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Biomechanical correlates of symptomatic and asymptomatic neurophysiological impairment in high school football ☆

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ABSTRACT

Concussion is a growing public health issue in the United States, and chronic traumatic encephalopathy (CTE) is the chief long-term concern linked to repeated concussions. Recently, attention has shifted toward subconcussive blows and the role they may play in the development of CTE. We recruited a cohort of high school football players for two seasons of observation. Acceleration sensors were placed in the helmets, and all contact activity was monitored. Pre-season computer-based neuropsychological tests and functional magnetic resonance imaging (fMRI) tests were also obtained in order to assess cognitive and neurophysiological health. In-season follow-up scans were then obtained both from individuals who had sustained a clinically-diagnosed concussion and those who had not. These changes were then related through stepwise regression to history of blows recorded throughout the football season up to the date of the scan. In addition to those subjects who had sustained a concussion, a substantial portion of our cohort who did not sustain concussions showed significant neurophysiological changes. Stepwise regression indicated significant relationships between the number of blows sustained by a subject and the ensuing neurophysiological change. Our findings reinforce the hypothesis that the effects of repetitive blows to the head are cumulative and that repeated exposure to subconcussive blows is connected to pathologically altered neurophysiology.

1. Introduction

An estimated 3.8 million sports-related traumatic brain injuries (TBIs) occur in the United States every year (Langlois et al., 2006), many of which are concussions (Gessel et al., 2007). Repeated concussions have been linked to early-onset Alzheimer's disease (Guskiewicz et al., 2005), depression (McCrory et al., 2009), dementia (Guskiewicz et al., 2005), and chronic traumatic encephalopathy (McKee et al., 2009). Currently the medical cost of TBI in the United States is approximately $60 billion per year without considering the increase in TBI associated with recent military conflicts. Yet despite the prevalence of concussions and the serious long-term consequences, the link between the injury biomechanics and the ensuing pathophysiology remains poorly characterized (Goldsmith and Monson, 2005; McCrory et al., 2001).

Talavage et al. (2010) recently reported observation of neurophysiological changes in high school football players without observable symptoms of concussion. The reported finding of degraded neurological performance in the absence of classical symptoms of concussion is consistent with prior observation of chronic traumatic encephalopathy (CTE) in the absence of history of concussion in three ex-NFL players, as reported in (Field Hearing: Legal Issues Football Head Injuries, 2010; Omalu et al., 2005, 2010). More recent discussion in the neuropathology community has implicated repetitive sub-concussive events as a significant source of accrued damage (Field Hearing: Legal Issues Football Head Injuries, 2010; McKee et al., 2009).

With the challenges of neural injury detection and the potential consequences if TBI goes unrecognized, it is critical that

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scientists, engineers, and medical professionals develop a better understanding of the mechanical events that lead to neurophysiological changes, how those events may accumulate over time, and how this accumulation affects healing processes. Toward this goal, neurophysiological changes and the biomechanical history of a cohort of high school football athletes were tracked for two seasons using instrumented helmets, functional magnetic resonance imaging (fMRI), and computer-based neuropsychological testing. This study expands upon our previous work (Talavage et al., 2010) by examining how the head collision histories of the athletes correlate with the observed changes in their neurophysiology, with the hypothesis being that the number and location of blows is directly correlated to the neurophysiological changes exhibited by the athlete.

2. Methods

All research methods were approved by an Institutional Review Board prior to the initiation of the study. Parental consent and participant assent were obtained from all subjects. The study is still ongoing, and the data reported here represents the aggregate data from two football seasons (2009 and 2010) (Talavage et al., 2010). In brief, the study consists of a cohort of high school football athletes for whom a neurophysiological and neuropsychological baseline was established in the pre-season. They were monitored throughout the season using a telemetry system embedded in their helmets. At least two players without a diagnosed concussion were recruited for follow-up neurophysiological and neuropsychological testing each week during the season. One was selected from the top 50% of players according to number of blows sustained in that week of play. The other was selected from the bottom 50%. Players with a diagnosed concussion were also recruited for follow-up testing (for additional details see the Appendix). Additional details of the neuropsychological testing, fMRI procedures, and statistical analyses are available (Supplementary material).

2.1. Subjects

Twenty four male high school football players between the ages of 15 and 18 (mean=17.0) were enrolled in the study for season 1, and 21 of the 24 participated throughout the entire season (Talavage et al., 2010). Twenty-eight male subjects between the ages of 14 and 18 (mean=16.8) were enrolled in the study for season 2, including 14 subjects from season 1 (Supplementary Table 1), and 25 of the 28 participated throughout the entire season. A self-reported history of concussion was obtained by a certified Athletic Trainer. No players were excluded from the study on the basis of previous concussions.

2.2. Helmet Telemetry

The Head Impact Telemetry (HIT^{TM}) System (Simbex; Lebanon, NH) was installed in subject helmets to monitor head impacts at every contact practice and game throughout both seasons. Each subject's helmet was outfitted with a sensor array comprising six uniaxial accelerometers, from which the location of blows and the head center-of-gravity linear acceleration were estimated (Crisco et al., 2004) (Table 1). A researcher was present at each practice, home game, and away game to ensure proper function of all sensors at all times.

