Development of a Novel Loss of Consciousness Injury Risk Function

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ABSTRACT

Most head injury risk functions (IRFs) focus on either severe brain injuries, such as diffuse axonal injury (DAI), or concussion. In sports contexts, particular emphasis has been placed on mitigating concussion risk, especially from repetitive head impacts, due to concerns about the long-term development of chronic traumatic encephalopathy (CTE). However, in non-sporting scenarios, a single head impact resulting in even brief loss of consciousness (LOC) may pose a substantial risk of serious injury or death. This is particularly critical in environments where escape, evasion, or egress from a post-crash fire is a critical concern. This research leverages real-world head injury data collected from sports to develop an IRF for LOC, applicable to a range of different impact conditions. An existing dataset of 61 reconstructed National Football League (NFL) head injury cases was used to generate a novel tissue-level IRF. Acceleration data from each case were used to load the Imperial College London 3D finite element model of the human head. The 90th percentile maximum principal strain (MPS90) and maximum principal strain rate (MPSR90) were extracted and analyzed. Survival analysis was employed to construct an IRF quantifying the probability of a LOC based on strain in each brain region of interest. The optimal model and distribution were identified using statistical tests in accordance with ISO/TS 20459:2023. Strain rate in the whole brain, brainstem and associated brainstem nuclei emerged as the most sensitive predictor of a LOC, with an AROC of 0.75. These findings reinforce the role of brainstem strain rate as a biomechanical correlate of LOC, consistent with previous studies. A novel tissue-level injury risk function has been developed for scenarios where a LOC introduces critical secondary risks. Potential applications include aviation, motorsports, and maritime environments, where this function may support the development of kinematics-based, use-case-specific IRFs.

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INTRODUCTION

Mechanical loading of the head can cause a loss of consciousness. Loss of consciousness is the loss of awareness for seconds to hours immediately after exposure. In sports, LOC is a clear indicator of large head impacts, leading to removal from the play and longer return to play. Even a brief incapacitation following loss of consciousness can have serious or fatal consequences in scenarios such as a sailor knocked into the water, a firefighter in a burning house, or a motorsports driver trapped in a post-crash fire. However, currently there are no strategies, e.g. refined helmet

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designs, for preventing loss of consciousness. This is partly because we still do not know what level of mechanical loading can produce a LOC.

Risk functions are developed to quantify the relationship between characteristics of head mechanical loading and the probability of brain injury. They relate mechanical measures such as peak linear acceleration to the probability of a defined outcome, such as skull fracture. In fact, the first and widely used injury risk functions were developed to predict the risk of skull fracture from head linear acceleration (Hutchinson et al., 1998). However, these risk functions have several limitations; they assume a link between skull fracture and brain injury, rely on linear acceleration data from frontal impacts, and do not account for head rotational motion. Several studies using porcine, cadaveric, and primate models have characterized the role of head rotational motion in pathology formation (Gennarelli et al., 1982, Ommaya et al., 1967, Gennarelli et al., 1972). These led to the development of a risk function for predicting diffuse axonal injury from head rotational velocity (Takhounts et al., 2013). However, currently there is no risk function available for loss of consciousness.

Risk functions have been developed to predict less severe pathologies in sporting disciplines, driven by concerns around repetitive head impacts and the formation of neurodegenerative diseases, such as chronic traumatic encephalopathy (CTE) (McKee et al., 2013, McKee et al., 2015, Daneshvar et al., 2023). These efforts have been focused primarily on predicting the risk of concussion, but this approach has important shortcomings. Firstly, concussion symptoms and diagnostic criteria are diverse, requiring highly trained medical staff to observe all players for subtle symptoms, some of which may only be reported by the individual (McCrory et al., 2017). Additionally, concussion does not predict risk of CTE, meaning that using concussion will lead to risk functions that predict concussive symptoms but not long-term effects. In contrast, loss of consciousness indicates large impacts producing direct and clearly observable effects on brain function.

