Quantifying Relative Brain Motion in a *Post Mortem* Human Subject

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ABSTRACT

Due to the increased vulnerability in the older population, motor vehicle crash (MVC) older occupants are more likely than younger occupants to sustain head injuries resulting in intracranial bleeding. Among the most lethal are acute subdual hematomas (ASDH), with mortality rates cited up to 50%. Bridging veins crossing from the surface of the brain cortex through the arachnoid and dura mater into the dural sinus are at risk for rupture during rotational loading as a result of relative motion between tissue layers. Previous post mortem human subject (PMHS) studies of relative brain motion are limited because motion near the surface of the brain was not quantified and time-consuming preparation procedures led to potentially substantial post mortem *degradation. The objective of the current study was to further refine the experimental techniques developed previously in order to quantify relative brain motion between the skull and the brain in a fresh PMHS using a fixture-mounted high speed, high-frequency B-mode ultrasound probe with emphasis on efforts to minimize brain tissue degradation. These efforts included introducing a preservative solution of antibiotics and sodium bicarbonate and targeting a brain temperature between 6-12°C. The head-neck complex was rotated in an anterior-posterior direction at three rotational severities. Kinematic data was obtained with accelerometers and angular rate sensors on the fixture and skull. The ultrasound probe was mounted directly to the cage so that it would move with the skull in contact with the dura. Two-dimensional brain motion images were collected using high-speed, high frequency B-mode ultrasound. Testing was completed within 60 hours* post mortem*. Results provide new insight on the relationship between gross head kinematics and motion between the brain and skull in PMHS at severities up to 3800 rad/s^2 using multiple strategies to minimize post mortem degradation.*

INTRODUCTION

Due to the increased vulnerability in the older population, motor vehicle crash (MVC) older occupants are more likely than younger occupants to sustain head injuries resulting in intracranial bleeding (Gennarelli et al., 2005; Sawauchi and Abe, 2008; Mallory, 2010). Among the more lethal of these bleeding injuries is acute subdural hematoma (ASDH), with mortality rates cited up to 50% (Sawauchi and Abe, 2008; Taussky et al. 2008). Previous analysis of MVC databases has suggested that the increased frequency of ASDH with age is primarily related to the rupture of bridging veins (Mallory, Herriot, and Rhule, 2011). The increased frequency of ASDH with age combined with poor outcome necessitates a better understanding of injury tolerance to ASDH associated with bridging vein bleeds in the older population.

Bridging vein failure has been recreated experimentally in both primates and human cadavers at angular accelerations of 4,500-10,000 rad/sec^2 over durations shorter than 10 milliseconds, or angular velocities over 50 rad/sec (Löwenhielm, 1974; Ommaya, 2002; Depreitere, 2006). Subdural hematomas associated with bridging vein damage are believed to result from stretching the veins to failure with motion of the brain relative to the skull during head rotation (Holbourn, 1943; Gennarelli, 1982). Bridging veins cross from the surface of the brain cortex through the arachnoid and dura mater into the dural sinuses, so any relative motion between these tissue layers may result in bridging vein failure.

Other documented research on relative brain motion started as early as 1944 with studies looking at direct, qualitative motion of the brain through transparent caps that replaced part or all of the skull and dura (Pudenz and Sheldon, 1944; Gosch et al, 1970; Ibrahim et al., 2010). However, direct observational studies of motion at the surface of animal brains removed the boundary condition of the meningeal layers and the literature remains unclear how the motion of animal brains correlates to the brain motion seen in humans. Radiographic studies have utilized x-rays to track radiopaque markers and intravascular contrast fluid in the *post mortem* human brain (Hodgson, 1966; Shatsky et al. 1974&1977; Nusholtz et al., 1984; Hardy et al., 2007). Other novel efforts to track brain motion have included the implantation of sonomicrometry crystals into the brain cortex to quantify brain deformation in response to dynamic rotational pulses (Alshareef et al., 2018), and insertion of accelerometers directly into the brain (Trosseille et al., 1992). While these studies tracked motion deeper in the brain, the results closer to the surface of the brain were limited, and motion between the surface of the brain and the meningeal layers or dura was not quantified. Advancements in magnetic resonance (MR) imaging have offered the opportunity to non-invasively measure brain motion in healthy volunteers. Most notably, a series of MR studies by Bayly and colleagues documented quantitative values for large displacements deep in the cortex with small, relative motions near the surface of the cortex as well (Feng, 2005). While volunteer studies of response to low severity impacts have come closer to tracking motion near the surface of the brain than *post mortem* studies, MR imaging is limited in close proximity to the skull and cannot capture motion right at the surface of the brain or between individual meningeal layers, and volunteer studies cannot predict response to trauma-level severity.