2.3. Definition of injury groups

All subjects were classified according to "clinically-observed impairment" (COI)—brain-injury induced changes that were detected by a clinician, such as concussion—and "functionally-observed impairment" (FOI)—changes that were detected using neuropsychological testing and fMRI (Talavage et al., 2010). Using this system, an individual with a diagnosed concussion is COI+/FOI+ (all of the individuals diagnosed with a concussion demonstrated functional impairment). Individuals with no diagnosed concussion and no functional impairment were COI−/FOI−. Individuals were defined as being COI−/FOI+ if they had no observable signs of concussion but nevertheless showed a statistically significant reduction in at least one of their visual composite score or verbal composite score categories for ImPACT (Talavage et al., 2010). The COI−/FOI− and COI−/FOI+ groups are collectively referred to as the COI−/FOI× group. Because FOI designations depend only on ImPACT scores, these designations are insensitive to the variability in fMRI.

Table 1
Regression model variables and descriptions.

Variable	Description
C_F	Cumulative blows to the facemask
C_TF	Cumulative blows to the top-front of the head
C_S	Cumulative blows to the side of the head
C_B	Cumulative blows to the back of the head
PW_F	Blows to the facemask in the previous week
PW_TF	Blows to the top-front of the head in the previous week
PW_S	Blows to the side of the head in the previous week
PW_B	Blows to the back of the head in the previous week

3. Results

There was no significant difference in the median peak linear acceleration for any of the three groups (Kruskal–Wallis, $\chi^2=1.28$, $p>0.52$, Fig. 1 and Table 2); however, a significant difference in the median total number of blows was found (Kruskal–Wallis, $\chi^2=6.1$, $p<0.05$, Table 2). Subsequent pairwise tests indicated that the COI−/FOI+ group sustained more blows than the COI−/FOI− group (Tukey–Kramer, $p<0.05$).

The number of side blows sustained by each of the groups (Fig. 2) was significantly different (Kruskal–Wallis, $\chi^2=6.29$, $p<0.04$), and pairwise tests indicated the COI−/FOI+ group sustained significantly more side blows than the COI+/FOI+ group (Tukey–Kramer, $p<0.05$). Scatterplots displaying a two-dimensional projection of recorded impact location and peak linear acceleration illustrated that the members of the COI−/FOI+ group sustained a majority of their blows to the top-front region of the helmet, especially those above 80 G (Fig. 3).

Of the 116 regions of interest (ROIs), 33 ROIs yielded significant regressions ($p<2\times10^{-16}$) relating changes in fMRI to the blows sustained by the COI−/FOI× group (Table 3, Fig. 4(A)). Of the 116 ROIs, 39 ROIs yielded significant regressions ($p<5\times10^{-22}$) relating changes in fMRI to the blows sustained by the COI+/FOI+ group (25 non-cerebellar ROIs, Table 4; 14 cerebellar ROIs, Table 5, Fig. 4(B)).

The spatial distributions of the ROIs in the COI+/FOI+ and COI−/FOI× groups for which a significant regression was obtained indicate distinct regions of correlation (Fig. 4(C and D)). While some overlap exists in the frontal, cerebellar, and basal ganglia regions, the COI−/FOI× group exhibited a concentration of correlations in the upper parietal and occipital regions,

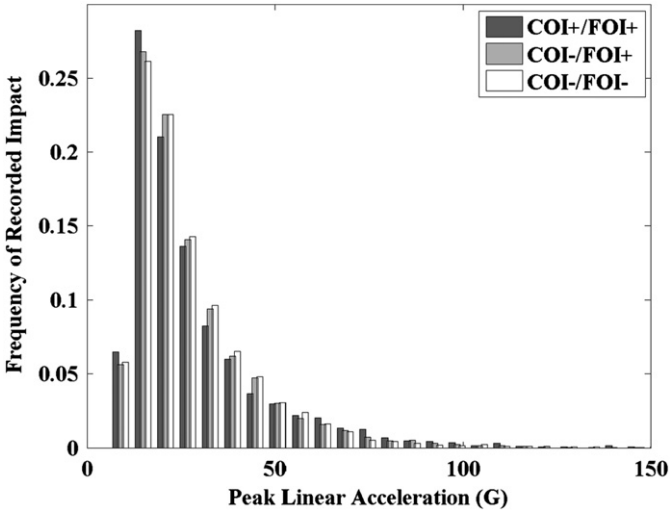

Fig. 1. Frequency distribution of peak linear acceleration for recorded impacts for each injury category. These distributions do not significantly differ (Kruskal–Wallis, $\chi^2=1.28$, $p>0.52$).

Table 2
Summary statistics for the distribution of number and peak linear magnitude of the recorded impacts for the three injury groups. The distributions of peak linear magnitude do not significantly differ (Kruskal–Wallis, $\chi^2=1.28$, $p>0.52$); however, the distributions of the number of blows sustained are significantly different (Kruskal–Wallis, $\chi^2=6.1$, $p<0.05$). Specifically, the COI−/FOI+ group sustained significantly more blows than the COI+/FOI+ group (Tukey–Kramer, $p<0.05$).