The relationship between head motion and loss of consciousness has been shown in several biomechanical studies (Cournoyer and Hoshizaki, 2019, Levin et al., 1997, Cournoyer and Hoshizaki, 2021). A recent work, utilizing Imperial College anatomically detailed finite element model of brain biomechanics, has shown larger strain and strain rates across the brain in NFL impacts leading to LOC than those leading to a negative head injury assessment (Zimmerman et al., 2023). Moreover, this study showed that in comparison to the asymptomatic case, the LOC cases had a concentration of strain rate within the brain stem and in nuclei involved in arousal and alertness. However, this work did not explore the relationship between brain strain and strain rate within brain stem and probability of sustaining an LOC, which is crucial for guiding the development of mitigation strategies.

Injury risk functions can be developed from kinematic and injury outcome data, ideally using high-quality datasets that pair head kinematics with injury outcomes. The resulting injury risk curve can then be used to estimate the probability of injury occurrence. These kinematic-level injury criteria are predictive for cases with impact conditions like those in the original dataset. However, their predictive power may diminish when applied to new data with variations in impact duration, location, or angle. One approach to improving the transferability of injury risk functions

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is to predict brain strain and strain rate for a given impact using finite element models of brain biomechanics. This technique has been used to predict the risk of mild traumatic brain injury (mTBI) and severe traumatic brain injury (sTBI)(Gabler et al., 2016, Gabler et al., 2019, Zhang et al., 2004, Kleiven, 2007).

An alternative method to kinematic-level IRFs is the strain-based or 'tissue-level' IRF. Rather than treating the head as a 'black box', strain within the brain can be calculated instead. Brain strain, a measure of brain deformation, is known to be directly linked with brain injury. Certain patterns of head kinematics have been shown to be associated with specific pathologies in specific areas of the brain. Several finite element models (FEMs) of the brain exist around the world, which have been developed and validated against real world brain injury data. These models allow strain to be measured in different brain structures for a given head impact. Using the same datasets as used in kinematic-level injury risk criteria, mathematical models such as logistic regression can predict the risk of injury for a given brain strain; whether global brain strain or strain within a particular structure. Tissue-level injury risk curves can be generated to estimate injury risk independently of specific impact conditions – this means that an injury risk function developed using injury data collected in one sport, can be used in a sport with different impact conditions or indeed non-sporting use cases.

Here we develop risk functions for loss of consciousness based on brain strain and strain rate. We use data from two groups of American Football impacts, one leading to LOC and another leading to no observable symptoms. The Imperial College anatomically detailed FE model of brain biomechanics is used to predict strain and strain rate within the brain and in brain stem and its nuclei involved in arousal.

