Published in final edited form as:

J Biomech. 2006 ; 39(6): 1086–1095.

In vivo imaging of rapid deformation and strain in an animal model of traumatic brain injury*

Philip V. Bayly^{a,b,*}, Erin E. Black^a, Rachel C. Pedersen^a, Elizabeth P. Leister^b, and Guy M. Genin^a

^a Mechanical and Aerospace Engineering, Washington University in St. Louis, 1 Brookings Drive, Box 1185, St. Louis, MO 63130, USA

^b Biomedical Engineering, Washington University in St. Louis, 1 Brookings Drive, Box 1185, St. Louis, MO 63130, USA

Abstract

In traumatic brain injury (TBI) rapid deformation of brain tissue leads to axonal injury and cell death. In vivo quantification of such fast deformations is extremely difficult, but important for understanding the mechanisms of degeneration post-trauma and for development of numerical models of injury biomechanics. In this paper, strain fields in the brain of the perinatal rat were estimated from data obtained in vivo during rapid indentation. Tagged magnetic resonance (MR) images were obtained with high spatial (0.2 mm) and temporal (3.9 ms) resolution by gated image acquisition during and after impact. Impacts were repeated either 64 or 128 times to obtain images of horizontal and vertical tag lines in coronal and sagittal planes. Strain fields were estimated by harmonic phase (HARP) analysis of the tagged images. The original MR data was filtered and Fourier-transformed to obtain HARP images, following a method originally developed by Osman et al. (IEEE Trans. Med. Imaging 19(3) (2000) 186). The displacements of material points were estimated from intersections of HARP contours and used to generate estimates of the deformation gradient and Lagrangian strain tensors. Maximum principal Lagrangian strains of >0.20 at strain rates $>40/s$ were observed during indentations of 2 mm depth and 21 ms duration.

Keywords

Brain injury; Concussion; Strain; Deformation; HARP; MRI

1. Introduction

In traumatic brain injury (TBI), rapid deformation of brain matter is believed to be associated with subsequent pathology. Tissue deformation can be described precisely and comprehensively by the mechanical strain tensor. However, it is challenging to obtain quantitative measurements of strain in relevant animal models; the brain is encased in the skull, injury events are rapid, and displacements must be measured accurately and with high spatial resolution.

In human TBI, abnormally high strain may be caused by high linear and angular accelerations of the skull (Holbourn, 1943) but the detailed relationships between skull motion and brain deformation are still incompletely understood. In some studies of TBI (e.g., Gennarelli et al., 1982; Margulies et al., 1990; Meaney et al., 1995) high angular acceleration has been used to

*Funding acknowledged from NIH Grant NS45237 (NINDS).

*Corresponding author. Mechanical and Aerospace Engineering, 1 Brookings Drive, Box 1185, St. Louis, MO 63130, USA. Tel.: +1 314 935 6081; fax: +1 314 935 4014. E-mail address: pvb@me.wustl.edu (P.V. Bayly)..

model injury. Other methods of inducing injury include fluid percussion (e.g., Dixon et al., 1987), pneumatic impact (e.g., Smith et al., 1995), and weight-drop (e.g., Bittigau et al., 1999). In these studies, injury is typically described in terms of indirect parameters such as acceleration, impact speed, or fluid pressure. None of these parameters is conserved between different models. However similar levels of strain are believed to cause similar neuropathology (Margulies et al., 1990). This belief is supported by in vitro studies such as those by Smith et al. (1999), Morrison et al. (2000), and Geddes et al. (2003), who investigated the response of cultured axons to stretching. Bain and Meaney (2000) determined thresholds for injury in the guinea pig optic nerve in terms of strain. Finite element models of the human head and brain have also been developed (e.g., Ruan et al., 1991; Zhang et al., 2001), but validation against quantitative, spatially resolved, strain data is still lacking.

To visualize the basic mechanism of acceleration-induced brain injury, Holbourn (1943), Margulies et al. (1990), and Meaney et al. (1995) examined shear deformation in gel-filled skulls. The deformation patterns offer insight into the expected strain fields, but the gel-filled skull is significantly different from the in vivo brain. High-speed biplanar X-ray measurement of a small number of radio-opaque targets embedded in cadaver brains during impact were obtained by Hardy et al. (1997, 2001) and Al-Bsharat et al. (1999). While the temporal resolution of these measurements is excellent, spatial resolution is limited by the small number of markers.

