# Functionally-Detected Cognitive Impairment in High School Football Players Without Clinically-Diagnosed Concussion

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**Conflict of Interest Notification**

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

**Abstract**

Head trauma and concussion in football players has recently received considerable attention. Post-mortem evidence suggests that accrual of damage to the brain may occur with repeated blows to the head, even when individual blows fail to produce clinical symptoms. There is an urgent need for improved detection and characterization of head trauma to reduce future injury risk and promote development of new therapies. This study examined neurologic performance and health in the presence of head collision events in high school football players, using longitudinal measures of collision events (HIT™ system), neurocognitive testing (ImPACT™), and functional MRI (fMRI). Longitudinal assessment (including baseline) was conducted in 11 males (ages 15-19) participating on the varsity and junior varsity football teams at a single high school. We expected and observed subjects in two previously described categories: *(1)* no clinically-diagnosed concussion and no changes in neurological behavior and *(2)* clinically-diagnosed concussion with changes in neurological behavior. Additionally, we observed players in a previously undiscovered third category who exhibited no clinically-observed symptoms associated with concussion, but who demonstrated measurable neurocognitive (primarily visual working memory) and neurophysiologic (altered activation in dorsolateral prefrontal cortex, DLPFC) impairments. This new category was associated with significantly higher numbers of head collision events to the top-front of the head, directly above DLPFC. Observation of this category suggests that more players are suffering neurologic injury than are presently detected via traditional concussion-assessment mechanisms. These individuals are unlikely to undergo clinical evaluation and thus continue to participate in football-related activities even when changes in brain physiology (and potential brain health) are present, likely increasing risk of future neurologic injury.

**Keywords:** MRI, Cognitive Function, Human Studies, Traumatic Brain Injury, Behavioral Assessment

## Introduction

The popular press recently reported a growing concern over the effects of concussions sustained while playing football ((2009), Schwarz, A. (2010)). A recent Congressional hearing on sports-related concussions brought particular attention to high school football players (Schwarz, A. (2009)), a group annually comprising over one million young males (http://www.nfhs.org), of which approximately 67,000 per year are clinically-diagnosed with a concussion (Broglio, S.P., et al. (2009), Gregory, S. (2010)). More significantly, it is estimated that a similar number of concussed players go undiagnosed (McCrea, M., et al. (2004)). Failure to diagnose concussions is a concern for two reasons. First, players with neurological damage not removed from play are at higher risk for additional concussions (Guskiewicz, K.M., et al. (2003)). Second, biomechanics research has suggested that injury may be accumulated (Goldsmith, W. and Monson, K.L. (2005), Ommaya, A.K., et al. (1994)), a finding supported by histological evaluation of deceased athletes (Omalu, B.I., et al. (2006), Omalu, B.I., et al. (2005), Omalu, B.I., et al. (2010)). Players who are not removed from play could thus accumulate injury in the form of multiple sub-concussive insults. Such a mechanism has been suggested by McKee, A.C., et al. (2009) based on observation in autopsies of long-term neurodegeneration that did not strictly correlate with a clinical history of concussion.

The effects of concussion—defined herein as a closed-head injury to the brain induced by mechanical insult—are part of a broader public concern about brain health. Concussion falls within the larger category of traumatic brain injury (TBI), which represents a significant component of brain health in the United States, with as many as 3.8 million sports-related incidents every year (Langlois, J.A., et al. (2006b)) and approximately 50,000 deaths and 235,000 hospitalizations from all causes (Langlois, J.A., et al. (2006a)). Previous TBI has been shown to be a significant risk factor for repeat concussions (McCrory, P., et al. (2009)) and other neurological conditions including early-onset Alzheimer's disease (Graves, A.B., et al. (1990), Rasmusson, D.X., et al. (1995)), chronic depression (Holsinger, T., et al. (2002)), epilepsy (Langlois, J.A., et al. (2006b)), and chronic traumatic encephalopathy (CTE) (McCrory, P., et al. (2007), Omalu, B.I., et al. (2005)). At least 17% of individuals who experience multiple concussions develop CTE (Roberts, G.W., et al. (1990)), with McKee *et al.* proposing that the incidence rate is likely higher (McKee, A.C., et al. (2009)). Athletes participating in sports involving a significant probability of head collisions, such as American football, represent a group that is at particularly high-risk for concussion and other forms of TBI.

Currently, on-site healthcare professionals evaluate athletes for presence of concussion by examination for symptoms such as loss of consciousness, amnesia, headaches, dizziness, and inability to respond correctly to specific, direct questions (McCrory, P., et al. (2009)). Drawbacks to this process include observation that symptoms often manifest themselves several hours after trauma (Guskiewicz, K.M., et al. (2003)), that symptoms do not clearly indicate a specific neurological dysfunction to treat (Levin, H.S., et al. (1992)), and that damage may accumulate over time as a result of injuries that do not produce symptoms meeting clinical criteria for concussions (McKee, A.C., et al. (2009)).

While concussion is inherently a mechanically-induced injury, efforts to determine the underlying biomechanical mechanisms have been inconclusive (El Sayed, T., et al. (2008), Goldsmith, W. and Monson, K.L. (2005), Hardy, W.N., et al. (1994), Ommaya, A.K., et al. (1994)). Attempts to correlate injury to kinematic input variables such as peak acceleration or the Head Injury Criterion have proven inadequate in their ability to accurately predict the occurrence of concussion (Goldsmith, W. and Monson, K.L. (2005), Greenwald, R.M., et al. (2008), King, A.I., et al. (2003)). Similarly, efforts to identify metabolic factors that predispose an individual to concussion have remained elusive (Begaz, T., et al. (2006)).

In order to model onset and development of cognitive impairment associated with head trauma in high school football, we monitored head collision events (HIT™ system) experienced throughout the course of a single season, including practices and games, by 21 members of a high school varsity football team. Based on the number and nature of collision events, we longitudinally evaluated 11 of these athletes (eight varsity starters, three reserves) for changes in neurocognitive function and neurophysiology. Linking these findings, we have identified a group of high school football players without clinically-observable signs of concussion who exhibited neurocognitive and neurophysiologic impairments comparable to or exceeding those exhibited by teammates who were diagnosed as concussed.

## Materials and Methods

*Subjects:* Twenty-four (24) male high school football players (range=15-18 years, mean=17.0) were enrolled. Twenty-one (21) participated in each aspect of the study throughout the 2009 season (Table 1). Of the three players who did not complete the study, two quit participation in football prior to the end of the season, and the third suffered a season-ending knee injury during the first game and did not participate in team activities thereafter.

*Head Collision Event Monitoring:* Participants in this study had Head Impact Telemetry (HIT$^{TM}$) system (Simbex; New Lebanon, NH) sensors installed in their helmets. This system utilizes six accelerometers that provide three components each of linear and angular acceleration, providing measurement of direction and intensity of collision events experienced by the head (Crisco, J.J., et al. (2004)). Each set of sensors is equipped with a wireless transmitter that provides real-time telemetry to a nearby laptop which records the linear accelerations and impact location for each event.

*Pre-Season Assessment:* Prior to the beginning of contact drills, 23 of the enrollees completed both “Pre-Season” neurocognitive (ImPACT$^{TM}$) and neurophysiologic (fMRI) assessment to quantify individual and group baselines. Neurocognitive testing was conducted at the high school, either in groups of up to 10 players in the library (19/23) or individually at the desk of the athletic trainer (4/23).

*Neurocognitive Testing:* The on-line version of ImPACT$^{TM}$ (http://www.impacttestonline.com) was used as a “gold standard” of neurocognitive assessment based on its widespread use in evaluating athletes. All participants selected the “High School” group for evaluation relative to an age-appropriate norm. Note that ImPACT$^{TM}$ was not used by the high school athletic training or medical staff in the return-to-play evaluation process.

