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S.I. : Concussions

Concussion Prone Scenarios: A Multi-Dimensional Exploration in Impact Directions, Brain Morphology, and Network Architectures Using Computational Models

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Abstract—While individual susceptibility to traumatic brain injury (TBI) has been speculated, past work does not provide an analysis considering how physical features of an individual's brain (e.g., brain size, shape), impact direction, and brain network features can holistically contribute to the risk of suffering a TBI from an impact. This work investigated each of these features simultaneously using computational modeling and analyses of simulated functional connectivity. Unlike the past studies that assess the severity of TBI based on the quantification of brain tissue damage (e.g., principal strain), we approached the brain as a complex network in which neuronal oscillations orchestrate to produce normal brain function (estimated by functional connectivity) and, to this end, both the anatomical damage location and its topological characteristics within the brain network contribute to the severity of brain function disruption and injury. To represent the variations in the population, we analyzed a publicly available database of brain imaging data and selected five distinct network architectures, seven different brain sizes, and three uniaxial head rotational conditions to study the consequences of 74 virtual impact scenarios. Results show impact direction produces the most significant change in connections across brain areas (structural connectome) and the functional coupling of activity across these brain areas (functional connectivity). Axial rotations were more injurious than those with sagittal and coronal rotations when the head kinematics were the same for each condition. When the impact direction was held constant, brain network architecture showed a significantly different vulnerability across axial and sagittal, but not coronal rotations. As expected, brain size significantly affected the expected change in structural and functional connectivity after impact. Together, these results provided groupings of predicted vulnerability to impact—a subgroup of male brain architectures exposed to axial impacts were most vulnerable, while a subgroup of female brain architectures was the most tolerant to the sagittal impacts studied. These findings lay essential groundwork for subject-specific analyses of concussion and provide invaluable guidance for designing personalized protection equipment.

Keywords—Functional connectivity, Kuramoto model, Finite element model, Subject-specific analysis.

INTRODUCTION

More than two million individuals experience a concussion (also known as mild traumatic brain injury) every year in the United States.[53] Despite the increased awareness and promising progress in the past decades to establish biomarkers for concussion,[8, 34] to investigate the potential causes of cognitive impairments in some concussion patients,[28, 50] and to improve protective equipment to reduce its incidence,[19] the underlying pathophysiology for concussion is not fully understood. Experimental work demonstrates the severity of diffuse brain injuries is generally associated with the magnitude of head kinematics[41, 42, 48] and implies a threshold exists that separates safe from un-

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safe impacts. However, concussions have been diagnosed in athletes within a large range of impact severity,[59] and it is common to observe impacts of similar severity will produce concussions in some individuals but not others. With improvements in technology to accurately measure the exposure during an impact in contact and non-contact sports,[23, 51] these datasets will become increasingly important to capture the range of real-world impacts associated with concussion.

Certainly, one primary factor for determining relative injury risk is the characteristics of external loading inputs to the head and the resulting kinematics. With similar magnitudes of impact severity, different impact directions can result in significantly different biomechanical responses according to human *in-situ* experiments and finite element (FE) simulations[1, 69] and would significantly affect physiological and neurocognitive outcomes as reported in experiments on non-human primates,[24, 60] pigs,[9, 15] and piglets.[65]

A second, much less studied, aspect associated with concussion risk is the many inter-subject variations that exist in a population. Even simple anatomical features of the brain, such as its size and general shape, show a wide range in the population. These physical differences motivated studies to investigate the influences of brain sizes by global scaling.[37] In addition, considerable variability in white matter architecture exists among the population.[12] Subject-specific changes to white matter architecture may explain at least a portion of variants on biomechanical responses[25] and result in diverse injury outcomes of a head impact based on brain network analysis.[4] Admittedly, the factors mentioned above are only some of the variants that might affect injury susceptibility. Several additional features, some of which relate to the physical properties of the braincase and its contents and others relating to the potential variation in pathobiological response among a population, can contribute further to differences in injury risk.

In the past decade, many advances emerged to facilitate a more thorough examination of individual risk to head impact. Advanced mesh morphing techniques efficiently generate subject-specific models from a generic FE model template while maintaining the same high mesh quality.[26, 70] Likewise, voxel-based modeling techniques are a rapid and efficient way to develop anatomically accurate FE models by directly converting voxels of neuroimaging to hexahedral elements.[27, 46] Although these subject-specific FE models were able to address the inter-subject variability introduced by brain anatomy from a biomechanical perspective, the influences of these variables on the susceptibility to brain injuries cannot be assessed by FE modeling alone. These existing models are effective to relate an impact to the expected areas of tissue damage throughout the brain, especially in combination with tissue-specific injury criteria. However, these models are unable to predict the functional consequences of an impact and therefore can only provide a limited estimation of how one impact may be more damaging than another.

In response to this analysis gap, we take advantage of past work which studies the brain as a complex network, whose cognitive functions are dictated by the oscillatory and coherent activity of anatomically distinct brain regions.[20] The structural links among brain regions are revealed through advanced brain imaging, and the functional coupling among brain areas is measured directly in human subjects. Models to merge brain structure and function exist, and are utilized to simulate biophysically plausible neural activity and mimic the synchronization and self-organization phenomena of the brain network.[11, 22, 40] These large-scale computational models, coupled with hemodynamic models, have enriched our understanding of the alterations on functional networks when the brain's structure is attacked by diseases like tumors, Alzheimer's disease, and traumatic brain injury.[3, 10, 18, 32, 66] Recently, an interdisciplinary computational model for predicting traumatic brain injury was developed by coupling biomechanical models with neurodynamic models,[73] which provides a novel perspective to studying the brain's organization and functioning following an injurious impact and a tool for characterizing these variabilities using a common scale—functional connectivity (FC).