Non-invasive measurement of strain in biological tissue is feasible using magnetic resonance imaging (MRI). Deformation of cardiac tissue has been visualized and quantified using MR images with reference “tag lines” since the work of Zerhouni et al. (1988). Axel and Dougherty (1989a,b) developed a scheme (“spatial modulation of magnetization” or SPAMM) for generating tag lines in images using a sequence of radio-frequency pulses and magnetic field gradients. In cardiac cine MRI, a trigger signal from the ECG initiates the tagging sequence, then the grid of tag lines is imaged at specified times during the cardiac cycle. Imaging is performed over a number of cardiac cycles to obtain fully resolved images of the deformed tag lines.

Osman et al. (2000) proposed the “harmonic phase” (HARP) method for estimation of strain in cardiac MRI. In the HARP approach, deformation is estimated from the phase angle of the complex image derived by selectively filtering, then inverting, the Fourier transform of the tagged image. The HARP method allows automated strain estimation and facilitates rapid image acquisition, because only data from a limited set of spatial frequencies (a limited section of k -space) is needed. Kuijer et al. (2001), Kraitchman et al. (2003), and Sampath et al. (2003) among others have extended the original technique. Validation of HARP strain analysis has been performed by Liu et al. (2004) and Bayly et al. (2004).

In the current study, strain fields were obtained during rapid indentation of the flexible skull of anesthetized perinatal (P7) rat pups. Controlled impact in the P7 rat has been used as a model of developmental brain injury (e.g., Bittigau et al., 1999). Our general approach is based on acquisition of tagged MR images in coronal and sagittal planes during controlled impacts. A modified HARP analysis is used to estimate displacements of material points. These displacements are then used to calculate the Lagrangian strain tensor.

2. Methods and materials

An MR-compatible device was developed to apply controlled rapid indentations to the head of a seven-day old (P7) Sprague–Dawley rat pup ($n = 11$) inside a 4.7 T MR scanner (Varian UNITY/INOVA 200/400). A rigid Delrin impactor, 3 mm diameter tip, was driven by a motor outside the scanner’s magnetic field. The impact tip was placed 3 mm anterior to the lambdoid

suture and 2 mm lateral to midline. Indentation of the flexible skull produces parasagittal deformation of the parietal cortex. Depth of indentation was controlled by screw adjustment of the impact tip. Impact speed and duration of contact are determined by motor speed, which was precisely controlled by a digital servo-system (PIC-SERVO, J.R. Kerr, Inc.).

Each animal was anesthetized with 5% isoflurane in air, placed in an MR-compatible holder (Fig. 1) with its head supported in a polyvinylsiloxane (dental impression material) mold that maintained head position during indentation. The impactor/holder assembly was inserted into the 10-cm bore of the magnet. Anesthesia was maintained with 2% isoflurane in air delivered via a nose cone. The skull of the animal was exposed by midline incision and the scalp reflected. The skull was repeatedly indented (1 or 2 mm) rapidly (6 impacts/s at 42 ms duration, or 12 impacts/s of 21 ms duration) during image acquisition. For 2 mm impacts at 6 impacts/s, the impact speed was 0.17 m/s; at 12 impacts/s the impact speed was 0.34 m/s. Animals that were imaged in only the coronal plane received 64 impacts; animals that were imaged in both coronal and sagittal planes received 128 impacts. The impact sequence took from 5.3 to 21.2 s, depending on the number and speed of impacts. Each animal spent approximately 25 min under anesthesia. Animals were euthanized by injection of sodium pentobarbital before recovery from anesthesia. Procedures were reviewed by the Washington University Animal Studies Committee and performed in accordance with the Animal Welfare Act and the NIH Guide for the Care and Use of Laboratory Animals.

The MR imaging sequence (Fig. 2) was initiated when the impactor interrupted an optical sensor. MR tagging of the brain was performed with a SPAMM 1–1 sequence (Axel and Dougherty, 1989a) after triggering and before impact. Tag lines were first placed horizontally, perpendicular to the “readout” direction of the image. Tagging was followed by 15 repeated acquisitions of one k -space line at temporal intervals of 3.9 ms. Each k -space line is a single “phase-encode” step containing 128 points in the readout direction. Indentation was performed again to obtain a second line of k -space data at the same time points. A total of 32 lines of k -space were acquired to obtain a complete set of images. The set consisted of 15 MR cine frames, at 3.9 ms/frame, with horizontal tag lines. The procedures were then repeated with the readout and phase-encode directions switched to obtain 15 more frames with vertical tag lines. This sequential procedure effectively provides 128×128 resolution for tracking tag lines in both directions but requires only 64 phase-encode steps.