*Neurophysiologic Testing:* Functional MRI was performed at the Purdue MRI Facility (West Lafayette, IN) on a 3T General Electric (Waukesha, WI) Signa HDx. This system is equipped with real-time monitoring, permitting excessive (greater than 0.5mm) within-acquisition motion to be identified on-site and acquisitions repeated as necessary until subject compliance is achieved. All 30-minute imaging sessions used a 16-channel brain array (Nova Medical; Wilmington, MA). For registration, whole-brain high-resolution images (3D-FSPGR; 1mm isotropic resolution) were acquired, including cerebellum.

Three functional runs were conducted of a visual working memory (N-back) paradigm, using gradient-echo echo planar imaging (TR/TE=1500/26ms; matrix=64x64; FOV=20cm; 34 slices; 3.8mm thickness; 117 volumes). In each run subjects performed one block (15 presentations, 3s interval, 5 targets per block) each of 0-, 1- and 2-back tasks for single letters (Lovell, M.R., et al. (2007), Ragland, J.D., et al. (2002)). Visual presentation was via fiber optic goggles (NordicNeuroLab; Bergen, Norway). Subjects responded by dominant index finger, via fiber-optic button box (Current Designs; Philadelpha, PA). Presentations and responses were implemented using E-Prime (Psychology Software Tools; Sharpsburg, PA). The order of the task blocks in the three runs was counter-balanced within each session, and across assessments.

*In-Season Assessment:* During each of the 10 weeks in the season, 1-3 players were invited to undergo “In-Season” assessment. Players were invited if *(a)* they were diagnosed by the team physician as having experienced a concussion, *(b)* they were not identified by the physician as being concussed, but their HIT™ system data indicated they had accrued unusually large numbers of collision events or at least one high magnitude (i.e., >100G) acceleration during that week’s practices and game(s), and *(c)* athletes who participated in both practices and games but did not experience either a large number of collision events or a high magnitude acceleration. Participant compliance with these invitations was 75%, and 15 In-Season assessments were initiated. All 15 ImPACT™ assessments were completed. Due to a network malfunction, only 14 fMRI sessions were performed in whole and included in our analysis.

In-Season assessments were conducted within 48 hours of a game or 72 hours of diagnosis of concussion. ImPACT™ testing was conducted at the MRI Facility with the player isolated in an office, and fMRI was conducted as above. The 11 players undergoing In-Season assessment included eight (8) who were invited on the basis of criteria *(b)* or *(c)*, above. Players invited under criterion *(b)* were primarily recruited from among those who had accrued large numbers (i.e., top 25%) of head collision events, as assessed by the HIT™ system. The three remaining players undergoing In-Season assessment represented three of the four players who were diagnosed by the team physician as having experienced a concussion. Note that one of the eight players receiving an In-Season assessment while exhibiting no symptoms associated with concussion later received a diagnosed concussion, but declined to participate in further assessments. Because this player had not yet experienced a concussion at the time of Pre- and In-season assessment, his data have been included with the group of players who exhibited no symptoms of concussion.

*Post-Season Assessment:* 10 of the 11 players (excluding the player noted above) who underwent In-Season assessment returned 1-3 months after the end of the season for “Post-Season” assessment. ImPACT™ testing was conducted at the MRI Facility (nine players) or in the high school athletic training room (one player). fMRI was conducted as above.

*Player Categorization:* Observed changes in neurologic health were subsequently examined in the context of clinical history of diagnosis or non-diagnosis of concussion during the course of the season and by detection or non-detection of abnormal re-test behavior using ImPACT™. To this end a 2×2 categorization matrix was defined for group evaluation (see Fig. 1). Players who were diagnosed by the team physician with a concussion were deemed to be positive for *clinically-observed impairment*, and are labeled COI+. Players who were not diagnosed with a concussion were negative for this feature, and are labeled COI-. Players who exhibited deviant ImPACT™ re-tests were said to be positive for a *functionally-observed impairment* (FOI+), while those whose ImPACT™ scores fell within the 99% confidence intervals were negative for this feature (FOI-).

*Statistical Analysis:* Three categories of data were evaluated in this work: neurocognitive scores (ImPACT™), collision events (HIT™ system), and neurophysiologic signal changes (fMRI). In addition, the statistical significance of the observed frequencies of player categories was evaluated.

The consequences of the multiple environments in which ImPACT™ testing was performed were modeled via regression to most accurately identify abnormal re-test performance—the documented range of reliable test/re-test performance is based on a single site (Iverson, G.L., et al. (2003)). Verbal and Visual Memory Composite scores from re-tests for which ImPACT™ did not indicate performance outside the reliability range were regressed on a population basis to compute the effect of site, permitting prediction of re-test performance at either site. Population variances were computed for ImPACT™ scores based on the Pre-Season tests conducted at the high school. 99% confidence intervals were generated around each player's re-test scores—on a site-specific basis—using the Pre-Season test variances scaled to account for observation of a higher mean for MRI Facility re-tests. Verbal and Visual Memory Composite re-test scores outside of these intervals were deemed to be "abnormal" (see Table 1). Note this approach is conservative, being biased toward non-detection of abnormal re-test performance.

Collision events recorded by the HIT™ system for each player were analyzed using a one-way ANOVA to identify differences between categories of players (see above). Observed differences were assessed for significance using a Bonferroni-corrected one-tailed *t*-test, with the alternative hypothesis being that that COI-/FOI+ group exhibited the highest number of events under given location and magnitude constraints.

The fMRI data were analyzed using AFNI (Cox, R.W. (1996)). Pre-processing included slice timing correction, motion correction, normalization to Talairach space, and 8mm Gaussian smoothing for inter-subject comparison. Individual runs (no more than one per subject) were discarded if extensive mid-sagittal ventricular "activity" was observed, suggestive of stress-induced, stimulus-correlated changes in physiologic behavior (e.g., cardiac rate, respiratory cycle), likely arising from participants being uncomfortable in the MRI environment. Final analysis for each subject was effected on concatenated data, using a general linear model approach with Gamma Variate hemodynamic response function (without derivatives). The contrast of interest is a comparison between 2-back and 1-back working memory tasks, with statistically significant activation identified using a threshold of $p < 0.05$, corrected for false discovery rate (FDR). Changes in fMRI activation were assessed using the 116 anatomically-defined regions of interest (ROIs) from MarsBaR (Brett, M., et al. (2002)). For each player category (see below), a given ROI was said to exhibit significantly altered neurophysiologic activity if the mean *t*-statistic fell outside the 99.9% confidence interval derived for that ROI using the Pre-Season data (23 players) for both *(a)* the group fixed-effects mean, and *(b)* a majority of players within the group.

Cross-modality analyses were performed to assess whether subsequently observed changes in fMRI assessment of physiology were correlated with head collision events. To evaluate possible short-term neurophysiologic effects of head collision events, alteration of hemodynamic response signal amplitudes observed during In-Season fMRI relative to that observed within the same subject in the Pre-Season assessment (i.e., $\%SignalChange_{In\text{-}Season}$ - $\%SignalChange_{Pre\text{-}Season}$) was compared to the number of head collision events measured by the HIT™ system in the week prior to the In-Season assessment. This assessment was performed both on an anatomical ROI basis (i.e., for all 116 anatomical ROIs) and on a more global basis, for an aggregated ROI encompassing the almost the entirety of the frontal lobe, excluding only the precentral gyrus (i.e., motor cortex, expected to be equally active in all tasks).

