Prediction of brain strain across head impact subtypes using 18 brain injury criteria

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Abstract

Multiple brain injury criteria (BIC) are developed to quickly quantify brain injury risks after head impacts. These BIC originated from different types of head impacts (e.g., sports and car crashes) are widely used in risk evaluation. However, the predictability of the BIC on different types of head impacts has not been evaluated. Physiologically, the brain strain is often considered the key parameter of brain injury. To evaluate the BIC’s ability to predict brain strain across five datasets comprising different head impact subtypes, linear regression was used to model 95% maximum principal strain, 95% maximum principal strain at corpus callosum, and cumulative strain damage (15%) on 18 BIC. The results show significant differences in the relationship between BIC and brain strain across datasets, indicating the same BIC value may indicate different brain strain in different head impact subtypes. The accuracy of regression is generally decreasing if the BIC regression models are fit on a dataset with a different head impact subtype rather than on the dataset with the same subtype. Given this finding, this study raises concerns for applying BIC to predict the brain strain for head impacts different from the head impacts on which the BIC was developed.

Key words Traumatic brain injury, Brain injury criteria, Brain strain, Head impact

1. Introduction

Traumatic brain injury (TBI), frequently caused by head impacts in sports, traffic accidents and unintentional falls, has become a global health challenge and affects over 50 million children and adults worldwide (1). Additionally, mild traumatic brain injury (mTBI) is associated with long-term cognitive and emotional sequelae (2), cerebral blood flow alterations (3) and even neurological degenerative diseases (4). If mTBI goes undetected, the accumulation of brain damage causes higher risks of long-term consequences (5), which calls for better monitoring of brain injury after head impacts.

To evaluate the brain injury risk associated with a head impact, multiple brain injury criteria (BIC) have been developed with reduced-order physical models (6–9) and statistical model fitting (10,11). These BIC predict the risk of brain injury based on the measured kinematics of head movement caused by an impact. Additionally, the peak values of head movement kinematics, such as the linear acceleration at the brain center of gravity, angular velocity and angular acceleration, can also be directly used as a BIC (8,12,13).

Because the brain can be injured when head movement deforms brain tissue by the inertial force (6–8,14–16), brain strain, particularly the maximum principal strain (MPS), is a key parameter in evaluating the brain injury risk (3,17–19), and has been widely used as an indicator for mTBI. To evaluate the accuracy of predicting brain injury risks of the BIC, typically Pearson correlation between the BIC and the brain strain (particularly 95% MPS), and the coefficient of determination of the linear regression of brain strain on the BIC, have been used (6–8,20).

Although the BIC are typically designed for specific types of head impacts, many BIC are used regardless of their development background. For instance, head injury criterion (HIC) originated in the dummy test of the automobile crashworthiness and in the field of motor vehicle regulation (21), but is now used in mTBI research (22). However, when applied to different types of head impacts, even for the same values of MPS, some BIC give different values. As is shown in Fig. 1, the impacts of college football and mixed martial arts show different characteristics in their kinematics and the BIC calculated based on the kinematics (Section 2.2) show clear distinctions. However, these two impacts reach the same peak value of 95% MPS. That different BIC values indicate potentially the same brain strain in different types of head impacts, poses a risk to the use of these metrics across the mTBI field.
Figure 1 Comparison between two impacts in college football (A) and in mixed martial arts (B). The traces of 95% MPS (left axis) and angular acceleration (Ang. Acc., right axis) magnitudes are plotted in (A, B), and these two impacts have the same peak value of 95% MPS as shown by the dash line across (A) and (B). The 95% MPS peak value and BIC values are given in (C). The blue and red bars indicate college football and mixed martial arts, respectively. The information of BIC is introduced in Section 2.2.

To better understand the risk of using one BIC for a general metric, in this work a number of datasets from various sports and various types of head impacts are used for comparison. Linear regression models were built with 18 different BIC as predictors for 95% MPS (MPS95), 95% MPS at corpus callosum (MPSCC95) and cumulative strain damage (CSDM,15%, indicating the volume fraction of brain with MPS exceeding the threshold of 0.15 (23)), to investigate the regression coefficients of the BIC and the brain strain prediction generalizability. These models were tested against the datasets in a variety of statistical strategies to best determine the efficacy of these different approaches.