In this study, we examine the relative importance of head impact direction, brain morphology, and anatomical connectivity on the susceptibility of different subpopulations to head impacts that could cause concussion. Rather than attempting to identify the relative risk from every possible impact for every individual brain architecture, we concentrate our efforts on studying idealized impacts that are approximately at the threshold for causing a concussion, and we studied the response to these impacts for five prototypical brain (white matter) architectures and seven brain sizes. Our work shows the most prominent features that can disrupt the brain functional connections after impact and finds the important variables to consider when studying subject-specific concussion risk and thus provide guidelines for developing better personal head protection equipment.

METHODS

A complete overview of the methods can be found in Fig. 1.

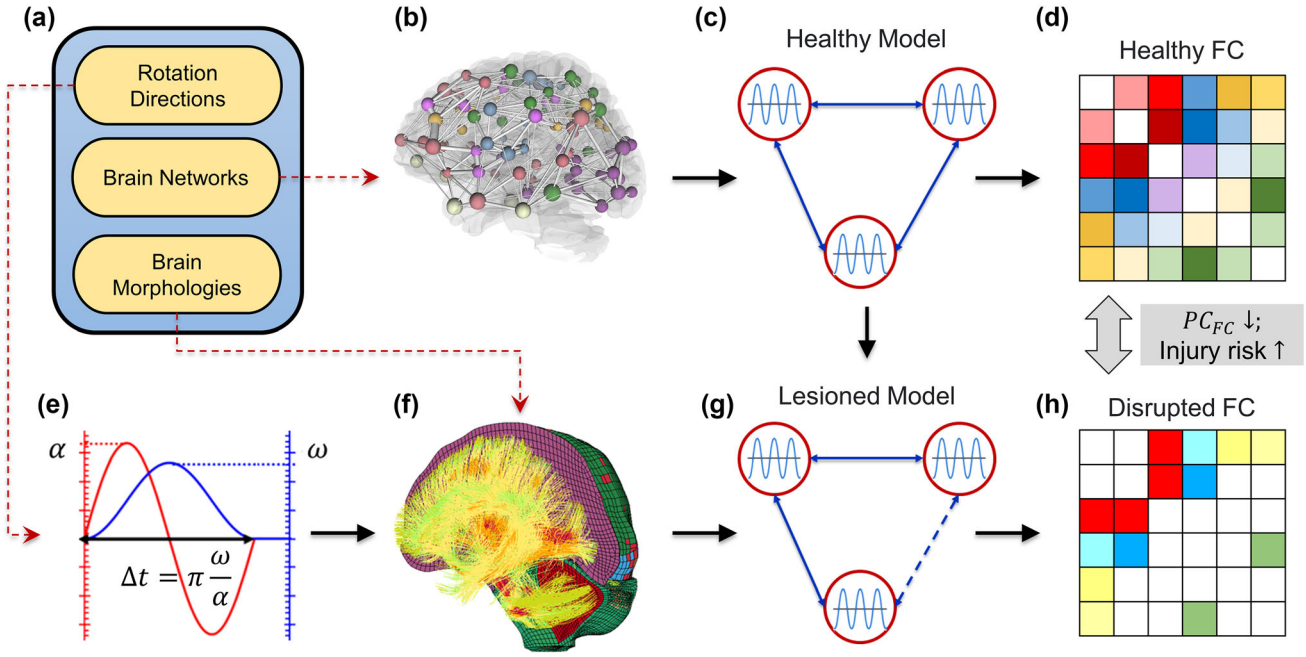

FIGURE 1. Overview of methods. (a) Variables in this parametric study; (b) Structural connectivity; (c) Computational neurodynamic and hemodynamic models of the healthy subject; (d) Simulated functional connectivity of the healthy subject; (e) Idealized sinusoidal head kinematic pulse; (f) Finite element brain model; (g) Computational neurodynamic and hemodynamic models following an impact; (h) Simulated functional connectivity following an impact, the alterations of the simulated FCs after an impact indicate the risk of injury. *FC* functional connectivity, PC_{FC} Pearson correlation score that measures the changes between healthy and disrupted functional connectivity matrices.

Computational Modeling

Finite Element Modeling

We used the anisotropic FE brain model developed in Wu *et al.*[70] with macroscale anatomy representative of the 50th percentile male (based on anthropometry: 175 cm height, 78 kg weight) as the baseline model. Axonal tracts were explicitly modeled as one-dimensional cable elements based on a population-averaged tractography atlas. Both the tracts and brain tissue were modeled using a hyper-viscoelastic constitutive model calibrated with brain-tissue experimental data. In the model, elastic membranes envelop the brain with fluid-filled cavities modeled as linear viscoelastic materials. The FE model was previously evaluated with brain deformation under blunt impacts and rapid rotation,[2, 70] and demonstrated good biofidelity compared to the other state-of-the-art models.

