Proceedings of 2017 IEEE International Conference on Biomedical and Health Informatics, Feb 16-19, 2017, Orlando, FL.

A Candidate Neuromechanical Biomarker and Dosimeter for Monitoring Cumulative Head Impact Trauma

John D. Ralston, *Member*, *IEEE*, Jonathan Woodard, Matthew Cieslak, Alex Asturias, Wendy Meiring, and Scott Grafton

***Abstract*— A candidate neuromechanical biomarker is demonstrated for monitoring cumulative head impact trauma. This biomarker demonstrates a pronounced threshold behavior, corresponding to the onset of physiological changes observed using high resolution brain imaging, and may enable a universally deployable wearable dosimeter.**

I. Introduction

Participation in many sports, military training and deployments, and industrial workplace activities all present risks of physical injuries that can be caused by both direct and indirect mechanical impacts to the head. Because of the wide range of tissue deformations and damage that can arise from the mechanical energy transferred from the external environment to the brain [1], the resulting cognitive, motor, and sensory impairments, as well as changes in mood, behavior, and personality, this issue is now recognized as a significant public health challenge.

Although attention has been directed predominantly at concussion injuries, a growing body of evidence has revealed that significant brain injuries can result from the cumulative effects of multiple lower intensity head impacts, none of which on their own lead to reported or clinically diagnosed concussion symptoms [2,3,4]. There currently exists no effective dosimeter to provide effective and universally deployable monitoring of cumulative head impact loading, or to alert users of pending but avoidable injury risks.

Standard neuropsychological testing of neurofunctional biomarkers [5] relies on self-reported or physician-diagnosed concussion symptoms, and is thus not effective for monitoring, assessing, or reducing injury risks due to cumulative sub-concussive head impact exposure.

A variety of neurochemical fluid biomarkers are being investigated for the detection of concussions [5,6], some of which may have sufficient sensitivity and specificity to detect physiological changes in the brain even in the absence of concussion symptoms. However, bio-assay costs, stability, and logistics, as well as difficulties in interpreting the results across large populations [6], limit their use as a dosimeter.

*Research supported in part by a General Electric-National Football League Head Health Challenge award.

J. D. Ralston is with Protxx, Inc., Menlo Park, CA, USA (phone: 650.215.8418; e-mail: john.ralston@protxx.com).

J. Woodard is with Globatom, Seattle, WA, USA.

M. Cieslak, A. Asturias, and S. Grafton are with the Department of Psychological and Brain Sciences, University of California, Santa Barbara, CA, USA (email: scott.grafton@psych.ucsb.edu)

W. Meiring is with the Department of Statistics and Applied Probability, University of California, Santa Barbara, CA, USA.

High resolution MRI brain imaging has emerged as the most powerful research tool to assess sub-concussive injuries. A variety of neuroimaging biomarkers based on both diffusion tensor imaging (DTI) and functional MRI (fMRI) have been shown to change following repetitive sub-concussive head impact exposures [3,4]. However, it remains unclear how many head impact exposures, and at what level of severity, are required to induce either reversible or persistent changes that are reliably detectable using brain imaging techniques. Equipment costs and analysis times also severely constrain the use of these techniques.

A variety of wearable devices have been developed and utilized in attempts to predict the occurrence of concussion injuries based on measured impact biomechanics. These devices all incorporate MEMS accelerometers and gyroscopes, with form factors that include skin-affixed patches, mouth guards, helmets, chin straps, headbands, skull caps, and clip-on devices. However, to accurately monitor motion of the user's head, the device must be well-coupled to the skull, which is only the case for skin affixed patches and fitted mouth guards.