To document that the designated player categories were statistically meaningful, the predictive power of player category with respect to fMRI activation was evaluated using a one-tailed version of Fisher's Exact Test (Agresti, A. (1992)). Fisher’s Exact Test is a more conservative version of the chi-square that is appropriate for smaller study populations. A 3×2 implementation of the test was used, where the player categories are considered the treatments and the observation is either a decrease or non-decrease in the In-Season frontal lobe hemodynamic response signal amplitude, relative to that obtained from the Pre-Season assessment, evaluated on a per-subject basis. The alternative was that the COI-/FOI+ player category was significantly associated with increased probability of observation of decreases in the aggregate frontal lobe response amplitude. The null hypothesis is that observation of decrease in aggregate frontal lobe response amplitude is not associated with the COI-/FOI+ categorization. Note that categorization was made from ImPACT™ scores without knowledge of the aggregate frontal lobe signal change.

**Results**

Four of the 21 full-season participants were diagnosed with a concussion (i.e., were COI+) as a consequence of activities related to a practice or a game. Three of these players participated in an In-Season assessment within 72 hours of the diagnosis. One player (100) was obligated to cease participating in football due to persistent symptoms following the injury. A second player (118) was injured near the end of the season and was not cleared to play prior to the last game. A third player (103) missed one game and returned to play the following week. As expected, all three of these COI+ players examined within 72 hours of diagnosis of concussion were found to exhibit significantly lower neurocognitive performance in one or both of the Verbal and Visual Memory Composite scores on ImPACT™. Based on joint observation of impairment by the team physician and the athlete's neurologic assessment scores, these players are categorized as COI+/FOI+. fMRI data for these players revealed alterations in the pattern and amplitude of signal differences observed when contrasting the 2-back and 1-back memory tasks, particularly in posterior middle and superior temporal gyri, regions associated with accessing linguistic representations of external stimuli (Fig. 2).

Four (105, 107, 112, 122) of the eight players invited to undergo In-Season assessment in the absence of a clinical diagnosis of concussion (i.e., designated as COI-) exhibited no statistically significant deviations in ImPACT™ (see Table 1). These players were categorized as COI-/FOI-. The In-Season fMRI data for this group remained consistent with Pre-Season evaluation in 115 of the 116 regions of interest, both on a within-player basis, and relative to the group random effects analysis (Figs. 2-3). The only exception was in *right cerebellum 3*, which exhibited decreased activation in three players. Three of the four COI-/FOI- players completed participation in a Post-Season assessment, at which time ImPACT™ scores and task performance were again found to be within test/re-test limits.

Unexpectedly, four (102, 115, 120, 121) of the eight COI- players evaluated during the season, while exhibiting no symptoms that would prompt evaluation for concussion by the team healthcare personnel, were found to exhibit statistically significant reductions in ImPACT™ scores (Verbal and/or Visual Memory Composite scores; see Table 1). On this basis, these players are categorized as COI-/FOI+. This finding was augmented by observation (Fig. 3), in all such individuals at all In-Season assessments (7 total, across 4 players), of significantly decreased fMRI activation levels in dorsolateral prefrontal cortex (DLPFC; middle and superior frontal gyri) and cerebellum, regions of the brain strongly associated with working memory (Gruber, O. and von Cramon, D.Y. (2003), Kwon, H., et al. (2002)). In particular, when the 2-back and 1-back working memory conditions were contrasted, activation in the DLPFC changed from favoring (i.e., being greater for) the 2-back condition, to favoring the 1-back condition (Fig. 2). Note that DLPFC has previously been documented to favor the 2-back condition in healthy controls (Ragland, J.D., et al. (2002)) and was also found to favor the 2-back condition in our participants who did not exhibit deviant ImPACT™ performance (i.e., COI-/FOI-; see Figs. 2 and 3). When compared with those players clinically-diagnosed as having been concussed (i.e., COI+/FOI+), the COI-/FOI+ players were found to be at least as impaired (demonstrated by both ImPACT™ and fMRI measures) as the known concussed group.

The observed player categories were found to be statistically meaningful with the null hypothesis rejected at the $p < 0.04$ level (Fisher's Exact Test). Therefore, the COI-/FOI+ category is a justifiable segmentation of the subjects with respect to fMRI signal change.

Evaluation of HIT™ system data indicated that the COI-/FOI+ group was different from the other two groups with regard to the total number and distribution of collision events. The 21 players participating in our study throughout the season experienced 15,264 collision events—i.e., a motion/action during which at least one accelerometer registered a magnitude in excess of 14.4G (Greenwald, R.M., et al. (2008))—across 48 practices and games (varsity and junior varsity; including pre-game warm-up sessions), an average of 15.5 collision events per player per organized activity. Among players who started for either the varsity or junior varsity, per player collision event totals ranged from a high of 1855 (Player 121; COI-/FOI+; 38.6 events per session) down to a low of 226 (Player 107; COI-/FOI-; 4.7 events per session). The total number of collision events experienced by the COI-/FOI+ group was significantly greater than any other group. This difference becomes even more pronounced when the number of collision events is examined on the basis of both region and magnitude (Fig. 4). Specifically, the COI-/FOI+ group exhibited more high magnitude (greater than 80G) collision events directed to the top front of the helmet—immediately above the DLPFC in which functional changes were observed (Fig. 3).

Further evaluation of the head collision events experienced by the 11 players assessed during the season revealed that the number of events experienced in the week immediately preceding an In-Season assessment (N=14) was significantly correlated with changes in fMRI activation for the 2-back vs. 1-back contrast of interest. At the level of anatomical ROIs (Table 2), statistically significantly ($p < 0.05$; $|r| \geq 0.53$) correlations were observed for collision events with the deviation of the 2-back vs. 1-back signal change from that observed for the individual in the Pre-Season assessment. For all of the ROIs listed in Table 2, fMRI signal changes became less biased in the favor of the 2-back task (i.e., lesser activation for the 2-back task, relative to that evidenced for the 1-back task) as number of head collision events increased. While the most consistent changes in activation were located in the DLPFC, the majority of anatomical structures associated with this region (e.g., L MFG, L SFG, R SFG) are not indicated in Table 2. However, comparison of collision events to calculated changes in hemodynamic response signal amplitude for the aggregated frontal lobe ROI yields a trend that is well described by a linear regression model ($R^2$ = 0.46; see Fig. 5).

**Discussion**

The goal of this study was to evaluate neurocognitive and neurophysiologic deficits in high school football players as a function of head collision events, using pre-season baselines to quantify observed deficits. Athletes with collision event distributions similar to those diagnosed with concussion were intended as controls—as opposed to non-athletes—representing the first time that such a control population has been examined. Unexpectedly, half of these controls demonstrated both neurocognitive and neurophysiologic deficits, prompting the designation of a new group without observable signs of concussion who nevertheless exhibited cognitive impairments (COI-/FOI+; Fig. 1).

Athletes are a particularly high-risk population for TBI, especially amateur hockey and football players (Gilchrist, J., et al. (2007), Guskiewicz, K.M., et al. (2000)). Of the two, football is the more commonly played sport, with approximately 1.1 million high school participants in the United States during 2008-2009 (http://www.nfhs.org). Each year, between 43,000 and 67,000 of these players are diagnosed with concussions (Broglio, S.P., et al. (2009), Gregory, S. (2010)). Unfortunately, many young athletes do not appreciate the seriousness of concussion and fail to self-report symptoms—sometimes intentionally, as they seek to remain on the field—likely doubling the number of actual concussions (McCrea, M., et al. (2004)). Those with undiagnosed impairment who are not removed from play are of critical concern, because they continue to experience repeated head collision events.