	COI+/FOI+	COI−/FOI+	COI−/FOI−
Peak linear magnitude (G) (median; mean ± std. dev.)	21.9; 28.5 ± 20.1	22.2; 27.7 ± 17.5	22.4; 27.5 ± 16.6
Peak linear magnitude (G) (Range; 1st quartile; 3rd quartile)	10.0–279.0; 15.8; 33.7	10.0–255.6; 16.3; 33.3	10.0–194.1; 16.3; 33.4
Hits sustained (count) (median; mean ± std. dev.)	438; 546 ± 464	1103; 1090 ± 570	593; 656 ± 378
Hits sustained (count) (Range; 1st quartile; 3rd quartile)	218–1551; 246; 567	396–1855; 567; 1783	226–1463; 354; 900

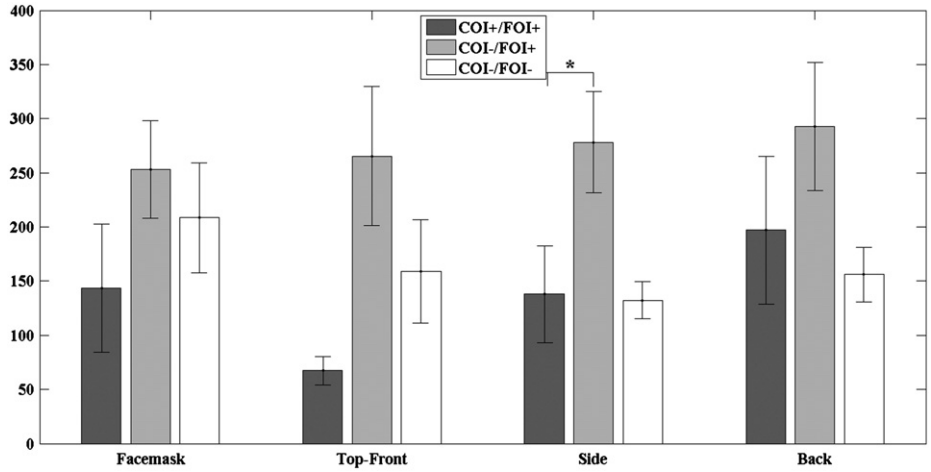

Fig. 2. Count of impacts sustained per season by each injury group reported for the four contact regions on the helmet (mean ± std. error). The injury groups sustained significantly different numbers of side impacts (Kruskal–Wallis, $\chi^2=6.29$, $p<0.05$). Specifically, pairwise tests indicate that the COI−/FOI+ group sustained significantly more side impacts than the COI+/FOI+ group (indicated by the asterisk, Tukey–Kramer, $p<0.05$). The average number of impacts to the facemask, top-front, and back of the helmet were not statistically different among the groups.

corresponding to visual processing (Fig. 4(g), Fig. 4(i) slice 2); in contrast, the COI+/FOI+ group exhibited an additional concentration of correlations in the temporal and lower parietal regions, corresponding to language processing (Fig. 4(l) slice 4).

4. Discussion

The purpose of this study was to characterize the magnitude, location, and number of blows sustained by athletes participating in high school football and to establish correlations between these blows and ensuing changes in neurophysiology. According to Talavage et al. (2010), three distinct impairment groups are observable among high school football athletes: those with clinically observed impairment and functional impairment as measured by fMRI and neuropsychological testing (COI+/FOI+), those with no outward symptoms and no functional impairment (COI−/FOI−), and those with no outward symptoms but substantial functional impairment (COI−/FOI+). This work extended that study with the incorporation of a second season of data, also classifying subjects into one of the three impairment groups, and identified the biomechanical characteristics that correspond with their classification. Having obtained data for 23 subjects over the course of two seasons, we found significant regressions for the COI−/FOI× and COI+/FOI+ groups consistent with progressive neurophysiological changes with accumulated blows to the head. These findings are consistent with our season 1 results (Talavage et al., 2010) and support the hypothesis of cumulative subconcussive damage (Field Hearing: Legal Issues Football Head Injuries, 2010; McKee et al., 2009).

The majority of previous concussion research has emphasized the magnitude and duration of individual blows (Goldsmith, 2001; Goldsmith and Monson, 2005). While identifying the characteristics of the specific blow that caused concussion was beyond the scope of the present work, it was found that the distributions of all blows sustained by COI+/FOI+, COI−/FOI+, and COI−/FOI− were not significantly different (Fig. 1; Table 2). This is consistent with the findings of Guskiewicz et al. (2007) that the magnitude of a blow in football was neither correlated with the probability of concussion nor the severity.

The primary difference between the groups was the number of blows sustained and their distribution (Table 3, Fig. 2). Talavage et al. (2010) had previously reported that the number of top-front blows between 20 G and 80 G sustained by the COI−/FOI+ group was a significant biomechanical differentiator. Consideration of subsets of blows according to magnitude was beyond the scope of this study; therefore, it is likely that the COI−/FOI+ population reported here also received more top-front hits than the other impairment groups if the blows are restricted to the 20 G–80 G magnitude range. In fact, the scatterplots showing both the location and magnitude of recorded impacts for characteristic individuals indicate that the COI−/FOI+ group received a substantial number of top-front impacts in the larger magnitude range (Fig. 3). Future work should consider the combined effects of impact magnitude and location with neurophysiological changes in more detail.

