felines, whom are used commonly in studies of brain disease – an outcome that may have resulted from several factors. Most importantly, feline brains are much smaller than human brains, and thus, had a correspondingly much smaller number of displacement measurements. Secondly, the variation could be associated with the level of shear strain produced in the tissue. Low strains provide less elasticity information and low SNR, allowing noise to have a greater effect on the recovered elasticity distribution. Measuring the shear strain energy during an exam will aid in achieving the best level of strain. Thirdly, the variations observed in this study may represent the true inter-subject variability between feline brain tissue. Certainly, the reproducibility of our MRE technique in phantoms and *in vivo* in past studies has been high, yielding variations of less than 10% which are well below the variability observed between felines in this study. While other experiments provide smaller inter- and intra-subject variation in property estimates (Green et al. (2008); Sack et al. (2008)), the removal of motion effects resulting from true small-scale modulus variations, which are filtered as noise in direct inversion schemes, may have occurred. No filtering was used in the iterative approach presented here, which may allow such small-scale modulus variations to be resolved; however, it may also lead to greater variability in the reconstructed distribution, most notably at low SNRs.

Another possible improvement in the current technique is the incorporation of more advanced mechanical models of tissue. Since cerebral tissue consists of nearly 80% extracellular fluid, if vibrated at a certain frequency, it may be better characterized by a viscoelastic (Cheng et al. (2007); Sack et al. (2009a)) or poroelastic model (Cheng and Bilston (2007); Perrinez et al. (2009)) relative to the linear elasticity used here. Another advancement would be the modeling of the anisotropic properties of the brain, specifically white matter. Currently, anisotropic material properties are being explored in simulations,

based on the equilibrium equations for a nearly incompressible orthotropic solid. These assumptions eliminate the need for Poisson's ratio and a known fiber orientation (no reconstruction of rotation angles), making the nonlinear optimization update occur in terms of two similar parameters (Young's and shear moduli). Incorporation of diffusion tensor imaging as directional priors throughout the brain volume is well worth pursuing because the information is likely to help stabilize the recovery of the anisotropic moduli estimates from the measured MRE response. Improvements in both the understanding of the appropriate brain model and the eliciting of shear waves at an appropriate frequency will be evaluated in future studies.

The number of studies reporting measurements of mechanical properties of brain tissue has been growing. MRE is advantageous because it provides a way to measure mechanical properties *in vivo*, whereas most shear modulus estimates have arisen from post mortem or *ex vivo* tissue evaluations, which lack the effects of blood circulation and interstitial pressure. Estimation of the mechanical properties of brain tissue *in vivo* would potentially allow for a non-invasive diagnosis of intracranial pathologies such as hydrocephalus (HC) and Alzheimer's disease. By quantifying the mechanical property distribution, especially in cerebral tissue constituents such as grey and white matter, baseline stiffness values become available for interpreting future studies of brain tissue pathologies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. MRE acquisition setup including the pneumatic actuator (left) and the complete experiment (right) with the subject laid prone on the MR table. Two circular RF coils are shown perpendicular to the MR table (right).

Figure 2. Examples images of the calculated octahedral shear (left image) and normal (right image) strain in the feline brain with use of the pneumatic actuator. Shear strain is one to two orders of magnitude greater in the interior brain tissue structures.

Figure 3.

Example images of the measured *in vivo* displacement in the *x*, *y*, and *z* directions. Image (d) shows a trace of the displacement in one direction, depicting one period of the sinusoidal actuation. Red line on (c) indicates where the values in image (d) are from. Scale is in micrometers.

Figure 4.
T2-weighted coronal image of a typical feline brain. Contours denote segmented grey matter (left) and white matter regions (right).

Figure 5. T2-weighted image (top row) and the corresponding reconstructed shear modulus elastogram (bottom row). Number 1 marks the falx and number 2 marks the lateral ventricles which were excluded from the analysis.

Figure 6.
Plot of the average grey and white matter values (in Pascals) of each feline subject.

Table 1

Current mechanical property estimates of brain tissue using MRE.

	Actuation	Inversion	G' (kPa)	G'' (kPa)
Green et al. (2008) (N=5)	Bite Bar	DI		
Grey Matter			3.1	2.5
White Matter			2.7	2.5
Kruse et al. (2008) (N=25)	Bite Bar	LFE		
Grey Matter			5.22	N/A
White Matter			13.6	N/A
Sack et al. (2008) (N=6)	Head Rocker	PWI	1.5	3.4*
Sack et al. (2009a) (N=55)	Head Rocker	PWI	2.01	0.8
Atay et al. (2008) (N=6)	Head Rocker	DI	12–19	N/A

Direct Inversion = DI, Local Frequency Estimation = LFE, Planar Wave Inversion = PWI.

* value given as viscosity (Pa-s)

Table 2

Mean shear modulus values for grey and white matter.

	White Matter (Pa)		Grey Matter (Pa)	
	μ	σ	μ	σ
<i>Mean:</i>	8322.97	± 3672.12	7085.88	± 2784.76
<i>Difference:</i>	1237.09			
<i>H₀:</i>	$p < 0.01$			