In addition to players that do not report their symptoms, the results presented here indicate that additional athletes—those that would be considered COI-/FOI+—may be accruing damage that does not immediately result in symptoms that are typically observed by a clinician. The analysis performed using Fisher's Exact Test demonstrates that the COI-/FOI+ category is statistically distinct from the *a priori* expected COI+/FOI+ and COI-/FOI- categories. This analysis examined the probability of decreased aggregate frontal lobe activation, which is a region associated with working memory (Gruber, O. and von Cramon, D.Y. (2003), Kwon, H., et al. (2002)). The frontal lobe was a structure of interest both because working memory scores from ImPACT™ were used to make the original categorizations and because frontal lobe damage has received considerable attention in the literature (Bayly, P.V., et al. (2005), McKee, A.C., et al. (2009), Ommaya, A.K., et al. (1971)). It is therefore notable that significant changes in signal amplitude in working memory structures were statistically more frequent in COI-/FOI+ subjects. This correspondence is consistent with the hypothesis of the existence of the COI-/FOI+ category.

While our data do not provide statistical confidence that 50% of all COI- subjects will exhibit functional impairment—this proportion has inherit scatter that must be measured through several replicates across different player populations—we nevertheless observed that 4 of the original 23 volunteer subjects, about 17%, were COI-/FOI+, which is still a sufficiently large proportion to raise concern. Further, use of our method for identifying COI-/FOI+ players based on decreases in ImPACT™ scores indicates that 12 of the 23 non-concussed contact sport athletes studied in (Beckwith, J.G., et al. (2010)) would be considered COI-/FOI+. This substantiates the proportion we have observed and indicates that the actual proportion of functional impairment among players who do not exhibit signs of concussion (i.e., COI- players) may indeed be quite high. It should also be noted that there is expected to be considerable variation in neurological response based on player size, speed, skill level, position and technique, as well as field conditions and level of competition. Consequently, additional studies are needed to elucidate the effects of these parameters and further generalize the results.

It is suspected that the COI-/FOI+ group comprises players who experienced neurologic trauma arising from repeated, sub-concussive head collision events, each of which likely produces sub-clinical stress on neural tissue (Geddes, J.F., et al. (1999)). In this case, the players failed to accrue sufficient short-term damage to integrative neural systems that they exhibited externally observable symptoms. As such, these players continued to participate in practices and games throughout the season with neurocognitive and neurophysiologic impairments persisting over time (Fig. 3), but never exhibiting symptoms that would trigger evaluation by a healthcare professional. These players not only may be representative of the group associated with "unreported" concussions, but are also likely to meet the criterion of McKee *et al.* (2009), wherein having received repetitive, sub-concussive blows to the head they may have an increased likelihood of long-term neurodegeneration (Geddes, J.F., et al. (1999), Ommaya, A.K., et al. (1994)).

Of particular interest, this functionally (but not clinically) impaired group was primarily comprised of linemen, who experience helmet-to-helmet contact on nearly every play from scrimmage, often to the top front of the head. This finding of degraded neurological performance in the absence of classical symptoms of concussion is consistent with prior observation of CTE in the absence of a commensurate history of concussion in two ex-NFL offensive linemen and a defensive back (Omalu, B.I., et al. (2006), Omalu, B.I., et al. (2005), Omalu, B.I., et al. (2010)). Given the dire outcomes observed as a consequence of CTE, and given that such a functional observation suggests that present clinical practice does not succeed in detecting the neurological deficits in these individuals, it is important that we develop a means to detect when such injury occurs or, perhaps more importantly, to predict and prevent injuries of this nature.

Our observation of two groups (COI+/FOI+ and COI-/FOI+) exhibiting neurocognitive and neurophysiologic impairment that is distinguished by the presence or absence of externally-observable behavioral symptoms implies that these groups have experienced injuries that differ by mechanism and associated location(s) of damage. The COI+/FOI+ group exhibits onset and extent of behavioral deficits consistent with damage to integrative centers of the brain associated with auditory (especially language) processing, with such damage likely produced in locations unique to each individual by a singular, deleterious collision event. In contrast, the COI-/FOI+ group predominantly exhibits behavioral deficits in working memory (predominantly visual), that likely are produced by repeated sub-clinical trauma to specific locations in the brain, though the nature of the trauma is as yet unclear.

Regardless of the uncertainty surrounding the specific injury incurred in the COI-/FOI+ group, the similarities of the fMRI impairment associated with members of this group (Fig. 3), suggests that future work may be able to identify the underlying causes of deficits within this population. It is worth noting that previous studies involving positron emission tomography (PET) have observed that changes in metabolism associated with TBI are spatially diffuse relative to the actual site of mechanically-induced injury (Wu, H.M., et al. (2004a)), and not necessarily localized to regions experiencing (transient) ischemia (Xu, Y., et al. (2010)). Therefore, alterations in fMRI signal changes may not take place at the precise location of mechanically-induced injury, but these alterations would be an expected consequence of the changes in metabolism associated with damage. Thus, players experiencing clinically-diagnosable concussions (i.e., COI+/FOI+) due to subject-specific injuries would not be expected to exhibit group-wise consistency in the alteration of fMRI activations, but players experiencing a specific injury (i.e., possibly the COI-/FOI+ group) could.

Initial assessment (Fig. 4) of the mechanical insults (as assessed by the HIT™ system) to the athletes in the two FOI+ groups indicates that they did, in fact, experience different collision event histories, and supports the above hypotheses regarding the potential for identifying a common underlying injury in the COI-/FOI+ group. Note that these data also support the argument that peak acceleration is not a sufficient measure to predict cognitive deficit (Goldsmith, W. and Monson, K.L. (2005), Greenwald, R.M., et al. (2008), Hardy, W.N., et al. (1994), Ommaya, A.K., et al. (1994)). Currently, the location of the postulated injuries in the COI-/FOI+ group (DLPFC and other working memory brain areas) and their apparent focal behavioral effect make it difficult to identify this group on-site. If an individual has not suffered damage to integration centers associated with language, or to auditory processing pathways, he is unlikely to exhibit the symptoms necessary for identification as being concussed. Further, if working memory deficits are sufficiently small, the individual may not be aware of the additional effort required to complete everyday tasks, perhaps only becoming aware that a deficit is present under the duress of probes such as neurocognitive tests.

The findings of this study suggest that functional MRI can be a valuable tool for detecting neurophysiologic deficit after head injury, as previously suggested (McCrory, P., et al. (2009)) and supported by PET literature related to the study of changes in metabolism following TBI (Wu, H.M., et al. (2004a), Wu, H.M., et al. (2004b), Xu, Y., et al. (2010)). To better evaluate the structure-function relationships that cause neurological damage, it will be essential to expand the range of neurological testing done within the MRI and to add structural assessments such as diffusion tensor imaging (Sundgren, P.C., et al. (2004)), and susceptibility-weighted imaging (Sehgal, V., et al. (2005)) modalities. In addition, better characterization of the mechanical insults and the complex, heterogeneous effects they have on the brain itself must be developed.

This study was strengthened by acquisition of baseline data prior to the commencement of athletic activities, greatly increasing the ability to detect changes at both an individual and group level. Despite the small sample size, a precise correlation was found between deficits observed using an established neurocognitive assessment tool (ImPACT™) and neurophysiologic changes observed with fMRI during a verbal working memory task. Consistent with the hypothesis that the different observed cognitive and neurophysiologic deficits arise from distinct mechanical insult histories, significant differences were observed between groups of players categorized by changes in ImPACT™ score.

Therefore, these data indicate the presence of a previously unknown, but suspected (McKee, A.C., et al. (2009)), group of athletes exhibiting neurocognitive deficits that persist over time, but which does not present observable symptoms. This group continues to participate in contact sports, and may be at risk of further, long-term neurological injury. Consequently, high priority should be given to the development of procedures that may lead to identification of these at-risk individuals.