Neurophysiological changes were measured using fMRI. Such measurements paired with working memory tasks, such as the N-back task, have been reported to be sensitive to the effects of neurotrauma (Chen et al., 2008) and accumulated subconcussive blows (Talavage et al., 2010). While substantial spurious inter-subject variability is possible in a general fMRI experiment, the experimental design and post-processing procedures employed here specifically controlled for these factors. For instance, several studies have shown the N-back task to be generally insensitive to drug use, except in cases of overt intoxication (Gundersen et al., 2008a;

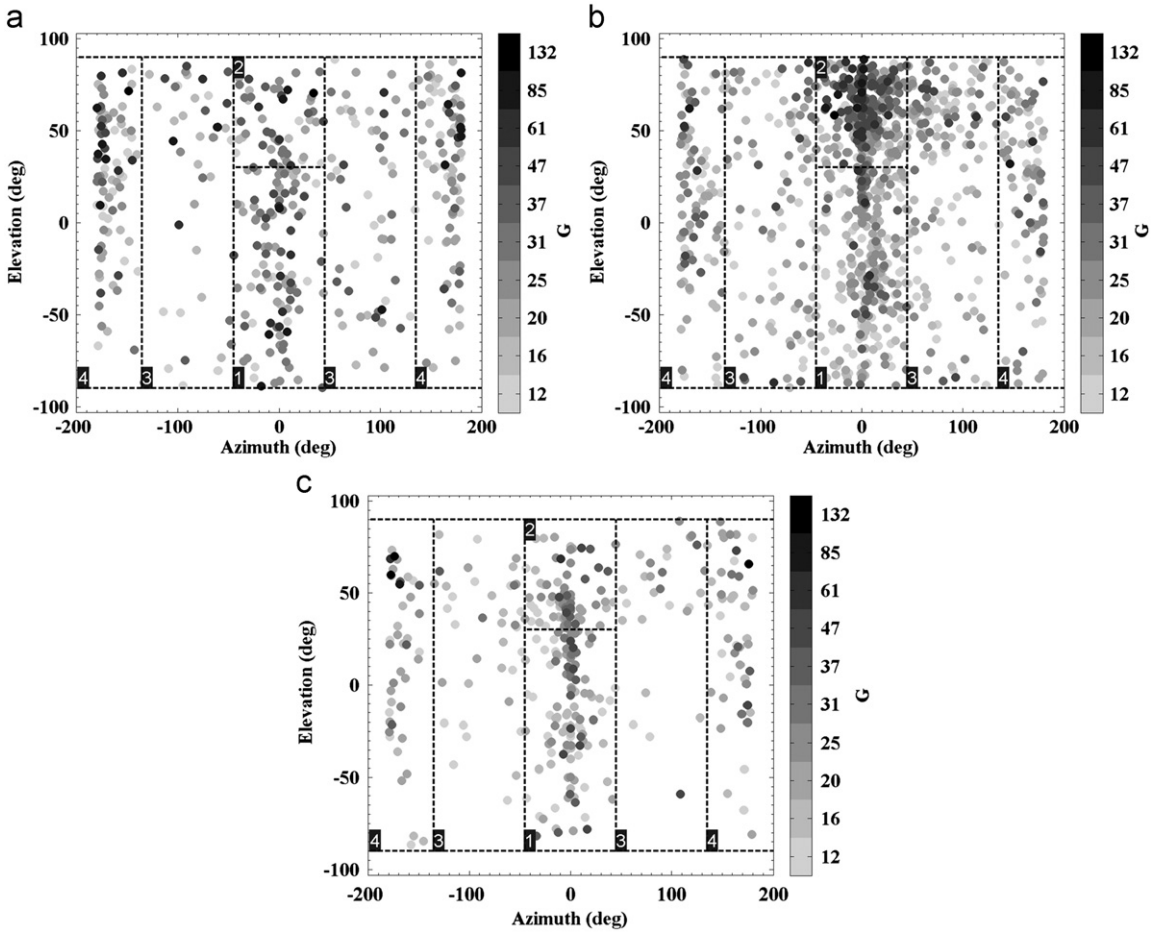

Fig. 3. Scatterplots showing both the location and intensity of blows taken by representative players from each group during a single season. The scatterplot displays a two-dimensional projection of the helmet surface. The numbers indicate the four contact regions on the helmet: (1) facemask, (2) top-front, (3) side, and (4) back. Each dot represents a blow measured during practice or a game. The peak linear acceleration of the blow is represented by the grayscale, with the hardest blows corresponding to black dots. The scale is not linear because of the high degree of skew in the blow magnitude distribution. This non-linear scale permits better resolution at lower blow magnitudes, where most of the blows are concentrated. Player 119 (a) sustained a concussion during the final week of practice in season 2. Player 115 (b) was an offensive lineman for both season 1 and season 2 and never sustained a concussion. Player 203 (c) was a defensive lineman during season 2. (a) COI+/FOI+, Player 119, Season 2, (b) COI−/FOI+, Player 115, Season 1 and (c) COI−/FOI−, Player 203, Season 2.