Although these efforts have revealed information about relative motion between the deep brain and the skull, no studies have yet non-invasively measured relative motion between the cortical surface and meningeal layers during trauma level loading. For this reason, a series of studies by Mallory et al. worked to quantify relative motion between the surface of the brain and the meninges during anterior-posterior rotation under a variety of loading conditions. The selection of high-speed, high frequency, B-mode ultrasound served as a means to measure relative motion between the brain and the meningeal layers (Mallory, 2014). However, the stationary ultrasound probe was mounted adjacent to the rotating head, which limited the collection of data to only low-level severities.

One of the major limitations that affects brain research is the rate at which brain tissue decays post mortem. Variation in elapsed *post mortem* time and storage conditions in previous testing, makes the comparison of previous work difficult. A review of the literature on the effects of temperature on brain degradation reveals large gaps in the research, and indicates that in as little

as 12 hours brain tissue samples at room temperature becomes unreliable for both mechanical and material property testing (Rashid et al., 2013; Ferrer, 2007; Puymirat, 2006; Peters et al., 2002; Brands et al., 2000; Forte et al., 2017; Hrapko, 2008). Studies have shown that for samples stored at 6°C, brain tissue can be used for reliable biomechanical measurements until 48 hours (Rashid et al., 2013, Puymirat, 2016). While this is useful information concerning materials testing, there are still gaps concerning how whole brain degradation is affected by the temperature at which the brain is tested.

The objective of the current study was to further refine the experimental techniques developed previously in order to quantify relative brain motion between the skull and the brain in a fresh *post mortem* human subject using a fixture-mounted high-frequency B-mode ultrasound probe with emphasis on efforts to minimize brain tissue degradation.

Methods

B-mode ultrasound was used to image the relative motion of the tissues near the surface of the brain in a PMHS head during anterior-posterior rotations. The methods followed were previously outlined by Mallory et al. (2014, 2015) with updates to improve efficiency of preparation and to introduce new methods to reduce the effects of *post mortem* degradation. The ultrasound probe was mounted on the custom rotation fixture in order to rotate with the skull and image the relative motion of the underlying tissues. The efforts to reduce *post mortem* degradation included cooling the brain tissue and flushing of the vasculature with antibiotics and sodium bicarbonate. Perfusion of the subarachnoid space was attempted.

PMHS Selection

Post mortem human subjects for this testing were ethically obtained from the Ohio State University's Anatomy Body Donor Program. Acceptance criteria included:

- Subject access at no more than 36 hours *post mortem*
- Medical history does not include history of major head trauma, brain surgery, brain cancer or death by strangulation

Selection criteria of potential subjects was not limited by height, weight, age, or sex, and was also not limited by neurological disease or stroke. The subject used for this round of testing was a 77-year-old female obtained at 31 hours *post mortem.* The subject's cause of death was kidney disease.

Initial Body Preparation

During initial body preparation, temperature monitoring and control began immediately through the application of ice bags to the head and neck to begin cooling the brain temperature. Temperature was monitored by probes in the ear and nose to approximate brain temperature. The desired range for brain temperature was 6-12°C.

Prior to separation of the head and neck from the rest of the body, the external carotids were ligated to avoid pressurizing the subject's face. The internal jugulars, vertebral arteries, and

internal carotid arteries were identified and saved for later use during pressurization trials following rotation testing.

The head and neck were separated from the rest of the body by cutting through the C6-C7 vertebral level, severing the spinal cord last. Immediately following the severing of the spinal cord, the space between the cervical vertebral dura and the arachnoid was plugged with yarn coated in petroleum jelly and paraffin wax in order to limit the introduction of air or fluid into the space. A Foley catheter was then inserted between the spinal cord and arachnoid in order to perfuse the subarachnoid space with artificial cerebrospinal fluid (aCSF) prepared according to Sugawara et al. (1996) plus antibiotics (ceftazidime, ampicillin, and amphotericin) and sodium bicarbonate (Wetli et al., 2018) in an effort both to re-introduce fluid back into the cranial subarachnoid space, and also to slow *post mortem* degradation. The aCSF with preservatives is further referred to as aCSF+.

Flushing with Preservatives

Access to the cranial vascular system via the superior sagittal sinus (SSS) was selected in order to introduce aCSF+ as a method for reducing *post mortem* degradation, to remove any potential blood clots, and to prepare for post-test pressurization. The SSS target hole location was 6 cm anterior to the external occipital protuberance (EOP). This location was confirmed to be over the SSS by placing a lead fishing sinker at the target location and taking an x-ray in an anterior-posterior orientation. The hole was created using a surgical craniotome with a size 302 craniotome drill bit (Figure 1). The venous system was flushed via the SSS opening and out of both internal jugulars, and the arterial system was flushed via the internal carotid arteries and out of the vertebral arteries.