Other MR imaging parameters were: tag spacing 1 mm; echo time (TE), 2 ms; field of view 2 cm $\times$ 2 cm (coronal), 3 cm $\times$ 3 cm (sagittal); final matrix size 128×128 ; slice thickness 1.0 mm. 2-D images were acquired in the coronal and sagittal planes centered below the impact tip. Coronal and sagittal untagged scout images of one animal (Fig. 3) illustrate the location of the image planes. The series of tagged images in both the coronal and sagittal planes show visible deformation (Fig. 4). These images were taken during 1 mm impacts at 6 impacts/s.

The imaging procedure caused no obvious physical change (such as laceration or visible fracture) to the impact site. To assess if any gross changes in mechanical properties occurred due to repeated impact, force was measured directly during MR imaging with a fiber Bragg grating optical strain gage system (Blue Road Research, 1300-1.0-A-P-5). The strain gage was mounted on the impact arm and excited by a superluminescent diode (Kamelian SLD-02-01-13-FP, 1300 nm wavelength). When force is applied to the tip of the arm, the resulting strain induces a change in the wavelength of reflected light. The change in wavelength is detected with a tunable grating filter (Blue Road TGF-001) and high-speed detector (Blue Road HSD-002). The combined strain gage system has a range of $\pm 500 \mu\epsilon$ and a bandwidth of 10 kHz; a force measurement range of approximately ± 2 N was obtained. Signals were acquired with 16-bit resolution at 5120 samples/s, bandpass filtered between 2.5 and 200 Hz to remove drift and high-frequency noise.

Representative force measurements (Fig. 5) for the two different speeds used in this study show negative pulses representing the force of indentation. Noise in the data may reflect both vibration and electromagnetic interference with electronics. Overall, the amplitude of impact force is quite stable during this sequence.

The major challenges in image acquisition are: (1) temporal resolution; (2) spatial resolution; (3) limiting the number of impacts. The current temporal resolution (3.9 ms) produces images without significant blurring or artifact. Algorithms to increase temporal resolution remain topics of current research. The current spatial resolution is 0.16–0.23 mm/pixel. Increasing spatial resolution would require slightly longer acquisition times (more samples in the readout direction) or an increased number of impacts (more samples in the phase-encode direction). For example, increasing from 128 to 256 lines in the readout direction would increase the actual data acquisition time from 0.77 to 1.54 ms. This change would increase the 3.9 ms repetition time to 4.7 ms, and also decrease the “shutter speed” of the imaging process. Tag line intersections can be estimated with sub-pixel resolution using the effective interpolation of the HARP algorithm. Impacts were delivered vertically, and images taken under the impactor’s central planes, so that 2-D analysis of the 3-D strain field is expected to capture the dominant modes of deformation.

2.1. HARP image analysis

The Fourier transform of a tagged MR image has peaks corresponding to the spatial frequencies of the periodic tagging pattern. If the Fourier transform is filtered, retaining only data from spatial frequencies near such a peak, then inverted, the resulting image is complex. The phase of this complex image, called “harmonic phase”, is a material property of the tagged tissue (Osman et al., 2000), which can be used to track 2-D displacement and strain.

HARP was implemented in a “*displacement-based*” analysis (Bayly et al., 2004). Contours of constant phase provide precise locations of synthetic tag lines in the reference and deformed images (Fig. 6a,b). The inter-sections of the isophase contours were found automatically and used as vertices of a triangular mesh in the reference image (Fig. 6c). The same triangular mesh-ordering scheme is applied to the corresponding intersection points in the deformed image (Fig. 6d). The result is a set of undeformed and deformed triangles. A strain tensor is estimated for each triangle, under the assumption that the strain field is locally homogeneous. If a side of a triangle in the reference image is described by the vector $\mathbf{DX}_i$, $i = 1, 2, 3$ and the corresponding side of the corresponding triangle in the deformed image is $\mathbf{dx}_i$, the elements of the deformation gradient tensor F can be estimated by solving Eq. (1) (in the least squares sense) simultaneously for $i = 1, 2, 3$.

$$\mathbf{dx}_i = F \mathbf{DX}_i \quad i = 1, 2, 3. \quad (1)$$

The 2-D apparent Lagrangian strain tensor is computed directly from F and written with respect to Cartesian coordinates of the image plane:

$$E = (F^T F - I) / 2 = \begin{bmatrix} \epsilon_{xx} & \epsilon_{xy} \\ \epsilon_{xy} & \epsilon_{yy} \end{bmatrix}. \quad (2)$$

We characterized the degree of deformation at a point by ϵ_1 , the maximum principal Lagrangian strain (the maximum eigenvalue of E).