Gundersen et al., 2008b; Murphy et al., 2006). The remaining factors, such as diet and sleep, certainly affect the resulting effect size (Gonzalez-Castillo and Talavage, 2011); however, the subtracted global contrast average is believed to largely account for these effects. In particular, the global contrast average did not exhibit any significant correlations with the regression variables ($p > 0.1$), indicating that the global contrast average only captures session-specific variation unrelated to cumulative neurotrauma. Furthermore, while substantial inter-subject variability may exist in the raw value of the *t*-statistic in any given scanning session, this study focuses on the changes in *t*-statistic between the pre-season scan and an in-season scan. Given the good repeatability of the N-back task in non-athletes (Gradin et al., 2010), substantial inter-subject variability in the change from pre-season values is not expected, except for that variability arising from blows to the head during football gameplay. Therefore, the relative insensitivity of the N-back task to outside factors and the use of pre-season data to obtain changes in fMRI allowed us to connect neurophysiological changes to biomechanical insults sustained during football-related activity.

The models relating the left and right middle frontal gyrus (MFG; Tables 3 and 4) are of particular interest because neuropsychological tests have indicated that changes in MFG activation are related to measureable decreases in verbal and visual working memory that have been documented in concussed indivdiuals (Hoskison et al., 2009). Disruption and/or degredation of gray-matter tissue in the MFG has also been documented in boxers who have sustained repeated blows to the head (Chappell et al., 2006). Finally, the MFG has been identified as a region where strains are particularly large for impacts in the sagittal plane (Bayly et al., 2005), which corresponds with the dependence of the models on PW_TF.

Significant models were also found for both the COI−/FOI× and COI+/FOI+ groups relating history of blows to structures of the basal ganglia and limbic circuits, such as the putamen, caudate nucleus, globus pallidus, cingulate cortex, hippocampus, and parahippocampal gyri (Tables 2 and 3). Neurodegeneration in these ROIs has been documented in cases of CTE and is believed to be the cause of emotional and behavioral disorders that are commonly reported in patients diagnosed postmortem with CTE (McKee et al., 2009; Omalu et al., 2005, 2006). These ROIs show correspondence with both cumulative and previous week hits sustained to the top-front and side of the head and have been identified as high-risk regions for neurotrauma (Bayly et al., 2005; Ommaya et al., 1971; Sabet et al., 2008).

Several models were also identified for cerebellar ROIs with both the COI−/FOI× and COI+/FOI+ groups (Tables 2 and 4). Moderate to severe levels of cerebellar neurodegeneration have been reported on autopsy of persons with CTE (McKee et al., 2009),

Table 3
Results of stepwise regressions relating changes in the average *t*-statistic in ROIs for the COI−/FOI× group to their respective history of blows to the head throughout the season and in the week preceding scanning. The slopes (β_n) and intercept (β_0) relate to the general regression model (1) and correspond to the respective model variables reported below. All slopes are significant at the $\alpha=0.05$ level except where noted. ROIs in which CTE-related neurodegeneration has been reported are indicated by superscripts identifying the relevant literature.

ROI	R^2	Variables (X1;X2)	β_0	β_1	β_2
Calcarine fissure, L	0.13	C_TF	−0.346	0.341	
Calcarine fissure, R	0.18	C_TF	−0.371	0.421	
Caudate nucleus, R[b]	0.17	PW_F	−0.523	0.413	
Cuneus, L	0.22	C_TF	−0.526	0.579*	
Cuneus, R	0.23	C_F	−0.608	0.542*	
Declive, R[a]	0.31	C_F; C_B	−0.342	0.518*	−0.316
Frontal operculum, inf. L	0.18	C_F	0.674	−0.517	
Frontal operculum, inf. R	0.19	PW_B	0.199	−0.540*	
Globus pallidus, L[b]	0.14	PW_B	−0.295	0.303	
Hippocampus, L[b]	0.14	C_S	0.574	−0.339	
Inf. occipital gyrus, R	0.18	C_S	−0.498	0.517	
Inf. parietal gyrus, R	0.20	PW_B	1.091	−0.763*	
Inf. temporal gyrus, R	0.13	C_S	0.312	−0.244	
Lingual gyrus, R	0.15	C_F	−0.379	0.321	
Lingula II, L[a]	0.40	PW_S; PW_B	0.011	−1.218*	1.097*
Mid. frontal gyrus, L[a]	0.22	PW_TF	0.216	−0.369	
Mid. frontal gyrus, R[a]	0.18	PW_TF	0.060	−0.442*	
Orbitofrontal gyrus, sup. R[a]	0.14	C_F	0.352	−0.283	
Paracentral lobule, L	0.20	PW_TF	0.089	0.397*	
Paracentral lobule, R	0.45	PW_TF; PW_B	0.145	0.877*	−0.606*
Pars triangularis, L	0.23	C_F	0.497	−0.451*	
Postcentral gyrus, L	0.16	C_S	−0.288	0.391	
Precuneus, L	0.22	PW_TF	−0.329	0.407*	
Precuneus, R	0.15	PW_S	−0.403	0.327	
Rectus, R	0.12	C_F	0.709	−0.354	
Rolandic operculum, L	0.15	C_B	−0.273	0.489	
Sup. frontal gyrus, lateral R[a]	0.16	PW_TF	0.138	−0.328	
Sup. occipital gyrus, L	0.14	C_TF	−0.124	0.405	
Sup. occipital gyrus, R	0.12	C_B	−0.381	0.394	
Suppl. motor area, L	0.14	PW_F	0.436	−0.246	
Supramarginal gyrus, L	0.25	PW_B	−0.686	0.576*	
Vermis IX[a]	0.13	C_B	0.460	−0.331	
Vermis VI[a]	0.13	PW_TF	0.089	−0.447	