None of the corresponding biomechanical metrics derived from impact sensor data have achieved widespread acceptance. Several do not correspond to measurable physical quantities, and/or require empirical fitting parameters with wide ranges of potential values [7,8]. Many studies limit impact data analyses to extracting peak linear or rotational velocities or accelerations [9], which neglects important biomechanical considerations such as the temporal duration of the impact and the physical displacement of the head during the impact. Both quantities influence the overall energy and power transferred to the head, which in turn determine the severity and corresponding brain injury risk of the impact. Furthermore, the above metrics have all been developed to try and predict concussions from single impacts, and do not address the critical issue of cumulative brain injuries resulting from sub-concussive head impacts.

In this paper, we examine the effects of cumulative head impacts on a group of college athletes throughout a soccer season. Data from skin-affixed wearable accelerometers were used to quantify the number and severity of head impacts. In parallel, high angular resolution diffusion spectrum MRI (DSI) of white matter (WM) and voxel-wise multi-dimensional diffusion anisotropy (MDA) data were acquired and used to quantify corresponding physiological changes in the brain. The cumulative impact power transferred to the brain is shown to be a promising neuromechanical biomarker for real-time monitoring of cumulative head impact exposure and injury risks, and, with improved device design, may enable a universally deployable wearable impact dosimeter.

II. METHODS

In this prospective cohort study, an NCAA Division I women's soccer team was monitored for head impacts throughout a 3-month soccer season and a 3-month post-season washout period. Twelve players began the study. One athlete suffered a concussion, was removed from play for neurocognitive testing, entered a supervised return-to-play protocol, and was not able to participate further in the study. Two athletes suffered ACL injuries and were not able to participate further in the study. Results are presented here for the remaining nine players, along with nine age-matched female controls.

A. Impact Measurements

Skin-affixed wearable accelerometers (X2 Biosystems X-Patch) were applied to the mastoid of each player during practices and games, and used to record linear and rotational accelerations for all impact events.

Known potential sources of X-Patch data errors [9] were addressed as follows. The devices were firmly attached to each player's mastoid process behind the ear, to minimize soft tissue motion artifacts observed when the devices are placed too low and partially on the neck. All data analyses and power calculations were carried out using raw sensor data, and did not rely on algorithms provided by X2 with the X-Patch sensors. Zero level offset errors due to mechanical distortions within the sensors were nulled out prior to processing the data. Sensor data generated by running and other low-impact-intensity motion were removed by filtering out all impacts with linear acceleration < 10G. Accelerometer and gyroscope traces generated by loosely attached sensors, device handling, and other spurious motion, which have easily identifiable linear and rotational acceleration characteristics, were removed from the data set using manual inspection. These traces were also utilized as a training set in a data analytics pipeline to numerically cluster traces for additional classification and filtering of spurious impact traces, yielding an expected false positive rate below 5% and a true positive rate above 93%.

Following the above data classification, no attempts were made to further classify the remaining individual head impacts in terms of direct vs. indirect, location and direction, or risk/probability of injury or concussion, as has been typically done in most other studies utilizing wearable head impact monitoring devices. Instead, data for all remaining impact events were used to calculate the cumulative impact power transferred to the brain.

For the current cohort of athletes, calculations of linear power transferred to the brain using the accelerometer data utilized an average female brain mass of 1.2 kg. Calculations of rotational power transferred to the brain using the gyroscope data utilized a 3D ellipsoidal brain model with average female volume of 1120 cm^3, radii of 8.3 cm (front to back), 7.0 cm (side to side), and 4.6 cm (top to bottom), and corresponding moment of inertia I=0.004 kg • m^2 (assuming rotation about axes through the base of the brain / neck).

B. Imaging Measurements

MRI diffusion weighted images (DWI) using diffusion spectrum image (DSI) sampling were acquired for each athlete, using a Siemens 3T Prisma scanner, at four time points throughout the season: scan 1 at the beginning of the season, scan 2 in the middle of the season, scan 3 at the end of the season, and scan 4 three months after the season was over (washout period and pseudo-baseline). Four DSI scans spaced over a 16-week sampling period were also acquired for each of nine age- and gender-matched control subjects without high risks for head trauma or history of concussion. Both local and global diffusion changes within brain white matter were assessed for the players vs. the controls.