Kuramoto Model and Hemodynamic Model

The resting-state neural activity was simulated using the time-delay Kuramoto model of oscillators,[38, 75] whose coherent behavior obeys the following delay differential equations.

$$\dot{\theta}_i = \omega_i + K\sum_{j=1}^{N} C_{ij}\sin(\theta_j(t-\tau * D_{ij}) - \theta_i(t)), i = 1, \dot{s}, N$$

In which the oscillators, whose phases (θ_i) were initialized randomly with uniform distribution, correspond to cortical regions of interest (ROI) and connect based on information of network architectures. ω_i is the intrinsic frequency of each oscillator, uniformly distributed with 60 Hz mean and 1 Hz standard deviation to simulate fast oscillatory activity in the gamma frequency band.[10] C_{ij} is the coupling strength between nodes i and j, determined by structural connectivity normalized by the mean non-zero edge weights. D_{ij} is the distance matrix normalized by the mean fiber length. The global coupling strength (K) and mean delay (τ) are 7.6 and 5.9 ms respectively to achieve moderate synchronization and high degree of metastability,[73] where the model best approximates empirical resting-state functional magnetic resonance imaging.[11, 22] The Balloon–Windkessel hemodynamic model[21] was used to simulate the blood-oxygen-level-dependent (BOLD) signal by taking $\sin(\theta_i)$ as neural activity input. Simulations were run for 200 s, the first 20 s were discarded to remove transient effects, and the remaining 180 s of the simulated BOLD were used to calculate the simulated FC matrix based on the Pear-

son correlation between these regional activities. The model assumes that neuronal ensembles exhibit self-sustained oscillations in the gamma frequency band and the local gamma neural activity alone can induce correlations at the BOLD level. Several electrophysiological studies have reported the existence of oscillations in this frequency band[7] and much experimental and theoretical evidence supports a strong association between gamma-band modulations and BOLD variations.[39, 47, 62]

Lesion Method

Mounting evidence indicates concussion involves a range of axonal pathophysiology because of mechanical damage to the white matter tracts.[63, 64] Correspondingly the functional deficits induced by concussion would be a result of lesions to the edges from the neural network perspective. The edge-based method detailed in Refs. [73] was used to correlate strain results from the FE simulations to the alterations in the structural brain networks. For a given head impact, the maximum tensile strain of the axonal tracts connecting each pair of ROIs was computed, resulting in a maximum axonal strain (MAS) matrix (100 × 100). Based on the *in-vivo*, tissue-level, mechanical risk function of axonal damage with respect to axonal strain ($P(MAS)$),[5] the structural connectome ($\overline{C}_{ij}$) after a certain impact can be weakened based on the strain matrix in each edge: $\overline{C}_{ij} = C_{ij}(1 - P(MAS))$. Subsequent neurodynamic and hemodynamic simulation using the lesioned structural connectome generated the disrupted functional connectivity after the impact. Lesion effects could then be evaluated by comparison of the disrupted and healthy functional connectivity matrices.

Parametric Space

Loading Conditions

We applied idealized rotational pulses of sinusoidal pulse shape to the FE models about each anatomical axis of the head to better characterize the influence of impact directions on the susceptibility to concussions. The x-axis was defined along the intersection of the Frankfort and mid-sagittal planes in the posterior-to-anterior direction (corresponding to coronal rotation). The y-axis was defined along the line joining the two superior edges of the auditory meatus in the left-to-right direction (corresponding to sagittal rotation). The z-axis is laid in the mid-sagittal plane perpendicular to the Frankfort plane and in the superior-to-inferior direction (corresponding to axial rotation). As concussion is widely understood to be an injury primarily caused by rotational motion, translational kinematics were not investigated in this study.[43] The selected angular acceleration and angular velocity magnitudes were $\omega = 60\text{rad/s}$, $\alpha = 5\text{Krad/s}^2$, informed by existing concussion data,[52, 58, 61, 74] and represent a relevant level of head kinematics for a high probability of concussion.

Variability in Brain Morphology

To reflect the variability of brain morphology and connectivity in the young adult population, we used high-quality neuroimaging data from the healthy participants of the human connectome project (HCP), including over 1200 healthy adults with a range of ages from 22 to 35 years. To reduce the dimension and complexity of the parametric space, we characterized the variability of brain morphology using a single metric: intracranial volume. Male and female subjects with the closest intracranial volume to the 5th, 50th, and 95th percentile in the HCP database were selected as samples to reflect the variation in brain morphology (Fig. 2).

Subject-specific FE models were generated by mesh morphing from the baseline FE model. The morphing technique was implemented to precisely match the inner cranial geometry of the FE brain models to the target subjects. An in-depth explanation of the morphing methodology was presented in Alshareef *et al.*[2]. The dura surface was used to match the segmented brain geometry from magnetic resonance imaging (MRI) through rigid-body alignment and affine transformation. The registration between the two surfaces was used to interpolate a 3D volume registration, using radial basis functions with thin-plate spline, to morph the baseline model to match the subject-specific brain. We used this technique to generate morphed models with comparable element quality to the baseline brain model.

Variability in Structural Networks

We used the diffusion MRI from the same HCP data to infer the variability of structural connectivity (SC) in the young adult population. SC matrices were generated using Schaeffer 100 parcellation following the same procedure described in Refs. [73]. A recent study[55] showed the SC matrices in HCP data ($n = 1065$) can be categorized into four non-overlapping groups (two male and two female groups) by performing modularity analyses. A representative structural network was selected for each group by identifying the closest geodesic distance[67] to the average SC matrix for the group (the mean weights of each edge). A baseline structural network was also selected