Ultrasound Window Preparation

Three holes were created on the test side, subject's left, using the surgical craniotome with bit size 302 (Figure 1). The location for the primary transducer window was 3 cm posterior to the bregma, and 3 cm lateral to the centerline. The two additional holes were created to check location sensitivities, however those results are not presented in this study.

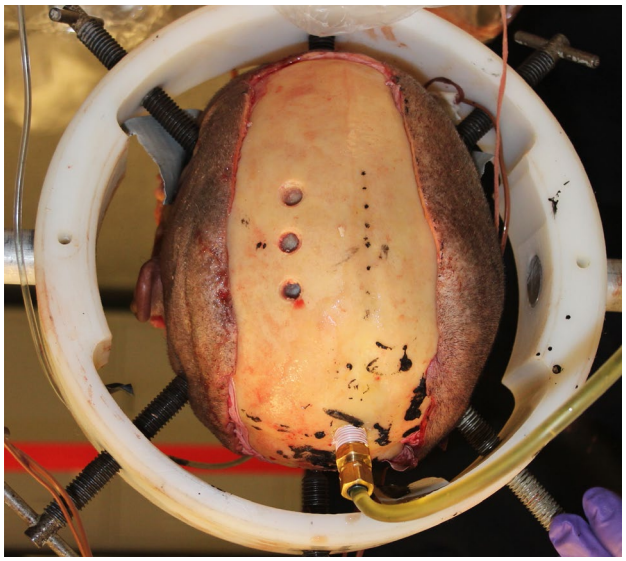

Figure 1: SSS (bottom, with plumbing inserted) and transducer holes before grinding (left of centerline)

Positioning the Head

The head was secured in a structure referred to as a cage, which ensured the head rotated on an axle in the anterior-posterior direction. The head was secured using threaded locator bolts that held the head in place without penetrating the skull. The head was positioned in the cage such that the dura underneath the ultrasound probe was at an 8 cm radius of rotation from the rotation axis of the fixture. The center of rotation of the subject was found using the Head Alignment Tool (HAT), developed for increasing the efficacy of aligning each subject on its specific axis of rotation while maintaining the radial location where brain motion is measured. The laser of the HAT is aligned such that it runs along the center of the superior sagittal suture between the nasion and the posterior occiput (Figure 2). Left and right center of rotation pins were then inserted to confirm and mark the center of rotation.

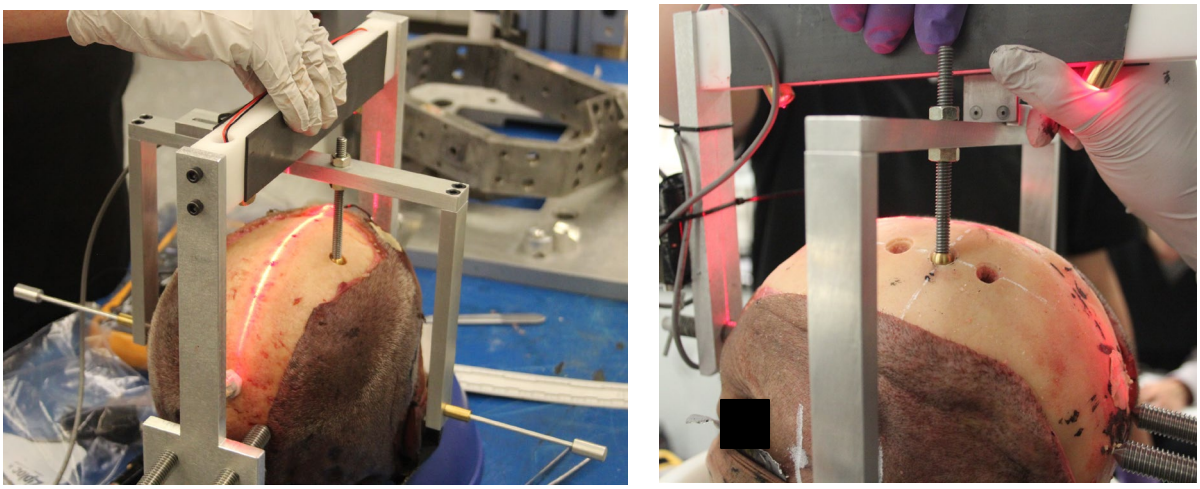

Figure 2: Head Alignment Tool (HAT)

In order to ensure that the ultrasound probe could be positioned close to the dura, the skull adjacent to the transducer viewing windows were grinded down until only a thin layer of skull remained around the periphery of each opening. Care was taken to ensure that the dura was not cut. With the cage installed in the rotation fixture, a superstructure was installed to house the ultrasound probe, allowing the ultrasound probe to rotate in close proximity to the dura, as well as a chin bar to increase stability (Figure 3). High-speed, high frequency motion images of the dura and underlying cortex were collected using a Vevo 2100 ultrasound imaging system (VisualSonics Inc., Toronto, Ontario, Canada) with a 550S probe. Images were collected at 693 frames per second at an image width of 4.08 mm and a focal depth of 6 mm.

