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The Relationship of Three-Dimensional Human Skull Motion to Brain Tissue Deformation in Magnetic Resonance Elastography Studies

In traumatic brain injury (TBI), membranes such as the dura mater, arachnoid mater, and pia mater play a vital role in transmitting motion from the skull to brain tissue. Magnetic resonance elastography (MRE) is an imaging technique developed for noninvasive estimation of soft tissue material parameters. In MRE, dynamic deformation of brain tissue is induced by skull vibrations during magnetic resonance imaging (MRI); however, skull motion and its mode of transmission to the brain remain largely uncharacterized. In this study, displacements of points in the skull, reconstructed using data from an array of MRI-safe accelerometers, were compared to displacements of neighboring material points in brain tissue, estimated from MRE measurements. Comparison of the relative amplitudes, directions, and temporal phases of harmonic motion in the skulls and brains of six human subjects shows that the skull–brain interface significantly attenuates and delays transmission of motion from skull to brain. In contrast, in a cylindrical gelatin “phantom,” displacements of the rigid case (reconstructed from accelerometer data) were transmitted to the gelatin inside (estimated from MRE data) with little attenuation or phase lag. This quantitative characterization of the skull–brain interface will be valuable in the parameterization and validation of computer models of TBI. [DOI: 10.1115/1.4036146]

Keywords: magnetic resonance elastography, mechanical characterization, brain deformation, tissue

1 Introduction

Traumatic brain injury (TBI) is a prevalent neurological disorder where brain tissue is damaged by an external force [1]. Diffuse axonal injury, or shearing and stretching of axonal fibers, is a common type of TBI often caused by sudden linear or angular accelerations of the head [2]. While the effects of TBI are well documented, the mechanisms linking mechanical insult and neurological injury are not well understood. Mathematical modeling and computer simulation of TBI can provide insight into these mechanisms, and guide the development of new methods for injury prediction, prevention, diagnosis, and management. However, to be useful, computer models require accurate descriptions of material behavior, boundary conditions, and loading. Recent research has largely focused on the material properties of brain tissue; however, quantitative characterization of the skull–brain interface *in vivo* remains an important need.

Magnetic resonance elastography (MRE) is a prominent tool for assessing the properties of brain tissue *in vivo*. MRE is a non-invasive MRI technique that enables assessment of the dynamic mechanical properties of living biological tissues [3,4]. In MRE of the brain, vibrations are applied to the skull in order to induce

shear waves throughout the brain [5–7]. These shear waves are observed using MRE imaging sequences with motion-encoding gradients that oscillate at the vibration frequency, producing phase contrast images proportional to displacement [3,4]. The speeds of shear waves in soft tissue are determined by its mechanical properties [5–7]. Previous studies have demonstrated the ability of MRE to provide local estimates of the mechanical properties of healthy brain tissue [8–11], as well as changes in brain material properties due to development, aging, injury, or disease [12–15]. MRE is also a valuable tool for parameterizing and validating computational models of TBI [16,17]. A number of methods exist to estimate material properties in soft tissue, such as local direct inversion (LDI) [18], nonlinear inversion (NLI) [19,20], or local frequency estimation (LFE) [21].

In contrast to the substantial progress on estimation of brain material properties, the transmission of skull motion to brain tissue motion has not been extensively characterized. Inside the skull, the brain is encased in multiple membranes including the dura mater, arachnoid mater, and pia mater. As the skull moves, these membranes, together with the cerebrospinal fluid (CSF) and blood contained between the various layers, cushion the brain and limit its displacement [22,23]. Together, these membranes and fluid layers comprise the skull–brain interface and play an important role in injury mechanics. Modeling the characteristics of the skull–brain interface is challenging, however [24]. While experimental studies of *ex vivo* tissue samples have provided some

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Fig. 1 Schematic illustration of the accelerometer mouth guard array (MGA) and its positioning for a human subject. (a) Spacing of the three accelerometers within the MGA. (b) The subject bites down firmly on the mouth guard while lying supine on the pillow actuator. (c) Three-dimensional rendering of the relative placement of the subject, pillow actuator, and MGA inside the head coil.

insight into the properties of the constituent materials [5,6,8], characterization of the intact skull–brain interface in vivo is desirable [22–24].

To characterize the role of the intact skull–brain interface in transmitting forces and motion to brain tissue, we record skull motion during MRE studies using an array of three MRI-safe tri-axial accelerometers, and then compare skull kinematics to brain tissue displacements estimated from MRE measurements. By contrasting the transmission of motion from skull to brain in human subjects to the analogous motion transmission from case to gel in a homogenous gelatin phantom, we quantify how the skull–brain interface attenuates and delays the brain’s response to skull motion.

2 Methods

2.1 MRE Imaging Procedures and Instrumentation. MRE imaging of six adult, male human subjects and a cylindrical gelatin phantom was performed on Siemens Trio® 3T MRI scanners located at the Beckman Institute at University of Illinois in Urbana-Champaign and the Center for Clinical Imaging Research at Washington University in St. Louis, MO. All studies were approved by the Institutional Review Board (IRB) of the respective institutions.