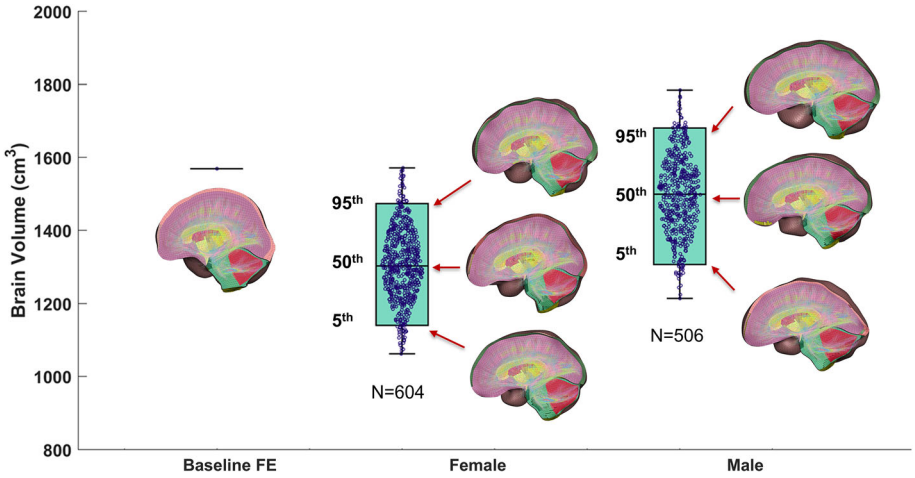

FIGURE 2. Brain volume variations and morphed subject-specific finite element models. F95:95th percentile female, F50:50th percentile female, F5:5th percentile female, M95:95th percentile male, M50:50th percentile male, M5:5th percentile male, *B baseline FE model, the baseline FE model represents the brain of a 50th percentile male based on height and weight.**

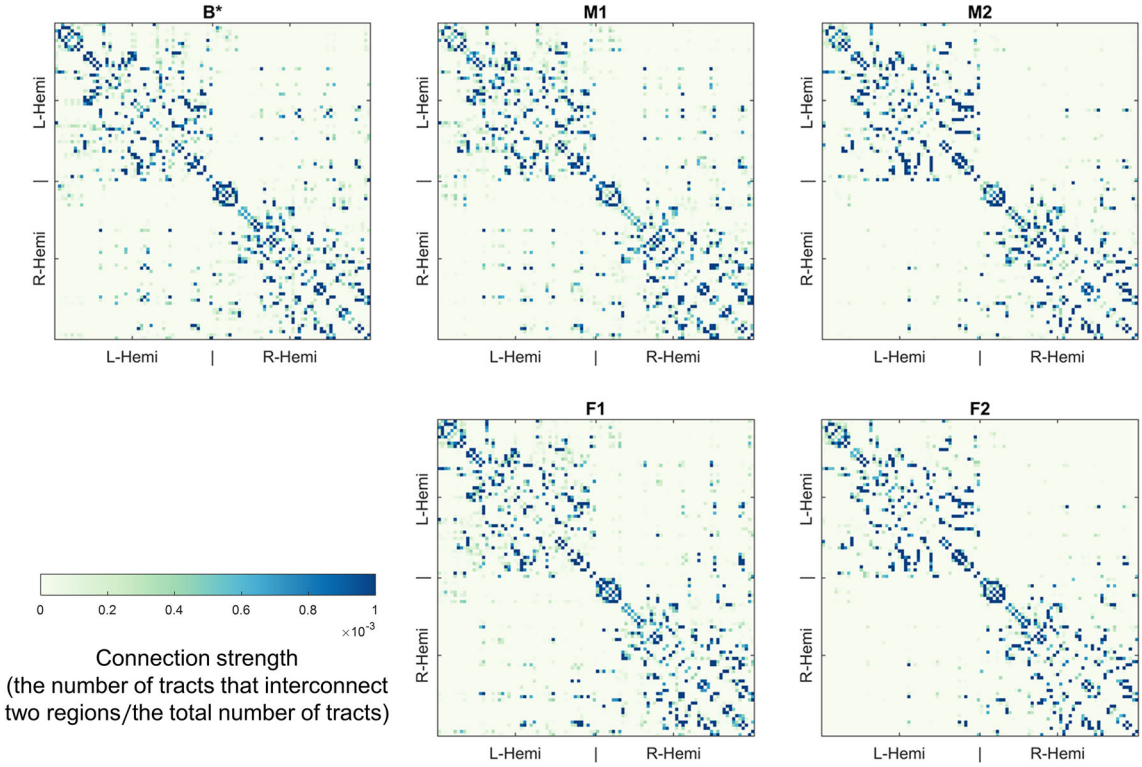

FIGURE 3. Representative matrices of structural connectivity in the HCP database. *B baseline subject 108020, *M1* male 1 module, *M2* male 2 module, *F1* female 1 module, *F2* female 2 module.**

as its closest geodesic distance[67] to the average SC matrix of the whole HCP database. Together, five structural networks (Fig. 3) and their distance matrices (D_{ij}) were used to represent the variability in the young adult population and perform neurodynamic simulations.

Simulation Matrix

Combinations of the independent variables lead to a total number of 108 simulated scenarios (Fig. 4). Among them, the healthy subjects of different brain sizes are repeated scenarios, and the total number of unique simulations is 87. All FE simulations were solved using LS-DYNA (v971 R9.2.0, double precision; LSTC, Livermore, CA). The neurodynamic and hemodynamic simulations were solved using the Runge–Kutta methods implemented in MATLAB (2019b, The MathWorks Inc., Natick, MA).

Data Analysis

The integrated FE, neurodynamic, and hemodynamic simulations predicted the simulated functional connectivity for each scenario. The differences between simulated FC of the impact scenarios and their healthy status FC were quantified by the Pearson correlation (PC_{FC}) score through unrolling the FC matrices into vectors. References [73, 74] showed a good negative correlation between the Pearson correlation of FC and the probability of injury by reconstructing head impacts in professional American football athletes. Lower PC_{FC} indicates a higher risk of brain injury for the specific impact scenario. ANOVA (analysis of variance) analysis with hierarchical type II sums of squares method was used to test the significance of the variables after fitting a multiple regression model between PC_{FC} and the predictors (direction, networks, sizes) and their interactions. During the ANOVA analysis, direction and networks were considered as categorical variables and size was considered as a continuous variable. Once the variables were deemed significant, Kruskal–Wallis tests with Bonferroni correction were conducted between all categories to elucidate the differences.