The displacement-based method allows quantities that are estimated in the deformed image to be mapped back to the reference image (Fig. 6e); it works well even when the reference tagging

pattern is not exactly uniform (due to spatial variations in the magnetic fields) or if the tag spacing is wide (Bayly et al., 2004).

2.2. Analysis details

The analysis was implemented in Matlab v.6.1 (The Mathworks, Natick, MA), which includes a built-in function for mesh generation via Delaunay triangulation. The filter $\Gamma(r)$ used to isolate spectral peaks in the Fourier transformed images was a circular band-pass filter with rapid fall-off (following Osman et al., 2000).

$$\Gamma(r) = \begin{cases} 1, & r \leq R, \\ \exp[-(r-R)/(2\sigma^2)], & r > R, \end{cases} \quad (3)$$

where r is the “distance” from spatial frequency $\mathbf{k}$ to the reference frequency $\mathbf{w}_i$: $r = \|\mathbf{k} - \mathbf{w}_i\|$. The decay variable $\sigma = 0.07$ and the filter radius $R = 1.28$ rad/mm, which was chosen as a small fraction of the dominant frequency of the tagging pattern (6.28 rad/mm for tag lines spaced 1 mm apart).

3. Results

Strain fields were computed in a total of 11 animals from 2 litters of P7 rat pups. 2-D strain fields were computed in the coronal plane for the following cases: (I) 2 mm at 6 impacts/s ($n = 3$); (II) 1 mm at 6 impacts/s ($n = 3$); and (III) 2 mm at 12 impacts/s ($n = 5$). Sagittal strain fields were computed for the same parameter values in 9 of the animals: Case (I), $n = 2$; Case (II), $n = 3$; Case (III), $n = 4$. The maximum principal Lagrangian strain magnitude ($|\epsilon_1|$) field superimposed on the coronal scout image for Case (II): 1 mm deformation at 6 impacts/s was shown previously (Fig. 6e). Example strain fields are shown in the coronal plane (Fig. 7) and sagittal plane (Fig. 8) for various parameter combinations.

In coronal images of the components of the strain tensor (Fig. 7) consistent features include the area of compression (large vertical strain, $\epsilon_{yy} > 0.10$) underneath the impactor. In this same area, the horizontal strain ϵ_{xx} is positive, indicating that material is being squeezed out as it is compressed. Bands of high shear strain, $\epsilon_{xy} > 0.10$; are seen under the corners of the indenter. The sense of the shear strain is positive on one side of the indenter and negative on the other side. The $|\epsilon_1|$ field captures the area of greatest deformation. Case (II), the case with 1 mm indentation depth, exhibits smaller areas of high strain than the two cases with 2 mm depth.

In sagittal images of strain components (Fig. 8) areas of vertical compression and horizontal stretching are again evident under the impactor. Areas of high shear, of opposite sign, are again found at the anterior and posterior edges of the indenter and extending downward. Principal strain magnitudes are again smaller for the 1 mm indentation depth, Case (II).

Summary statistics (Figs. 9 and 10) were estimated from the complete set of strain fields. The fraction of the field exhibiting maximum principal Lagrangian strain magnitude $|\epsilon_1|$ greater than 0.10, the mean value of $|\epsilon_1|$, and the maximum value of $|\epsilon_1|$ are plotted for each animal. While there is some scatter, and relatively few samples, there are clear differences between strain fields caused by 1 and 2 mm indentation. Differences between all summary statistics of strain in coronal sections from 1 and 2 mm indentation depths are statistically significant with $p < 0.01$ (Tables 1 and 2). There were fewer sagittal strain fields estimated, but in each statistic from sagittal sections the probability that the increase occurred by chance as impact depth was increased from 1 to 2 mm was $p < 0.075$ (Tables 3 and 4). No statistically significant differences in strain fields were observed between slower (0.17 m/s) and faster (0.34 m/s) impacts.

The magnitude of strain rate may be estimated approximately from these data. The quotient of the strain tensor divided by the time to peak indentation (1/2 the impact duration, or 11 ms for 12 impacts/s, for example) is a conservative estimate of strain rate. Using this method, mean strain rates of about 10/s and maximum strain rates of at least 40/s are observed in 2 mm impacts at 12 impacts/s.

4. Discussion

Strain fields were obtained in vivo during rapid indentation of the P7 rat brain. The current method is based on HARP analysis of tagged MR images acquired with high spatial and temporal resolution. Qualitative features of estimated strain fields are consistent among animals and consistent with expectations of basic continuum mechanics. Values of maximum principal strain greater than 0.20 and strain rates greater than 40/s were observed in several animals exposed to 2 mm impacts of 21 ms duration. Strain magnitudes appear to depend on indentation depth, as expected, but not on rate of loading.