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METHODS

NFL Loss of Consciousness Database

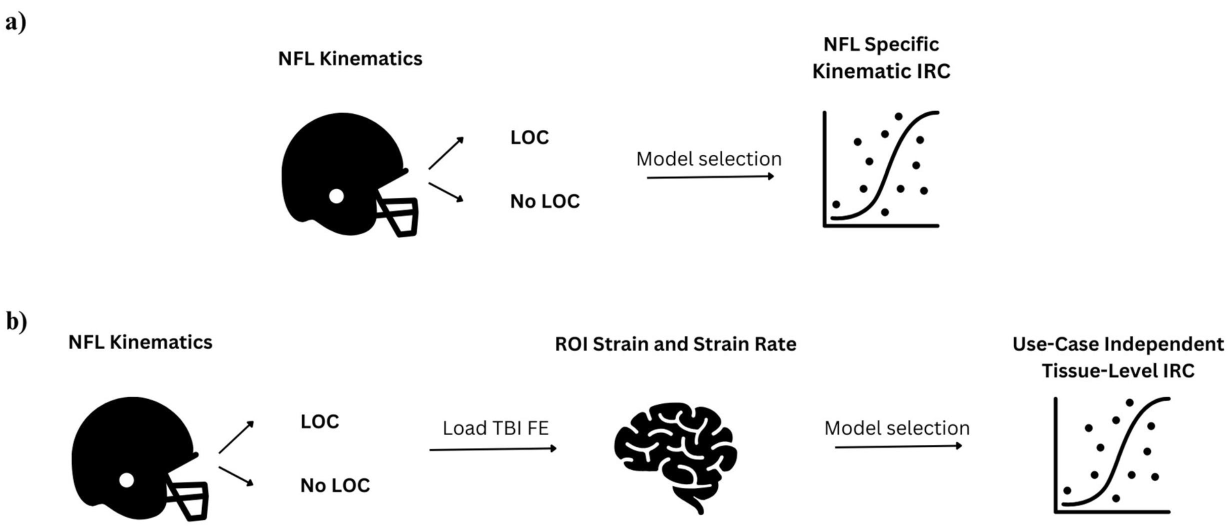
An existing database of 61 concussive head impacts from 1,280 National Football League (NFL) games was analyzed. Of these cases, 20 involved a loss of consciousness, while 41 showed no visible signs of impairment. Loss of consciousness was defined as complete loss of motor tone or a failure to protect themselves against the fall within 2s after the impact. Full details of the database and subsequent laboratory reconstructions are available in Zimmerman et al 2023 (open access) (Zimmerman et al., 2023). For each reconstructed head impact, six degrees-of-freedom head kinematics data were available along with documentation of whether a loss of consciousness occurred.

The head kinematic NFL data were used to predict strain and strain rate within brain tissue to develop a new tissue-level risk function (Tissue IRF) for LOC.

Brain Strain and Strain Rate Prediction

Kinematic injury data from real-world NFL cases were used to load the Imperial College FE model of the human brain (Zimmerman et al., 2023, Yu et al., 2022, Ghajari et al., 2017). The model predicts brain deformation for each impact and generates a NIfTI (Neuroimaging Informatics Technology Initiative) file for subsequent analysis. The 90th maximum principal strain (MPS90) and strain rate (MPSR90) data were collected from voxels across the whole brain and brainstem ROIs using the fMRIB Software Library (FSL) v6.07. This was done to exclude abnormally large variations in values in poorly defined elements. In addition, masks derived from the Harvard Ascending Arousal Network (AAN) atlas were used to measure the strain and strain rate in nuclei of the brainstem known to be important in arousal. These nuclei are the dorsal raphe, locus coeruleus, laterodorsal tegmental nucleus, median raphe, mesencephalic reticular formation, periaqueductal grey, parabrachial complex, pontine reticular formation, pedunculotegmental nucleus and the ventral tegmental area (Edlow et al., 2012). An overview of this approach compared to a use-case specific injury risk function can be seen in **Error! Reference source not found.**.

Figure 1: Development of a tissue-based injury risk function for a loss of consciousness, a) use-case specific kinematic injury risk curve, b) use-case independent tissue-level injury risk curve. ROI = region of interest



Developing Tissue-Level LOC Risk Functions

We used a survival analysis to build risk functions based on the brain tissue strain and strain rate data in the LOC or no LOC groups. Historically, injury risk functions derived from binary biomechanical data have been modelled using simple logistic regression. However, logistic regression curves are generally reliable in the middle of the dataset, where most data points are concentrated, but they may not extrapolate well at the extremes, leading to inaccurate predictions

(McMurry and Poplin, 2015). For example, logistic regression injury risk curves do not always pass through the origin (0,0), resulting in a nonzero injury risk (y-axis) for zero stimulus (x-axis). An alternative approach is survival analysis, which provides a similar fit to the data in the central region but performs better when extrapolating to higher or lower stimulus levels. As a result, injury risk curves developed using survival analysis naturally pass through the origin, ensuring a more realistic representation of injury risk at low stimuli.

