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Improved prediction of direction-dependent, acute axonal injury in piglets

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Abstract

To guide development of safety equipment that reduces sports-related head injuries, we sought to enhance predictive relationships between head movement and acute axonal injury severity. The severity of traumatic brain injury (TBI) is influenced by the magnitude and direction of head kinematics. Previous studies have demonstrated correlation between rotational head kinematics and symptom severity in the adult. More recent studies have demonstrated brain injury age- and direction- dependence, relating head kinematics to white matter tract-oriented strains (TOS). Now, we have developed and assessed novel rotational head kinematic parameters as predictors of white matter damage in the female, immature piglet. We show that many previously published rotational kinematic injury predictor metrics poorly predict acute axonal pathology induced by rapid, non-impact head rotations; and that inclusion of cerebral moments of inertia (MOI) in rotational head injury metrics refines prediction of diffuse axonal injury following rapid head rotations for two immature age groups. Rotational Work (RotWork) was the best significant predictor of traumatic axonal injury in both newborn and pre-adolescent piglets following head rotations in the axial, coronal and sagittal planes. An improvement over current metrics, we find that RotWork, which incorporates head rotation rate, direction and brain shape, significantly enhanced acute traumatic axonal injury prediction. For similar injury extent, the RotWork threshold is lower for the newborn piglet than the pre-adolescent.

Graphical Abstract

Correspondence to: Susan S. Margulies.

Conflict of interest

Authors have no conflicts of interest.

Author Roles:

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: LA. Acquisition of data: SSM, CS. Analysis and interpretation of data: LA, SSM. Drafting of the manuscript: LA, SSM. Critical revision of the manuscript for important intellectual content: LA, SSM. Statistical analysis: LA.

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To guide development of safety equipment that reduces sports-related head injuries, we compared eight published and three new metrics for predicting acute axonal injury severity. Rotational work, a new metric which incorporates head rotation rate, direction, and brain shape, significantly enhanced acute axonal injury prediction in two pediatric populations.

Keywords

rotational; kinematics; biomechanics; brain trauma; pediatric

Introduction

The Center for Disease Control has designated traumatic brain injury (TBI) as a silent epidemic that affects as many as 1.9 million children aged 18 years annually in the United States (Bryan, et al., 2016; Faul, et al., 2010). The need for effective TBI prevention is underscored by the 1 billion USD cost of hospitalization and care (Schneider, et al., 2006). The ability to predict pediatric traumatic brain injury from head kinematic parameters is necessary for the effective design of child safety equipment and for accurate assessment of brain injury risk during recreation and transportation. Motor vehicle traffic-related crashes account for the majority of TBI-related deaths in youth 0–14 years old in the United States (CDC Injury Center, 2016) and across the world (Diamond et al., 2009; Gawryszeski, 2007; Kypridis et al., 2000; Wang et al., 2003; Wu et al., 2008).

Previous research has increased our understanding of the mechanisms behind TBI through computational simulations, analysis of helmet kinematics during sports games and animal models of TBI. Rotational head motion, as opposed to linear head motion, is widely believed to cause TBI by excessive shearing of brain tissue, which is a consequence of its low shear modulus and high bulk modulus (Gennarelli, 1994; Kimpara & Iwamoto, 2012; Ommaya, et al., 2002). Most published brain injury criteria use either rotational or linear head motion for brain injury prediction. Even fewer criteria, such as HIP (Newman, et. al, 2000), utilize both linear and rotational components of motion.

Most TBI prediction metrics were formulated from unspecific, non-functional brain trauma severity classification systems. Previously published rotational injury predictors, such as BRIC, were correlated to the head component of the Abbreviated Injury Scale (AIS), which is a general measure of the threat of injury to a subject's life, rather than a direct and

objective measure of the severity of brain injury. Several studies show that axonal damage strongly correlates to head injury severity (Benson et al., (2007); Johnson, et al., (2013); Sullivan et al., (2013)), whereas AIS and other injury severity assessments, such as Glasgow Coma Scale and Injury Severity Score, have been shown to poorly predict 12 month outcomes after TBI (Foreman et al., 2007). In order to better inform new injury predictors through increased accuracy of TBI severity measurement, we utilized immuno-histological assessment of axonal damage 6 hours following TBI.