Subjects lay supine with their heads centered in a Siemens 12 channel head coil. Skull vibrations were induced at a frequency of 50 Hz through a commercially available mechanical actuator (Resoundant™, Rochester, MN) using a pillow-like actuator (Mayo Clinic, Rochester, MN) positioned on the back of the subject’s head at the skull occipital protuberance [12]. The head rests on the pillow, and is stabilized by pads placed laterally. Skull vibrations were induced at 18% Resoundant™ amplitude. Three-dimensional skull kinematics were measured using three MRI safe tri-axial accelerometers (TSD109C2-MRI, BIOPAC®, Goleta, CA) embedded in an array constructed from a commercial sports mouth guard and three-dimensional (3D)-printed interface (Fig. 1). This accelerometer mouth-guard array (MGA) was designed to allow for rigid placement of the accelerometers and easy retrieval from the subject during the scanning protocol. The relative positions of the MGA and the pillow actuator were identified with vitamin E capsules that appeared with high signal in the field of view of T₁-weighted magnetic resonance (MR) images. Subject brain volume ($1378 \pm 192 \text{ cm}^3$) was calculated through segmentation of gray and white matter tracts in T₁-weighted MRI data [25].

A multishot spiral MRE sequence with 2 mm isotropic voxels was used to measure brain tissue displacement, which is encoded as phase in the resulting MR images [20]. Imaging parameters included 26 mT/m motion-encoding gradient strength (MEGS), 6 k-space interleaves, eight phase offsets, and twenty axial slice acquisition in the region of the corpus callosum (Fig. 2(b)), with an image volume of $240 \text{ mm} \times 240 \text{ mm} \times 40 \text{ mm}$ and a scan duration of approximately 11 min. The accelerometers are MRI-safe,

meaning they are composed of material that poses no hazard within an MRI environment. While MRI-safe, the accelerometers induced imaging artifacts, thus a single slice scan with duration of approximately 36 s was performed in order to record skull acceleration during the MRE sequence. After this scan, The MGA was removed while the subject’s head remained in the head coil and the full, 20 slice MRE scan was performed.

To provide an MR phantom with simpler properties that could be used to validate techniques and compare behavior, a cylindrical phantom ($\sim 13 \text{ cm}$ long and 13 cm in diameter) was fabricated

Fig. 2 Three-dimensional kinematics are estimated at four points around the skull. (a) Schematic diagram of the accelerometer positions relative to the origin. (b) Sagittal MR image showing the relative distance, $r_{A^1/O}$, between the skull origin, approximated as the posterior clinoid process (circle), and accelerometer 1 (A^1) within the MGA. The relative location of the pillow actuator is outlined as the rectangle. The MRE acquisition planes, encompassing twenty slices at 2 mm voxel resolution, are shown. (c) Anatomical (T1-weighted) images are used to determine the position of the four reconstruction points anterior (A), right (R), left (L), and posterior (P) relative to the origin. (d) Regional analysis of MRE measurements is performed by segmenting the MRE images into three rings and four quadrants. A mask based on image amplitude was applied to isolate brain tissue from the skull (dotted oval).

from a plastic case filled with 1.65 L (1.81 kg) of a gelatin-glycerol-water solution (4% gelatin, 48% glycerol, and 48% water by weight [26]). For brevity, this mixture is referred to as gelatin. The gelatin phantom was refrigerated for a minimum of 12 h to allow the gelatin to set. The gelatin phantom was equilibrated for 3 h at room temperature before imaging. The storage modulus, or real part of the viscoelastic shear modulus, of gelatin samples was 1.8 kPa, as measured with dynamic shear testing at 50 Hz [26]. A 3D printed holder was used to rigidly attach the MGA to the outer surface of the gelatin phantom's cylindrical plastic case. The gelatin phantom was positioned in the head coil, stabilized laterally with pads, and vibrated using the pillow actuator at 50 Hz. The lower weight of the gelatin phantom, 1.8 kg compared to approximately 3.5–4.5 kg for the human skull [27], necessitated a Resonant™ actuation amplitude of 3% to minimize phase wrapping of the MRE images.

Our experimental protocol thus involved the following steps:

- (1) Position subject outside the scanner bore with the accelerometer MGA.
- (2) Record skull accelerations in response to the pillow actuator without the spiral MRE sequence running.
- (3) Move subject into the scanner bore and acquire accelerometer data from a single-slice MRE sequence.
- (4) Remove the MGA without removing the subject's head from the coil.
- (5) Run anatomical scan (T_1 -weighted: 3D magnetization prepared rapid gradient, 0.9 mm isotropic voxels) and 20-slice spiral MRE sequence.

This protocol enabled comparison of skull dynamics (reconstructed from accelerometer data) and brain tissue displacement (estimated from MRE measurements) in the same subject.

2.2 Estimation of 3D Skull Kinematics. Skull motion during MRE at 50 Hz is well approximated as rigid-body motion [28]; standard 3D kinematic equations for rigid-body acceleration (Eqs. (1a)–(1c)) [29] are used. Here, $\mathbf{a}$ is linear acceleration, $\boldsymbol{\alpha}$ is angular acceleration, $\mathbf{r}$ defines the distance between some point and the skull origin (approximated as the posterior clinoid process), and $\boldsymbol{\omega}$ is angular velocity. Each of these vectors consists of three components, denoted as x , y , and z , to represent the right-left (RL), anterior-posterior (AP), and superior-inferior (SI) directions. Thus, (a_x^O, a_y^O, a_z^O) are, respectively, the RL, AP, and SI linear accelerations of the skull origin; $(\omega_x, \omega_y, \omega_z)$ are rates of rotation (angular velocity) about the RL, AP, and SI directions, respectively; and $(\alpha_x, \alpha_y, \alpha_z)$ are the components of angular acceleration. (a_x, a_y, a_z) are the components of linear acceleration of a point whose position, measured from the skull origin, is (r_x, r_y, r_z) . The right-hand side of these equations will contain nine unknowns (three components of motion for each of $\mathbf{a}$, $\boldsymbol{\alpha}$, and $\boldsymbol{\omega}$ at the skull origin), which can be solved using the known values of linear acceleration at the positions of the tri-axial accelerometers

$$a_x = a_x^O + (\alpha_y r_z - \alpha_z r_y) + (\omega_x (\omega_y r_y + \omega_z r_z) - r_x (\omega_y^2 + \omega_z^2)) \quad (1a)$$

$$a_y = a_y^O + (\alpha_z r_x - \alpha_x r_z) + (\omega_y (\omega_z r_z + \omega_x r_x) - r_y (\omega_x^2 + \omega_z^2)) \quad (1b)$$