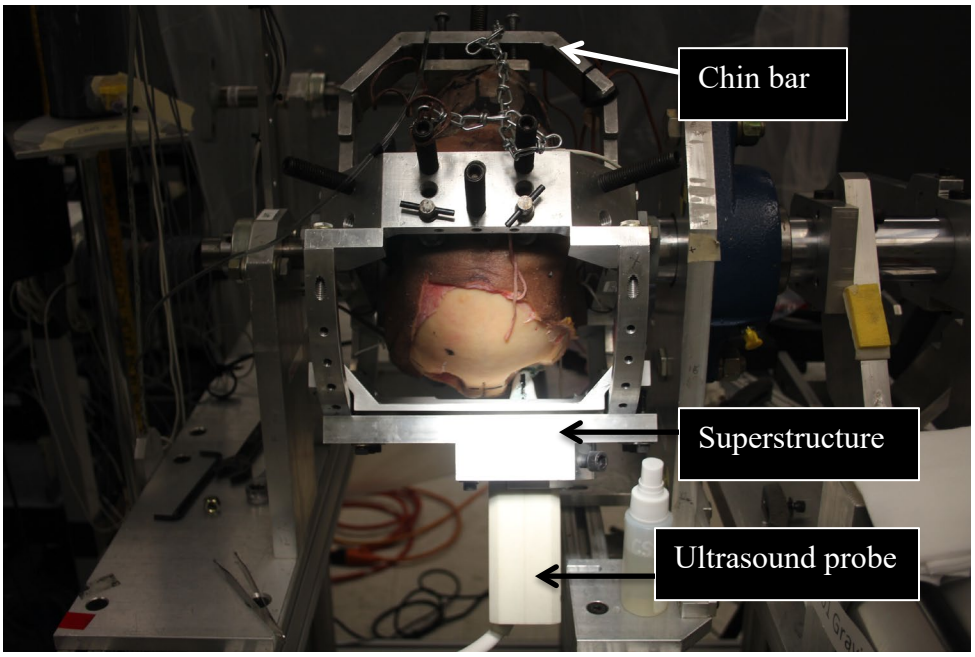

Figure 3: Head in cage installed in rotation fixture with chin bar at top, ultrasound probe mounted in superstructure at bottom

Test Set-up

To date, the results of three tests have been analyzed, including one test with rotational kinematics comparable to the volunteer data collected by Feng et al. (2005). An additional low-rate test with added mass was conducted, as well as a higher-rate test conducted through the pressurization of a pneumatic ram. The custom built rotational fixture is shown in Figure 4. All acceleration and braking of the head is achieved through the application of forces to the moment arms extending from the fixture's rotation axle.

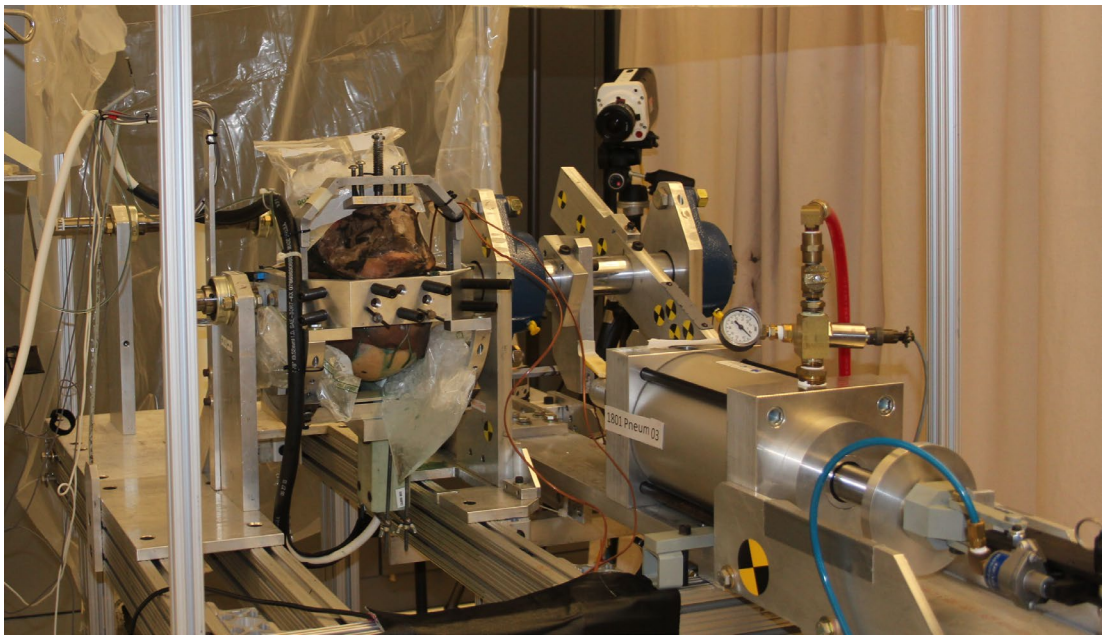

Figure 4: Custom rotation fixture, inverted head in cage (left), pneumatic piston in contact with shaft-mounted loading arm (right)