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**Table 1:** Dates and results of ImPACT™ tests and dates of fMRI assessments for all players enrolled in study.

| Assessment | ImPACT™ Test Date(s) | ImPACT™ Memory Composite (Verbal) | ImPACT™ Memory Composite (Visual) | fMRI Session Date(s) |
|---|---|---|---|---|
| | | ***Player 100*** [1] | | |
| Pre-Season | 5 August[a] | 85 | 93 | 1 August |
| In-Season | 29 August[b] | 75†,‡ | 57†,‡ | 29 August |
| Post-Season | 29 November[b] | 93 | 68†,‡ | 29 November |
| | | ***Player 101*** | | |
| Pre-Season | 5 August[a] | 93 | 81 | 1 August |
| | | ***Player 102*** | | |
| Pre-Season | 5 August[a] | 93 | 59 | 2 August |
| | 19 September | 96 | 56† | 19 September |
| In-Season | 1 October[a] | 97 | 75 | |
| | 7 October[b] | 83†,‡ | 79 | 7 October |
| Post-Season | 23 November[b] | 91†,‡ | 79 | 23 November |
| | | ***Player 103*** | | |
| Pre-Season | 5 August[a] | 98 | 70 | 2 August |
| In-Season | 6 September[b] | 82†,‡ | 76 | 6 September |

| | | | | |
|---|---|---|---|---|
| | 7 October[b] | 78†,‡ | 61†,‡ | 7 October[A] |
| Post-Season | 29 November[b] | 84†,‡ | 84 | 29 November |
| | | ***Player 104***[2] | | |
| Pre-Season | 5 August[a] | 77 | 86 | 2 August |
| | | ***Player 105*** | | |
| Pre-Season | 5 August[a] | 87 | 67 | 2 August |
| In-Season | 18 October[b] | 99 | 78 | 18 October |
| Post-Season | 21 November[b] | 95 | 72 | 21 November |
| | | ***Player 106*** | | |
| Pre-Season | 5 August[a] | 90 | 81 | 2 August |
| | | ***Player 107*** | | |
| Pre-Season | 5 August[a] | 94 | 75 | 2 August |
| In-Season | 20 September[b] | 99 | 83 | 20 September |
| | | ***Player 108*** | | |
| Pre-Season | 5 August[a] | 63 | 80 | 2 August |
| | | ***Player 109***[2] | | |
| Pre-Season | 5 August[a] | 80 | 59 | 2 August |
| | | ***Player 110***[3] | | |
| Pre-Season | --- | --- | --- | 2 August |
| | | ***Player 111*** | | |
| Pre-Season | 5 August[a] | 84 | 70 | 2 August |
| | | ***Player 112*** | | |

| | | | | |
|---|---|---|---|---|
| Pre-Season | 5 August[a] | 92 | 78 | 2 August |
| In-Season | 6 September[b] | 97 | 80 | 6 September |
| Post-Season | 5 January[a,c] | 86 | 77 | 18 November |
| | | ***Player 113[1,2]*** | | |
| Pre-Season | 14 August[a] | 67 | 85 | 2 August |
| | | ***Player 114*** | | |
| Pre-Season | 7 August[a,d] | 61 | 49 | 2 August |
| | | ***Player 115*** | | |
| Pre-Season | 5 August[a] | 94 | 73 | 3 August |
| In-Season | 5 September[b] | 94 | 66† | 5 September |
| Post-Season | 18 November[b] | 100 | 65† | 18 November |
| | | ***Player 116*** | | |
| Pre-Season | 6 August[a] | 98 | 95 | 3 August |
| | | ***Player 117*** | | |
| Pre-Season | 5 August[a] | 84 | 66 | 4 August |
| | | ***Player 118[1]*** | | |
| Pre-Season | 5 August[a] | 91 | 75 | 4 August |
| In-Season | 18 October[b] | 88†,‡ | 61† | 18 October |
| Post-Season | 23 November[b] | 96 | 84 | 23 November |
| | | ***Player 119*** | | |
| Pre-Season | 5 August[a] | 100 | 78 | 5 August |
| | | ***Player 120*** | | |

| | | | | |
|---|---|---|---|---|
| Pre-Season | 5 August[a] | 88 | 96 | 5 August |
| In-Season | 29 August[b] | 98 | 76†,‡ | 29 August |
| | 10 October[b] | 100 | 73†,‡ | 10 October |
| Post-Season | 19 November[b] | 93 | 75†,‡ | 19 November |
| | | ***Player 121*** | | |
| Pre-Season | 5 August[a] | 77 | 91 | 6 August |
| In-Season | 26 September[b] | 76 | 79† | 26 September |
| | 25 October[b] | 88 | 70†,‡ | 25 October |
| Post-Season | 23 November[b] | 93 | 75†,‡ | 23 November |
| | | ***Player 122*** | | |
| Pre-Season | 6 August[a] | 78 | 52 | 7 August |
| In-Season | 16 September[b] | 91 | 68 | 16 September |
| Post-Season | 23 January[b] | 89 | 81 | 23 January |
| | | ***Player 123*** | | |
| Pre-Season | 11 August[a] | 93 | 59 | 10 August |

*Player Footnotes*

[1] Injured during season, did not return to play

[2] Quit participation in football prior to or during season

[3] Injured prior to practice, ImPACT™ not administered; HIT™ system monitored after return to play

*ImPACT™ Assessment Footnotes*

[a] Test administered at high school

[b] Test administered at Purdue MRI Facility

[c] Scores for test administered on day of fMRI Session not saved due to known on-line bug

[d] Test flagged by ImPACT™ as possibly invalid

*ImPACT™ Score Footnotes*

† Score outside 99% confidence interval

‡ Score outside 99% confidence interval and flagged by ImPACT™ as significantly decreased

*fMRI Assessment Footnotes*

[A] Computer network failure precluded completion of fMRI assessment; not included in analyses

**Table 2:** Anatomical regions of interest from MarsBaR (Brett, M., et al. (2002)) exhibiting statistically significant correlations ($p < 0.05$; N=14) between the total number of head collision events (HIT™ system) experienced by a player in the week prior to In-Season assessment and the fMRI percent signal change observed during that assessment for the 2-back vs. 1-back contrast. (*) = $p < 0.01$

| Anatomical Region of Interest (MarsBaR ROI #) | Correlation between fMRI Contrast and Collision Events |
|---|---|
| Frontal Medial Orbital L (41) | -0.70 (*) |
| Frontal Medial Orbital R (42) | -0.72 (*) |
| Frontal Middle R (46) | -0.55 |
| Frontal Superior Orbital L (50) | -0.71 (*) |
| Fusiform R (54) | -0.56 |
| Hippocampus L (57) | -0.60 |
| Hippocampus R (58) | -0.68 (*) |
| Parahippocampal R (76) | -0.58 |
| Rectus L (89) | -0.59 |
| Rectus R (90) | -0.62 |
| Temporal Superior Pole L (103) | -0.59 |
| Temporal Superior Pole R (104) | -0.53 |

**Figure Captions**

**Figure 1:** Summary of observed player categories, with representative functional magnetic resonance imaging (fMRI) observations. Categories are based on both clinical observation by the team physician of impairment associated with concussion (COI+ or COI-) and presence or absence of significantly neurocognitive impairment via ImPACT™ (FOI+ or FOI-). Functional MRI activations are depicted for all players using a sagittal slice through the left inferior parietal lobule (L IPL) to illustrate the presence of many changes, relative to Pre-Season assessment, for FOI+ players. Detail regarding the depicted fMRI activations may be found in Figs. 2 and 3. *(Bottom Right)* As expected, all (3/3) players who were diagnosed by the team physician as having experienced a concussion (COI+) were also found to exhibit significantly reduced ImPACT™ scores (FOI+), and are categorized as COI+/FOI+. See also Fig. 2. *(Top Left)* Half (4/8) of players brought in for assessment ostensibly for control purposes (i.e., presenting no clinically-observable impairment, COI-) were found to be neurocognitively consistent with Pre-Season assessment (FOI-), and are categorized as COI-/FOI-. *(Top Right)* The other half (4/8) of the intended "control" group, studied in the absence of diagnosed concussion (COI-), were found to exhibit significantly impaired ImPACT™ performance (FOI+), and are categorized as COI-/FOI+. See also Fig. 3. This group represents a newly observed category of possible neurological injury. *(Bottom Left)* No players who were diagnosed with a concussion (COI+) were found to exhibit ImPACT™ scores consistent with Pre-Season assessment (FOI-).