The DSI images were recorded at 2.0 x 2.0 x 2.0 mm^3 resolution. Each dataset was reconstructed using the generalized q-ball imaging (GQI) algorithm as implemented in DSI-Studio [10]. Spatial normalization (ANTs) [11] and per voxel analyses [12] were utilized to explore statistical variations across the full image set. For each scan and voxel, primary (MDA0) and second order (MDA1) anisotropy values [13] were calculated. To explore local changes of primary anisotropy (MDA0), each player's and control's end-of-season scan (scan 3) was normalized (as a % change) with the same participant's out-of-season washout scan (scan 4). Differences in these normalized scan 3 MDA0 values between players and controls were estimated in SPM12 with an unpaired t-test (exploratory threshold, $p < 0.005$).

To estimate global changes of MDA0 and MDA1 diffusion, a 99.9% confidence limit of expected diffusion values was defined from the out-of-season washout scan (scan 4) at each voxel; this procedure was done separately for the players and controls. The numbers of voxels in WM surpassing the expected limit were then summed for each player and control in each of their respective scans 1, 2 and 3. A t-test was used to determine if there was a significantly greater than expected number of outlier values of MDA0 or MDA1 in the players for scans 1, 2 and 3.

III. RESULTS

A. Impact Data

Impact data were available for ~85% of all games and practices over the entire season. A total of 1938 head impacts were registered by the nine athletes over the 11 weeks for which data was recorded, corresponding to an average of 215 head impacts per player over the season (low = 128, high = 327), or ~20 impacts per player per week. Fig. 1 shows the histogram of the calculated cumulative total power transferred to the brain for all nine athletes over the entire 11-week period.

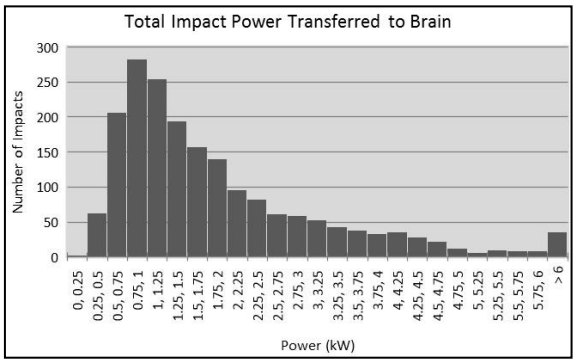

Figure 1. Histogram of cumulative total impact power (linear + rotational) transferred to the brain for all nine athletes throughout 3-month season.

Although the relative magnitude of linear vs. rotational power varied widely across individual impacts, the histograms for linear and rotational impact power components were similar, with both peaked between 0.25 and 0.75kW. The total impact power distribution peaks between 0.5kW and 1.5kW per impact, with few impacts beyond 5kW. The individual impact values reported here are all significantly lower than those reported to have a high probability of causing a concussion [8], and none of the nine players were diagnosed with any concussion symptoms.

B. Imaging Data

Changes in local WM diffusion between end-of-season images (MDA0 scan 3) normalized by the out-of-season washout/pseudo-baseline image (scan 4) were calculated for each subject and compared with similarly normalized scans for the age-matched controls. As shown in Fig. 2, clusters of WM changes are observed for the players vs. controls in both deep WM and at the white matter-cortical border, including at the cortical sulci.