In order to build the LOC risk function using survival analysis, we combined the recommendations from the International Organization for Standardization (ISO/TS 18506:2014) and the recommended modifications to these steps to address its nuances and deficiencies (Yoganandan et al., 2016).

Survival Function Development. Survival analysis is typically used to study the time until an event of interest occurs and is most commonly used in medicine to track cancer survival rates or drug treatment effects. Data are classified as either right-censored, where the event has not occurred by the time of observation, or left-censored, where the event occurred before the observation began. Injury risk curves developed using survival analysis typically plot time on the x-axis and survival probability on the y-axis. To adapt this approach for injury risk curves, time was replaced by the variable of interest, such as brain strain, while survival probability was replaced by the likelihood of loss of consciousness. Injury cases were treated as left-censored and non-injury cases as right-censored. The following equation describes the survival function:

$$S(\varepsilon) = e^{-\left(\frac{\varepsilon}{\lambda}\right)^{k}}, \qquad (1)$$

where $S(\varepsilon)$ is the probability of no injury beyond strain ε, λ is the scale parameter and k is the shape parameter.

Area under the Receiver Operator Curve (AROC). The area under the receiver operating characteristic curve (AUC-ROC) was used to evaluate the ability of each survival analysis model to distinguish between positive and negative cases. The trade-off between model sensitivity and specificity was assessed, yielding a value between 1.0 (perfect classifier) and 0.0 (worst classifier). The region of interest (ROI) with the highest AUC-ROC was selected for further analysis.

Probability Distributions and AIC Comparison. Survival analysis was performed on the selected region of interest (ROI) using three probability distributions: log-normal, log-logistic, and Weibull. These distributions were chosen to evaluate model fit and distance to the parametric model. Akaike Information Criterion (AIC) and the Quality Index (QI) were used to rank the distributions. The distribution with the lowest AIC and highest QI was selected for further analysis.

Goodness of Fit. Goodness of fit was evaluated using Kolmogorov-Smirnov tests, which compare the empirical distribution of the data with the distribution of the model. A p-value above 0.05 indicates that the model is not significantly different from the empirical data, suggesting a better fit.

Difference in Beta Coefficients (DFBETA). Influential cases were identified using dfbeta statistics for each ROI. Dfbetas can be calculated from the following equations (Belsley, 1980).

$$DFBETA_{ij} = \hat{\beta}_j - \hat{\beta}_{(i)j} \tag{2}$$

$\hat{\beta}_j$ = j^{th} coefficient from the regression calculated using all the data, $\hat{\beta}_{(i)j}$ = j^{th} coefficient from the regression calculated without the i^{th} observation

The leave one out regression technique was considered as the most suitable for Weibull, log normal and log logistic models.

$$DFBETA_i = \frac{\hat{\beta}_j - \hat{\beta}_{(i)}}{SE(\hat{\beta})}, \tag{3}$$

where $SE(\hat{\beta})$ is the standard error.

If influential cases were identified, they were removed from the initial dataset, and the analysis steps were repeated. If a statistically significant difference was found in the AIC before and after case removal, their exclusion was considered for the final model.

Confidence Intervals. Confidence intervals (CI) and normalized confidence intervals (NCI) were calculated for the chosen metric.

Final Tissue-level Injury Risk Function. Using a Weibull cumulative distribution function (CDF) for the tissue-level injury risk function provides:

$$P(LOC|ROIStrain) = 1 - exp\left(-\left(\frac{ROIStrain^k}{\lambda}\right)\right) \tag{4}$$

Where (LOC|ROIStrain) = probability of LOC for a given ROIStrain, λ = scale and *k* = shape. All analyses were performed using RStudio v2024.12.0.

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RESULTS

NFL Injury Database

Strain and strain rate data were calculated for the 61 NFL head impacts in the whole brain, brainstem and each brain region of interest (ROI).