To relate head movements to axonal damage, sophisticated computational finite element models have been used to determine mechanistic underlying associations that relate head movements, tissue distortions and axonal injury. Finite element simulations of rapid head rotations in animals (Coats, et al., 2012; Maltese & Margulies, 2016; Sullivan et al., 2015) and humans (Post et al., 2015; Sahoo, et al., 2014; Weaver, et al., 2012; Zhao & Ji, 2015) demonstrate that high magnitude axonal tract strains strongly correlate with the direction of head rotation. Age, brain size and direction of head rotation (Eucker, et al., 2011; Ommaya, et al., 2002; Prange & Margulies, 2002; Sullivan et al., 2013) directly modulate brain injury risk. Of the rotational brain injury kinematic metrics, BRIC uses resultant rotational velocity and acceleration, which is independent of head rotation direction. Revised BrIC addresses directional rotational velocity sensitivity by including direction-specific critical thresholds of injury. In comparison to previously mentioned metrics, Power Rotational Head Injury Criterion (PRHIC36)(Kimpara & Iwamoto, 2012) and HIP include the head rotation direction by including moment of inertia (MOI) to capture directional and brain size sensitivity of axonal injury (Eucker et al., 2011; S. Sullivan et al., 2015). MOI is the resistance to rotational motion about an axis (x, y or z).

In this study, we hypothesized that kinematic injury predictor metrics that incorporate MOI, namely, Rotational Kinetic Energy (RotKE), Rotational Work (RotWork) and rate of RotKE (rKE), would provide improved correlation of acute axonal injury volume (AIV) in our animal model of diffuse TBI compared to previously published metrics. We evaluated these three novel rotational kinematic brain injury predictors and 8 published metrics for newborn and pre-adolescent pigs to identify those strongly correlated with volume of acute (6 hour post-injury) axonal injury assessed via histology. Using data obtained in two populations of piglets, representative of human infants and pre-adolescents, we examined the relationships between age, axonal injury and rotational kinematic metrics.

Methods & Materials

All studies were approved by the University of Pennsylvania Institution Animal Care and Use Committees (IACUC). Previously published axonal injury and angular velocity data (Eucker et al., 2011; Sullivan et al., 2015) from 3–5 day old (n=32) and new data from 2 month old (n=17) female piglets sacrificed at 6 hours after TBI were analyzed in a novel manner for this publication. These piglet ages correspond to human infants (<2 years) and pre-adolescents (10–13 years) respectively in brain development (Armstead, 2005). The use of pigs in neuroscience research has grown recently because the pig brain is similar to that of the human in anatomy (Lind et al., 2007), and piglets share similar cerebral hemodynamics and metabolism with humans (Buckley, 1986; Dickerson & Dobbing, 1967; Duhaime,

1998). The rate of myelination and cerebral electrical activity during development has been correlated with the human (Lind et al., 2007). Furthermore, the pathophysiology of TBI in piglets compares well with that in human children due to similar gyral pattern, overall brain shape and distribution of gray and white matter (Armstead, 2000, 2005).

Diffuse white matter injury was induced in juvenile female piglets using a well-characterized rotational acceleration device (Raghupathi & Margulies, 2002). A single non-impact, closed-head, rapid head rotation (12–20 ms) was applied in the purely coronal (COR), axial (AXI) or sagittal (SAG) plane, centered at the mid-cervical spine (Eucker et al., 2011). Angular velocity of head rotation was recorded at 10 kHz using angular rate sensor (ATA Engineering, Model#: ars--06, Inc., Herndon, VA) attached to the linkage sidearm of HYGE pneumatic actuator (via data acquisition system in LabView, National Instruments, Austin, TX). A 10 point binomial smoothing filter was applied to all triangular-shaped velocity-time histories. The mean and standard deviation of the peak angular velocities in each direction measured in the 3–5 day and 2 month old are summarized in Table 1. During AXI and COR rotations, the piglet head rotated 90°, while SAG spanned 60° because of limited cervical spine flexibility in this direction and we excluded hyperflexion and hyperextension. Our SAG standard deviations are smaller in our previous study because we limited the range of infant piglet head velocity due to increased mortality in this direction at lower velocities than those used in COR or AXI. The means and standard deviations of peak absolute angular acceleration were for $2.96\text{e}+8 \pm 1.48\text{e}+8$ and $1.58\text{e}+6 \pm 3.55\text{e}+5 \text{ rad/s}^2$ in the 5 day and 2 month old piglets respectively.