Low-rate Rotation of the Head During low-rate loading, the head was allowed to rotate in a posterior-anterior direction under the force of gravity from rest until contact with a padded stop, when it decelerates to a stop, i.e. accelerating in an anterior-posterior direction. This method was used to target the low-severity, non-injurious test speed and deceleration as outlined by Feng et al. The targeted ranges of rotational velocity and deceleration were between 2.0 - 2.2 rad/sec and 124-143 rad/sec^2, respectively. For the added mass test, 480 grams of additional weight was added to slightly increase the severity of the deceleration using the gravity-drop procedure.

Higher-rate Rotation of the Head The highest-severity of the three tests analyzed was accomplished by pressurizing the pneumatic ram. When accelerated, an applied linear force to the fixture's load arm initiated anterior-posterior rotational acceleration of the head about the axis on the fixture shaft. The cage was then decelerated by a damping brake in contact with an axle-mounted moment arm.

Instrumentation and Data Analysis

In order to attach instrumentation to the skull, a small area was grinded down and three orthogonally mounted angular rate sensors (DTS ARS18K PRO, Diversified Technical Systems, Seal Beach, CA) were glued to the skull to collect kinematic data during rotation testing.

The shaft and both sides of the cage were instrumented with ARS to measure rotational velocity about the Y-axis. Uniaxial accelerometers (7264C-2K, Endevco, San Juan Capistrano, CA) were fixed to the anterior and posterior cage for calculation of rotational acceleration about the Y-axis during post processing. Instrumentation locations are shown in Figure 5.

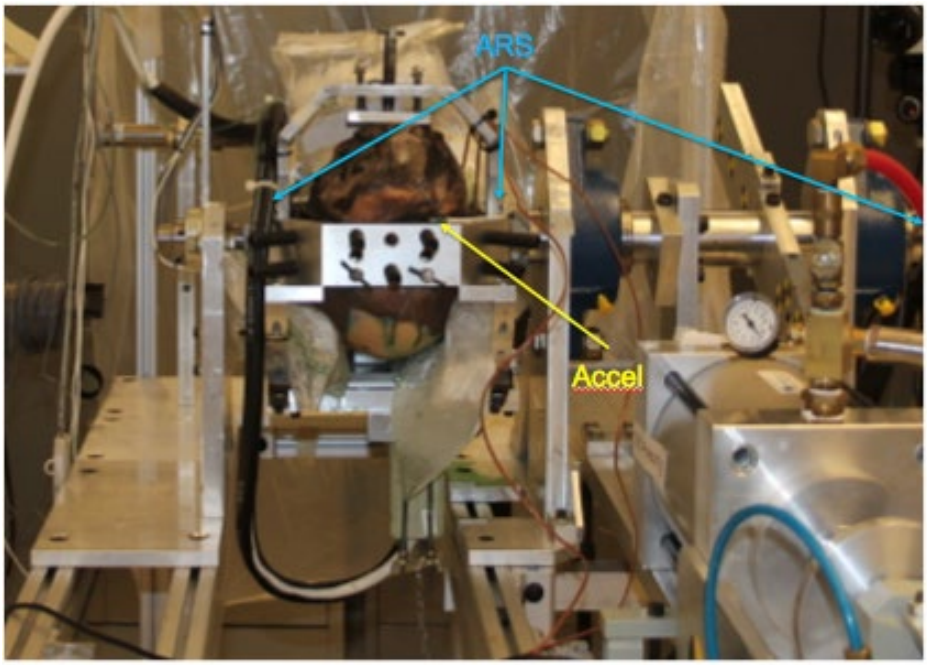

Figure 5: Fixture-mounted instrumentation locations

Rotational velocity and acceleration results were processed by removing offset prior to motion and filtered at CFC 180 using a commercial data analysis software (DIAdem, National Instruments, Austin, Texas). Rotational acceleration of the cage was found by calculating the difference between the front and rear cage accelerometers and dividing by the distance between them. Head rotation was calculated through the integration of the skull-mounted angular rate sensors.

Tissue tracking video sequences collected by B-mode ultrasound were analyzed using a commercial video tracking software (TEMA, Image Systems, Linköping, Sweden). The tracking of points on the dura, cortex surface, 1 mm deep into the cortex, and 2 mm deep into the cortex were tracked semi-automatically in the ultrasound images and time-histories were obtained. The motion of the points in the cortex was then used to estimate the displacement of the tracked points relative to the dura. As image lines across ultrasound images are collected sequentially, using the ultrasound probe during high-speed motion offers the potential for the collected images to be spatiotemporally distorted. Time correction was applied to each of the tests during post-processing (Mallory et al., 2018).