Fig. 3 Validation of accelerometer motion reconstruction using constrained angular and linear motion. (a-i) The accelerometer MGA was placed on the bottom disk of a torsional vibration demonstration system (ECP 205 Torsional Plant, ECP®, Bell Canyon, CA) and used to reconstruct in-plane motion at the location of a fourth reference accelerometer placed at the top of the platform. Oscillation frequency: 10 Hz. (a-ii) Normalized reconstruction RMS error in the AP direction, NRMSE = 0.04; (a-iii) normalized RMS error in the SI direction, NRMSE = 0.02. (b-i) A horizontal shaker (APS Electro-seis 113 Long Stroke Shaker, APS Dynamics®, San Juan Capistrano, CA) was used to validate translational motion reconstruction. The MGA was placed on the posterior of the platform while the reference accelerometer was placed on the side. Oscillation frequency: 50 Hz. (b-ii) AP direction NRMSE = 0.04, (b-iii) SI direction NRMSE = 0.08.

$$a_z = a_z^O + (\alpha_x r_y - \alpha_y r_x) + (\omega_z(\omega_x r_x + \omega_y r_y) - r_z(\omega_x^2 + \omega_y^2)) \quad (1c)$$

To provide additional information, rigid-body velocity expressions (Eqs. (2a)–(2c)) may also be used to estimate ω [29,30]. Velocity ($\mathbf{v}$) at each accelerometer position can be estimated through integration of the acceleration signal

$$v_x = v_x^O + \omega_y r_z - \omega_z r_y \quad (2a)$$

$$v_y = v_y^O + \omega_z r_x - \omega_x r_z \quad (2b)$$

$$v_z = v_z^O + \omega_x r_y - \omega_y r_x \quad (2c)$$

The acceleration signals are expressed as Fourier coefficients (sum of sinusoids) j , providing the ability to integrate acceleration in the frequency domain. Equations (3a)–(3c) demonstrate how velocity and displacement ($\mathbf{u}$) are calculated. Here Ω is angular frequency (rad/s), ϕ is phase shift, D is amplitude, t is time, the subscript j denotes the Fourier harmonic, and the subscript q refers to each of the three Cartesian components of motion

$$a_q = \sum_j D_{qj} \sin(\Omega_j t + \phi_j) \quad (3a)$$

$$\Rightarrow v_q = - \sum_j \frac{D_{qj}}{\Omega_j} \cos(\Omega_j t + \phi_j) \quad (3b)$$

$$\Rightarrow u_q = - \sum_j \frac{D_{qj}}{\Omega_j^2} \sin(\Omega_j t + \phi_j) \quad (3c)$$

Displacements at four discrete points: anterior (A) near the forehead, right (R) by the right temple, left (L) by the left temple, and posterior (P) near the skull occipital protuberance (Figs. 2(a) and 2(c)) were reconstructed from acceleration data. Reconstruction points and the skull origin were located from T₁-weighted anatomical scans (Fig. 2(b)). On the gelatin phantom, anterior, right, left, and posterior reconstruction points were similarly chosen as central points along each cylinder edge.

To test the accuracy of motion reconstruction, we performed known translational and rotational motions (Fig. 3), measured accelerations with an independent sensor, and compared these data to the accelerations reconstructed from simultaneous measurements with the accelerometer array (MGA). Oscillatory rotational motion was generated by a Torsional Plant 205 (ECP®, Bell Canyon, CA) at a frequency of 10 Hz while translational motion was generated with an Electro-seis 113 Long Stroke Shaker (APS Dynamics®, San Juan Capistrano, CA) at a frequency of 50 Hz. The MGA was mounted on the moving section of each device. An additional accelerometer was placed on each device to serve as a reference. For rotational experiments, the MGA was oriented so that the motion corresponded to rotation about the RL axis. For linear motion, the MGA was oriented so translation was in the AP direction. The normalized root-mean-square error (NRMSE) was calculated from the RMS difference between the acceleration reconstructed from the MGA and the recorded signal from the reference accelerometer, normalized by the reference acceleration magnitude. In the rotational experiment, NRMSE was 0.04 in the AP direction and 0.02 in the SI direction. In the translational experiment, NRMSE was 0.04 in the AP direction and 0.08 in the SI direction. Noise, nonrigid motion, and nonlinearity can contribute to reconstruction error; these are more apparent in low-amplitude harmonic signal, such as in the translational experiment SI motion. However, since the SI component is a small fraction of the acceleration magnitude, its contribution to the overall error is small.