Tissue-Level Injury Risk Function

Survival analysis, assuming a Weibull distribution, was performed for MPS90 and MPSR90 across the whole brain, brainstem, AAN-specific brainstem nuclei.

presents the regions of interest ranked by AROC. The five metrics with the highest AROC value of 0.75 were shortlisted for further analysis; brainstem, mesencephalic reticular formation, whole brain, ventral tegmental area, and periaqueductal grey strain rates. AIC and QI values for all five metrics supported the use of survival analysis with a Weibull cumulative distribution function (CDF). Additional analysis using Kolmogorov-Smirnov (K-S) testing returned p-values greater than 0.05, meeting the selection criteria. VTA SR was excluded due to its lower p-value. Analysis of the selected metrics using dfbetas did not identify any influential cases that significantly affected the AIC. Weibull CDF survival analysis curves for each of the final metrics, including 95th percentile confidence intervals can be seen in Figure 2.

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Table 1: Summary of statistical results ranked by Area Under the Receiver Operator Curve (AROC). ROI = region of interest. ROIs shaded in green represent the four selected metrics. AIC = Akaike Information Criterion. QI = Quality Index. K-S = Kolmogorov-Smirnov test. S = strain. SR = strain rate. DR = dorsal raphe, LC = locus coeruleus, LDTg = laterodorsal tegmental nucleus, MnR = median raphe, mRt = mesencephalic reticular formation, PAG = periaqueductal grey, PBC = parabrachial complex, PnO = pontis oralis, PTg = pedunculotegmental nucleus, VTA = ventral tegmental area

ROI	AROC	AIC	QI		K-S *p* value					
		LL	LN	WB	LL	LN	WB	LL	LN	WB
Brainstem SR	**0.75**	**-291.97**	**-294.93**	**-297.43**	**0.07**	**0.29**	**1.00**	**1.00**	**1.00**	**0.99**
mRt SR	**0.75**	**-255.74**	**-258.13**	**-266.17**	**0.01**	**0.02**	**1.00**	**0.95**	**0.95**	**1.00**
Brain SR	**0.75**	**-221.18**	**-223.29**	**-234.52**	**0.00**	**0.00**	**1.00**	**0.96**	**0.94**	**1.00**
VTA SR	0.75	-181.44	-277.86	-288.04	0.00	0.01	1.00	0.00	0.86	0.77
PTg SR	**0.75**	**-237.40**	**-239.66**	**-248.56**	**0.00**	**0.01**	**1.00**	**0.93**	**0.90**	**0.97**
BrainStem S	0.74	-113.01	-115.92	-119.38	0.04	0.18	1.00	0.96	0.93	0.83
MnR SR	0.74	-175.62	-272.19	-278.95	0.00	0.03	1.00	0.00	0.98	0.45
PAG SR	0.74	-268.53	-270.90	-281.16	0.00	0.01	1.00	0.98	0.99	0.93
PTg S	0.74	-96.73	-99.92	-101.26	0.10	0.51	1.00	0.73	0.82	0.91
mRt S	0.74	-110.04	-113.32	-115.02	0.08	0.43	1.00	0.90	0.95	0.88
PnO SR	0.74	-262.65	-264.84	-268.18	0.06	0.19	1.00	0.99	0.99	0.00
VTA S	0.74	-123.37	-126.40	-128.80	0.07	0.30	1.00	0.89	0.89	0.89
DR SR	0.74	-176.59	-273.12	-281.27	0.00	0.02	1.00	0.00	0.96	0.88
DR S	0.73	-124.49	-127.68	-130.20	0.06	0.28	1.00	0.96	0.95	0.95
MnR S	0.73	-123.59	-126.75	-129.42	0.05	0.26	1.00	0.88	0.89	0.96
PnO S	0.73	-114.29	-117.53	-119.57	0.07	0.36	1.00	0.91	0.95	0.94
Brain S	0.73	-90.16	-93.54	-95.79	0.06	0.32	1.00	0.92	0.93	0.95
PAG S	0.73	-123.12	-126.31	-128.70	0.06	0.30	1.00	0.95	0.97	0.94
LC SR	0.72	-174.00	-281.41	-285.67	0.00	0.12	1.00	0.00	0.93	0.98
LC S	0.70	-122.74	-126.00	-128.91	0.05	0.23	1.00	0.83	0.89	0.97
PBC SR	0.70	-159.52	-281.23	-281.77	0.00	0.76	1.00	0.00	0.97	0.97
PBC S	0.67	-124.33	-126.00	-126.98	0.27	0.61	1.00	0.98	0.99	0.96