Results

Preparation for rotation testing was completed within 47 hours *post mortem*, and completion of rotation testing was finished within about 58 hours *post mortem.* Timing breakdown for each individual procedure is summarized in Table 1.

Table 1: Summary of Test Timing (Includes Breaks)

Procedure	**Time to Complete**	**Total Elapsed Post Mortem Time**
Pre-Procedure Preparation	1 hour 11 minutes	32 hours 11 minutes
Initial Body Preparation and Disarticulation	1 hour 54 minutes	34 hours 5 minutes
Subarachnoid Perfusion	17 minutes	34 hours 22 minutes
Flush with Preservatives	5 hours 3 minutes	39 hours 25 minutes
Positioning the Head	1 hour 44 minutes	41 hours 9 minutes
Window Preparation and Head Instrumentation	2 hours 43 minutes	43 hours 52 minutes
Setup in Rotation Fixture	2 hours 57 minutes	46 hours 49 minutes
Rotation Testing	11 hours 13 minutes	58 hours 2 minutes

Of the tests conducted, only results from three tests across a range of severities tested are presented here (Table 2). Peak rotational velocity of the head measured by the skull-mounted angular rate sensors was 2.2 rad/sec in the test targeted at the kinematic parameters in previous non-injurious volunteer tests by Feng et al. That test, as well as the test that resulted in peak rotational velocity of 3.8 rad/sec was run using the gravity drop procedure. The 28 rad/sec test was run using the pneumatic gun pressurized to 50 psi. X-displacements, corresponding to the anterior motion of the tissue relative to the skull and skull-mounted probe in the parasagittal ultrasound image plane, of each of the three tests analyzed are shown in Figures 6-8.

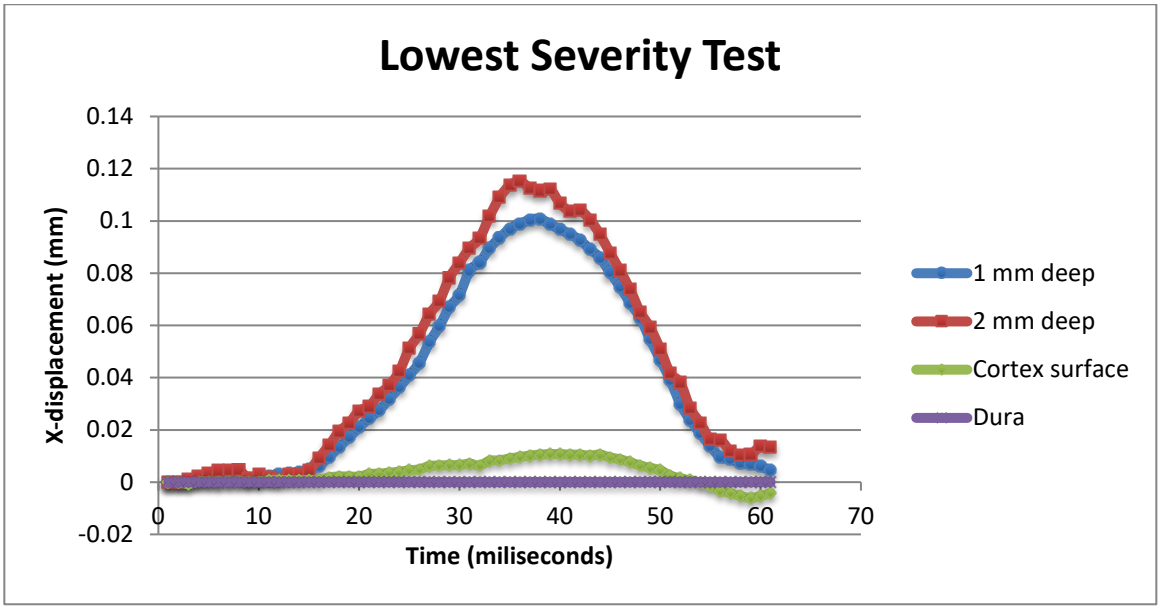

Figure 6: X-displacement relative to skull-mounted ultrasound probe for the lowest severity test analyzed