2. Methods
2.1 Data description and processing
To evaluate the generalizability of BIC across different types of head impacts, data from six individual sources were used to construct five datasets: 1) the dataset 1 contained 2183 lab impacts, among which 2130 were simulated by a validated finite element analysis (FEA) model of hybrid III anthropomorphic test dummy (ATD) headform impacted by the impactor for football testing (20,24,25). The remaining 53 were reconstructed head impacts in National Football League (26) using hybrid III ATD headform. The data from these two sources were merged because they both represented the responses of hybrid III ATD headform under football-type impacts; 2) the dataset 2 contained 302 on-site college football head impacts collected by the Stanford instrumented mouthguards (27–29); 3) the dataset 3 contained 457 on-site mixed martial arts (MMA) head impacts collected by the Stanford instrumented mouthguard (3,30); 4) the dataset 4 contained 48 head impacts in automobile crashworthiness tests from the National Highway Traffic Safety Administration (NHTSA) (31); 5) the dataset 5 contained 272 numerically reconstructed head impacts in National Association for Stock Car Auto Racing (NASCAR) by hybrid III ATD headform.

Since finite element (FE) modeling is the state-of-the-art biomechanics modeling tool for brain strain in head impacts, the validated KTH model (32) was used to calculate the MPS95, MPSCC95 and CSDM since these are widely used in mTBI research (6,7,23,33,34). The KTH model includes the brain, skull, scalp meninges, cerebrospinal fluid (CSF) and 11 pairs of bridging veins. The modeling was performed using the commercially available FE software LS-DYNA (Livermore, CA, USA). The accuracy in predicting the MPS95/MPSCC95/CSDM was then used to evaluate the brain strain prediction ability of the BIC. The distributions and the summary statistics of the MPS95, MPSCC95 and CSDM in the five datasets are shown in Fig. 2.

**Figure 2** The normalized distribution and the summary statistics of MPS95, MPSCC95 and CSDM on five datasets. (A) The normalized distribution of MPS95 on five datasets. (B) The normalized distribution of MPSCC95 on five datasets. (C) The normalized distribution of CSDM on five datasets. (D) The summary statistics (mean values, standard deviations (STD) and maximum values) of MPS95/MPSCC95/CSDM on five datasets.
2.2 Brain Injury Criteria

In this study, 18 BIC were included which have been used in mTBI research. These are listed in Table 1 (Lin. Acc.: Linear Acceleration, Ang. Acc.: Angular Acceleration, Ang. Vel.: Angular Velocity). These BIC were based on one or a combination of translational and rotational parameters in the head movement kinematics with experimental data fitting or reduced-order mechanical models (6–8).

The peak values of the magnitudes of the linear acceleration at the brain center of gravity $|\alpha(t)|$ (lin_acc.CG_max) (12), angular velocity $|\omega(t)|$ (ang_vel_max) (13) and angular acceleration $|\dot{\alpha}(t)|$ (ang_acc_max) (13, 20) are the most fundamental BIC definitions. They are calculated by taking the maximum of the magnitude of the respective translational or rotational parameters. In addition to these three BIC, 15 other BIC used in this study are described as follows:

Severity Index (SI), also known as Gadd Severity Index (GSI), was developed by Gadd (35) based on curve fitting the Wayne State Tolerance Curve with skull fracture data in head form simulation. It is calculated based on the following equation, and the integral is calculated from when the signal first exceeds 4g m/s² to when it returns to 4g m/s² after the highest peak:

$$SI = \int |\alpha(t)|^{2.5} dt$$  \hspace{1cm} (Eqn. 1)

Head Injury Criterion (HIC) was developed by Versace et al. (21). It is the most widely used injury criteria developed in the assessment of head injury risks in motor vehicle regulation. HIC is calculated based on the following equation, where $t_1, t_2$ are chosen to maximize the value of HIC. The duration was initially set as 36ms and under the current standard $t_2 - t_1 \leq 15$ms, and the resultant term is expressed as HIC\textsubscript{15}.

$$HIC = \max_{t_1, t_2} \left\{ \left[ \int_{t_1}^{t_2} |\alpha(t)| dt \right]^{2.5} (t_2 - t_1) \right\}$$  \hspace{1cm} (Eqn. 2)

Generalized Acceleration Model for Brain Injury Threshold (GAMBIT) was developed by Newman et al. (36). It was designed to combine rotational and translational components of head accelerations, as an analogue in the kinematics to maximum shear stress/strain theory. It is calculated based on the following equation, where $a_c, \alpha_c$ are the thresholds for the corresponding acceleration and the constants are: $n = m = s = 2, a_c = 250g$ and $\alpha_c = 25000 rad/s^2$.

$$GAMBIT = \left\{ \left[ \left( \frac{|a(t)|}{a_c} \right)^n + \left( \frac{|\alpha(t)|}{\alpha_c} \right)^m \right]^{1/5} \right\}$$  \hspace{1cm} (Eqn. 3)

Head Impact Power (HIP) was developed by Newman (37). It was based on the hypothesis that the severity of head injury correlated with the head impact power. HIP is calculated based on the following equation, where $m$ denotes the mass and $I_i$ denotes the principal moments of head inertia, and $\dot{i}$ denotes the components of the acceleration in three spatial directions:

$$HIP = \max_{t} \left\{ m \sum a_i(t) \int a_i(t) dt + \sum I_i \alpha_i(t) \int a_i(t) dt \right\}$$  \hspace{1cm} (Eqn. 4)