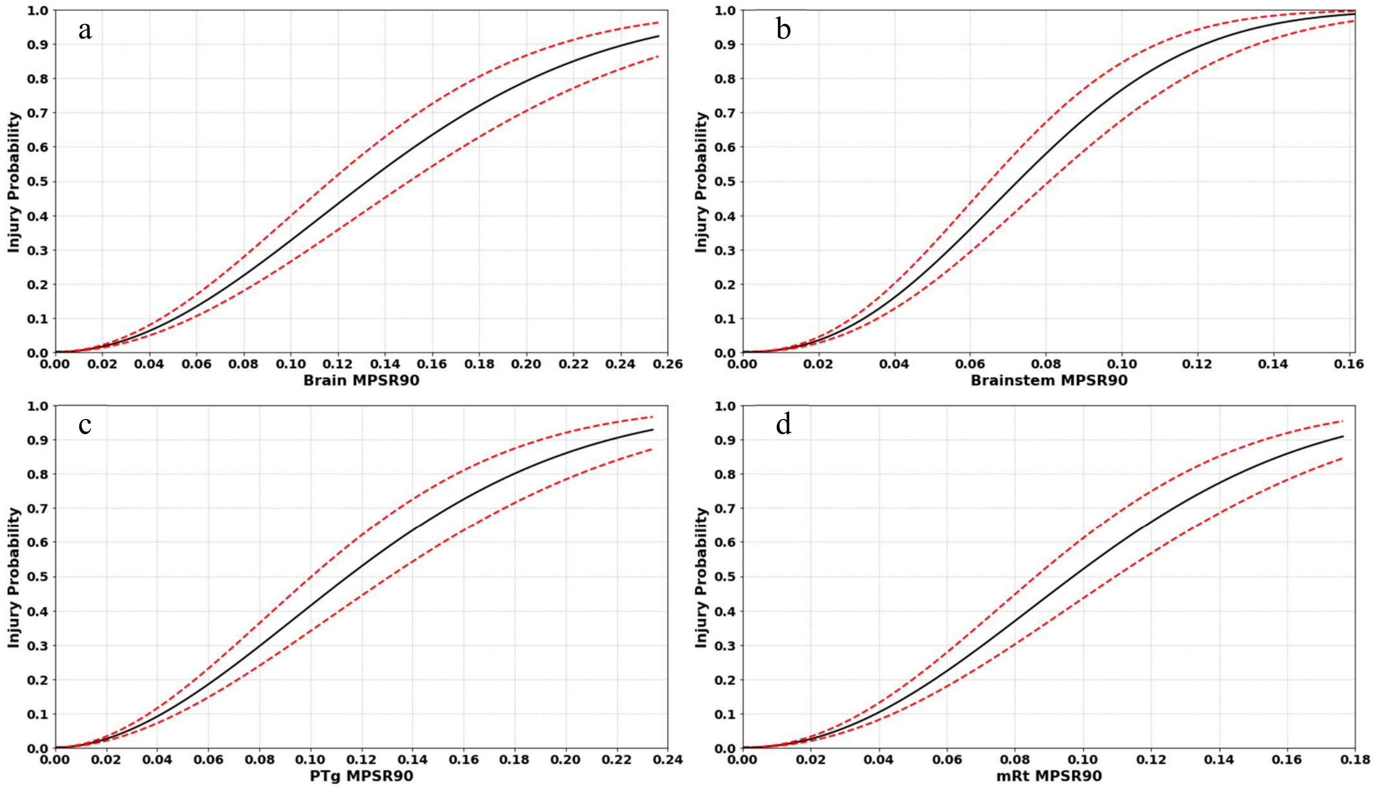

Figure 2: Risk of loss of consciousness based on a) brain, b) brainstem, c) PTg (pedunculotegmental nucleus) and d) mRt (mesencephalic reticular formation) 90th percentile maximum principal strain rate. Red dashed areas represent 5th and 95th percentile confidence intervals.

DISCUSSION

Existing rotationally focused injury risk criteria primarily assess either the risk of concussion at lower severity levels or the risk of diffuse axonal injury at higher severities. While concussion-based criteria are widely used, particularly in sports-related injury assessments, they do not directly address the risk of incapacitation, specifically loss of consciousness (LOC). This study aims to fill this gap by utilizing a novel database of NFL injury cases that incorporate LOC as the primary outcome measure rather than concussion, providing a more targeted risk criterion for incapacitation.

Currently, no injury criteria specifically consider the risk of incapacitation due to LOC. While typically transient, LOC can have severe consequences, particularly in situations with a high risk of death. Much of the focus on low-severity head impacts has centered on a broader definition of concussion, which may not be applicable in all scenarios. In contexts such as motorsports, aviation crashes, or environments where there is a risk of drowning, even a brief LOC significantly increases the likelihood of serious injury or death.

The proposed injury risk criterion could supplement or replace existing criteria in scenarios where LOC presents additional risks beyond those associated with concussion.

To develop injury risk functions applicable to various use cases, tissue-level injury risk functions were generated by calculating brain deformation in NFL head impacts. This was achieved by loading a finite element model (FEM) of the head with kinematic data obtained from real-world loss of consciousness injury cases. In accordance with ISO/TS 18506:2014, an injury risk function was developed using survival analysis, assuming a Weibull distribution. Curves for four regions of interest were produced, which represent the whole brain, brainstem and two brainstem nuclei known to be involved in arousal: the pedunculotegmental