* $p < 0.01$.
[a] McKee et al. (2009).
[b] McKee et al. (2010).

and disruption and/or degradation of the cerebellar tissue has been documented in boxers who have sustained repeated blows to the head (Chappell et al., 2006).

While the correlation of individual ROIs to a history of blows is informative, a full interpretation of any given regression is difficult. To the knowledge of the authors, this is the first time the number of blows a player has sustained has been related to changes in neurophysiology; therefore, individual ROIs are only interesting inasmuch as they exhibit correlation in a region known to be involved in the pathophysiology of concussion. A more useful interpretation relative to the existing literature arises from looking at a map of the ROIs for which a significant regression was found, regardless of the functional form of the regression (Fig. 4). The COI−/FOI× and COI+/FOI+ groups show some overlap in significant ROIs, including regions in the cerebellum, frontal lobe, and basal ganglia. The starkest difference is the substantial involvement of upper parietal and occipital visual processing systems in the COI−/FOI× group (Fig. 4(g), Fig. 4(i) slice 2) contrasted with the involvement of upper temporal and lower parietal verbal processing systems in the COI+/FOI+ group (Fig. 4(l) slice 4). This contrast is consistent with the observation that verbal working memory deficits were predominate in COI+/FOI+ individuals, while COI−/FOI× individuals tended to exhibit stronger deficits in visual working memory (Talavage et al., 2010). It is possible that the distinct history of blows between COI+/FOI+ and COI−/FOI+ subjects underlies this contrast in neural system involvement. This would imply that the changes in COI+/FOI+ and COI−/FOI+ individuals arise from distinct biomechanical processes.

More strikingly, both the COI+/FOI+ map and the COI−/FOI× map bear substantial resemblance to the strain patterns documented for sagittal motion by Bayly et al. (2005). There is further similarity with the pattern of lesions found on autopsy of fatal traumatic brain injury (Gurdjian, 1976). It has long been believed that tissue strain is the fundamental biomechanical process that engages pathophysiological sequelae (Goldsmith, 2001). Our findings support this hypothesis. Moreover, they indicate that the effects of strain linger in the tissue, so that the effect of cumulative blows on tissue health is akin to mechanical fatigue. However, the dependence of regression models for some ROIs on previous week blows instead of cumulative blows suggests that the cumulative effect is in competition with some sort of healing. The rate of damage accumulation and the relative rate of healing are critical components in understanding concussion and ultimately the link to progressive degenerative neuropathy.

The biomechanical correlates presented here do not present a complete picture of the insults sustained by our subjects and warrant future work. In particular, the HIT System does not measure angular accelerations (Rowson et al., 2009) and only estimates linear accelerations and direction (Crisco et al., 2004). Angular accelerations are of particular concern in the biomechanics of concussion. Holbourn (1943) originally hypothesized that rotational strain fields could be at least as large as linear strains, which Ommaya et al. (1968) later verified, showing that injury