Principal Component Score (PCS) was developed by Greenwald et al. (11) using football data and principal component analysis (PCA). It is calculated as a linear combination of HIC, SI, maximum magnitude of linear acceleration and maximum magnitude of angular acceleration, while each term of the kinematics is standardized and the coefficients are fitted empirically (11):

$$PCS = \beta_0 + \beta_1 |\alpha(t)| + \beta_2 SI + \beta_3 HIC + \beta_4 |\dot{\alpha}(t)|$$  \hspace{1cm} (Eqn. 5)

Kinematic rotational brain injury criterion (BRIC) was developed by Takhounts et al. (38) by adopting the effects of both angular acceleration and angular velocity. The critical values $\omega_{cr}$ and $\alpha_{cr}$ were design variables and decided by risk of diffuse axonal injury (DAI) and the best linear fit between CSDM...
and the BRIC. Different $\omega_{cr}$ and $\alpha_{cr}$ were given in (38) and the parameters used were obtained by the on-field football data.

$$\text{BRIC} = \frac{[\omega]}{\omega_{cr}} \frac{[\alpha]}{\alpha_{cr}}$$  \hspace{1cm} (Eqn. 6)

Power Rotation Head Injury Criterion (PRHIC) was developed by Kimpara et al. (39) with modifications on the HIC. It is calculated based on the following equation under the constraint $t_2 - t_1 \leq 36ms$, where $HIP_{rot}$ is the second part of HIP contributed by the rotation:

$$\text{PRHIC} = \left\{ \left( \int_{t_1}^{t_2} |HIP_{rot}(t)| dt \right)^{2.5} (t_2 - t_1) \right\}$$  \hspace{1cm} (Eqn. 7)

Kleiven’s Linear Combination (KLC) was proposed by Kleiven (40) as a brain injury predictor based on a combination of HIC$_{36}$ and the maximum magnitude of angular velocity. It is calculated according to the following formula:

$$\text{KLC} = 0.004718 \max_t |\omega(t)| + 0.000224 \text{HIC}_n$$  \hspace{1cm} (Eqn. 8)

Rotational Injury Criterion (RIC) was developed by Kimpara et al. (41) in a similar form to HIC but with the linear acceleration replaced by the angular acceleration. RIC is calculated based on the following equation under the constraint $t_2 - t_1 \leq 36ms$:

$$\text{RIC} = \left\{ \left( \int_{t_1}^{t_2} |\alpha(t)| dt \right)^{2.5} (t_2 - t_1) \right\}$$  \hspace{1cm} (Eqn. 9)

Brain Injury Criterion (BrIC) was developed by Takhounts et al. (42) based on the assumption that strains calculated by FE modeling can be predicted by angular velocity alone in pendulum and occupant crash tests. It is calculated based on the following formula, where $[\omega_x, \omega_y, \omega_z]$ are the maximum value of the angular velocity in three spatial directions, and $[\omega_{xcr}, \omega_{ycr}, \omega_{zcr}]$ are the corresponding critical values [66.2, 59.1, 44.2] rad/s found by experimental data:

$$\text{BrIC} = \sqrt{\left( \frac{\omega_x}{\omega_{xcr}} \right)^2 + \left( \frac{\omega_y}{\omega_{ycr}} \right)^2 + \left( \frac{\omega_z}{\omega_{zcr}} \right)^2}$$  \hspace{1cm} (Eqn. 10)

Combined Probability of Concussion (CP) was developed by Rowson et al. (10). It is based on the risk of concussion in the football head impacts with the logistic function. The metric is calculated as the basis of the logistic function in a linear combination of the maximum magnitude of translational and rotational accelerations and the interaction between these two terms, where each of the coefficients is determined by logistic regression:

$$\text{CP} = \beta_0 + \beta_1 |\alpha(t)| + \beta_2 |\alpha(t)| + \beta_3 |\alpha(t)| |\alpha(t)|$$  \hspace{1cm} (Eqn. 11)

Rotational Velocity Change Index (RVCI) was developed by Yanaoka et al. (43) based on pedestrian impact events. It assumed an analogy between the brain strain and the deformation of a spring-mass model. It is calculated based on the following formula, where $R_i$ are the weighing factors related to each axis, which is determined by FE model, and the duration constraint was chosen to be $t_2 - t_1 \leq 10ms$:

$$\text{RVCI} = \max_{(t_1,t_2)} \sqrt{R_x(\int_{t_1}^{t_2} \alpha_x dt)^2 + R_y(\int_{t_1}^{t_2} \alpha_y dt)^2 + R_z(\int_{t_1}^{t_2} \alpha_z dt)^2}$$  \hspace{1cm} (Eqn. 12)

Convolution of impulse response for Brain Injury Criterion (CIBIC) was developed by Takahashi et. al. (9). CIBIC used the similar lumped-mass system as Damage (7) but the coupling effects in different directions were not considered. Furthermore, brain strain caused by the impulse with 1ms was used to solve the system, and the displacement, which indicated the 95% MPS, was calculated by the convolution integral.