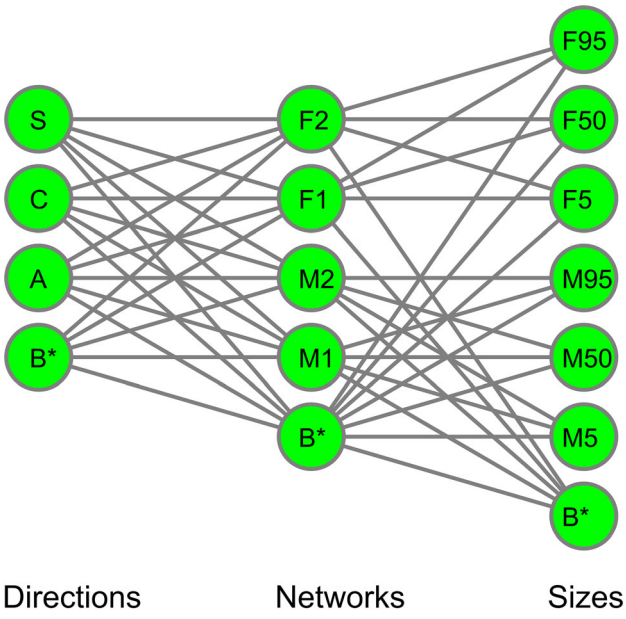

FIGURE 4. Summary of the simulation matrix. Each path represents a simulated scenario. In the 'Directions', *S* sagittal, *C* coronal, *A* axial. *B non-impact baseline simulation; In the 'Networks', *F2* female group 2, *F1* female group 1, *M2* male group 2, *M1* male group 1; *B** baseline subject 108020; In the 'Sizes', *F95* 95th percentile female, *F50* 50th percentile female, *F5* 5th percentile female, *M95* 95th percentile male, *M50* 50th percentile male, *M5* 5th percentile male, *B** baseline FE model.**

RESULTS

Pearson Correlation Analysis Results

The relationship between the variables, their interaction, and Pearson correlation scores (PC_{FC}) was well-characterized by a multiple regression model ($R^2 = 0.917$). The results of the subsequent ANOVA (Table 1) indicate that impact direction contributed significantly to the model ($p < 0.05$) and explain 67.1% of the variability. The other significant factors ranked by their contribution percentage were the interaction between impact direction and network architecture, brain size, and the interaction between impact direction and brain size ($p < 0.05$). Since impact direction was the most significant factor, we further conducted ANOVA for each impact direction. The variability was contributed largely by network architecture ($> 50\%$) for axial and sagittal impacts, while the variability during coronal impacts was mainly explained by brain size.

For comparison, similar ANOVAs were also done by considering the Pearson correlation between the SCs before and after impact (PC_{SC}) as the continuous outcome. Although the resulting significant variables were almost consistent with those of PC_{FC} analysis, the variability was less explained by the network architecture, which indicated the variation increased when the neural regions of the structural network interacted and coordinated to form a functional network.

The direction-dependent results showed the increased disparity of FC from the healthy status when the head motions change from axial to sagittal to coronal with decreased PC_{FC} scores (Fig. 5a). This result indicated the risk of injury was higher in axial rotation than that in sagittal rotation, and coronal motions had the lowest risk of injury. The size-dependent results showed decreased PC_{FC} scores, thus increased injury susceptibility as the brain size increased, although the influence of size on injury susceptibility was less significant than that of impact direction (Fig. 5b). When the results were grouped by different directions, the size-dependent injury suscep-

TABLE 1. Summary of ANOVA results.

Directions	Variables	PC_{FC}			PC_{SC}		
		DF	P-value	CP	DF	P-values	CP
All	Direction	2	0.000	67.1%	2	0.000	87.2%
	Network	4	0.079	1.5%	4	0.173	0.2%
	Size	1	0.000	7.7%	1	0.000	5.6%
	Direction: Network	8	0.000	10.2%	8	0.002	0.7%
	Direction: Size	2	0.000	4.5%	2	0.000	5.0%
	Network: Size	4	0.386	0.7%	4	0.511	0.1%
	Error	47		8.1%	47		1.2%
Axial	Network	4	0.001	53.1%	4	0.112	5.9%
	Size	1	0.003	19.2%	1	0.000	84.6%
	Network: Size	4	0.215	9.4%	4	0.776	1.1%
	Error	13		18.3%	13		8.3%
Coronal	Network	4	0.001	26.6%	4	0.386	12.4%
	Size	1	0.000	51.2%	1	0.001	49.1%
	Network: Size	4	0.03	11.9%	4	0.901	2.8%
	Error	13		10.3%	13		35.7%
Sagittal	Network	4	0.002	54.0%	4	0.000	31.6%
	Size	1	0.143	4.2%	1	0.000	56.6%
	Network: Size	4	0.072	19.2%	4	0.019	6.8%
	Error	13		22.5%	13		5.0%

DF degree of freedom, *CP* contribution percentage.
Darker green color indicates a higher contribution percentage, and darker yellow color indicates smaller P-values.