2.3 Analysis of MRE Displacement Measurements. In MRE, motion-encoding gradients in the MRI sequence encode displacement as phase of the MR signal [20,31]. Oscillating gradients are applied along three orthogonal directions to capture motion-induced phase at each voxel in space. The resulting motion-induced MRE phase contrast (Φ) is proportional to the component of the oscillatory displacement ($\mathbf{u}$) in the direction of the gradient [3,31]. MRE phase contrast includes the effects of oscillatory rigid-body motion, longitudinal wave motion, and shear wave motion. During imaging, oscillatory, rigid-body motion can be described through both translation in the x , y , and z directions along with rotation about each of those axes. Additionally, when the amplitude of motion is large, motion-induced phase wrapping may occur. This was commonly seen in the phase-encoded anterior–posterior component of motion. Wrapped phase was spatially unwrapped using FSL PRELUDE [32] and temporally unwrapped using a custom postprocessing algorithm described in Appendix A.1. A separate experiment using variable gradient strength in MRE of a single subject provided validation of the unwrapping approach used in this study (Fig. 10).

After unwrapping the MRE phase data, the three complex displacement components at each voxel were obtained by converting phase to displacement (Appendix A.2) and extracting the first harmonic using a temporal Fourier transform. Components of rigid-body displacement ($\bar{\mathbf{u}}$) were estimated for comparison with skull motion reconstructed from the accelerometers. A set of three rotation components (θ_x, θ_y , and θ_z) and three translation components ($\bar{u}_x^O, \bar{u}_y^O$, and $\bar{u}_z^O$) about the brain origin were used to describe 3D, rigid-body displacement in the brain at each voxel location (denoted by position $\mathbf{r}$ with respect to the brain origin). These complex components were solved by least squares fitting of the total displacement (estimated from MRE data) at all voxels within the brain to a model of rigid-body displacement

$$\bar{u}_x = \bar{u}_x^O + \theta_y r_z - \theta_z r_y \quad (4a)$$

$$\bar{u}_y = \bar{u}_y^O + \theta_z r_x - \theta_x r_z \quad (4b)$$

$$\bar{u}_z = \bar{u}_z^O + \theta_x r_y - \theta_y r_x \quad (4c)$$

The contribution of shear and longitudinal waves to the displacement field ($\bar{\mathbf{u}}$) was estimated by removing rigid-body motion from the total displacement field estimate. In addition, in an isotropic, uniform, elastic or viscoelastic material, the curl of the displacement field contains only contributions of shear waves. The curl (Γ) was estimated through local polynomial fitting and differentiation of the displacement field to provide a separate estimate of the contribution of shear waves. Wave motion for both human subjects and the gelatin phantom are reported in terms of both wave displacement and curl. Strain magnitudes resulting from wave propagation are reported as octahedral shear strain (ϵ_s) [33]. For comparison with estimates of strain and curl (nondimensional measures of displacement per unit length), the displacement of the case or skull was normalized by the radius of the case or the major semi-axis of the skull.

To characterize brain tissue displacements in different regions and compare them with skull motion at specific locations, MRE measurements were separated into twelve regions of interest (ROI) including three shells (outer, middle, and inner) and four quadrants (anterior, A; right, R; left, L; and posterior, P) (Fig. 2(d)). MRE measurements in the gelatin phantom were separated similarly into 12 ROIs: four corresponding A, P, R, and L quadrants, and three shells.

2.4 Comparison of Skull and Brain Displacements. Estimates of skull displacement at four material points in the skull (reconstructed from accelerometer measurements) were compared to analogous estimates of displacement at neighboring material

Fig. 4 Reconstructed acceleration profile (RL, AP, and SI components of motion) at skull anterior (A), right (R), and posterior (P) points during MRE of a typical human subject (actuator frequency: 50 Hz, actuator amplitude = 18%)

points in the brain (estimated from MRE measurements). In general harmonic motion, where the three components of motion are not exactly in phase, the 3D trajectory of each point in the brain and skull is an ellipse, represented as a complex coefficient vector, $\mathbf{u}_0$, multiplied by a complex exponential in time, $\mathbf{u}(t) = \mathbf{u}_0 \exp(i\Omega t)$ (Appendix A.3). The elliptical trajectories of material points in skull and brain tissue were described by their relative amplitudes, spatial orientations, and temporal phase. The amplitude of each elliptical trajectory is reported as its mean radius: the circumference of the corresponding ellipse divided by 2π .

Consider two 3D complex coefficient vectors $\mathbf{u}_0$ and $\mathbf{v}_0$, corresponding to elliptical trajectories of skull motion and brain tissue rigid-body motion, respectively. The vectors normal to the two elliptical trajectories are used to calculate the spatial, angle, β . The dot product of the two complex coefficient vectors can be used to calculate temporal phase shift, ϕ [34]. The vector normal to each ellipse is found from the cross product of the real and

imaginary components of the coefficient vectors, as shown in the below equations

$$\mathbf{N}_u = \text{Re}[\mathbf{u}_0] \times \text{Im}[\mathbf{u}_0] \quad (5)$$

$$\mathbf{N}_v = \text{Re}[\mathbf{v}_0] \times \text{Im}[\mathbf{v}_0] \quad (6)$$

The spatial angle, β , between the two ellipses is then found from the below equation

$$\cos \beta(\mathbf{u}_0, \mathbf{v}_0) = \frac{(\mathbf{N}_u \cdot \mathbf{N}_v)}{\|\mathbf{N}_u\| \|\mathbf{N}_v\|} \quad (7)$$

In order to compare the phases of skull and brain motion captured in their complex coefficient vectors, a common reference for $t = 0$ is needed to describe the relative timing between the MRE sequence and skull acceleration profile (Appendix A.2). The

Fig. 5 (a) and (d) Representative total MRE displacement fields in (a) the gelatin phantom and (d) a human subject at the first of eight time points; (b) and (e) corresponding wave displacement fields; (c) and (f) corresponding curl fields. Wave displacement is obtained by subtracting rigid-body motion from the total displacement field. Note the different displacement amplitudes in panels (d) and (e). The bar at the bottom of each image indicates the approximate location of the pillow actuator.