Damage was developed by Gabler et. al (7) based on a three-degree-of-freedom, 2nd-order lumped-mass system. To include the coupling effects between direction directions, the off-diagonal elements in the stiffness and damping matrices were assumed to be non-zero. The head angular acceleration was used as the input and the displacement of the mass was assumed to indicate the 95% MPS.
Brain Angle Metric (BAM) was developed by Laksari et al. (8) based on a 3 degree-of-freedom lumped parameter brain model and a combined dataset with head impacts from college football, high school football, navy sled tests, etc. BAM is calculated by taking the maximum brain angle $\theta_{\text{brain}}$ in each direction. It is based on the following equations, where the $k$ and $c$ are the stiffness and damping coefficient of the system and the $\theta_{\text{brain}}, \theta_{\text{skull}}$ denote the angles of the brain and the skull, with the related model parameters specified (8):

$$I(\dot{\theta}_{\text{brain}} + \dot{\theta}_{\text{skull}}) = -k\theta_{\text{brain}} - c\dot{\theta}_{\text{brain}}$$  

(Eqn. 13)

| BIC Name | Equation | Source Impact | Kinematics Included | FE model | Reference |
|----------|----------|---------------|---------------------|----------|-----------|
| SI       | 1        | Car Crash     | Lin. Acc.           | -        | (35)      |
| HIC      | 2        | Car Crash     | Lin. Acc.           | -        | (21)      |
| GAMBIT   | 3        | Car Crash     | Lin. Acc., Ang.     | -        | (36)      |
| HIP      | 4        | Simulation    | Lin. Acc., Ang.     | -        | (37)      |
| PCS      | 5        | Football      | Lin. Acc., Ang.     | -        | (11)      |
| BRIC     | 6        | Football      | Ang. Acc., Ang.     | SIMon(44)| (38)      |
| PRHIC    | 7        | Football      | Ang. Acc.           | THUMS(45)| (39)      |
| KLC      | 8        | Football      | Lin. Acc., Ang.     | KTH      | (40)      |
| RIC      | 9        | Football      | Ang. Acc.           | THUMS    | (41)      |
| BrIC     | 10       | Simulation, Football, Car Crash | Ang. Acc. | GHBMC(46)| (42)      |
| CP       | 11       | Football      | Lin. Acc., Ang.     | -        | (10)      |
| RVCI     | 12       | Car Crash     | Ang. Vel.*          | GHBMC    | (43)      |
| CIBIC    | -        | Car Crash     | Ang. Acc.           | GHBMC    | (9)       |
| Damage   | -        | Idealized Impact, Football | Ang. Acc. | GHBMC    | (7)       |
| BAM      | 13       | Football, Naval Sled tests | Ang. Acc. | KTH      | (8)       |
| lin_acc_CG_max | - | - | Lin. Acc. | - | - |
| ang_vel_max          | - | - | Ang. Vel. | - | -   |
| ang_acc_max            | - | - | Ang. Acc. | - | -    |

*The formula for RVCI is based on the angular acceleration, but the integral of angular acceleration is the change of angular velocity.

2.3 Evaluation of brain strain predictability based on BIC

To evaluate the ability to predict MPS95/MPSCC95/CSDM based on the 18 BIC, ordinary least squares (OLS) regression models were built with each BIC as the predictor and the MPS95/MPSCC95/CSDM as the outcome, respectively. OLS regression indicates the most direct predictive power of BIC in terms of explained variance (coefficient of determination), as such it has been widely used in evaluating the accuracy of BIC (6,8,21,26,42).
The regression coefficients were initially analyzed to investigate the relationship between the BIC and the brain strain. For OLS, the two key components are the curve’s slope and the intercept. Focus was placed on the slope because the slope determines the variance in the outcome that can be explained by the predictor. The intercept, which is in the same unit as the outcome, is used to balance the mean of the outcome in the regression to center the outcome data. To ensure robust results, the datasets were bootstrapped 1000 times (47). The mean and 95% confidence intervals of the regression slopes were recorded.

Next, the influence of different datasets on the ability of BIC to predict the brain strain was evaluated. The accuracy of brain strain prediction is recognized as higher if the coefficient of determination ($R^2$) of the OLS regression is higher (equivalent to that the Pearson coefficient of correlation ($r$) between the predictor and the outcome is higher in this single-predictor regression model).