The parameters of this study are based on those used in previous studies of developmental brain injury in the P7 rat. Depth of deformation and indenter size are based on the studies of Bittigau et al. (1999) and Black et al. (2004). The strains and strain rates observed overlap with: (i) the threshold for axonal injury (~0.2 strain at 30/s–60/s) measured by Bain and Meaney (2000) in guinea pig optic nerve; (ii) the threshold for axonal injury (~0.3 strain) predicted by Prange and Margulies (2001) in the infant pig; and (iii) the strain and strain rate (0.30 at 10/s) used by Geddes et al. (2003) to demonstrate membrane permeability changes in an in vitro preparation of rat cortical neurons.

The scope of the present study is restricted to the biomechanics of impact, specifically measurement of strain. However, the areas of high strain observed in this study clearly include the parietal cortex and inner structures of the brain, including the hippocampus, the corpus callosum, and the anterior sections of the thalamus. All these structures are known (e.g., Bittigau et al., 1999) to exhibit degenerative changes (cell death or axonal injury) post-trauma.

A number of technical limitations of the current method are acknowledged.

Temporal resolution

Temporal resolution is limited by the MRI sequence repetition time, which is currently 3.9 ms in our small animal scanner. This is easily sufficient for impacts of 20–40 ms duration, but needs to be improved to capture faster injury events. For example, with a 3.9 ms repetition time, the time of peak strain could be in error by almost 2 ms. However, for a half-sine pulse of 20 ms width, a 2-ms error in the time of peak strain would lead to an error of only 4.9% in the peak strain amplitude. Accordingly, in the current study 5% error in peak strains is a conservative upper bound on the error due to temporal sampling.

Repeatability of indentation

These imaging studies require repeated impacts. Each loading cycle must be nearly identical, since a single image contains data from many cycles. The tag line intensity in the final image represents a weighted average of its intensity over the sequence. Although Gefen et al. (2003) show that the mechanical properties of the infant rat brain are affected by pre-conditioning, force data (Fig. 5) provide some evidence of consistent impacts in this study.

2-D analysis of 3-D deformation

Indentation leads to a 3-D deformation. In this study, 2-D apparent strain fields were obtained in coronal and sagittal slices, through the mid-plane of the indenter. Out-of-plane deformation

is minimized by choosing these planes, but not eliminated, so that 2-D strain images are acknowledged to be approximate and partial pictures of the 3-D strain field.

Animal model

The perinatal rat is a useful model for the study of developmental brain injury. However, acceleration-induced deformation will need to be studied in human cadavers or larger animals, because of the scaling of strain with brain size (Margulies et al., 1990). The present imaging procedures can be generalized readily to acceleration-induced deformation.

Number of impacts

It should be possible to reduce the number of phase encode steps, and thus reduce the number of required impacts, by using only those data needed to define spectral peaks (Kraitchman et al., 2003; Sampath et al., 2003). Generalization to 3-D would be desirable, but would require an excessive number of impacts with our current method. For example, to obtain a 3D data set with six slices in a single direction, 384 impacts would be required. 2-D apparent strain remain very useful quantitative descriptions of deformation, though they must be interpreted carefully. Complementary acquisition and subtraction of inverted tagged images (C-SPAMM) has been recommended for HARP strain analysis (Kuijer et al., 2001) but C-SPAMM would require undesirable additional impacts.

The ability to characterize head injury on the basis of strain and strain rate will be essential for understanding the mechanism of neuronal injury in the in vivo brain. The current study cannot directly provide injury thresholds for single impacts, because impacts are repeated to obtain strain fields. Injury thresholds for repeated impacts will not be the same as for single impacts. However, the current approach provides new quantitative information on the strain levels that would be experienced in single impacts. Strain and strain rate, but not other mechanical parameters (force, acceleration, displacement, velocity), are conserved among different injury models. The methods and results of this study can provide high-quality data for interpretation of physiological studies, as well as for validation of computer models of brain mechanics.

Acknowledgements

We gratefully acknowledge the assistance of colleagues in the Washington University Biomedical MR Laboratory. MRI facilities support was provided by National Cancer Institute Small Animal Imaging Resource (SAIR) Program grant R24-CA83060; the Washington University Small Animal Imaging Resource (WUSAIR). Support from the NIH grant NS45237 is acknowledged.