Fig. 6 Rigid-body motion of the gelatin phantom (estimated from MRE measurements) compared with motion of the case (reconstructed from accelerometer data). (a) Motion reconstructed at individual points on the case anterior (A), right (R), left (L), and posterior (P) are compared with corresponding material points within the outermost shell of corresponding gelatin regions. Filled circles on the elliptical trajectory indicate the reference time, $t = 0$. (b) Rigid-body motion coefficients for translation and rotation about the gelatin phantom origin are compared between the phantom case and gelatin. (c) The component of displacement in the AP direction for the case and gelatin posterior reconstruction points is shown as a function of time.

center of the refocusing pulse of the MRE sequence was chosen as the common reference. The temporal phase shift, φ , between skull and brain tissue motion was estimated as the phase angle of the complex dot product

$$\varphi = \angle(\mathbf{u}_0^* \cdot \mathbf{v}_0) \quad (8)$$

3 Results

3.1 Motion of the Human Skull and Gelatin Phantom Case Reconstructed From Acceleration Data. During MRE imaging of human subjects, the ResoundantTM system causes the pillow actuator to vibrate the back of the skull. Examples of accelerations reconstructed at the anterior, right, and posterior points are shown in Fig. 4. The acceleration magnitudes typically ranged from 2 to 5 m/s². Acceleration components reconstructed at the left (L) and right (R) skull points were similar in magnitude and phase. The SI component of acceleration was largest at the posterior. AP acceleration magnitudes were similar at all reconstruction points. Data generally suggest a combination of AP linear acceleration and rotation of the skull about the RL axis. The mean magnitudes of

the components of skull acceleration for the six human subjects are compared to those of the gelatin phantom case in Table 1. The gelatin phantom case had lower acceleration amplitude than the human skull, and the largest component was consistently in the AP direction, even at the posterior reconstruction point.

To characterize the uncertainty in the accelerometer measurements obtained during MRE in the absence of a reference accelerometer, we compared the accelerations reconstructed at the positions of the embedded accelerometers to the recorded accelerometer data. NRMSE for each acceleration component was obtained by averaging the NRMSE of that component for the three accelerometers in the MGA. Normalized errors for reconstructed accelerations in human studies were: NRMSE = 0.05 (RL direction), NRMSE = 0.10 (AP direction), and NRMSE = 0.07 (SI direction). In the gelatin phantom, reconstructed data also showed reasonable agreement with recorded values: NRMSE = 0.13 (RL direction), NRMSE = 0.10 (AP direction), and NRMSE = 0.16 (SI direction). The higher NRMSE in the gel phantom is likely due to the lower amplitude of acceleration, which leads to a lower signal-to-noise ratio in the data.

Table 1 Reconstructed acceleration components for human skull and gelatin phantom case at the four reconstruction points. NRMSE characterizes the accuracy of reconstruction using the difference between the measured accelerations and the accelerations reconstructed at the accelerometer locations.

Position	Human skull ($n = 6$)			Gelatin phantom		
	a_{RL} (RMS m/s ²)	a_{AP} (RMS m/s ²)	a_{SI} (RMS m/s ²)	a_{RL} (RMS m/s ²)	a_{AP} (RMS m/s ²)	a_{SI} (RMS m/s ²)
Anterior	0.60 ± 0.38	2.23 ± 0.46	0.42 ± 0.11	0.15	0.77	0.51
Right	0.58 ± 0.35	2.31 ± 0.44	1.54 ± 1.06	0.09	0.81	0.33
Left	0.58 ± 0.35	2.16 ± 0.48	1.51 ± 0.71	0.09	0.73	0.41
Posterior	0.61 ± 0.36	2.23 ± 0.46	2.90 ± 1.58	0.05	0.77	0.23
NRMSE (dimensionless)	0.05	0.10	0.07	0.13	0.10	0.16

Table 2 Spatial angle (β) and temporal phase delay (ϕ) between harmonic motion of the gelatin phantom case and harmonic, rigid-body motion of gelatin

Position	Phantom case/gelatin	
	β (rad)	ϕ (rad)
Anterior	0.50	0.03
Right	0.30	0.17
Left	0.34	0.04
Posterior	0.11	0.17

3.2 Motion of Human Brain Tissue and Phantom Gelatin Estimated From MRE Measurements. Rigid-body motion and wave motion in both gelatin and brain tissue were estimated from MRE measurements, as described previously. In the gelatin phantom, most of the total displacement field is due to wave displacement (Figs. 5(a) and 5(b)). In human subjects, the MRE measurements reflect a relatively uniform displacement field with high amplitude in the AP direction (Fig. 5(d)), suggesting a larger contribution from rigid-body motion than from wave displacement fields. Amplitudes of wave displacement and curl in the gelatin phantom (Figs. 5(b) and 5(c)) were higher relative to total displacement than in human brain tissue.