Our rapid head rotation injury model captures the short, high deceleration aspects of impact events, without a contact event. To confirm, we scaled our piglet angular velocities and accelerations (using Ommaya's brain mass scaling laws) to that of three monkey species (rhesus, chimpanzee, and squirrel) presented in Ommaya's studies comparing head kinematics from separate whiplash and impact injuries (Ommaya et al., 1968, 1970; Ommaya & Hirsch, 1971; Ommaya et al., 1973). We observed that loading conditions for impact and whiplash associated with concussion overlap for all three nonhuman primate species. Furthermore, we note that when we scaled pig kinematics to each species' brain mass, the pig kinematics overlap with both impact and whiplash loading conditions for all three primate species. Our HYGE injury kinematics encompass both impact and whiplash. We conclude that our porcine rapid head rotation injury model captures whiplash kinematics as well as the short, high deceleration aspects of impact events, without a contact event.

The staining, imaging and quantification procedures for immunohistochemical processing of piglets brains are detailed elsewhere (Eucker et al., 2011) and are summarized here. Six hours after injury, brains were perfusion-fixed with 10% neutral buffered formalin for 24 hours. Fixed brains were weighed before being cut into serial coronal 3mm sections; from each section a thin slice (6 μm thickness) was examined for histopathology. Histopathological assessment of axonal damage was conducted by staining coronal slices for beta-amyloid precursor protein (βAPP). Positive βAPP immuno-staining indicates damaged axons with disrupted fast axonal transport. A neuropathologist blinded to the animal injury group then identified regions with > 2 positive βAPP -stained axonal profiles per field (scanning power 5–40x) in each slice. For every animal, the cumulative sum of positively

stained regional area throughout all examined brain slices (6 μm thickness) yielded an AIV, expressed as a percent of total cerebral volume. AIV is individual-specific response.

In our new analysis, we sought to identify a biomechanical “biomarker” that related to acute axonal injury. We computed the MOI (I_{ij}), or the resistance to rotational motion, for each age group using our previously published (Sullivan et al., 2015) finite element models of the piglet head in Abaqus Explicit v6.9-EF1 (Dassault Systèmes, Vélizy-Villacoublay, France). We did not use individual MOI measurements because brain mass within an age group was very consistent (coefficient of variation <10%); we did not obtain individual MRI images from each pig. Instead, we obtained one representative MRI for each age, and calculated the MOI from that image. For this new analysis, we determined the MOI (about the x-, y- and z-axes) with respect to the center of rotation for our typical 3–5 day old and 2 month old piglet. For the 3–5 day old piglet mesh, the MOI with respect to the mid-cervical spine about the x-axis (SAG rotations), y-axis (AXI rotations) and z-axis (COR rotations) were defined from Abaqus to be 81.57 gmm^2 , 61.68 gmm^2 and 25.05 gmm^2 respectively. The MOI (about the x-, y- and z- axes) for the 2 month old piglet brain mesh were determined to be 254.63 gmm^2 , 172.83 gmm^2 and 102.11 gmm^2 respectively. Due to brain geometry, in both ages, piglet MOI was largest for SAG rotations, because the caudal-rostral (x) dimension is the largest in the pig brain, and smallest for COR rotations.

