Predicting Sport-Related Brain Injury via Head Kinematics, Finite Element Brain Modelling, and Plasma Biomarkers

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I. INTRODUCTION

Identifying head impacts that carry a risk of traumatic brain injury in sport remains challenging. Current screening relies on witnessed events, observable signs, or self-reported symptoms, which may not reflect the presence or severity of underlying brain injury [1]. Instrumented mouthguards (iMG) enable in vivo quantification of head impact kinematics [2], and finite element (FE) brain models can translate these data into estimates of brain strain that may better capture injury risk than kinematics alone [3]. However, most studies have validated these measures against subjective clinical diagnoses rather than objective biological markers such as blood-based biomarkers. Here, we aimed to examine the association between iMG kinematics, FE-modelled brain strain, and plasma biomarkers, glial fibrillary acidic protein (GFAP; astroglial injury) and neurofilament light (NfL; axonal injury) [4], across a range of impact magnitudes sustained in Australian football, including those resulting in concussion, a medically cleared sideline assessment (HIA-), and those not requiring assessment.

II. METHODS

Participants*:* The analysis included 41 video-verified impacts from male amateur Australian football players: 17 resulting in concussion, five assessed but cleared (HIA-), and 19 not requiring assessment.

Kinematic data: Head impact kinematics were recorded using custom-fit iMGs (HIT-IQ Nexus, Melbourne, Australia), which has been validated previously [2]. Six-degree-of-freedom kinematics were measured using a tri-axial accelerometer and gyroscope at 1 kHz and filtered at 300 Hz cut-off frequency, from which peak linear acceleration (PLA), peak rotational acceleration (PRA), and peak rotational velocity (PRV) were derived.

Computational modelling: We used the Imperial College FE brain model, which incorporates detailed anatomical representation of intracranial structures, validated against cadaver experiments [5] (Fig. 1). Linear and rotational accelerations were applied to the rigid skull (referenced to the centre of gravity), and simulations were performed using an explicit FE solver (LS-DYNA). Maximum principal Green-Lagrange strain was computed for all elements. Strain data were output to NIfTI format and spatially aligned to the MNI152 standard space. The 90th percentile strain values were extracted for whole-brain, white-matter, grey-matter, and brainstem.

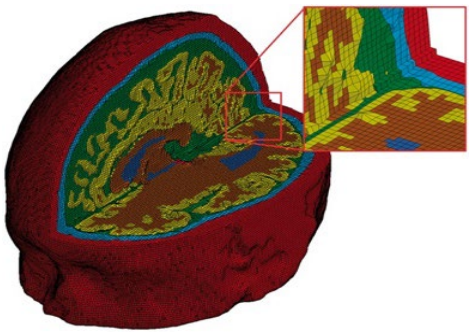

Fig. 1. Brain tissue segmentation includes skin (red), skull (light blue), cerebrospinal fluid (green), grey matter (yellow), white matter (brown), and ventricles (dark blue).

Plasma biomarkers: Venous blood samples were collected at timepoints aligned with expected biomarker peaks (24 hours for GFAP; six days for NfL). Plasma GFAP and NfL concentrations were quantified using a Simoa HD-X Analyzer.

Data analysis: Spearman's rank correlation coefficient (ρ) assessed associations between biomarkers and biomechanical measures due to right-skewed biomarker distributions. Multiple linear regression models adjusted for age, body mass index, and time since injury/match were used to confirm these associations after accounting for potential confounders. Correlations were analysed for impacts overall (n=41) and for concussive impacts only (n=17). Steiger's Z test was used to compare strength of correlations between metrics. Piecewise regression models, adjusted for age, body mass index, and time since injury/match, assessed the relationship between biomechanical measures and log-transformed GFAP, with breakpoint identification and slope differences tested using wild bootstrapping.

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III. INITIAL FINDINGS

Associations with plasma GFAP: For impacts overall, plasma GFAP was moderately correlated with PLA (ρ=0.46, 95% CI: 0.20–0.66), PRV (ρ=0.53, 95% CI: 0.20–0.78), and whole-brain strain (ρ=0.60, 95% CI: 0.32–0.80) (Fig. 2). Associations were stronger within concussion cases for whole-brain strain (ρ=0.86, 95% CI: 0.58–0.97) and PRV (ρ=0.64, 95% CI: 0.15–0.93). Overall, GFAP correlated more strongly with whole-brain strain than PRA (Z = 2.60, *P* = 0.009). Within concussion cases, correlations between GFAP and whole-brain strain were stronger than PLA (Z = 3.10, *P* = 0.002), PRA (Z = 3.68, *P* < 0.001) and PRV (Z = 2.30, *P* = 0.02).

Fig. 2: Raw GFAP levels are displayed on a $\log_{10}$ scale. Trendlines and 95% CIs were fitted using generalised additive models for overall impacts. Spearman correlation coefficients (ρ), 95% CIs and P-values are shown for overall (black) and concussive impacts (red).

Associations with plasma NfL: No unadjusted associations were detected between kinematic or strain measures and NfL after Bonferroni correction. However, linear regression models adjusting for age, body mass index, and time-since-injury demonstrated moderate standardised beta coefficients (β) between PRV (β = 0.54, 95% CI: 0.36-0.81, *P* < 0.001), and whole-brain strain (β = 0.43, 95% CI: 0.12-0.74, *P* = 0.005) with NfL for impacts overall.

Biomechanical tipping point: Piecewise regression identified strain levels above which associations with plasma GFAP steepened across PRV (breakpoint = 21.0 rad/s, 95% CI: 14–28; Δslope: 0.09, 95% CI: 0.01–0.16; *P* = 0.039), whole-brain (breakpoint = 0.21, 95% CI: 0.14–0.28; Δslope: 9.73, 95% CI: 2.60–17.01; *P* = 0.009) and brainstem strain (breakpoint = 0.19, 95% CI: 0.13–0.25; Δslope: 12.20, 95% CI: 4.46–19.91; *P* = 0.034) (Figure 3A). In concussion cases, players with supra-threshold brainstem strain had greater symptom severity scores at 24 hours (25, 13–43), compared to those below the 0.19 threshold (10, 6–11; *P* = 0.043) (Figure 3B).

Fig. 3: (A) Relationship between brainstem strain and log-transformed GFAP levels. Individual impacts resulting in concussion (red), medically cleared head injury assessment (HIA-; blue) and control (green are shown. (B) Sport Concussion Assessment Tool (SCAT) 24 hour symptom severity levels were compared above and below brainstem threshold of 0.19.

IV. DISCUSSION

By anchoring biomechanical measures to plasma biomarkers of brain injury, this study addresses a key limitation of prior iMG and FE studies that have relied largely on binary clinical diagnosis. FE-derived brain strain showed stronger associations with plasma levels of GFAP than peak kinematic metrics, supporting the theoretical advantage of strain-based measures, which account for the combined effects of impact magnitude, direction, duration, and brain anatomy. The observed non-linear strain-GFAP relationship, together with greater symptom severity among players exceeding the brainstem strain breakpoint, supports the concept of a biomechanical tipping point above which measurable brain injury is more likely. Future work should increase number of subjects and explore cumulative effects. Collectively, these findings support FE-derived brain strain as a biologically relevant representation of tissue deformation, and its use in further defining injury thresholds and future injury risk modelling.

V. REFERENCES

[1] Harmon *et al., JAMA Netw Open*, 2024 [2] Jones *et al*., *Br J Sport Med*, 2022 [3] Ghajari *et al., Brain*, 2017
[4] O'Brien *et al., JAMA Netw Open*, 2024. [5] Zimmerman *et al., J. Biomech,* 2021