References

- Al-Bsharat, A., Hardy, W.N., Yang, K.H., Khalil, T.B., King, A.I., Tashman, S., 1999. Brain/skull relative displacement due to blunt head impact: new experimental data and model. Proceedings of the 43rd Stapp Car Crash Conference, SAE Paper 99S-86.
- Axel L, Dougherty L. MR imaging of motion with spatial modulation of magnetization. Journal of Biomechanics 1989a;171 (3):841–845.
- Axel L, Dougherty L. Heart wall motion: improved method of spatial modulation of magnetization for MR imaging. Radiology 1989b;172 (2):349–350. [PubMed: 2748813]
- Bain AC, Meaney DF. Tissue-level thresholds for axonal damage in an experimental model of central nervous system white matter injury. Journal of Biomechanical Engineering 2000;122:615–622. [PubMed: 11192383]
- Bayly PV, Ji S, Song SK, Okamoto RJ, Massouros P, Genin GM. Measurement of strain in physical models of brain injury: a method based on HARP analysis of tagged magnetic resonance images. Journal of Biomechanical Engineering 2004;126:523–528. [PubMed: 15543872]

- Bittigau P, Sifringer M, Pohl D, Stadthaus D, Ishimaru M, Shimizu H, Ikeda M, Lang D, Speer A, Olney JW, Ikonomidou C. Apoptotic neurodegeneration following trauma is markedly enhanced in the immature brain. *Annals of Neurology* 1999;45:724–735. [PubMed: 10360764]
- Black EE, Young C, Olney JW, Bayly PV. Graded traumatic brain injury in the P7 rat pup. *Journal of Neurotrauma* 2004;21(9):1276.(abstract)
- Dixon CE, Lyeth BG, Povlishock JT, Findling RL, Harmon RJ, Marmarou A, Young HF, Hayes RL. A fluid percussion model of experimental brain injury in the rat. *Journal of Neurosurgery* 1987;67:110–119. [PubMed: 3598659]
- Geddes DM, Cargill RS, LaPlaca MC. Mechanical stretch to neurons results in a strain rate and magnitude-dependent increase in plasma membrane permeability. *Journal of Neurotrauma* 2003;20(10):1039–1049. [PubMed: 14588120]
- Gefen A, Gefen N, Zhu Q, Raghupathi R, Margulies SS. Age-dependent changes in material properties of the brain and braincase of the rat. *Journal of Neurotrauma* 2003;20(11):1163–1177. [PubMed: 14651804]
- Gennarelli TA, Thibault LE, Adams JH, Graham DI, Thompson CJ, Marcincin RP. Diffuse axonal injury and traumatic coma in the primate. *Annals of Neurology* 1982;12:564–574. [PubMed: 7159060]
- Hardy, W.N., Foster, C.D., King, A.I., Tashman, S., 1997. Investigation of brain injury kinematics: introduction of a new technique. *Proceedings of Crashworthiness, Occupant Protection, and Biomechanics in Transportation Systems*, ASME Publication AMD-vol. 225, pp. 241–254.
- Hardy WN, Foster CD, Mason MJ, Yang KH, King AI, Tashman S. Investigation of head injury mechanisms using neutral density technology and high-speed biplanar X-ray. *Stapp Car Crash Journal* 2001;45:337–368. [PubMed: 17458753]
- Holbourn AHS. The mechanics of head injuries. *Lancet* 1943:438–441.
- Kraitchman DL, Sampath S, Castillo E, Derbyshire JA, Boston RC, Bluemke DA, Gerber BL, Prince JL, Osman NF. Quantitative ischemia detection during cardiac magnetic resonance stress testing by use of FastHARP. *Circulation* 2003;107:2025–2030. [PubMed: 12668517]
- Kuijper JPA, Jansen E, Marcus JT, van Rossum AC, Heethaar RM. Improved harmonic phase myocardial strain maps. *Magnetic Resonance in Medicine* 2001;46:993–999. [PubMed: 11675652]
- Liu W, Chen J, Ji S, Allen S, Bayly PV, Wickline SA, Yu X. HARP MRI tagging for direct quantification of Lagrangian strain in rat hearts after myocardial infarction. *Magnetic Resonance in Medicine* 2004;52:1282–1290. [PubMed: 15562486]
- Margulies SS, Thibault LE, Gennarelli TA. Physical model simulations of brain injury in the primate. *Journal of Biomechanics* 1990;23:832–836.
- Meaney DF, Smith DH, Ross DT, Gennarelli TA. Biomechanical analysis of experimental diffuse axonal injury in the miniature pig. *Journal of Neurotrauma* 1995;12(4):689–695. [PubMed: 8683620]
- Morrison B III, Meaney DF, Margulies SS, McIntosh TK. Dynamic mechanical stretch of organotypic brain slice cultures induces genomic expression: relationship to mechanical parameters. *Journal of Biomechanical Engineering* 2000;122:224–230. [PubMed: 10923289]
- Osman NF, McVeigh ER, Prince JL. Imaging heart motion using harmonic phase MRI. *IEEE Transactions on Medical Imaging* 2000;19(3):186–202. [PubMed: 10875703]
- Prange, M.T., Margulies, S.S., 2001. Tissue strain thresholds for axonal injury in the infant brain. *Proceedings of the ASME Bioengineering Conference, BED-vol. 50*, pp. 833–834.
- Ruan JS, Khalil T, King AI. Human head dynamic response to side impact by finite element modeling. *Journal of Biomechanical Engineering* 1991;113(3):276–283. [PubMed: 1921354]
- Sampath S, Derbyshire JA, Atalar E, Osman NF, Prince JL. Real-time imaging of two-dimensional cardiac strain using a Harmonic Phase Magnetic Resonance Imaging (HARP-MRI) pulse sequence. *Magnetic Resonance in Medicine* 2003;50:154–163. [PubMed: 12815690]
- Smith DH, Soares HD, Pierce J, Perlman KG, Saatman KE, Meaney DF, Dixon CE, McIntosh TK. A model of controlled cortical impact in the mouse: cognitive and histopathologic effects. *Journal of Neurotrauma* 1995;12(2):169–178. [PubMed: 7629863]
- Smith DH, Wolf JA, Lusardi TA, Lee VM, Meaney DF. High tolerance and delayed elastic response of cultured axons to dynamic stretch injury. *Journal of Neuroscience* 1999;19(11):4263–4269. [PubMed: 10341230]