For each animal (n=32 newborn piglets, n=17 pre-adolescent piglets), the filtered angular velocity-time profiles were used to calculate eight previously published rotational head injury prediction metrics: peak angular velocity (VEL_i), peak angular acceleration (ACCEL_i), Rotational Injury Criterion (RIC36)(Kimpura & Iwamoto, 2012), Head Impact Power (HIP) (Newman et al., 2000), Brain Rotational Injury Criteria (BRIC) (Takhounts, et al., 2011), Revised Brain Rotational Injury Criteria (Revised BrIC) (Takhounts, et. al, 2013), Power Rotational Head Injury Criterion (PRHIC36)(Kimpura & Iwamoto, 2012) and Rotational Velocity Change Index (RVCI) (Yanaoka & Takahashi, 2015).

Peak Angular Velocity (VEL_i):

$$\text{VEL}_i = \max(\omega_i(t)) \quad (\text{Equation 1})$$

where $\omega_i(t)$ is the absolute value of the head’s angular velocity-time history from a rotation about axis i (e.g. x, y, or z).

Peak Angular Acceleration (ACCEL_i):

$$\text{ACCEL}_i = \max(\alpha_i(t)) \quad (\text{Equation 2})$$

where $\alpha_i(t)$ is the absolute value of the head’s rotational acceleration-time history from a rotation about axis i (e.g. x, y, or z). Angular acceleration was calculated by differentiating the angular velocity time history.

Rotational Injury Criterion (RIC36):

$$RIC36 = \left[(t_2 - t_1) \left\{ \frac{1}{(t_2 - t_1)} \int_{t_1}^{t_2} \alpha_i(t) dt \right\}^{2.5} \right]_{\max} \quad (\text{Equation 3})$$

where $t_2 - t_1 = 36$ ms and $\alpha_i(t)$ is defined above (Kimpara & Iwamoto, 2012).

Head Impact Power (HIP):

$$HIP = \left(\sum m \cdot a_i \cdot \int a_i(t) dt \right) + \left(\sum I_{ii} \cdot ACCEL_i \int \alpha_i dt \right) \quad (\text{Equation 4})$$

where m is mass of head (kg), a_i is linear acceleration (ms^{-2}) and I_{ii} is MOI about axis i (kgm^2), where the skull is assumed to be rigid. Linear (tangential) accelerations from the center of mass to the center of rotation for each animal were used in the HIP calculation.

Brain Injury Rotational Injury (BRIC):

$$BRIC = \frac{VEL_i}{\omega_{cr}} + \frac{ACCEL_i}{\alpha_{cr}} \quad (\text{Equation 5})$$

where ω_{cr} and α_{cr} are newborn pig's mass scaled critical angular velocity (415 rad/s) and acceleration ($2.55 \times 10^5 \text{ rad/s}^2$) from diffuse axonal injury (DAI) threshold load values in the baboon as published in (Margulies & Thibault, 1992).

Revised Brain Injury Rotational Injury (Revised BrIC):

$$\text{Revised BrIC} = \sqrt{\left(\frac{VEL_x}{\omega_{xC}} \right)^2 + \left(\frac{VEL_y}{\omega_{yC}} \right)^2 + \left(\frac{VEL_z}{\omega_{zC}} \right)^2} \quad (\text{Equation 6})$$

where $\omega_{xC} = 330$ rad/s, $\omega_{yC} = 281$ rad/s and $\omega_{zC} = 213$ rad/s for newborn pig's mass scaled critical angular velocities in their respective directions based on the average of cumulative strain damage measure and max principal strain in simulated injury monitor from (Takhounts, et al., 2013).

Power Rotational Head Injury Criterion (PRHIC36):

$$PRHIC36 = \left[(t_2 - t_1) \left\{ \frac{1}{(t_2 - t_1)} \int_{t_1}^{t_2} \left(\sum I_{ii} \cdot \alpha_i \right) dt \right\}^{2.5} \right]_{\max} \quad (\text{Equation 7})$$

where the maximum integral time duration was set to 36 ms (Kimpara & Iwamoto, 2012). The contents under the initial integral correspond to rotational component of HIP.