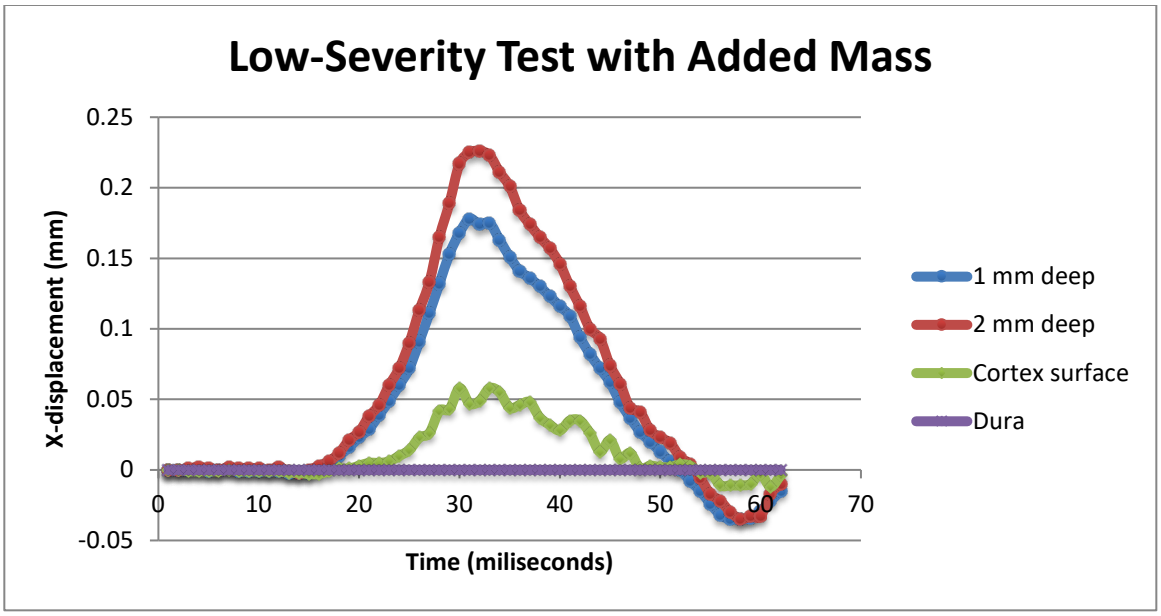

Figure 7: X-displacement relative to skull-mounted ultrasound probe for the low-severity test with added mass

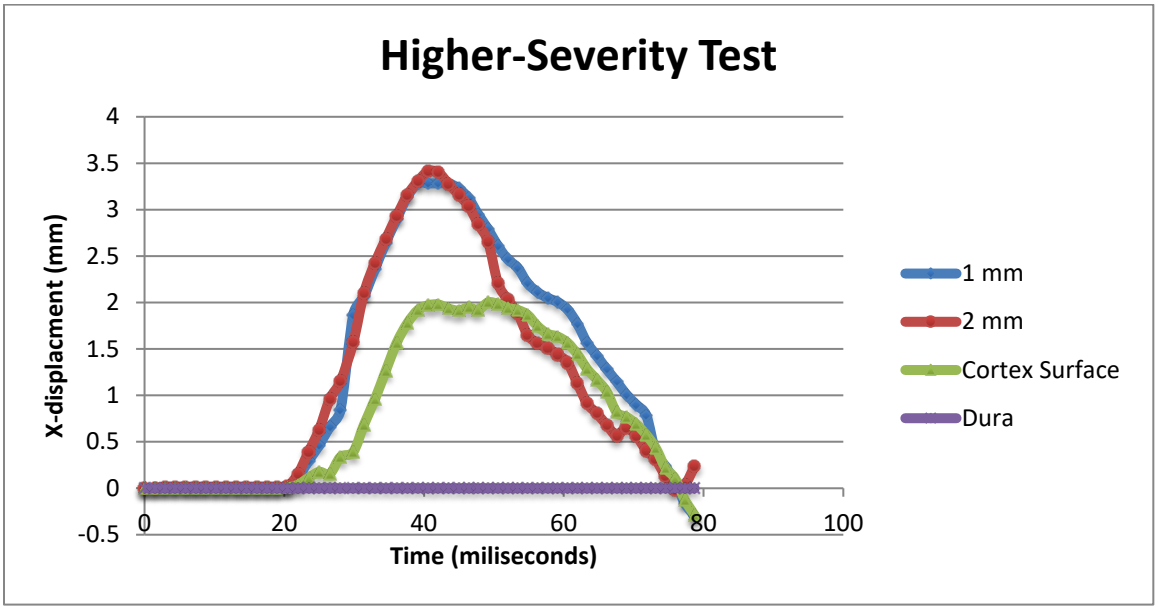

Figure 8: X-displacement relative to skull-mounted ultrasound probe for the 50 PSI pneumatic test

Maximum displacement from each of the three severities recorded for the cortex surface, 1 mm deep, and 2 mm deep are recorded below in Table 2. Since the dura was firmly attached to the skull, it was assumed that any motion relative to the dura could be used to estimate motion relative to the skull.