**Figure 2:** Significant alteration in fMRI activation during In-Season assessment was found in left middle and superior temporal gyri (L MTG and L STG; green circles) under a MarsBaR-based (Brett, M., et al. (2002)) region-of-interest (ROI) analysis for COI+/FOI+ players, but not for COI-/FOI- players. For the COI+/FOI+ group, In-Season assessments took place within 72 hours of diagnosis of concussion by the team physician. fMRI activations are depicted for a contrast between 2-back and 1-back working memory tasks, with observation of

greater activation for the 2-back (1-back) task indicated using the red-yellow (blue-cyan) colorscale, thresholded at a statistical significance level of $p < 0.05$, corrected for false discovery rate. MarsBaR ROIs were said to exhibit significant alteration if the mean *t*-statistic fell outside the ROI-specific 99.9% confidence interval (derived from the Pre-Season data, 23 players) for both the group fixed-effects mean, and in a majority of the players within the group. For the COI+/FOI+ group, the L MTG and L STG were two of five ROIs that exhibited such significant alteration. Other anatomical ROIs were *left middle occipital gyrus*, *left cerebellum 10*, and *right cerebellum 3*. The L MTG persisted in exhibiting significant deviation in the Post-Season data. For the COI-/FOI- group, only the *right cerebellum 3* anatomical ROI was found to exhibit significant deviation during In-Season assessment. It is important to note that all players performed the working-memory task at a consistent near-ceiling level over all sessions.

**Figure 3:** Significant alteration in fMRI activation during In-Season assessment was found in left middle and superior frontal gyri (L MFG and L SFG; green circles) under a MarsBaR-based (Brett, M., et al. (2002)) region-of-interest (ROI) analysis for COI-/FOI+ players, but not for COI-/FOI- players. These ROIs represent much of dorsolateral prefrontal cortex (DLPFC). Coupled with observation of significantly reduced ImPACT™ scores, the COI-/FOI+ group represents a newly observed category of neurological injury, as these players are functionally impaired, yet do not exhibit symptoms associated with clinical diagnosis of concussion. See Fig. 2 for information regarding depicted fMRI activations. For the COI-/FOI+ group, the L MFG and L SFG were two of eight ROIs that exhibited significant alteration in multiple In-Season assessments. Other anatomical ROIs were *right middle* and *superior frontal gyrus* (R MFG, R SFG), both *right* and *left superior parietal lobule* (R SPL, L SPL), *right pars triangularis*, and *right cerebellum crus1*. Three of these ROIs (L MFG, L SFG, R SFG) exhibited deviant activation in all In-Season assessments for all COI-/FOI+ subjects. For the COI-/FOI- group, only the *right cerebellum 3*

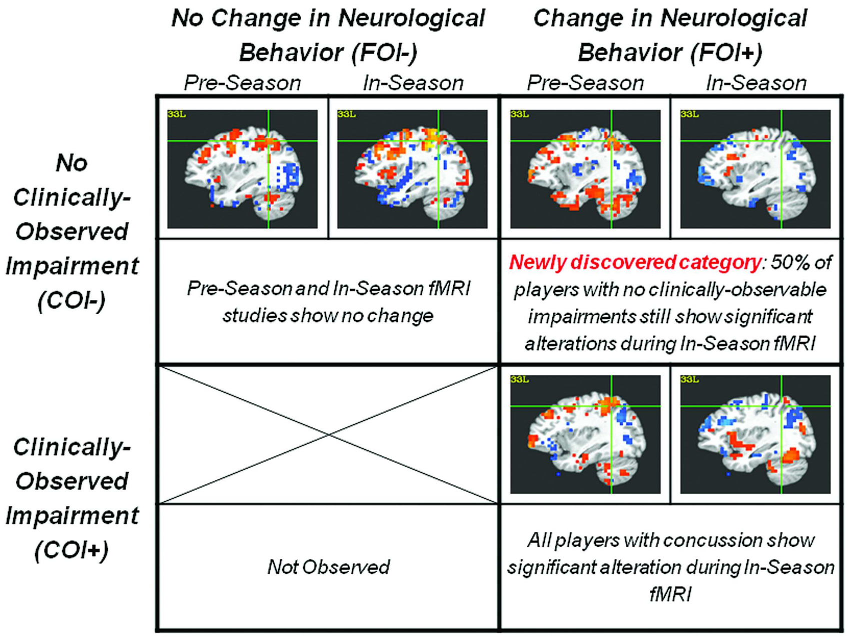
anatomical ROI was found to exhibit significant deviation during In-Season assessment. It is important to note that all players performed the working-memory task at a consistent near-ceiling level over all sessions.

**Figure 4:** While peak linear acceleration is not predictive for neurological trauma, the pattern of average collision events per individual is significantly related to the concussion group as identified using neurocognitive testing (ImPACT™). Each participant wore a Riddell® Revolution™ helmet (Riddell; Elyria, OH) outfitted with a sensor array (HIT™ system; Simbex, New Lebanon, NH) to record head accelerations in practices and games once the season started (Crisco, J.J., et al. (2004)). Overall the COI-/FOI+ group experienced the greatest number of collision events to each region of the helmet. The COI-/FOI- group accumulated more collisions per player in each location than did the COI+/FOI+ group, suggesting the latter's injuries were not the result of the number of blows, but likely rather a single or small number of deleterious collisions. *(a)* For collision events less than 20G, the COI-/FOI+ group experienced significantly more collision events to the side and the top-front of the helmet ($p < 0.05$, group-wise one-way ANOVA and Bonferroni-corrected one-tailed $t$-test). *(b)* Between 20G and 80G, the COI-/FOI+ group experienced a greater number of collision events to each region of the helmet, but the only location where it reached significance was the top-front. *(c)* Above 80G, the COI+/FOI+ group experienced significantly more blows to the side of the head, while the COI-/FOI+ group continued to experience a statistically greater number of blows to the top-front of the helmet.

**Figure 5:** The number of head collision events exceeding 14.4G experienced by a player was found to be inversely correlated with the fMRI contrast (2-back vs. 1-back) observed during In-Season assessments (see also Table 3). All "Frontal" regions of interest in MarsBaR (Brett, M., et al. (2002)) were aggregated to obtain a frontal lobe ROI from which an average percent signal change was computed for this contrast in each of the 14