Rotational Velocity Change Index (RVCI):

$$RVCI = \left[\sqrt{R_x \left(\int_{t_2}^{t_1} \alpha_x dt \right)^2 + R_y \left(\int_{t_2}^{t_1} \alpha_y dt \right)^2 + R_z \left(\int_{t_2}^{t_1} \alpha_z dt \right)^2} \right]_{\max} \quad (\text{Equation 8})$$

where R_x , R_y and R_z are weighting factors about the x, y and z axes respectively and t_1 and t_2 are the initial and final times over a 10ms duration (Yanaoka & Takahashi, 2015). The Cumulative Strain Damage Measure weighting factors, $R_x = 1$, $R_y = 2.29$ and $R_z = 1.98$, were used because they were more appropriate for predicting diffuse injuries than weighting factors determined from correlation with Max Principal Strain (Yanaoka & Takahashi, 2015).

In addition to the eight previously published metrics, three novel metrics were calculated using the rotational MOI we identified. The novel head injury metrics calculated for each animal includes: rotational kinetic energy (RotKE), rotational work (RotWork) and rate of change of rotational kinetic energy (rKE), shown in Equations 9–11 respectively. Each piglet within an age group was assumed to have the same direction-specific MOI (I_{ii}). RotKE, RotWork and rKE of the head during rotation may describe the global forces on the brain responsible for axonal injury through deformation of tissue.

$$\text{RotKE} = \frac{1}{2} I_{ii} \text{VEL}_i^2 \quad (\text{Equation 9})$$

$$\text{RotWork} = \text{ACCEL}_i I_{ii} \theta \quad (\text{Equation 10})$$

$$\text{rKE} = \frac{\frac{1}{2} I_{ii} \text{VEL}_i^2}{t_{\max}} \quad (\text{Equation 11})$$

where θ is maximum change in angular displacement; t is number of seconds to reach max angular velocity, VEL_i .

For each age group and metric, we performed separate linear regressions between each metric and AIV(R, version 3.2.4, 2016-03-10). Our objective was to identify all metrics with promising injury predictive capability (defined as $R^2 > 0.5$ with slopes greater than zero) and then determine which of these metrics are strong in both age groups. While we recognize that metrics may have some co-dependency (e.g. on acceleration), collinearities between metrics were not assessed. We evaluated outliers, and excluded all data greater than three standard deviations from the metric mean for that age cohort. We excluded one outlier pre-adolescent animal from the ACCEL, HIP, RVCI and rKE metrics and removed a single infant animal from the PRHIC36, HIP and RotWork metrics.

Results

Rotational Head Injury Metrics and Axonal Injury

We calculated the mean tangential accelerations: $23,499 \pm 836 \text{ m/s}^2$ (infants) and $26,426 \pm 1,287 \text{ m/s}^2$ (pre-adolescents). The mean and standard errors of angular accelerations were: $43,071 \pm 13,018 \text{ rad/s}^2$ (infants) and $34,594 \pm 8,608 \text{ rad/s}^2$ (pre-adolescents). For both ages, animals injured in the COR plane (Fig. 1, triangles) had relatively low AIV, while rotations in the AXI and SAG planes resulted in markedly higher AIV (Fig. 1, circles, squares respectively). Eight rotational kinematic metrics had positive and significant linear relationships with AIV in one or both ages (Table 2). Ellipses in Fig. 1 indicate 95% confidence intervals for these relationships, where stronger relationships ($R^2 > 0.5$) are designated by gray-filled ellipses and are bolded in Table 2. Although Revised BrIC accounted for the effect of head rotation direction on head injury by weighting peak head velocities by critical threshold velocities, Revised BrIC did not correlate significantly with axonal injury. For all of the strong metrics shown in Fig. 1, all slopes in the newborn age group exceeded that of the pre-adolescent.

All rotational head injury metrics that used MOI and rotational kinematics had strong, significantly positive correlations with axonal injury in one or both age groups. RotKE had the strongest correlation for all 3–5 day old piglets, and PRHIC36 performed the best in pre-adolescent piglets (Table 2, Fig. 1). Both HIP and rKE are head power measures and are strong predictors of AIV for the infant, but not for the pre-adolescent pig. HIP quantifies the summation of both translational and rotational head power, while rKE only measures rotational power. RotWork was the only strong metric in both age groups (Fig. 2). The RotWork-AIV slope for the 3–5 day old is more than six times larger than that of the 2 month old pig (Fig. 2), indicating that the newborn-aged pig sustained much more AIV per joule of RotWork than the pre-adolescent piglet.