3.3 Comparison of Case and Gelatin Motion in the Gelatin Phantom. Motion trajectories at four points on the case (estimated from accelerometer measurements) were compared to trajectories at four material points inside the gelatin (estimated from MRE measurements). These comparisons were characterized by

relative amplitude, orientation, and phase (Fig. 6). The rigid-body motion of the gelatin and case were similar in amplitude, particularly the dominant components of rotation (θ_{RL}) and translation ($\bar{u}_{AP}^0$). The spatial angle between rigid-body motion of the gelatin and rigid-body motion of the case indicated high alignment of gel and case motion (Table 2). The phase shift between case and gelatin rigid-body motion was consistently low.

The magnitudes of wave displacement in gelatin were larger than the amplitudes of rigid-body motion of both the case and gelatin (Fig. 7). No qualitative differences in curl, displacement, or strain amplitudes were seen between shells or quadrants.

3.4 Comparison of Skull and Brain Motion in Human Subjects. Brain motion (estimated from MRE measurements) and skull motion (reconstructed from accelerometer measurements) were compared for six subjects. As in the gelatin phantom, elliptical trajectories of neighboring material points were used to compare brain and skull rigid-body motion (Fig. 8). In contrast to the gelatin phantom, the amplitude of rigid-body motion in the brain differed from the amplitude of nearby skull motion. At each of the brain material points, the AP component of translation was consistently the highest amplitude, while the skull experienced high amplitudes in both AP and SI directions. Rigid-body motion of the brain and skull exhibited greater differences in spatial angle than were seen between the case and contents of the gelatin phantom (Table 3). The phase shift between rigid-body motion in brain and skull was consistently longer than between case and gelatin in the gelatin phantom.

The amplitude of wave motion in brain tissue was lower than the amplitude of reconstructed skull motion (Fig. 9) in all quadrants and shells. The displacement amplitudes in the outer and

Fig. 7 Magnitudes (RMS) of (b) wave displacement; (c) curl; and (d) octahedral shear strain in the gelatin phantom. Values are shown for each quadrant-shell ROI (a). For comparison to curl and strain (dimensionless measures of displacement/length), the case displacement magnitude is normalized by the radius of the case (striped). Error bars in all three plots represent the standard deviation of each quantity within the shell ROI.

Fig. 8 Rigid-body motion of human brain tissue estimated from MRE measurements, compared with skull motion reconstructed from accelerometer data. (a) Trajectories at individual reconstruction points on the skull anterior (A), right (R), left (L), and posterior (P) are compared with analogous trajectories of neighboring brain tissue material points selected from the outer shell ROI. Filled circles on the elliptical trajectories indicate the reference time, $t=0$. (b) The amplitude of the rigid-body motion coefficients for translation and rotation about the skull origin are compared between the skull and brain ($n=6$). Error bars indicate standard deviation between subjects. (c) The component of displacement in the AP direction is plotted for the skull and brain posterior reconstruction points.

middle shells were typically higher than in the inner shell. The amplitudes of curl and strain also decreased progressively in regions closer to the center of the brain.

4 Discussion and Conclusion

In this study, we directly characterized skull kinematics using accelerometers in order to relate skull motion to brain tissue

motion. To describe brain tissue motion, MRE measurements of displacement were decomposed into wave motion and rigid-body motion. Comparing skull kinematics with brain tissue motion in vivo enables assessment of relative motion and deformation. Furthermore, comparison of data from human subjects to data from a gelatin phantom (in which the gelatin adheres to the cylindrical case) provides insight into how the skull–brain interface (a more complex material interface) affects motion transmission.

Fig. 9 Magnitudes (RMS) of (a) wave displacement; (b) curl; and (c) octahedral shear strain, in the human brain. Values are shown for each quadrant-shell ROI. For comparison with curl and strain (dimensionless measures of displacement/length), skull displacement magnitude is normalized by the major semi-axis of the skull (striped). Error bars in all three plots show the standard deviation among subjects ($n=6$).

Table 3 Spatial angle (β) and temporal phase delay (ϕ) between harmonic motion of the human skull and harmonic, rigid-body motion of brain tissue

Position	Human skull/brain ($n = 6$)	
	β (rad)	ϕ (rad)
Anterior	0.76 ± 0.48	3.97 ± 0.95
Right	0.63 ± 0.40	3.91 ± 0.96
Left	0.75 ± 0.51	4.01 ± 0.85
Posterior	1.19 ± 0.37	3.94 ± 0.91

The effects of the skull–brain interface are illuminated by comparison to the coupling of case to gelatin in the gelatin phantom. In the phantom, harmonic, rigid-body displacements of both gelatin and case were similar. Material points in the case and material points in gelatin exhibited elliptical trajectories due to rigid-body motion. The elliptical trajectories of neighboring points on opposite sides of the adherent interface exhibited similar amplitude, direction (spatial angle), and temporal phase. While we expect particles in the case and in the gelatin at the interface to have almost identical trajectories, discrepancies in the rigid-body motions are apparent (for example, Fig. 6). There are several likely reasons: (i) gelatin motion includes both rigid-body and wave motion; (ii) the case is not perfectly rigid (which introduces some error into the estimate of case motion); (iii) motion estimates from MRE are average values within a finite region of interest. Displacements in the gelatin due to waves were consistently higher than the displacements due to rigid-body motion of the gelatin and case. It is likely that harmonic excitation at 50 Hz induces constructive wave interactions in the weakly dissipative gelatin, causing higher displacement fields in the interior.