### 2.4 Statistic analysis and prediction tasks

In the analysis of the regression, the underlying relationship between the BIC and the brain strain across datasets were analyzed. Two statistical tests were performed: 1) the one-way ANOVA tests to find whether the regression slopes were statistically significantly different across datasets; 2) the pairwise Wilcoxon signed rank tests (48) to find statistical significance in the regression slope difference between each pair of two datasets. Paired t-tests were not used because the Shapiro Wilk tests (49) rejected the normal distribution hypothesis on some of the regression slope results, and the Wilcoxon signed rank test does not rely on the normal assumption of data distribution of the bootstrapped regression slope. Although the values given by different BIC were in different scales, this study compared each BIC across datasets.

Additionally, because the different regression slopes indicate the varying relationship between the BIC and the brain strain, the cross-dataset brain strain prediction accuracy may be different from that in the single-dataset prediction. To analyze the generalizability of the BIC model in predicting brain strain, three different prediction tasks were designed:

1. **Single-dataset regression and prediction**: to test the ability of the BIC to predict brain strain in the same type of head impacts, on each dataset, 80% of the impacts were randomly selected as the training dataset and the remaining 20% impacts as the testing dataset. The remaining 20% impacts were assumed to represent the distribution of the entire dataset from which they were randomly sampled. 100 iterations of bootstrapping were performed to ensure the result robustness. OLS models were fit on the training dataset and predicted on the testing dataset, with the mean $R^2$ recorded to assess the accuracy. Five models corresponding to five datasets were built and evaluated.

2. **Cross-dataset regression and prediction**: to test the ability of the BIC to predict brain strain on a different type of head impacts, a cross-dataset prediction task was conducted by using one dataset as the training dataset and another dataset as the testing dataset. 100 iterations of bootstrapping resampling were performed on the training dataset and the mean $R^2$ were recorded. Twenty models were built and evaluated because each of the five datasets could be either the training dataset or the testing dataset.

3. **Leave-one-dataset-out regression and prediction**: this task was completed to further simulate potential real-world applications when the brain strain of a new type of head impact needs to be evaluated. To do this, four datasets were combined to be the training dataset with the remaining dataset as the testing dataset. The same pattern of bootstrapping resampling was conducted. Five
models were built and evaluated, because each of the five datasets was once regarded as the testing dataset.

3. Results
3.1 Analysis of regression slope

To test whether the relationship between the BIC and the brain strain is the same across datasets, the slopes in the OLS regression models were analyzed with the outcomes (MPS95/MPSCC95/CSDM) on the predictor (each of the BIC). One-way ANOVA tests show statistical significance of the different slopes across datasets on each of the three outcome variables (p<0.001). Fig. 3 and Supplementary Fig. 1 show the regression slopes on the different datasets and the pairwise comparison Wilcoxon test p-values. The results show that 535 out of the 540 pairwise comparisons manifest statistical significance at the p-value threshold of 0.05, and 527 out of the 540 pairwise comparisons manifest statistical significance at the p-value threshold of 0.001. Although the regression slopes are all positive values, which means that larger values in BIC indicate higher brain strain, the statistically significant difference of regression slopes indicates that the exact relationship between the BIC and the brain strain varies with different types of head impacts.
Figure 3 The p-values of pairwise comparisons of regression slopes on different datasets of head impacts with 1000 iterations of bootstrapping resampling based on Wilcoxon signed rank tests. Dataset 1-5: lab impacts, college football, MMA, NHTSA, NASCAR. (A) The p-values of pairwise comparisons in the regression of MPS95. (B) The p-values of pairwise comparisons in the regression of MPSCC95. (C) The p-values of pairwise comparisons in the regression of CSDM.
3.2 Single-dataset prediction (task 1) and cross-dataset prediction (task 2)