Translation to the Human Pediatric Population

Based on observations made in the neonatal pig, the largest MOI was in the SAG direction and correlated with the largest volume of axonal injury. To translate our findings to humans, we hypothesized that the principal axis with the highest MOI for the human head would exhibit the largest sensitivity to head injury. In a child, the skull is more spherical than that of an adult, due in part to increased skull bone curvature (Winkelstein, 2012). Up to the time of publication, we found one study that reported 14 children (aged 5 months to 16 years) head MOI values for all three principal axes (Loyd et al., 2010). We note that only measurements of head (not brain) MOI about all three principal axes in humans were previously published and that developmental changes in the geometry of the skull are non-linear (Loyd et al., 2010) and may differ from that of the brain over time. In this study, COR rotations corresponded to head movement about the x-axis, defined from the dorsum sellae to the nasion; SAG head rotations corresponded to movement about the y-axis, defined as left to right; while AXI rotations corresponded to rotations about the z-axis, defined as inferior to superior along the spine. We observed that across all ages, MOI values about the y-axis (SAG) were consistently the largest. To determine if brain development altered the shape (MOI) of the head, we performed a linear regression of MOI (for each axis) by age

(Fig. 3). Comparison of each axis' regressions by analysis of covariance revealed that the MOI in all directions increases significantly ($p < 0.0001$) with development (y axis slope with age 12.82 ± 1.40 ; x axis 10.21 ± 1.40 ; z axis 9.57 ± 1.40 , all in units of $\text{kg}\cdot\text{cm}^2/\text{year}$), but ANOVA revealed no interaction between the effect of age and direction ($p = 0.23$). The lack of significant interaction between age and direction on MOI indicates that the brain grows in an isotropic manner, without a significant change in shape. Future studies should collect more data from children to confirm how MOI varies with development.

Discussion

Our goal was to identify TBI mechanisms that inform motor vehicle and protective equipment design strategies. We believe that the novel predictors of rotational head injury presented in this study are scientifically valuable as well as potentially clinically relevant to injury prevention and public health. In this study, our objective was to compare previously published rotational head kinematic metrics with new kinematic metrics that included MOI and to correlate these metrics with acute, histopathological axonal injury in the newborn- and pre-adolescent-aged piglet populations.

Rotational Moment of Inertia Improves Prediction of Axonal Injury

Consistent with our hypothesis, kinematic metrics that included MOI and rotational direction improved prediction of axonal injury. The strongest metrics were RotKE, RotWork and rKE for newborn piglets and PRHIC36 and RotWork for the pre-adolescent pigs. RotKE was the strongest predictor of axonal injury severity for newborn animals, and PRHIC36 was the strongest predictor for pre-adolescent pigs. RotWork had strong predictive capability in both ages. Therefore, we recommend that future rotational injury metrics should consider including RotWork to enhance robustness of brain injury prediction.

Age Influences the Axonal Injury Threshold

For both pigs and children, the increase in head size with age significantly increased the magnitude of MOI about each axis. We hypothesized that acute axonal injury would increase with MOI and increasing rotational injury metric values. Thus, we expected older larger brains with larger MOI and RotWork to have more severe axonal injury than the newborn. However, with larger brains, pre-adolescent-aged piglets experienced less AIV for many rotational head injury metrics than newborn-aged piglets (Fig. 1). For example, comparison of AIV-RotWork relationships across age suggests that newborn-aged pigs have a lower RotWork threshold to axonal injury (Fig 2). Experimentally, even when accelerations were scaled by brain mass alone (Ommaya, et al., 1967), we expected larger, older brains exposed to similar accelerations to have more severe axonal injury. Instead, rapid head rotations caused newborn piglets to sustain worse outcomes (Maltese, 2012b; Sullivan et al., 2015; Sullivan et al., 2013) and larger AIV (Fig. 1) than that experienced by pre-adolescent pigs. Thus, scaling by brain mass and size is inappropriate when comparing across age because injury risk in the young brain is not mitigated by its small size. Potential mechanisms responsible for these findings include differences in material properties, white matter tract orientation or deformations experienced in the older brain that are protective. Previously we incorporated tract and age-related constitutive property differences into a computational