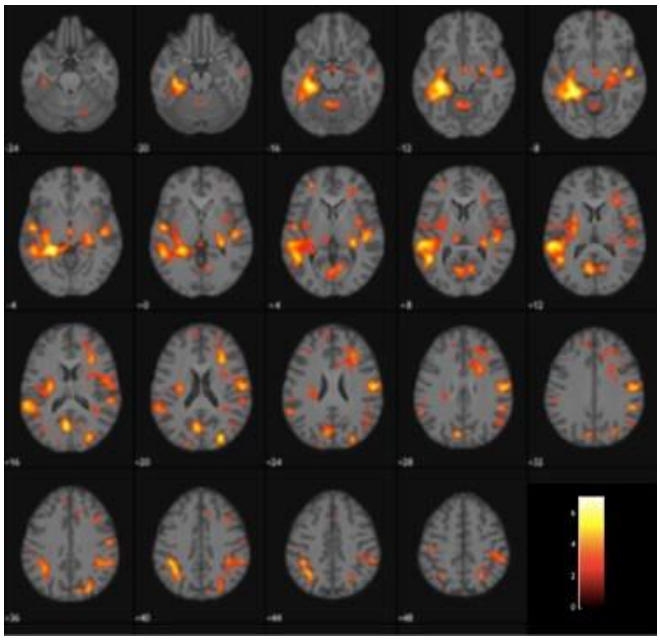

Figure 2. Local differences in WM primary diffusion direction between players and age matched controls (MDA0, in-season scan 3 normalized with respect to out-of-season scan 4, $p < 0.005$).

Global changes of WM were estimated by calculating the number of outlier voxels based on MDA0 and MDA1 values for players and controls at each voxel, using the out-of-season washout/pseudo baseline (scan 4) as a relative control. As shown in Fig. 3, compared to those of the controls, all 3 in-season scans (scans 1, 2, and 3) for the players show more voxels with outlying changes of white matter diffusion in both primary and second order fiber pathways relative to the baseline (all pairwise comparisons significant by unpaired t-test). These changes correlate more strongly with the total cumulative power in the period prior to the scan than with the total number of impacts in the same period.

Fig. 4 shows the calculated difference between the number of outlier voxels calculated for each player's mid-season scan and the average for all controls, plotted as a function of the total cumulative power measured over the 2, 3, and 4 week periods immediately preceding each scan. The data exhibit a non-linear relationship between the number of outlier voxels and the cumulative head trauma load, with a pronounced threshold behavior. In the specific example shown in Fig. 4, the cumulative power threshold above which outlier voxels are observed is on the order of 50 kW over a 2-week period, which falls within the range of typical cumulative impact powers for all athletes in this study.

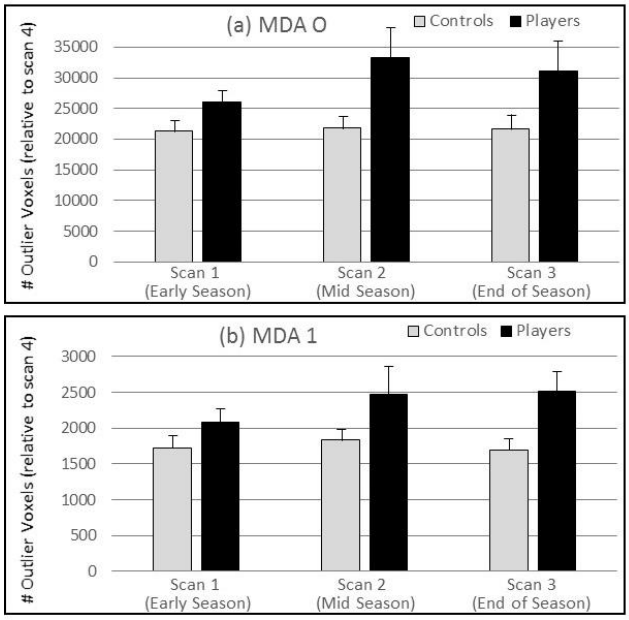

Figure 3. (a) MDA0 and (b) MDA1 WM diffusion in the players is globally different than age matched controls (scans 1, 2, and 3 vs. scan 4).

The differences between the results for 2, 3, and 4 weeks indicate that a significant fraction of the observed outlier voxel groupings emerge and persist during the two-week period following impact exposure, and that some fraction then begins to dissipate.