As the analysis of regression slopes indicates the varying relationship between the BIC and the brain strain on different datasets, further testing was performed of the accuracy and generalizability of predicting MPS95/MPSCC95/CSDM on the single-dataset or across datasets. The diagonal elements in each plot of Figs. 4-6 show the coefficients of determination ($R^2$) in single-dataset prediction tasks, in which, the testing dataset comprised 20% data of the entire dataset while the training set comprised 80% data of the dataset to fit the OLS regression model. The off-diagonal elements in each plot of Figs. 4-6 show the coefficients of determination ($R^2$) in cross-dataset prediction in which one dataset was used as the training dataset and another dataset as the testing dataset for prediction evaluation. The root mean squared error (RMSE) results are shown in Supplementary Figs. 2-4. The diagonal elements in each plot generally show the higher $R^2$ in single-dataset prediction tasks than the off-diagonal elements which are the cross-dataset prediction. There is also a high variance in the performance of different BIC.
Figure 4 The mean $R^2$ in the single-dataset prediction and cross-dataset prediction of MPS95 based on 18 BIC with 100 iterations of bootstrapping resampling. The color indicates the same training dataset. Dataset 1: lab impacts; Dataset 2: college football; Dataset 3: MMA; Dataset 4: NHTSA; Dataset 5: NASCAR.
Figure 5 The mean $R^2$ in the single-dataset prediction and cross-dataset prediction of MPSCC95 based on 18 BIC with 100 iterations of bootstrapping resampling. The color indicates the same training dataset. Dataset 1: lab impacts; Dataset 2: college football; Dataset 3: MMA; Dataset 4: NHTSA; Dataset 5: NASCAR.
Figure 6 The mean $R^2$ in the single-dataset prediction and cross-dataset prediction of CSDM based on 18 BIC with 100 iterations of bootstrapping resampling. The color indicates the same training dataset. Dataset 1: lab impacts; Dataset 2: college football; Dataset 3: MMA; Dataset 4: NHTSA; Dataset 5: NASCAR.
3.3 Leave-one-dataset-out prediction (task 3)

To better simulate the real-world application of BIC where the brain strain in a new dataset needs to be evaluated, the leave-one-dataset-out prediction was performed by leaving one dataset completely out as the testing datasets and the combination of remaining datasets as the training dataset. As is shown in Fig. 7, the mean $R^2$ was used as the accuracy metric, the accuracy of single-dataset prediction tasks generally outperforms the accuracy of the leave-one-dataset-out prediction tasks on the same dataset and with the same type of BIC. This result repeats on MPS95, MPSCC95 and CSDM regression, which shows that combining all the data not from the same type of head impacts in the testing dataset leads to lower accuracy in the brain strain prediction.
Figure 7 Comparison of mean $R^2$ in the single-dataset prediction task and the leave-one-dataset-out prediction task on each dataset and each BIC with 100 iterations of bootstrapping resampling. (A) The mean $R^2$ in the regression of MPS95. (B) The mean $R^2$ in the regression of MPSSC95. (C) The mean $R^2$ in the regression of CSDM.
4. Discussion

As different BIC have been developed based on different types of head impacts, the predictability of the BIC across different types of head impacts has previously not been investigated. This study investigated the regression slopes in the OLS regression models of MPS95/MPSCCC95/CSDM on 18 BIC and the generalizability of the regression models to predict the brain strain if the models are fitted on a different dataset, with five datasets of different types of head impacts (lab impacts, college football impacts, MMA impacts, NHTSA impacts, NASCAR impacts). This study found that the regression slopes in most of the OLS regression models showed statistically significantly differences across datasets in Fig. 3 and Supplementary Fig. 1. This indicates that the underlying relationship between BIC and brain strain varies with different types of head impacts. A potential explanation is that the characteristics of the kinematics used by BIC to predict brain strain vary among different types of head impacts. Furthermore, the difference in the relationship between BIC and brain strain suggests that the risks of brain injury vary among different types of head impacts.

The influence of the datasets on the accuracy of the brain strain prediction were shown in Figs. 4-6 and Supplementary Figs. 2-4. The bars were generally higher on the diagonal than off diagonal, indicating that the single-dataset prediction tasks generally showed higher mean R² than those in the cross-dataset prediction tasks. In other words, the models were more accurate in the prediction of MPS95/MPSCCC95/CSDM if it was fit on the same type of head impacts. It should be noted that exceptions did exist when the off-diagonal prediction accuracy was higher, and the potential reasons may be the insignificant slope difference in the regression of the two datasets and the randomness in a small dataset. This finding suggests that the accuracy of the BIC should be evaluated according to the type of head impact. In previous studies related to BIC, the evaluation of the accuracy in brain strain prediction has been mainly done on the same dataset. Although different types of head impacts were combined to develop BIC in previous studies (Table.1), it was only until recently that researchers started to investigate the declining performance of the brain strain prediction models when applied to a different type of head impacts. Zhan et al (20) developed a deep learning head model for predicting brain strain of the entire brain and showed that the model accuracy deteriorates when the model was trained on a dataset mainly comprising simulated head impacts and applied to MMA head impacts. According to the finding in this study, concerns may arise if the BIC is used to evaluate the brain strain if the BIC regression model is fit on a different type of head impacts. Therefore, the BIC, the reduced-order head models and deep learning head models developed by researchers to predict brain injury risks need to be validated across different types of head impacts if they are ever intended to be used that way.