model to evaluate the contributions of these factors, and found smaller tract-oriented deformation thresholds for acute axonal injury in the newborn than pre-adolescent piglets (Sullivan et al., 2015). Future studies should focus on the biological and physiological mechanism responsible for the vulnerability in the newborn.

Axonal Injury Vulnerability to Sagittal Head Rotations

MOI may be considered a weighting factor for each axis when predicting injury from head rotations about combinations of the x, y and z axes. In both ages, RotWork, MOI and AIV were both highest when the piglet brain was rotated in the SAG plane and lowest in the COR plane. For newborn-aged pigs, SAG head rotations were previously shown to cause global reductions in cerebral blood flow, persistent axonal injury and significant functional deficits, which were absent following COR and AXI rotations (Eucker et al., 2011; Sullivan et al., 2013). Similarly, newborn-aged pigs rotated in the SAG direction had significantly longer unconscious durations than the sham group, as did AXI head rotations at similar angular velocities (Eucker, 2011). For the 2 month old pigs, SAG had comparable mean AIV (at 6 hours post-injury) to AXI over a range of angular velocities, but SAG was the only direction with significantly longer time to return of pinch reflex (return to consciousness) compared to sham (Maltese, 2012b). Finite element simulations of rapid head rotations in the pig reveal that white matter tract orientation relative to the deformation field may be a key driver of head rotation direction-dependent axonal damage (Sullivan et al., 2015), whereby larger stretching along white matter tracts produces higher AIV. We propose that MOI and white matter tract orientation both contribute to axonal vulnerability to sagittal head rotations in the pig.

The translational applications of our results from pig to human must incorporate differences in brain size, architecture and tissue properties. In the nonhuman primate, more severe brainstem injury was observed following coronal head rotations, compared to horizontal and sagittal rotations (Gennarelli et al., 1982, Gennarelli et al., 1987). The orientation of white matter tracts and brainstem may account for discrepancy between bipedal non-human primates and quadrupedal pigs. The presence of the cerebrospinal fluid-filled pontine cistern that separates the primate brain stem from the skull in the sagittal plane may dampen stresses caused by sagittal rotations in the primate relative to the piglet. These cross-species direction-dependent responses are important avenues of future study.

Fortunately, well-correlated pig brain development timelines to humans allows us to draw valuable insight into biomechanical changes across age in the piglet that may be relevant to the human child. For both pigs and children, we observed that MOI (or resistance to rotational motion) about the axis corresponding to SAG rotations was largest at all ages, compared to COR or AXI. Because SAG rotations correlated with the largest volume of axonal injury in the piglet, we speculate that SAG rotations would cause the most severe axonal injury in the human child compared to other axes, if important white matter tracts in pigs and humans have similar spatial orientation. Future studies should test this hypothesis with human study data.

Limitations

We note several limitations in our study. First, the sample sizes for pigs and humans are small and we assumed normality in our analyses. Samples sizes per direction are also uneven. We recommend more data be collected to validate the importance of MOI in predicting direction-sensitive axonal injury in pigs and humans. Second, we estimated the MOI of the piglet head for both ages using finite element models based on magnetic resonance imaging of a single animal per age. There was inherent biological variance in the MOI from animal to animal that was not accounted for in this study, however we found that the brain mass coefficient of variation to be less than 10% for both ages. Future studies could include individual MOI to evaluate increased accuracy of RotWork correlations with axonal injury. Third, in order to calculate critical velocity and acceleration values specific to both piglet age groups for BRIC and Revised BrIC, we used mass-scaling laws (Ommaya, et al., 1967), which assume similar brain shape and composition across species. We acknowledge the complexity and challenge to the translation of our work, performed in pigs, to humans due to differences in brain size, shape and tissue properties. The conclusions drawn from Fig. 3 are limited because the published sample size is small, and more acute histopathological data are needed to definitively assess whether MOI is useful for predicting direction-sensitive axonal injury in humans. Few human studies report axonal injury volumes immediately following a single TBI, without complications from ischemia or previous brain injuries. Finally, our study was limited to acute axonal injury, and future studies should investigate if RotWork is predictive of sustained (chronic) axonal injury.