nucleus and the mesencephalic reticular formation (Edlow et al., 2012). These brain regions were selected based on the AROC scores and whether they met the statistical tests outlined in the ISO standard. These regions were all based on strain rate, rather than brain strain, which may indicate greater rate sensitivity in the areas of the brain which regulate arousal. One limitation of this study is the relatively small number of left-censored cases, despite an extensive review of NFL game footage. Such injury data are inherently difficult to obtain outside of televised games, and the quantity reported here is consistent with that in comparable studies. An advantage of using loss of consciousness as an outcome measure is its relative objectivity compared to the broader and more variable symptomatology associated with concussion.

The tissue-based injury risk functions generated in this study can be used to develop a kinematic injury risk function for any use-case where high quality kinematic head impact data exists. For example, head kinematic data obtained from anthropomorphic test devices (ATD) generated during automotive or aerospace crash tests could also be used to load the same FEM brain model to predict brain deformation. This approach would allow the head kinematics in this use-case to be directly linked to the tissue-based risk function developed from the NFL injury dataset, using brain deformation as an intermediary. This process would enable the development of an injury risk function specific to any use-case of interest, even if the impact conditions are different from those encountered in the NFL.

CONCLUSIONS

This study has produced a novel loss of consciousness injury risk function which could be used for use-cases where incapacitation is associated with additional risks of death or serious injury, including in motorsports, maritime and aerospace environments. In addition, this study provides an alternative to concussion-based criteria, which are based on subjective clinical assessments of sporting head impacts. This research is preliminary, and future work is required to test these novel injury risk functions using specific use-case kinematic datasets.

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