- Zerhouni EA, Parish DM, Rogers WJ, Yang A, Shapiro EP. Human heart tagging with MR imaging—a method for noninvasive assessment of myocardial motion. *Radiology* 1988;169:59–63. [PubMed: 3420283]
- Zhang, L., Hardy, W., Kiyoshi, O., King, H.Y., King, A.I., 2001. Recent advances in brain injury research: a new model and new experimental data. *Proceedings of the ASME Bioengineering Conference, BED-vol. 50*, pp. 831–832.

Fig. 1.
(a) CAD drawing of the head-holder/impact/anesthesia device with animal. The inset shows the 4.7 T small-animal MR scanner (10 cm bore) into which the device and impacting apparatus are inserted. (b) Photograph of the head-holding device showing the molded head side supports, palate support and nose cone.

Fig. 2.

Timing diagram of MR sequence. The diagram is approximately scaled for an impact duration of 21 ms, and an inter-impact interval of 83 ms (12 impacts/s). Before each impact, an optical detector triggers the MR sequence. Tag lines are applied before impact begins. Data is then acquired for one spatial frequency, k_N , in the “phase-encode” direction (i.e., one line in k -space). Acquisition of the same k -space line is repeated 15 times during and after the impact. Temporal resolution of the data set is determined by the time increment between each acquisition: 3.9 ms. The actual time during which data is acquired is ~ 1 ms. Impact is repeated to acquire the next line of k -space, k_{N+1} , until 32 lines of k -space are acquired for each of the two tagging directions.

Fig. 3.

(a) Coronal and (b) sagittal “scout” MR images of the rat brain showing the anatomical planes in which strain is measured. These images are obtained just prior to the impact sequence. The skull has been exposed and the scalp reflected.

Fig. 4. Series of coronal (top) and sagittal tagged images of the P7 rat brain during 1 mm deformation, 6 impacts/s. Temporal resolution is 3.9 ms/frame.

Fig. 5. Impact force measurement obtained with fiber optic (Bragg grating) force transducer during MR imaging at (a) 6 impacts/s, 2 mm depth (42 ms impact duration, 0.17 m/s impact speed), and (b) 12 impacts/s, 2 mm depth (21 ms impact duration, 0.34 m/s impact speed).

Fig. 6.

Illustration of strain analysis procedures. (a–b) Contour lines of constant “harmonic phase” (HARP) superimposed on (a) undeformed and (b) deformed tagged images. (c) Reference and (d) deformed triangular meshes formed from the intersection points of contour lines. (e) Contour plot of maximum principal Lagrangian strain magnitude $|\epsilon_1|$ plotted with respect to referential location and superimposed on the MR image of the undeformed brain (red = 0.20, blue = 0.0).

Fig. 7.