Conclusions

Rotational kinematic injury metrics that include MOI, such as Rotational Work (RotWork), strengthen the predictive relationship between head movement and acute axonal injury by accounting for the directional-dependence of axonal injury. SAG rotations have the largest MOI and RotWork in pigs and, due to the white matter tract orientation, have the largest AIV. If tracts are aligned similarly in humans and because children also have a large MOI in the SAG direction, we would expect that SAG rotations may create more severe acute axonal injury in children. For the same MOI or Rotational Work, we find that newborn brains have more axonal injury than pre-adolescent brains. We conclude that head injury kinematic metrics should use rotational kinematics and MOI to enhance directional-sensitivity of brain injury predictions, and future studies should identify age-specific metric thresholds for brain injury in children.

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Significance

Traumatic Brain Injury (TBI) disproportionately affects millions of children each year and costs millions of dollars in healthcare. The ability to predict pediatric TBI from head movement metrics during recreation and transportation is critical to effective design of child safety equipment and accurate assessment of brain injury risk. The severity of TBI is influenced by the magnitude and direction of head movement. We have developed and assessed novel rotational head kinematic metrics as predictors of acute axonal pathology in the immature brain that show enhanced predictive capability over previously published metrics for two age groups.

Figure 1.

Figure 3.

Table 1

Sample size, mean and standard deviations of average peak angular velocities for porcine subjects.

	Coronal VEL _{avg} (rad/s)	Axial VEL _{avg} (rad/s)	Sagittal VEL _{avg} (rad/s)
Newborn Pig (average brain mass = 35.74 g)	199.81 ± 17.76 (n=6)	171.65 ± 29.03 (n=21)	158.66 ± 2.21 (n=5)
Pre-adolescent Pig (average brain mass =81.11 g)	170.72 ± 12.12 (n=5)	142.27 ± 18.47 (n=9)	126.08 ± 21.25 (n=3)

Table 2

Rotational Head Injury Metric	Use moment of inertia	3–5 day old piglet			Pre-adolescent piglet		
		R ²	p-value	Slope	R ²	p-value	Slope
VEL ₁	No	0.132	0.04056 *	6.4278e–3	0.022	0.570	2.872e–3
ACCEL ₁	No	0.199	0.0105 *	1.6743e–5	0.146	0.134	6.061e–6
RIC36	No	0.068	0.1490	1.955e–10	0.227	0.053	4.923e–10
HIP	Yes	0.677	<0.0001 *	8.100e–7	0.405	0.008 *	3.925e–8
BRIC	No	0.117	0.0558	1.4760	0.396	0.0068 *	0.8404
Revised BrIC	No	0.004	0.7205	–0.18395	0.030	0.5034	–0.3812
PRHIC36	Yes	0.280	2.203e–3 *	4.778e–04	0.610	0.0002 *	4.339e–6
RVC1	No	0.125	0.0474 *	9.58e–3	0.233	0.058	8.822e–3
RotKE	Yes	0.717	<0.0001 *	1.377e+3	0.457	0.0029 *	5.927e+2
RotWork	Yes	0.632	<0.0001 *	7.02	0.600	0.0003 *	0.92797
rKE	Yes	0.601	<0.0001 *	2.559	0.391	0.0096 *	0.658

Table of all rotational head injury predictors (and whether moment of inertia in their calculation), R² values (greater than 0.5 shown in bold), p-values (asterisk indicates p-value <0.05) and slopes from separate linear regressions with AIV in 3–5 day (n=32) and 2 month old (n=17) piglets.