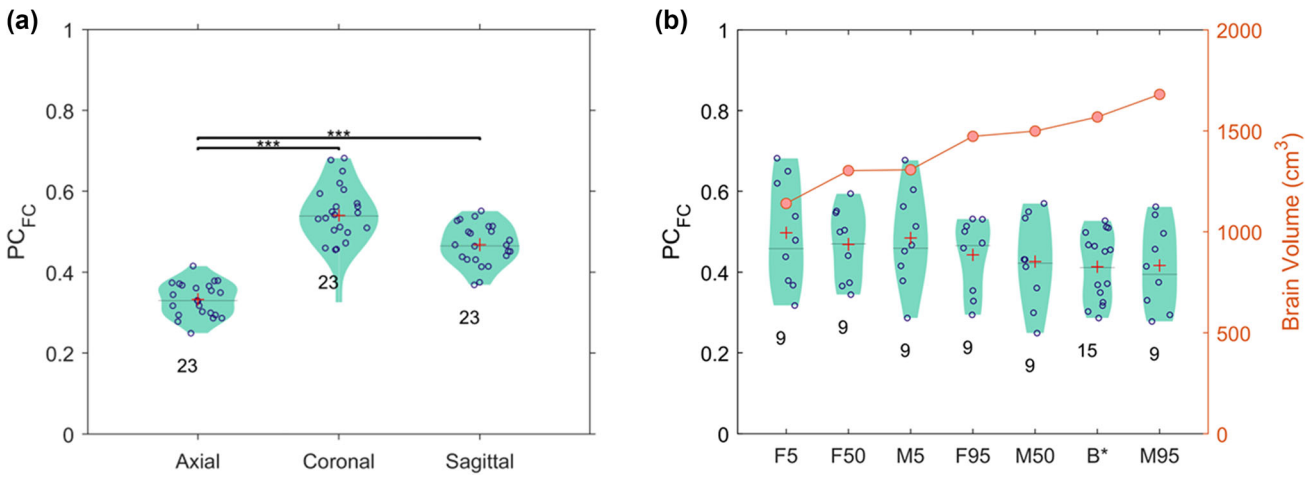

FIGURE 5. Distribution of Pearson correlation scores between lesioned and healthy functional connectivity. (a) Influence of impact directions; (b) Influence of brain sizes. Stars and lines are drawn to highlight significant differences between pairs of groups according to Kruskal–Wallis one-way analysis of variance with Bonferroni correction: *$p \leq 0.05$, **$p \leq 0.001$, ***$p \leq 0.0001$. The number of data points in each category is indicated below the violin.

tibility was more pronounced with a negative correlation between brain size and PC_{FC} in coronal scenarios (Fig. 6). When distinguishing by directions, the influence of network architecture also emerged, the PC_{FC}

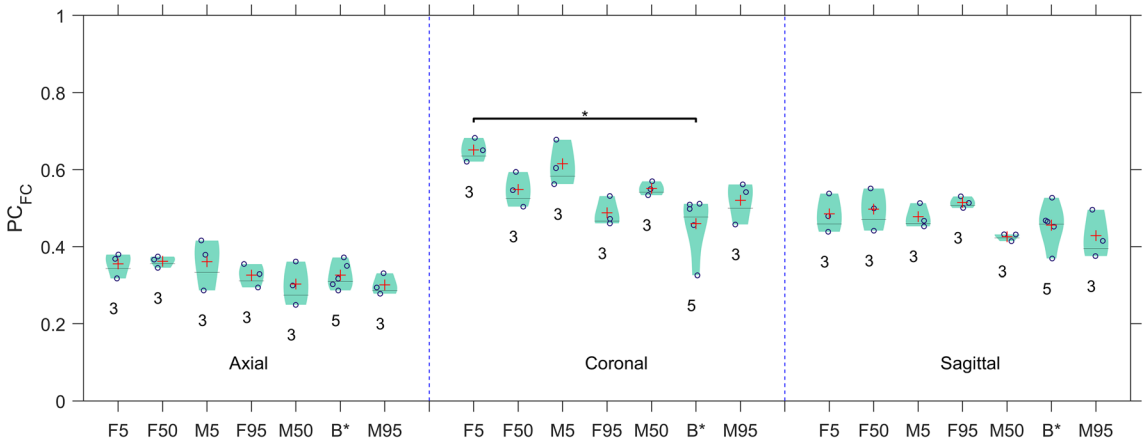

FIGURE 6. Distribution of Pearson correlation scores between lesioned and healthy functional connectivity to show the influence of brain sizes per impact direction. Stars and lines are drawn to highlight significant differences between pairs of groups according to Kruskal–Wallis one-way analysis of variance with Bonferroni correction: *$p \leq 0.05$, **$p \leq 0.001$, ***$p \leq 0.0001$. The number of data points in each category is indicated below the violin.

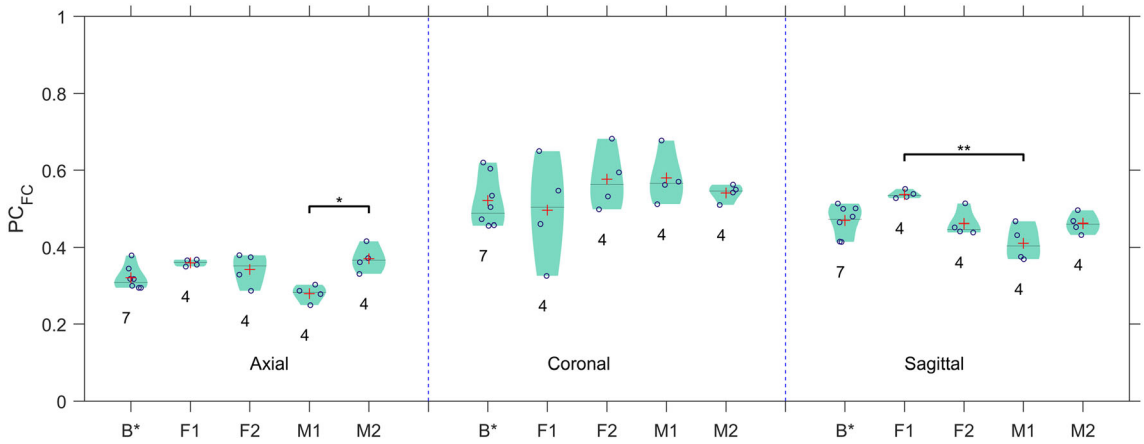

FIGURE 7. Distribution of Pearson correlation scores between lesioned and healthy functional connectivity to show the influence of brain networks per impact direction. Stars and lines are drawn to highlight significant differences between pairs of groups according to Kruskal–Wallis one-way analysis of variance with Bonferroni correction: *$p \leq 0.05$, **$p \leq 0.001$, ***$p \leq 0.0001$. The number of data points in each category is indicated below the violin.

scores of some types of network architecture are significantly different from the others under certain rotations (Fig. 7). For example, the male 1 module (M1) is more vulnerable than male 2 module (M2) in axial rotation; the female 1 module (F1) has a higher tolerance to injury than M1 in sagittal rotation.