Lagrangian strain fields estimated from coronal tagged images. (I) 2 mm depth, 6 impacts/s (0.17 m/s). (II) 1 mm depth, 6 impacts/s (III) 2 mm depth, 12 impacts/s (0.34 m/s). Qualitative features consistent with indentation appear in each case. Negative ϵ_{yy} (compressive strain in the vertical, or y direction) and positive ϵ_{xx} (tension in the horizontal, or x direction) appear under the indenter. Shear bands (ϵ_{xy}) of opposite sense occur under the edges of the indenter. Maximum principal Lagrangian strain, $|\epsilon_1|$, characterizes the magnitude of deformation.

Fig. 8.

Strain fields estimated from sagittal tagged images. (I) 2 mm depth, 6 impacts/s (0.17 m/s). (II) 1 mm depth, 6 impacts/s. (III) 2 mm depth, 12 impacts/s (0.34 m/s). Qualitative features consistent with indentation appear in each case. Negative ϵ_{yy} (compressive strain in the vertical, or y direction) and positive ϵ_{xx} (tension in the horizontal, or x direction) appear under the indenter. Shear bands (ϵ_{xy}) of opposite sense occur under the edges of the indenter. Maximum principal Lagrangian strain magnitude, $|\epsilon_1|$, characterizes the degree of deformation.

Fig. 9.

Summary statistics for coronal strain images. (a) Fraction of the strain field in which maximum principal Lagrangian strain magnitude $|\epsilon_1|$ exceeds 0.10. (b) Mean value of $|\epsilon_1|$. (c) Maximum value of $|\epsilon_1|$. (v1 = 6 impacts/s; v2 = 12 impacts/s.) Average values and estimated probabilities that differences in strain fields would occur by chance are given in Tables 1 and 2.

Fig. 10.

Summary statistics for sagittal strain images. (a) Fraction of the strain field in which maximum principal Lagrangian strain magnitude $|e_1|$ exceeds 0.10. (b) Mean value of $|e_1|$. (c) Maximum value of $|e_1|$. ($v1 = 6$ impacts/s; $v2 = 12$ impacts/s.) Average values and estimated probabilities that differences in strain statistics would occur by chance are given in Tables 3 and 4.

Table 1 Average values $\pm$ standard deviations of coronal strain field statistics^a

Coronal	Proportion $ \epsilon_1 > 0.10$	Mean $ \epsilon_1 $	Max. $ \epsilon_1 $
1 mm, 6 impacts/s ($N = 3$)	0.155 ± 0.022	0.060 ± 0.007	0.246 ± 0.030
2 mm, 6 impacts/s ($N = 3$)	0.368 ± 0.102	0.094 ± 0.010	0.416 ± 0.164
2 mm, 12 impacts/s ($N = 5$)	0.322 ± 0.092	0.089 ± 0.008	0.387 ± 0.079

^aSee Fig. 8 for data and Table 2 for statistical significance.

Table 2

Estimated probabilities that differences in statistics of coronal strain field would occur by chance (Student's *t*-test)

Coronal	Proportion $ \mathbf{e}_1 > 0.10$	Mean $ \mathbf{e}_1 $	Max. $ \mathbf{e}_1 $
1 mm vs. 2 mm depth	$p = 0.0005$	$p = 0.0001$	$p = 0.0035$
v1 vs. v2 speed (2 mm depth)	$p = 0.256$	$p = 0.174$	$p = 0.386$

Speeds: v1 = 6 impacts/s (0.17 m/s); v2 = 12 impacts/s (0.34 m/s).

Table 3 Average values $\pm$ standard deviations of sagittal strain field statistics^a

Sagittal	Proportion $ \epsilon_1 > 0.10$	Mean $ \epsilon_1 $	Max. $ \epsilon_1 $
1 mm, 6 impacts/s ($N = 3$)	0.090 ± 0.065	0.048 ± 0.012	0.197 ± 0.013
2 mm, 6 impacts/s ($N = 2$)	0.148 ± 0.028	0.059 ± 0.009	0.376 ± 0.222
2 mm, 12 impacts/s ($N = 4$)	0.180 ± 0.071	0.069 ± 0.007	0.393 ± 0.163

^aSee Fig. 9 for data and Table 4 for statistical significance.

Table 4

Estimated probabilities that differences in statistics of sagittal strain fields would occur by chance (Student's *t*-test)

Sagittal	Proportion $ \epsilon_1 > 0.10$	Mean $ \epsilon_1 $	Max. $ \epsilon_1 $
1 mm vs. 2 mm depth	$p = 0.071$	$p = 0.051$	$p = 0.017$
v1 vs. v2 speed (2 mm depth)	$p = 0.223$	$p = 0.143$	$p = 0.465$

Speeds: v1 = 6 impacts/s (0.17 m/s); v2 = 12 impacts/s (0.34 m/s).