In contrast, displacement fields in the human brain exhibited higher amplitudes of rigid-body motion than wave motion. Furthermore, rigid-body motion of the brain differed strongly from rigid-body motion of the skull. Considering first the rigid-body components of motion, elliptical trajectories of material points in the brain exhibited significant differences in amplitude, orientation (spatial angle), and temporal phase compared to elliptical trajectories of neighboring points on the skull. Wave components of displacement in the brain were even smaller relative to skull motion; displacements due to waves at material points in the brain were an order of magnitude smaller than displacements of neighboring material points in the skull. In addition, waves were attenuated significantly as they propagated inward from the outer cortical surface toward the midbrain.

These results indicate significant mechanical compliance and dissipation at the skull–brain interface. These properties are attributable to the dural membranes, blood vessels, and fluids that comprise the interface. In contrast, the gelatin phantom has none of these structures, and the adherent interface between gelatin and case exhibits dramatically simpler behavior.

Some experimental limitations are acknowledged. All analyses performed in this study assumed perfect coupling between the accelerometers and the skull. In practice, this is unlikely; slip or compliance will affect the transmission of motion from the jaw, via the commercial mouth guard, to the accelerometer array. However, by using the same array in the gel phantom, we demonstrate that these effects are not dominant. Accelerations were assumed to be harmonic; Fourier components at a single frequency were converted to displacement in the frequency domain for comparison with MRE measurements. As noted in the description of experimental methods, and in the Appendix, the methods for measurement and reconstruction of skull kinematics from accelerometer data were validated in separate experiments.

Substantial variation in acceleration (Table 1) and spatial angle (Table 3) between skull and brain motion is seen over the cohort of six subjects. These variations likely reflect intersubject differences

in head size, shape, and anatomy, as well as individual responses to actuation and variations in subject and actuator positioning. Despite intersubject variability, subjects consistently showed higher amplitudes of skull translation in the AP and SI directions, relative to RL translation, and higher amplitudes of rotation about the RL axis, relative to other rotation components. Additionally, recorded human MRE data are consistent with results reported by other groups using a similar actuation system [20].

Future work should explore the possibility of frequency-dependent, anisotropic, and nonlinear mechanical behavior of the skull–brain interface. Different actuation locations and frequencies could be used to investigate such behavior. Additionally, MRE data from the entire brain could be compared to a more extensive set of reconstruction points on the skull.

This study confirms that the skull–brain interface is a critical determinant of brain tissue deformation due to skull loading, and thus is a major factor in TBI. The properties of this interface are measurable; the quantitative data from this study should be of immediate use in the parameterization and validation of computer models and simulations of TBI. The properties of the skull–brain interface are also critical to the development of strategies for MRE of the brain, in which enhanced transmission of waves into the brain is desirable. The compliant and dissipative nature of the skull–brain interface clearly protects the brain during mild skull accelerations. Further studies are needed to determine the conditions under which this protective system may fail.

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Nomenclature

- a = linear acceleration (m/s^2)
- D = wave amplitude (m/s^2 , m/s , m)
- N = vector normal to an ellipse (m)
- r = position (m)
- u = displacement (m)
- $\bar{u}$ = rigid-body displacement (m)
- $\tilde{u}$ = wave displacement (m)
- x, y, z = vector components: right-left, anterior–posterior, and superior–inferior
- α = angular acceleration (rad/s^2)
- β = spatial angle (rad)
- θ = angular displacement (rad)
- v = velocity (m/s)
- ϕ = phase shift (rad)
- Φ = MRE phase contrast (rad)
- ω = angular velocity (rad/s)
- Ω = angular frequency (rad/s)

Appendix

A.1 Unwrapping MRE Phase Contrast

MRE phase contrast (Φ) is originally constrained to the principal range $(-\pi, \pi]$, which can cause wrapping and complicate recovery of the original amplitude. To validate our unwrapping approach, an echo planar imaging (EPI) sequence was used to acquire MRE data from a single human subject at motion-encoding gradient strengths (MEGS) between 4 and 25.9 mT/m (Fig. 10). Imaging parameters included 3 mm isotropic voxels, 240 mm field of view, and 24 axial slices. As in the two-dimensional spiral sequence, MRE data that encoded displacements in the AP direction were often wrapped when acquired at high motion-encoding gradient strengths. In addition to phase wrapping in space (which is already a challenging problem [35,36]), the harmonic data may also be wrapped in time. Unwrapping in time is further challenging due to the very coarse sampling: eight points per period. Therefore, to accurately recover

Fig. 10 Comparison of MRE phase contrast (Φ) captured by different motion-encoding gradient strengths (MEGS). (a) Visualization of the wrapped and unwrapped phase contrast encoded by the maximum MEGS of 25.9 mT/m at time point 2. (b) Comparison of wrapped and unwrapped MRE phase contrast at a single voxel (circle) between EPI-MRE trials at 4, 7, 10, and 25.9 mT/m. (c) Line plot of MRE phase contrast, normalized to the unwrapped phase contrast at 25.9 mT/m. Unwrapped data points were fitted to a linear model ($R^2 = 0.99$).

Fig. 11 Artifact in the accelerometer trace can be used to locate landmarks in the MR pulse sequence, such as the RF pulse, refocusing gradient, and spiral gradients. A two-dimensional spiral MRE pulse sequence diagram is shown in Ref. [20]. Bipolar motion-encoding gradients (dashed boxes) are applied sequentially.

the harmonic time series, we used a custom temporal postprocessing algorithm following initial spatial unwrapping of 3D volumes with a widely used, third-party algorithm (FSL PRELUDE [32]). The temporal postprocessing algorithm consisted of tabulating all possible permutations of the motion-encoded phase at a selected voxel, with a value of 0, -2π , or 2π added at each time point. This resulted in 3^8 , or 6561 permutations. The eight-point FFT of each permutation was calculated, and the permutation that contained the highest fraction of power at the fundamental frequency FFT, was then selected as the unwrapping solution. As Fig. 10 shows, the rigid-body motion is homogeneous across the field of view, meaning that the same unwrapping scheme was used for each voxel. We then acquired MRE data at lower MEGS to view an unwrapped AP phase contrast waveform in the same subject. Data from this protocol confirmed that MRE phase contrast was proportional to the strength of the motion encoding gradients. The MRE phase waveform acquired at lower MEGS was used as a template to check the unwrapped solution for the waveform at higher MEGS.