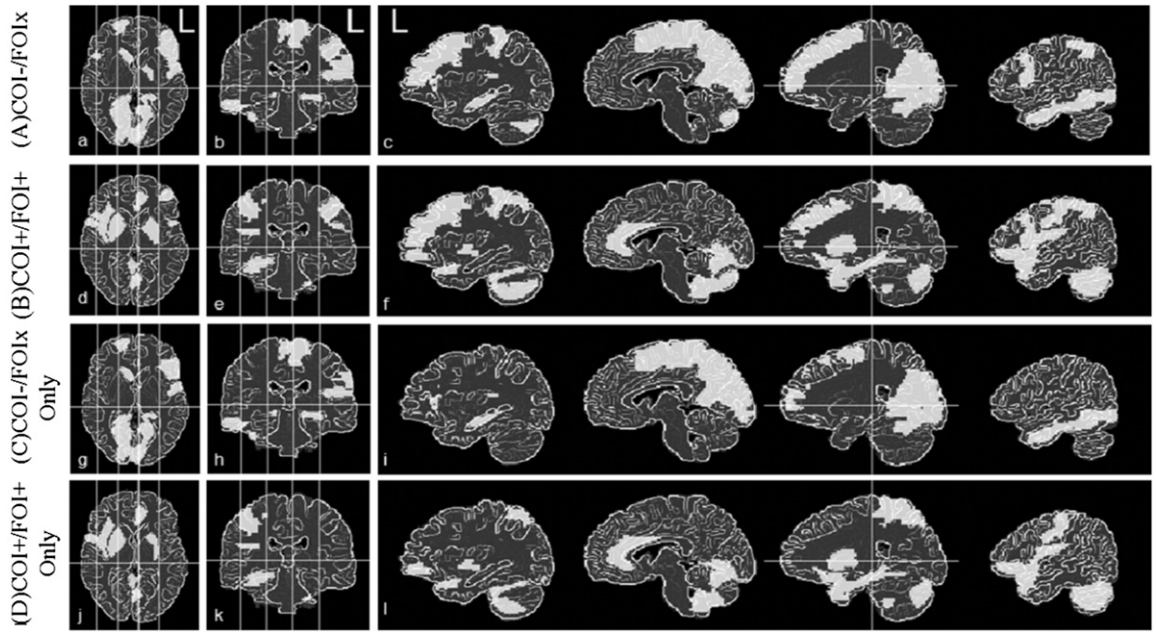

Fig. 4. Anatomical maps showing ROIs where a significant ($\alpha < 0.05$) regression was obtained for both the COI+/FOI+ and COI−/FOI× groups. The (A) COI−/FOI× group exhibits diffuse correlations that span every lobe of the cortex. The (B) COI+/FOI+ group also exhibited diffuse correlations in every lobe of the cortex. While both groups exhibited diffuse correlations, the distributions were only partially overlapping. Several parietal and occipital structures yielded significant regressions in the COI−/FOI× group but not the COI+/FOI+ group (C). In contrast, the COI+/FOI+ exhibited several correlations in the orbitofrontal lobe and upper parietal lobe that were not exhibited in the COI−/FOI× group (D). Maps were constructed from the Talairach atlas, and the sagittal slices proceed from left to right, with slices taken at the locations indicated in the coronal and axial images. Regressions indicate substantial correlation with a history of blows in the hippocampus and basal ganglia for both groups.

Table 4
Results of stepwise regressions relating changes in the average *t*-statistic in non-cerebellar ROIs for the COI+/FOI+ group to their respective history of blows to the head throughout the season and in the week preceding scanning. The slopes (β_n) and intercept (β_0) relate to the general regression model (1) and correspond to the respective model variables (X_n) reported below. All slopes are significant at the $\alpha = 0.05$ level except where noted. ROIs in which CTE-related neurodegeneration has been reported are indicated by superscripts identifying the relevant literature.

ROI	R^2	Variables (X_1;X_2)	β_0	β_1	β_2
Cingulate gyrus, ant. L[b]	0.59	PW_B	0.964	−0.558	
Cingulate gyrus, post. R[b]	0.83	C_F	−0.969	0.540*	
Frontal operculum, inf. L[a]	0.73	C_F	1.815	−0.575	
Frontal operculum, inf. R[a]	0.95	PW_TF; PW_B	−0.034	−0.527*	0.890*
Fusiform gyrus, R	0.73	C_F	−1.332	0.593	
Globus pallidus, L[b]	0.90	PW_S	1.088	−0.386*	
Globus pallidus, R[b]	0.63	PW_B	0.194	−0.451	
Inf. parietal gyrus, R	0.84	PW_S	−1.181	0.714*	
Insula, R	0.82	PW_B	0.943	−0.539*	
Lingual gyrus, L	0.62	PW_F	−0.472	0.397	
Mid. frontal gyrus, L[a]	0.61	PW_TF	0.702	−0.606	
Mid. frontal gyrus, R[a]	0.61	PW_S	−0.983	0.610	
Mid. temporal pole, R	0.59	PW_TF	−1.475	0.648	
Olfactory bulb, R	0.59	PW_B	1.163	−0.599	
Orbitofrontal gyrus, inf. R[a]	0.96	C_S; PW_B	0.544	0.510*	−0.856*
Orbitofrontal gyrus, mid. L[a]	0.58	PW_TF	1.465	−0.729	
Parahippocampal gyrus, R[b]	0.58	C_F	0.914	−0.597	
Postcentral gyrus, L	0.93	C_TF; PW_B	−0.804	0.271	−0.174
Postcentral gyrus, R	0.93	C_F; PW_B	−0.210	−0.359	0.589*
Putamen, L[b]	0.64	C_S	1.192	−0.896	
Putamen, R[b]	0.77	C_B	1.761	−0.836*	
Sup. parietal gyrus, L	0.70	PW_F	0.723	−0.917	
Sup. parietal gyrus, R	0.59	PW_TF	0.689	−0.514	
Sup. temporal pole, L	0.76	C_S	0.648	−0.786	
Sup. temporal pole, R	0.60	C_B	0.422	−0.372	

* $p < 0.01$.
[a] McKee et al. (2009).
[b] McKee et al. (2010).

thresholds double when head rotation is disallowed. Sabet et al. (2008) have also shown that rotational accelerations generate substantial strain fields, which are believed to result in more severe injury. The inability of the HIT System to reliably determine the angular accelerations, and consequently the inability to relate angular accelerations to our fMRI findings, is a regrettable deficit in the present work. Considerable progress is certainly warranted in the field of sports telemetry technology if biomechanics researchers are to formulate a more complete picture of what happens in football gameplay.