Supplemental Analysis

We conducted several reliability analyses as detailed in the supplemental material to examine the effect of (a) time delay, (b) damage thresholds/injury severities, (c) lesion method (node-based method as detailed in Refs. [73]), (d) sex as a variable and considering the sex-differences in axonal damage threshold. These results confirmed that (i) the greatest variability was attributed to impact direction, and under specific impact direction, injury susceptibility could be affected by brain size and/or network architecture; (ii) the variability of functional susceptibility (PC_{FC}) contributed by network differences was more significant than the variability of structural susceptibility (PC_{SC}) contributed by the variances in network architecture. These results also showed that (i) the consideration of time delay and nodal lesion had minimal effects on the findings; (ii) the influence of the structural network may also depend on injury severity, and differences caused by network architectures started to disappear when the injury becomes more extensive; (iii) The significance of sex as a covariate only appeared when assuming the female axonal damage threshold was lower than the male axonal damage threshold. For example, when the female threshold was lowered by 5% strain (from 15 to 10%), the sex only explained

7.9% of the variation, far less than the 45.1 and 15.4% contributed respectively by impact directions and network architectures.

DISCUSSION

This work investigated the influence of impact directions, brain morphology, and network architectures on the susceptibility of concussion among the adult population using computational modeling. Consistent with past work, our results show a primary effect of impact direction on the outcome (predicted by functional connectivity) after impact, with axial motions more injurious than either sagittal or coronal rotations. The heterogeneous outcome of an impact could also be explained by brain morphology alone or the combination of brain morphology and impact direction. Although not statistically significant, larger brains generally had a higher risk of injury. Statistically, the baseline male brain (B) was more vulnerable to the small female brain (F5) under coronal impact. In certain loading directions, different network architectures also contribute to heterogeneous injury outcomes, but determining if there exist specific types of network architectures that are always more vulnerable to concussion in real-world loading conditions remains to be elucidated.

The direction-dependent susceptibility of brain injury found in this study is consistent with the biomechanical responses of human *in-situ* brain experiments and FE simulations,[1, 69] assuming brain deformation correlates with injury risk. However, this finding is unable to corroborate with the *in-vivo* experiments on non-human primates and piglets. Gennarelli *et al.*[24] found that non-human primates are most susceptible to axonal damage in coronal rotation, most tolerant in sagittal motions, with axial motion showing an intermediate level of impairment. In another primate study, however, coronal impact tolerance of concussion was estimated about twice as high as sagittal impact tolerance.[60] More recent studies on piglets show coronal rotations induce lower axonal injury volumes than axial and sagittal head rotations, and sagittal rotations led to increased behavioral deficits compared to axial rotations.[65] These findings are not consistent with the current study and the past human *in-situ* and FE studies, but the significant inter-species differences in the brain–skull anatomy and relative brain/brainstem orientation may provide the most direct explanation of these differences. For example, piglets lack pronounced falx cerebri, a meningeal partition between the two hemispheres in the human brain, which was believed to significantly influence the biomechanical response.[30, 31] The contradictory results would also result from different viewpoints on TBI severity. The above studies classified the severity of TBI based on either subjective symptoms as outcomes or quantification of brain tissue damage, while this study assesses the severity of TBI by the quantitative changes of functional connectivity. Our study approaches the brain as a complex network in which neuronal ensembles act in concert to ensure normal function, therefore, both the anatomical damage site and its topological characteristics within the brain network play an essential role in disrupting brain function and causing injury. For these network alterations to become clinically useful, though, much more multimodal quantifiable data (including imaging and biomarkers) is required to unravel exactly how network organization changes in response to different types and stages of brain damage, as well as a consensus approach on network construction and analysis. Once these obstacles are resolved, the network method carries the potential to allow more objective diagnosis, to monitor recovery processes, and to evaluate effective treatment options.

The size of the brain is a significant factor influencing injury susceptibility. Larger brains tend to have an increased risk of injury, though not necessarily following a strictly monotonic increasing trend due to the other factors. Influences of brain size on mechanical brain response have been long known and can be analytically explained by dimensional analysis and scaling laws.[49, 71] Characterizing morphological variations by intracranial volume is a simplification and leaves out several other factors influencing the brain's biomechanical responses. The shape of the brain can be very different, as evident by the six HCP specimens selected in this study (Fig. 2), although its influence may be minimal according to previous studies.[2] The current study also lacks the consideration of subject-specific internal brain anatomy[26] and physical properties of the brain,[76] as well as the brain–skull interface,[78] to alter the biomechanical response of the brain. Quantifying the variation of these factors in the population is a challenging open question and requires further investigation and better data collection.