A.2 Relating MR Sequence Timing With Accelerometer Recordings

Artifacts such as aliasing and sudden changes in amplitude in the accelerometer trace corresponded with landmarks in the MRE sequence such as the spiral gradients and refocusing pulse (Fig. 11). To relate the phases of skull motion and brain motion, the center of the 180 deg refocusing pulse was chosen as a common temporal landmark for synchronizing the accelerometer and MRE signals. The relative phase of the accelerometer recordings was determined from the FFT of the accelerometer time series, setting the initial time point at the center of the refocusing pulse. The relative phase shift of the MRE signal was found directly from the FFT of the time series of MRE phase contrast, which is already referenced to the center of the refocusing pulse.

The MRE phase contrast, Φ , for time-varying (square wave) motion-encoding gradients, $G(t)$, as shown in Fig. 11, and harmonic displacement field $u(r, t)$ is

Fig. 12 During 3D harmonic motion, the trajectory of each point depends on the amplitude and phase of each component. (a) The trajectory is a straight line when all three components have the same temporal phase, ψ , even if the component magnitudes, r_n , are different. (b) The trajectory becomes an ellipse when the three components have different temporal phase. (c) The spatial angle, β , between the vectors normal to the plane of each ellipse (arrows) was used to describe the difference in spatial orientation of motion ($\beta = 0.9$ rad in this example).

$$\Phi = N\gamma \int_0^T \mathbf{G}(t) \cdot \mathbf{u}(\mathbf{r}, t) dt \quad (\text{A1})$$

where γ is the gyromagnetic ratio of ^1H , T is the period, N is the number of motion-encoding gradients, and $\mathbf{u}(\mathbf{r}, t) = \mathbf{u}_0 e^{i(\Omega t - \psi)}$ is the vector of displacement at position $\mathbf{r}$ and time t . Here, Ω is angular frequency (rad/s) and $\psi = \psi(\mathbf{r})$ is the temporal phase shift, $2\pi\Delta t(\mathbf{r})/T$, of the displacement at that voxel. Evaluation of this integral yields an expression for the MRE phase contrast Φ , including the temporal phase shift relative to the refocusing pulse

$$\Phi = \frac{4N\gamma G u_G e^{-i(\psi - \frac{\pi}{2})}}{\Omega} \quad (\text{A2})$$

Here, u_G is the component of $\mathbf{u}_0$ in the direction of the gradient: $u_G = \mathbf{G} \cdot \mathbf{u}_0 / G$ and G is the motion encoding gradient strength. From this equation, we find that the temporal phase of the MRE measurements must be shifted $\pi/2$ rad to reference them to the center of the refocusing pulse. After computing this shift, the relative phase of the accelerometer data and MRE measurements is then calculated using Eq. (8).

The sensitivity of the sequence was doubled by computing the phase difference between acquisitions using positively (P) and negatively (N) polarized motion-encoding gradients.

$$\Phi_T = \Phi_P - \Phi_N = 2\Phi_P = \frac{8N\gamma G u_G e^{-i(\psi - \frac{\pi}{2})}}{\Omega} \quad (\text{A3})$$

The magnitudes of the total (reported) phase Φ_T and of the displacement u_G are linearly related to each other by the ratio $u_G/\Phi_T = \Omega/(8N\gamma G)$. For the spiral sequence used in this study, $\Omega = 2\pi(50 \text{ s}^{-1})$, $N = 2$, $G = 26 \text{ mT/m}$ and γ of ^1H is $2.68(10^5) \text{ rad/(s mT)}$, so that $u_G / \Phi_T = 2.82 \text{ } \mu\text{m}$ per radian of MRE phase contrast.

A.3 Elliptical Trajectories Described by Complex Coefficient Vectors

Consider a complex vector $\mathbf{u}_0 = (u_0, v_0, w_0)$ describing 3D harmonic motion at a frequency, Ω : $\mathbf{u}(t) = \text{Re}[\mathbf{u}_0 e^{i\Omega t}]$. The components of this vector can be described by

$$u_0 = r_1 e^{i\psi_1} \quad (\text{A4})$$

$$v_0 = r_2 e^{i\psi_2} \quad (\text{A5})$$

$$w_0 = r_3 e^{i\psi_3} \quad (\text{A6})$$

where r_n is the amplitude and ψ_n is the phase of each component. In harmonic motion, the trajectory shape is determined by the relative amplitudes and phases of these components as shown in Fig. 12. When all three components are exactly in phase, that is $\psi_1 = \psi_2 = \psi_3$, the trajectory collapses to a straight line (Fig. 12(a)). If the three components have different temporal phase, however, then the resulting trajectory is an ellipse (Fig. 12(b)). For our analysis, we determined the relative spatial orientation of two elliptical trajectories by finding the spatial angle between the vectors normal to the plane of each ellipse (Fig. 12(c)). The normal vectors are calculated from the cross product of the real and imaginary parts of the coefficient vectors.

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