Additionally, although this study found statistically significant different regression slopes across datasets in Fig. 3, the findings also showed that there might be similarities between certain pairs of head impact types. In terms of the regression slopes in Fig. 3, on BrIC, statistical significance was not found in the pairwise comparison between lab impacts and NASCAR impacts, in the regression of MPS95. On CP, no statistical significance and weak significance were found in the pairwise comparison between MMA impacts and NHTSA impacts in the regression of MPS95 and CSDM, respectively. On RVCI, no statistical significance was found in the pairwise comparison between lab impacts and college football impacts; weak statistical significance was found in the regression of MPSCCC95 in the pairwise comparison between lab impacts and NHTSA impacts. On CIBIC, no statistical significance and weak significance were found in the pairwise comparison between lab impacts and NASCAR impacts, and between college football impacts and NASCAR impacts, in the regression of CSDM. In addition, weak significance was also found on some BIC between college football impacts and NHTSA impacts, and
between lab impacts and college football impacts. These similarities among different types of head impacts can also be indicated in the cross-dataset prediction results in which there were several high bars off the diagonal. For example, high mean $R^2$ was shown in the pairs (training dataset listed first in each pair): NASCAR impacts-lab impacts, NASCAR impacts-college football impacts, college football impacts-NASCAR impacts, college football impacts-lab impacts, and MMA impacts-college football impacts. The possible explanations may be: 1) the lab impacts were generally simulated for the research of head impacts in football matches, which may explain the similarity between lab impacts and college football impacts; 2) the MMA head impacts and NHTSA car crash dummy head impacts were measured without protective helmets, while the college football head impacts and the NASCAR head impacts were measured with protective helmets that protect the players/drivers from concussion. The helmet can effectively change the impact response of the head (50), which may explain the similarity between MMA impacts and NHTSA impacts, as well as among NASCAR impacts, college football impacts and lab impacts.

Comparing the performances of BIC in single-dataset task in Figs. 4-6, most of BIC definitions can accurately predict brain strain, and the BIC that included angular velocity as input (BRIC, BrIC, RVCI, ang vel max) as well as the BIC developed by solving the mass-lumped systems (Damage, CIBIC. BAM) generally showed higher accuracy (the high diagonal bars), which agrees with the results published in (7,15,51). Furthermore, these two types of BIC also provided the generally accurate prediction in the cross-dataset task (the high off diagonal bars) with the exception of BAM. The different performances of BIC in cross-dataset tasks derive from the fact that each BIC was designed to capture certain characteristics of the head kinematics to predict the brain strain, and these characteristics varied among different datasets. Although the mechanism underlying how the head kinematics caused the brain strain was not clear, a potential factor might influence the performance in the cross-dataset task was the impulse duration. As observed in (6) and explained in (16), the MPS95 depends on the angular velocity peak when the impulse duration was short, and on the angular acceleration peak when the impulse duration was longer. The impulse duration was only defined for idealized impact instead of the on-field impact. It is possible that the difference in impulse duration contributed to the difference in BIC performances. Aside from the impulse duration, the multiple peaks (Fig.1A) and the different profiles (51–53) were also potential factors that influenced the cross-dataset performance.

The lower accuracy in leave-one-dataset-out prediction in Fig.7 suggested that combining several different types of head impacts as the training dataset may fail to predict the brain strain in the unknown type of head impacts. As shown in Table.1, most of the BIC were developed based on the football and traffic accident datasets. Therefore, researchers and medical professionals should carefully interpret the results of applying BIC to other type of head impacts. For the type of head impact in which the head kinematics characteristic is unknown, sufficient impact cases should be collected and analyzed by an FE model before using the BIC. Furthermore, deep learning head models were recently developed based on football dataset (54) and football, MMA, and lab impact datasets (20), and these models have achieved promising accuracy. Although different types of dataset were used in (20), the ability of the model to predict the brain strain in an unknown type of head impact was not examined.

Furthermore, multiple negative mean $R^2$ occurred in this study in Fig. 4-7, mainly in the cross-dataset prediction tasks and leave-one-dataset-out prediction tasks but also in the single-dataset prediction tasks. The negative mean $R^2$ in the results may be explained by the significantly different distributions of the training dataset and the test dataset. In the cross-datasets and leave-one-dataset-out tasks, the negative values indicate that the distribution of the other datasets may be insufficient to represent the distribution of the selected testing dataset so that the regression models showed high bias. In the single-dataset tasks, the
negative values may be caused by the fact that the random sampled 20% testing data may not be well covered by some of the bootstrapping resampled training dataset distributions. For instance, the MMA dataset had two peaks with significantly different kernel densities, which indicates that there are much fewer data points in the minor peak region (as is shown in the red box in Fig. 2). These may be caused by several exceptionally fierce fights with severe head impacts and the collection of more data may address this issue. The data points located in the minor peak of the MPS95/MPSCC95 distributions of the MMA dataset in the testing dataset might not be well covered by the distribution of the bootstrapping resampled training dataset because the bootstrapping resampled training datasets theoretically covers 63.2% samples in the training data (55). The NHTSA dataset, which only contains 48 head impacts, may also suffer from the distributional mismatch between the testing dataset and the training dataset.