Besides the main study variables (loading directions, size, network architecture) investigated, there is growing interest in sex as a biological variable affecting TBI vulnerability. The prevalence of concussion in some sports-related and military-related activities is reported to be higher in females than males but the overall picture is not clear with complicated and often contradictory findings.[29, 45] Whether there are differences in outcome from TBI in males and females can be approached by examining whether there are correlations between sex and the independent variables studied here. First, there may be differences in loading

conditions related to how males and females acquire their injuries, females are more likely to receive injuries from assault or violence, while males are more likely to receive work-related injuries and motor vehicle collisions.[14] Second, brain size is correlated with sex, as males normally have larger brains (Fig. 2). Third, the sex category is not a major predictor of the variability of human brain network architecture.[55] Fourth, sexual dimorphism of axon structure in the brain may also contribute to different axonal damage thresholds, as investigated in the supplemental analysis. The mixture of these factors might influence the outcome in studies of sex differences in TBI, without considering the epidemiological characterization of head impact exposure and precise characterization of the effect of sexual dimorphism, our results suggested that if the effects of size was accounted for, sex alone did not contribute significantly to the variability of brain injury risk.

Variability across structural connectivity and their potential influence on the susceptibility of concussion has been noticed in the past.[4, 25] This is the first study that attempted to quantify this effect on concussion compared to the other factors inferred by a relatively large MRI database. Despite its large sample size, the HCP subjects represent a tight demographic profile of healthy adults between the ages of 22 and 35 with twins and siblings. Thus, by using this dataset, we have likely underestimated the variations of network architectures in the general population. It will be essential to see how findings from this particular set of subjects generalize to broader age ranges. Both the functional and structural connectivity patterns seem to be similarly affected by older age and the observed changes seem to particularly affect the default mode network.[16] Another limitation of this study is only incorporating the FE models with a simplified generic mesoscopic fiber architecture extracted from the population-averaged tractography for all the scenarios. Considering the inclusion of axonal tracts only introduced minimal effects on strain outcomes in previous studies,[70, 77] the influence of the variation in fiber architecture from the biomechanical aspect is expected to be negligible.

In this study, the underlying assumption is that the disruption of functional connectivity is associated with concussion. Although growing clinical evidence suggests that TBI may cause changes in (resting-state) functional connectivity,[13, 44, 54, 68] these findings were obtained from relatively small sample sizes with a cross-sectional design. It is unknown how the brain function of the injured subjects compared to pre-injury brain function. Concussion patients were normally examined at least days post-injury in those clinical studies. It is still an open question about how significantly the length of post-injury time would affect the functional response. The validity of this connection between concussion and the functional network remains to be strictly examined. On the other hand, structural connectivity is known to shape functional connectivity, but this relationship remains complex. For example, functional connections can exist between two brain regions despite the absence of direct structural connectivity.[33] Our results did demonstrate the benefit of functional network analysis compared with structural networks as the variability contributed by the network architecture increased.

The validity of the findings in this study also depends on the fidelity of the computational models. To directly validate our models would require injury data with an amount of subject-specific information including head kinematics, diffusion and functional MRI before and after impact, and clinical outcomes. A single set of data including such information currently does not exist. Efforts have been made to construct and validate each model with full use of the data available. The brain FE model was validated using *in-situ* experimental brain deformation under high-rate rotational head motion.[2] The current model showed better biofidelity than the other two commonly used FE models (GHBMC and SIMon) when validating against approximately 5000 individual point displacement time histories from six specimens, each with four loading severities in the three directions of controlled rotation. The construction of the Kuramoto model was guided by the resting-state functional connectivity of the healthy HCP subjects.[73] The main assumption made when applying the Kuramoto model to simulate large-scale neural dynamics is that the self-sustained gamma-frequency oscillations are responsible for resting brain activity. The role of ongoing neural oscillations in the processing and perception of information across distributed neuronal ensembles is not well understood, previous research provided evidence for the relevance of different frequency band oscillations for the different mechanisms underlying multisensory processing.[36] Although the Kuramoto oscillators with a gamma-band intrinsic frequency can generate slow fluctuations (falling in the alpha and beta frequency bands) resembling magnetoencephalography data,[11] the brain is likely to operate on multiple frequency channels during rest,[17] which may require a more complex model than the Kuramoto implemented here. The lesion method was based on the correlation between axonal stretch and axonal injury demonstrated in the *in-vivo* animal model,[5] in which the MAS tolerances for the occurrence of electrophysiological impairment and the occurrence of morphological damage for axonal tracts are 15% and 17% respectively. Due to the pitfall of numerical methods, caution should be taken in applying the *in-vivo* thresholds to the FE simula-

tion.[27] To further check our results, we note the tolerance for 50% risk of concussion using the same FE model was 12.3% in terms of 95th percentile global MAS.[72] It seems plausible, therefore, that using the *in-vivo* thresholds of axonal tracts in this FE model would generate realistic injury outcomes.

We believe this work is the first study to characterize the disparities in vulnerability to concussion caused by the variations in impact directions, brain morphology, and network architectures. Our work does not attempt to consider the possibility of an individualized risk for concussion, a possibility that is raised in some previous biomechanical studies.[56, 57] Besides the factors investigated here, additional poorly understood variabilities, such as biomechanical factors (mechanical properties of brain components), pathophysiological differences[6] and neuroplasticity,[35] could also contribute to concussion tolerance but require future investigation. As a result of the limited validation data, we can only infer how important these factors could play a role in concussion relative to each other. The predicted alterations to the functional networks and the risk of concussion for a given scenario should be interpreted with caution. We showed that, in descending order of importance, impact directions, the interaction between impact direction and network architecture, brain size, and interaction between impact direction and brain size contribute significantly to the heterogeneous injury outcomes. This work highlights the prerequisite information to collect for subject-specific analyses with the ultimate goal of mitigating concussions and facilitates the development of more effective protective equipment in the long term.

SUPPLEMENTARY INFORMATION

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CONFLICT OF INTEREST

No competing financial interests exist.

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