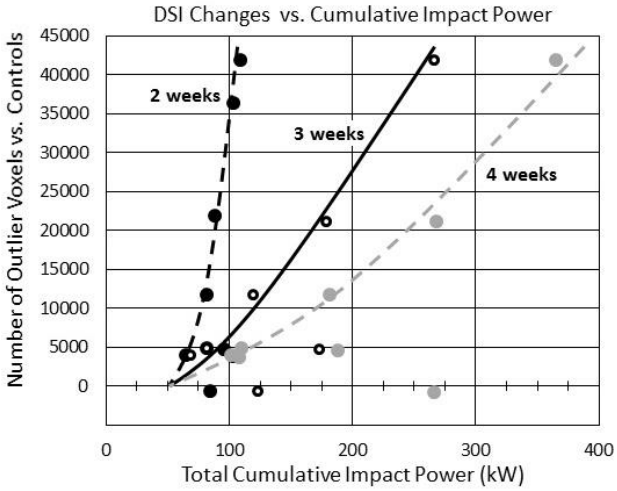

Figure 4. Calculated number of outlier voxels vs. total cumulative impact power transferred to the brain measured over 2, 3, and 4 week periods immediately preceding each player's mid-season DSI scan.

IV. Discussion

Physiological changes, biochemical responses, injuries, and any observed symptoms are all triggered by the

mechanical energy transferred to the head/neck/brain during direct or indirect head impacts [1]. Since many of these changes are cumulative, any metric used to characterize the corresponding impact injury risks and potential severity should be directly measurable and cumulative. The present work builds on earlier studies of automobile collisions and sports impacts, in which the maximum head impact power during a single impact was found to be a good predictor of concussion [8], and that effective thresholds for 50% / 95% probability of a concussion injury due to a single impact were on the order of 13 kW / 21 kW, respectively. Impact power transferred to the brain has not been investigated, nor has the application of cumulative impact power to assess cumulative brain trauma due to lower-intensity head impacts.

This paper demonstrates that the mechanical power transferred to the brain is a valid neuromechanical biomarker for cumulative impact trauma, and that the linear, rotational, and total transferred power can be calculated directly from the outputs of a MEMS accelerometer and MEMS gyroscope in a wearable device. With improved device design, most spurious impacts will have small durations and physical displacements, even if they register high peak linear and rotational accelerations, and hence contribute minimal errors to the above measurements of cumulative impact power.

The observation that global diffusion changes emerge throughout the soccer season as players accumulate head impacts (Fig. 3) is consistent with finite element modeling of head impacts, which predict that relative displacements and deformations are widely distributed throughout the brain due to coupling of linear and rotational degrees of freedom [14].

More advanced finite element brain models that include tissue-specific mechanical properties and detailed structural morphologies have predicted several additional important impact responses, including spatial localization of stress fields and tissue damage at morphologic features such as the cortical sulci [15, 16]. One implication of this finding is that even modest impacts, at levels traditionally thought to be safe, may generate localized regions of high stress and damage in the brain. This damage localization has been proposed as one possible explanation for recent observations that beta amyloid deposition is concentrated at the cortical sulci in the brains of professional football players who were diagnosed post mortem to have suffered from CTE [17]. The spatially localized diffusion changes observed at the cortical sulci in Fig. 2 demonstrate the potential ability to measure the onset of localized damage *in-vivo* and much earlier in an athlete's career, which will be critical to understanding how such effects originate and evolve over time.

The present framework might also help to assess reorganization or recovery processes occurring after head trauma, and therefore enable the investigation of white matter plasticity. As shown in Fig. 4, head impact trauma at the levels investigated in this paper appears to induce both reversible and persistent changes that are detectable using brain imaging techniques.

This paper has shown that the measurement of longitudinal changes in white matter diffusion using high angular resolution DSI imaging and voxel-wise MDA estimates, combined with the measurement of head impact biomechanics using wearable sensors, is a promising framework for detecting and characterizing sub-concussive head trauma. Further research is needed to improve the design of wearable sensors for such applications, as well as to characterize localized mechanical damage thresholds and the temporal evolution of corresponding physiological, biochemical, and neuropsychological manifestations.

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