In addition, the decrease in the prediction accuracy from single-dataset tasks to cross-dataset tasks and leave-one-dataset-out tasks also indicates the issue of overfitting of the BIC models, even with simple OLS regression. As data fitting is widely used to assess BIC accuracy (e.g., fitting a regression model of 95% MPS on HIC) by evaluating the goodness of fit; however, to fit the model and to evaluate the goodness of fit on the same dataset may cause overfitting. The overfitting can lead to over-optimistic estimate of the accuracy of the BIC. Therefore, instead of fitting the BIC and evaluating the goodness of fit on the same dataset, the accuracy of the BIC across different head impact datasets also should to be validated.

There are a few important limitations of this study to note: firstly, most of the BIC definitions were developed with parameters by optimizing the prediction in certain datasets (Table.1). In this study, the BIC values were used directly with the parameters reported in the papers. It is possible that recalculating the parameters according to each dataset will generate higher accuracy than what was reported in this paper. Therefore, it is suggested that each BIC should be further improved for different types of head impacts in the future. Also, it was assumed that the testing dataset represented the head kinematics in the type of head impacts. This assumption should be examined particularly when the dataset distribution is skewed with multiple peaks or heavy tails. In the future, as more head impact data becomes available, this assumption will be more robust. Finally, the OLS regression model was the only method used to predict MPS95/MPSCC95/CSDM from the BIC because it directly shows the ability of brain strain prediction based on BIC; however, the underlying relationship between BIC and the brain strain may also be nonlinear (25). The simple linear regression may have certain biases. Neural-network-based classifiers may perform better across the cohort of comparisons listed here but may even more drastically overfit the data. Lastly, we regarded the ability to predict the brain strain as the ability to evaluate brain injury risk. More neurological studies need to be done to validate the brain strain as an accurate supplant of brain injury risk.

5. Conclusion

In this study, we investigated the varying relationship between the BIC and the brain strain and the different accuracy of brain strain prediction over different datasets of head impacts. The slope values of linear regression from BIC to brain strain (MPS95/MPSCC95/CSDM) manifest statistically significant differences across datasets. Furthermore, the accuracy of the regression models of MPS95/MPSCC95/CSDM on the BIC may be lower if the regression models are fitted on different training datasets and then used to predict the brain strain on another testing dataset. The findings indicate researchers and medical professionals who use the BIC to monitor the severity of head impact and to predict the brain strain to take extra caution to interpret the BIC results in different types of head impact. Based on the findings, it may also be advantageous to fit detailed BIC brain strain prediction models on the same type of head impacts as the head impacts which need to be evaluated.
Acknowledgements
The authors want to thank Dr. Kaveh Laksari, Dr. Lee F. Gabler and Dr. Toshiyuki Yanaoka for answering questions and providing help. This work is also supported by Stanford Department of Bioengineering.

Funding
This research was supported by the Pac-12 Conference’s Student-Athlete Health and Well-Being Initiative, the National Institutes of Health (R24NS098518), Taube Stanford Children’s Concussion Initiative.

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Supplementary Materials

Data and Code
The data and codes used in this study are reported at: https://github.com/xzhan96-stf/BIC.

Supplementary Figures
Supplementary Figure 1 The slopes in the OLS regression of MPS95/MPSCC95/CSDM on each of the 18 BIC on five datasets of head impacts with 1000 iterations of bootstrapping resampling. (A) The slopes in the regression of MPS95. (B) The slopes in the regression of MPSCC95. (C) The slopes in the regression of CSDM.
Supplementary Figure 2 The mean RMSE in the single-dataset prediction and cross-dataset prediction of MPS95 based on 18 BIC with 100 iterations of bootstrapping resampling. Dataset 1: lab impacts; Dataset 2: college football; Dataset 3: MMA; Dataset 4: NHTSA; Dataset 5: NASCAR.
Supplementary Figure 3 The mean RMSE in the single-dataset prediction and cross-dataset prediction of MPSCC95 based on 18 BIC with 100 iterations of bootstrapping resampling. Dataset 1: lab impacts; Dataset 2: college football; Dataset 3: MMA; Dataset 4: NHTSA; Dataset 5: NASCAR.
Supplementary Figure 4: The mean RMSE in the single-dataset prediction and cross-dataset prediction of CSDM based on 18 BIC with 100 iterations of bootstrapping resampling. Dataset 1: lab impacts; Dataset 2: college football; Dataset 3: MMA; Dataset 4: NHTSA; Dataset 5: NASCAR.