Table 2: Summary of results for rotational testing

		Max displacement relative to dura		
Rotational velocity (rad/s)	Rotational acceleration (rad/s^2)	Cortical surface (mm)	1 mm deep (mm)	2 mm deep (mm)
2.2	133	0.012	0.105	0.115
3.8	477	0.058	0.178	0.226
28	3800	2.001	3.283	3.414

DISCUSSION

Previous PMHS studies of relative brain motion are limited by the fact that motion near the surface of the brain is not quantified and time-consuming preparation procedures have led to potentially substantial *post mortem* degradation. The selection of high-speed, high frequency B-mode ultrasound has made it possible to measure surface motion of the brain during high-rate head motion without damage to the dura. Moving from a stationary probe to mounting the ultrasound probe on the rotation structure has increased the possibility for tracking tissue at higher velocities (Mallory, 2015).

Maximum displacements of 1 mm and 2 mm deep in the cortex, 0.105 mm and 0.115 mm, respectively, are comparable to the results obtained by Mallory et al. of around 0.10 mm and 0.15 mm, respectively (2014). Both series of testing were run at the same loading conditions. A sonomicrometry study by Alshareef and colleagues reported x-displacements around 3 mm at locations 3 cm deep into the brain at a 20 rad/sec pulse (2018), comparable to the results obtained here of 3.414 mm displacement, but at a depth of only 2 mm and pulse of 28 rad/sec. Although it is expected to see greater motion from a larger rotational pulse, it is difficult to make direct comparisons due to the differences in impact velocity and measurement location.

While it was possible to track tissues at rotational velocities up to 28 rad/sec, higher-rate tests showed evidence of potential out-of-plane tissue motion that limited motion tracking. Studies of motion of deeper tissues show out of plane motion up to 3 mm at anterior-posterior rotational pulses of 20 rad/sec, though none of the points tracked were at the surface of the brain (Alshareef, 2018). This potential for out-of-plane tissue motion creates a limitation for tracking two-dimensional ultrasound images, and necessitates reduction of lateral motion likely due to structural vibration of the rotation test fixture and further investigation into out of plane motion of the surface of the cortex.

It has been established that increased *post mortem* time leads to unreliable measurements in the PMHS brain tissue (Ferrer, 2007, Peters et al., 2002, Brands et al., 2000, Forte et al., 2017, Hrapko, 2008), placing increasing importance on addressing this limitation of brain research. Alshareef et al. reported a *post mortem* time of 60 hours (2018), previous studies by Mallory et al. reported times between 59 and 86 hours (2014), and Hardy reported times between 120 and 240 hours (2007). Efforts in this study were made to minimize preparation times as well as to slow the rate of tissue degradation during that time. Creation of the HAT device and other general streamlining of procedures has offered the potential to reduce the time needed to complete testing,

resulting in an overall lower *post mortem* time at the completion of rotation testing. A novel approach of addressing brain degradation was the addition of antibiotics and sodium bicarbonate into aCSF and the measurement and control of brain temperature throughout testing. Antibiotics have been used in previous studies to preserve *post mortem* human tissue (Csönge et al. 1995, Potier, 2010) and more recent work has shown the potential to use both antibiotics and sodium bicarbonate to slow degradation in the PMHS brain tissues (Wetli, 2018). Previous temperature trials by this research group have found that a temperature probe in the PMHS nose closely approximates temperatures measured 8 cm into the cortex towards the center of the brain, and a temperature probe inserted into the ear closely approximates temperatures measured epidurally. Thus, brain temperature could be measured non-invasively and controlled through the application of ice packs.

Although the primary goal of this test was for method development, these tests, along with the tests reported by Mallory et al. in 2014, provide valuable information about relative brain motion at the cortex relative to the dura during head rotation. Efforts to understand the relative motion between the deep brain and the skull have contributed greatly to the validation of human body models. Finite element (FE) models are powerful tools, and the anatomical complexity of brain models are proving potential in estimating injury tolerance. Among these are the Royal Institute of Technology KTH model (Kleiven and Holst, 2002), the Wayne State University Brain Injury Model (WSUBIM) (King et al., 2003), as well as the head models of full-body FE models such as the Total Human Model for Safety (THUMS) (Kimpara et al., 2006), and the Global Human Body Model Consortium (GHBMC) (Mao et al., 2013). The predictive power of FE models can only be utilized through adequate validation of biomechanical testing under a variety of loading scenarios. Of the models listed, all are validated by the deep brain results of Hardy et al (2007). Supplemental evaluation of model motion at the surface of the brain, even at the relatively low rates of rotation reported in the current study, would offer an opportunity to further optimize model biofidelity.

CONCLUSIONS

These results provide new insight on the relationship between gross head kinematics and motion between the between the brain and skull in post mortem human subjects at severities up to 3800 rad/s^2 using multiple strategies to minimize post mortem degradation. Further improvements to rotation test procedures are needed to extend these methods to the high-speed testing required to ultimately draw conclusions for estimating injury tolerance of the elderly in sustaining an acute subdural hematoma.

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