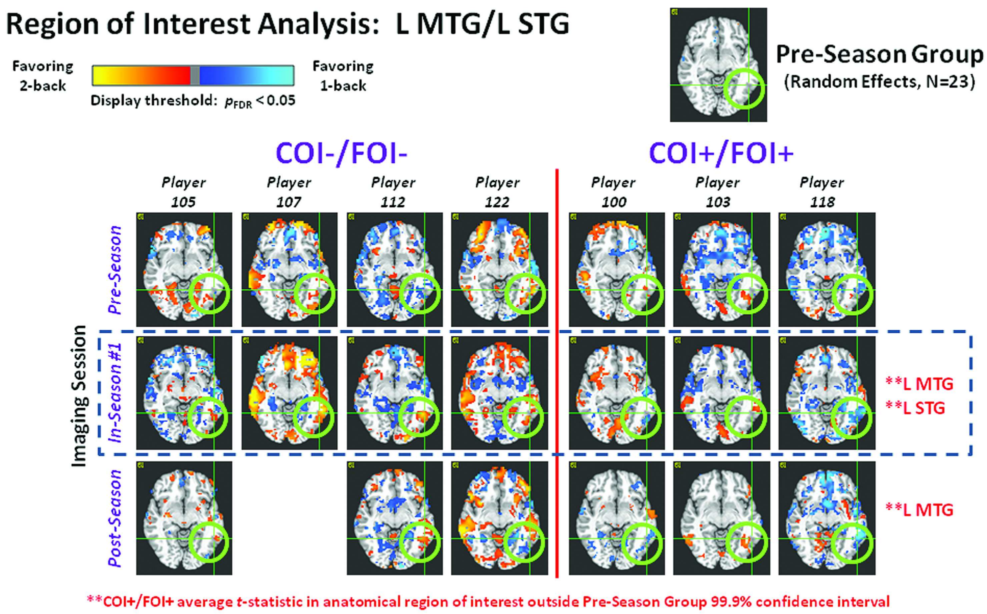
completed In-Season fMRI assessments and the corresponding Pre-Season assessment for the same subjects. The difference between these assessments is plotted against the total number of HIT™ system reported collision events. Different colors/symbols have been used to identify the three groups (COI-/FOI-, COI-/FOI+, COI+/FOI+) of players, further illustrating the greater number of collision events for the COI-/FOI+ group (see Fig. 4). The regression line across the 14 comparisons achieves $R^2 = 0.46$, indicating that the recent accrual of head collision events is meaningfully related to degree of change in neurophysiologic response.

Figure 1

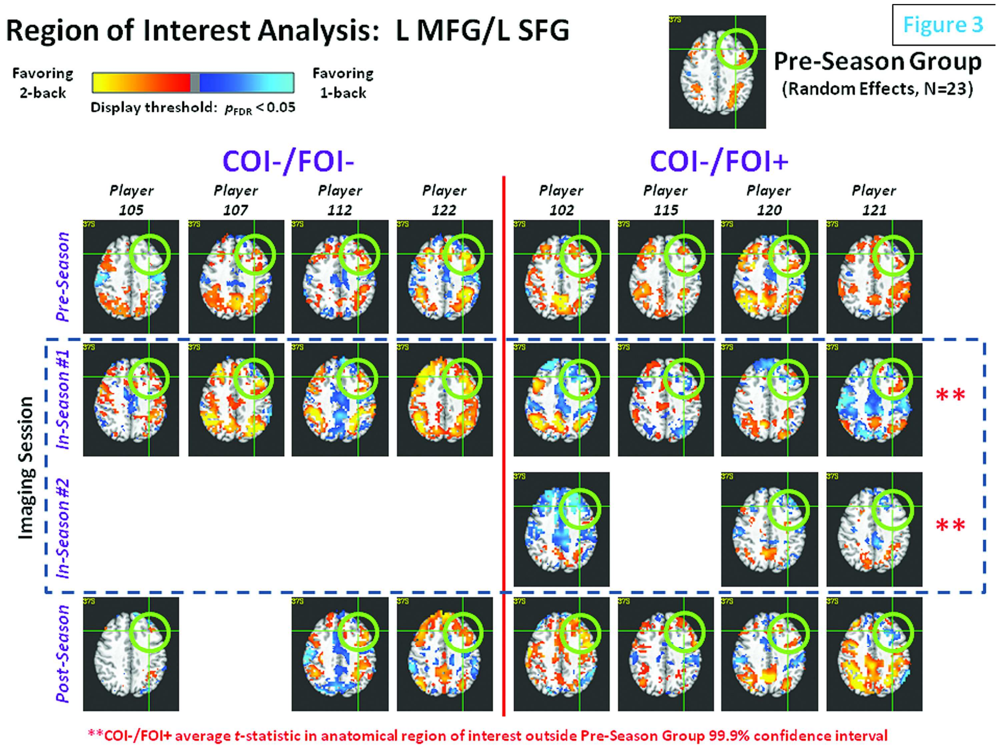



Summary of observed player categories, with representative functional magnetic resonance imaging (fMRI) observations. Categories are based on both clinical observation by the team physician of impairment associated with concussion (COI+ or COI-) and presence or absence of significantly neurocognitive impairment via ImPACTTM (FOI+ or FOI-). Functional MRI activations are depicted for all players using a sagittal slice through the left inferior parietal lobule (L IPL) to illustrate the presence of many changes, relative to Pre-Season assessment, for FOI+ players. Detail regarding the depicted fMRI activations may be found in Figs. 2 and 3. (Bottom Right) As expected, all (3/3) players who were diagnosed by the team physician as having experienced a concussion (COI+) were also found to exhibit significantly reduced ImPACTTM scores (FOI+), and are categorized as COI+/FOI+. See also Fig. 2. (Top Left) Half (4/8) of players brought in for assessment ostensibly for control purposes (i.e., presenting no clinically-observable impairment, COI-) were found to be neurocognitively consistent with Pre-Season assessment (FOI-), and are categorized as COI-/FOI-. (Top Right) The other half (4/8) of the intended "control" group, studied in the absence of diagnosed concussion (COI-), were found to exhibit significantly impaired ImPACTTM performance (FOI+), and are categorized as COI-/FOI+. See also Fig. 3. This group represents a newly observed category of possible neurological injury. (Bottom Left) No players who were diagnosed with a concussion (COI+) were found to exhibit ImPACTTM scores consistent with Pre-Season assessment (FOI-).
254x190mm (300 x 300 DPI)