Table 5
Results of stepwise regressions relating changes in the average *t*-statistic in cerebellar ROIs for the COI+/FOI+ group to their respective history of blows to the head throughout the season and in the week preceding scanning. The slopes (β_n) and intercept (β_0) relate to the general regression model (1) and correspond to the respective model variables (X_n) reported below. All slopes are significant at the $\alpha=0.05$ level except where noted. CTE-related neurodegeneration has been broadly documented in cerebellar ROIs (McKee et al., 2010).

ROI	R^2	Variables (X_1;X_2;X_3)	β_0	β_1	β_2	β_3
Caudal tuber valvulae, L	0.82	C_S	0.803	−0.720		
Caudal tuber valvulae, R	0.76	C_TF	−1.239	0.580		
Declive, L	0.76	PW_F	−0.706	0.688		
Lingula I, R	0.98	PW_F; PW_S; PW_B	0.232	0.661*	−0.213	−0.273
Lingula II, L	0.59	PW_S	0.695	−0.376		
Lingula II, R	0.77	C_S	0.273	−0.181*		
Nodulus, L	0.79	PW_S	2.071	−0.930		
Pyramis, L	1.00	C_F; C_S; PW_S	0.947	0.214*	−0.759*	−0.117*
Uvula, L	0.96	C_F; C_S	0.233	0.340	−0.656*	
Uvula, R	0.74	PW_S	0.739	−0.351		
Vermis I/II	0.95	C_TF; PW_B	2.558	−0.903	−1.806*	
Vermis III	0.64	PW_B	0.363	−0.937		
Vermis IV/V	0.80	C_F	0.074	−0.339		
Vermis VI	0.66	C_S	1.468	−0.710		

* $p < 0.01$.

It should also be noted that these regressions do not indicate the precise functional relationship between head collision history and ensuing neurophysiological changes. The exploratory nature of these regressions can only indicate likely connections between biomechanics and neurophysiology. Functional relationships should be based on a more complete theory for the biomechanical basis of neurotrauma; however, these regressions help to direct future research and the development of such a theory.

It should be noted that the effect of healing and recovery is not readily apparent in this study. The neurophysiological changes observed may not persist for a sufficiently long period of time to be connected to any later-life neurodegeneration, and this hypothesized recovery process should be more thoroughly explored. Nevertheless, the descriptive power of cumulative blow regressors suggests that the effects of blows may persist for a much longer period than previously believed. During this time, individuals may be in a vulnerable state, so that the blow that results in symptoms is the "straw that broke the camel's back." If this concern is valid, a particular blow may cause a "physiological bifurcation" that places the brain in a distinct pathophysiological regime, much in the way that minor injuries precondition an eventual catastrophic tear in musculoskeletal soft tissues. Certainly, if concussion were a purely acute injury, the very strong connection we observed between blow history and neurophysiological changes should not exist. It seems unlikely that this connection is due to concussed players playing more violent football, given that COI+/FOI+ players neither sustained more blows nor larger blows than their COI−/FOI× counterparts (Figs. 1 and 2). In light of these findings, a larger cohort of COI+/FOI+ subjects should be assembled to better test this hypothesis.

Finally, fMRI does not elucidate the cellular basis for the observed changes. Due to the interconnectedness of the brain, changes in neurophysiology for an ROI could be the result of pathological processes in the region, pathological processes in a connected region, or a combination of both. Furthermore, the BOLD contrast serves only as a surrogate for neural activity. Some work indicates a decoupling of neurometabolic activity from neural activity subsequent to concussion (Hovda et al., 1995), making it unclear whether our measurements of neurophysiology are vascular, neural, or both. Other imaging modalities, such as diffusion tensor imaging and susceptibility weighted MRI, may reveal the connections between the cellular basis and the observed neurophysiological changes; however, it is likely that more work is needed to elucidate how features of a mechanical insult to the brain—such as location, magnitude, duration, and eccentricity—engage one or more of several pathophysiological mechanisms.

Epidemiological studies have indicated that the effects of concussion are cumulative (Collins et al., 2002; Guskiewicz et al., 2003). Moreover, neurodegeneration found on autopsy of persons with CTE has not been commensurate with the reported clinical history of concussion, leading some to suggest that subconcussive blows may have a lasting and cumulative effect that is related to CTE (Field Hearing: Legal Issues Football Head Injuries, 2010; McKee et al., 2009). While it has been historically believed that some level of symptomatic neurotrauma may occur without lasting effects (Denny-Brown and Russell, 1941; Parkinson, 1992), the growing body of evidence indicates that the cumulative effect of repeated blows to the head is pathological. Our work, both here and elsewhere (Talavage et al., 2010), has provided direct evidence of this effect. Furthermore, we have shown that covert changes in neurophysiology correspond to regions of the brain that are known to experience large strains. The regressions and summary statistics presented here reinforce the observation that symptomatic (COI+/FOI+) and asymptomatic (COI−/FOI+) changes in neurophysiology arise from distinct biomechanical events and represent distinct changes in neurophysiology. Further work will elucidate why these two groups exhibit distinct pathophysiologies and how these differences relate to the possible development of acute neurological injury and long-term neurodegeneration, such as CTE.

Conflict of interest statament

The authors declare that they have no financial interest in this study or its outcomes.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jbiomech.2012.01.034.

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