Figure 2

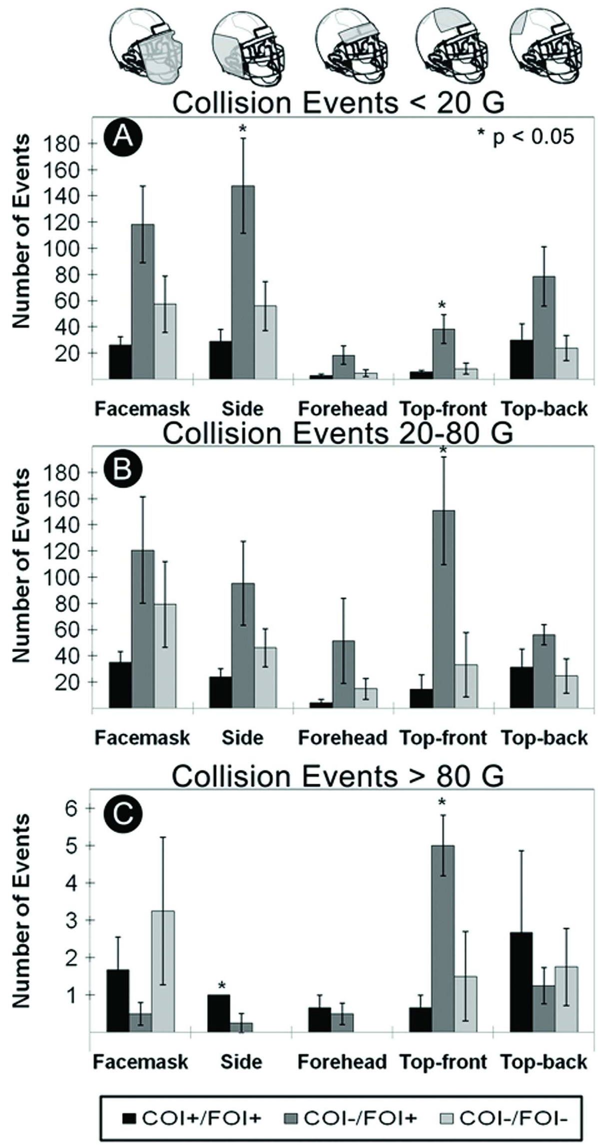



Significant alteration in fMRI activation during In-Season assessment was found in left middle and superior temporal gyri (L MTG and L STG; green circles) under a MarsBaR-based (Brett, M., et al. (2002)) region-of-interest (ROI) analysis for COI+/FOI+ players, but not for COI-/FOI- players. For the COI+/FOI+ group, In-Season assessments took place within 72 hours of diagnosis of concussion by the team physician. fMRI activations are depicted for a contrast between 2-back and 1-back working memory tasks, with observation of greater activation for the 2-back (1-back) task indicated using the red-yellow (blue-cyan) colorscale, thresholded at a statistical significance level of $p < 0.05$, corrected for false discovery rate. MarsBaR ROIs were said to exhibit significant alteration if the mean t-statistic fell outside the ROI-specific 99.9% confidence interval (derived from the Pre-Season data, 23 players) for both the group fixed-effects mean, and in a majority of the players within the group. For the COI+/FOI+ group, the L MTG and L STG were two of five ROIs that exhibited such significant alteration. Other anatomical ROIs were left middle occipital gyrus, left cerebellum 10, and right cerebellum 3. The L MTG persisted in exhibiting significant deviation in the Post-Season data. For the COI-/FOI- group, only the right cerebellum 3 anatomical ROI was found to exhibit significant deviation during In-Season assessment. It is important to note that all players performed the working-memory task at a consistent near-ceiling level over all sessions.
254x190mm (300 x 300 DPI)




Significant alteration in fMRI activation during In-Season assessment was found in left middle and superior frontal gyri (L MFG and L SFG; green circles) under a MarsBaR-based (Brett, M., et al. (2002)) region-of-interest (ROI) analysis for COI-/FOI+ players, but not for COI-/FOI- players. These ROIs represent much of dorsolateral prefrontal cortex (DLPFC). Coupled with observation of significantly reduced ImPACTTM scores, the COI-/FOI+ group represents a newly observed category of neurological injury, as these players are functionally impaired, yet do not exhibit symptoms associated with clinical diagnosis of concussion. See Fig. 2 for information regarding depicted fMRI activations. For the COI-/FOI+ group, the L MFG and L SFG were two of eight ROIs that exhibited significant alteration in multiple In-Season assessments. Other anatomical ROIs were right middle and superior frontal gyrus (R MFG, R SFG), both right and left superior parietal lobule (R SPL, L SPL), right pars triangularis, and right cerebellum crus1. Three of these ROIs (L MFG, L SFG, R SFG) exhibited deviant activation in all In-Season assessments for all COI-/FOI+ subjects. For the COI-/FOI- group, only the right cerebellum 3 anatomical ROI was found to exhibit significant deviation during In-Season assessment. It is important to note that all players performed the working-memory task at a consistent near-ceiling level over all sessions.
254x190mm (300 x 300 DPI)

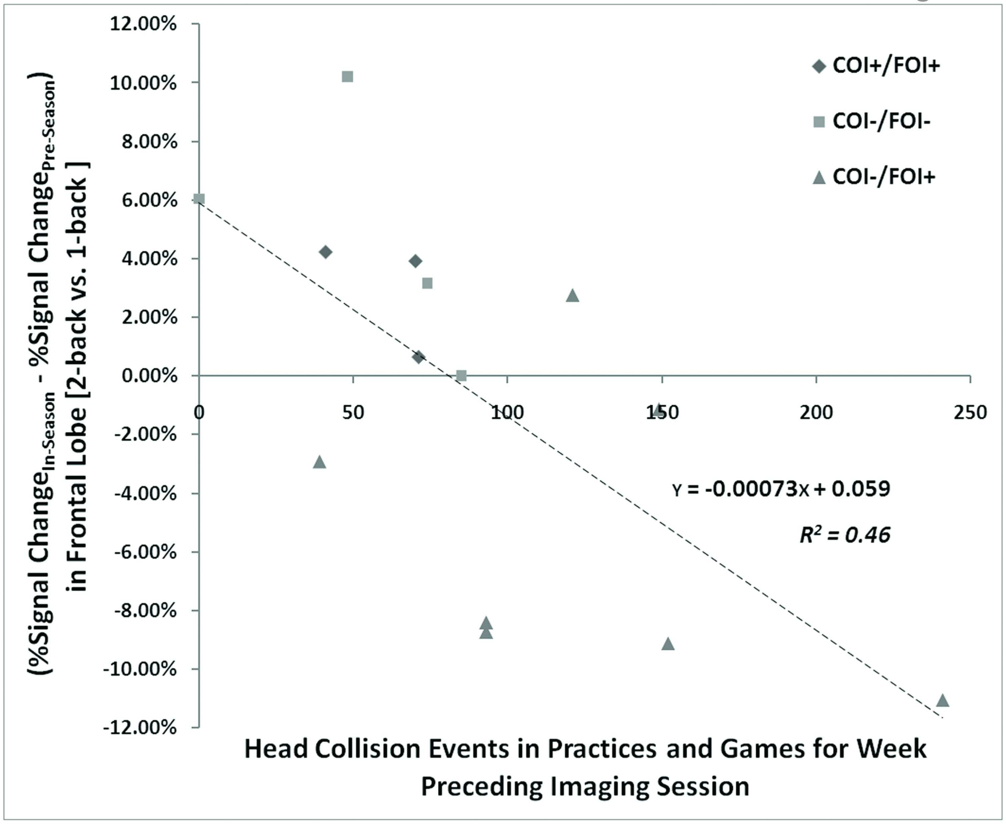
Figure 4




While peak linear acceleration is not predictive for neurological trauma, the pattern of average collision events per individual is significantly related to the concussion group as identified using neurocognitive testing (ImPACTTM). Each participant wore a Riddell® Revolution™ helmet (Riddell; Elyria, OH) outfitted with a sensor array (HIT™ system; Simbex, New Lebanon, NH) to record head accelerations in practices and games once the season started (Crisco, J.J., et al. (2004)). Overall the COI-/FOI+ group experienced the greatest number of collision events to each region of the helmet. The COI-/FOI- group accumulated more collisions per player in each location than did the COI+/FOI+ group, suggesting the latter's injuries were not the result of the number of blows, but likely rather a single or small number of deleterious collisions. (a) For collision events less than 20G, the COI-/FOI+ group experienced significantly more collision events to the side and the top-front of the helmet ($p < 0.05$, group-wise one-way ANOVA and Bonferroni-corrected one-tailed t-test). (b) Between 20G and 80G, the COI-/FOI+ group experienced a greater number of collision

events to each region of the helmet, but the only location where it reached significance was the top-front. (c) Above 80G, the COI+/FOI+ group experienced significantly more blows to the side of the head, while the COI-/FOI+ group continued to experience a statistically greater number of blows to the top-front of the helmet.
190x254mm (300 x 300 DPI)

Figure 5




The number of head collision events exceeding 14.4G experienced by a player was found to be inversely correlated with the fMRI contrast (2-back vs. 1-back) observed during In-Season assessments (see also Table 3). All "Frontal" regions of interest in MarsBaR (Brett, M., et al. (2002)) were aggregated to obtain a frontal lobe ROI from which an average percent signal change was computed for this contrast in each of the 14 completed In-Season fMRI assessments and the corresponding Pre-Season assessment for the same subjects. The difference between these assessments is plotted against the total number of HITTM system reported collision events. Different colors/symbols have been used to identify the three groups (COI-/FOI-, COI-/FOI+, COI+/FOI+) of players, further illustrating the greater number of collision events for the COI-/FOI+ group (see Fig. 4). The regression line across the 14 comparisons achieves R2 = 0.46, indicating that the recent accrual of head collision events is meaningfully related to degree of change in neurophysiologic response.
254x220mm (300 x 300 DPI)