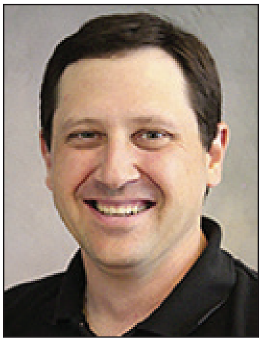
The lack of symptoms or clinically diagnosable dysfunction does not guarantee that an athlete is healthy.

Medical Imaging to Recharacterize Concussion for Improved Diagnosis in Asymptomatic Athletes



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The Purdue Neurotrauma Group began in 2009 to study causes and consequences of concussion in youth athletes in an effort to understand why, in a two-player collision that produced a diagnosed injury, it was only one—rather than each—athlete that evidenced symptoms. Our work applies the concept of structural health monitoring (Bond et al. 2014; Kim et al. 2014), without intervention, to characterize how the brain becomes predisposed to presentation of symptoms after exposure to head acceleration events (direct collisions or whiplash movements associated with contact to other portions of the body).

Assessing Concussion

From our initial work (Talavage et al. 2014), it quickly became apparent that although an athlete may be asymptomatic, the lack of clinically diagnosable dysfunction does not guarantee that the athlete is healthy.

Evidence from Brain Scans

Figure 1 illustrates the disparity of health outcomes for three high school football athletes, one from each category of clinically and functionally observed impairment (COI, FOI; identified in Talavage et al. 2014): COI−/FOI− denotes arguably healthy athletes; COI−/FOI+ represents athletes exhibiting neurophysiologic changes in the absence of symptoms; and COI+/FOI+

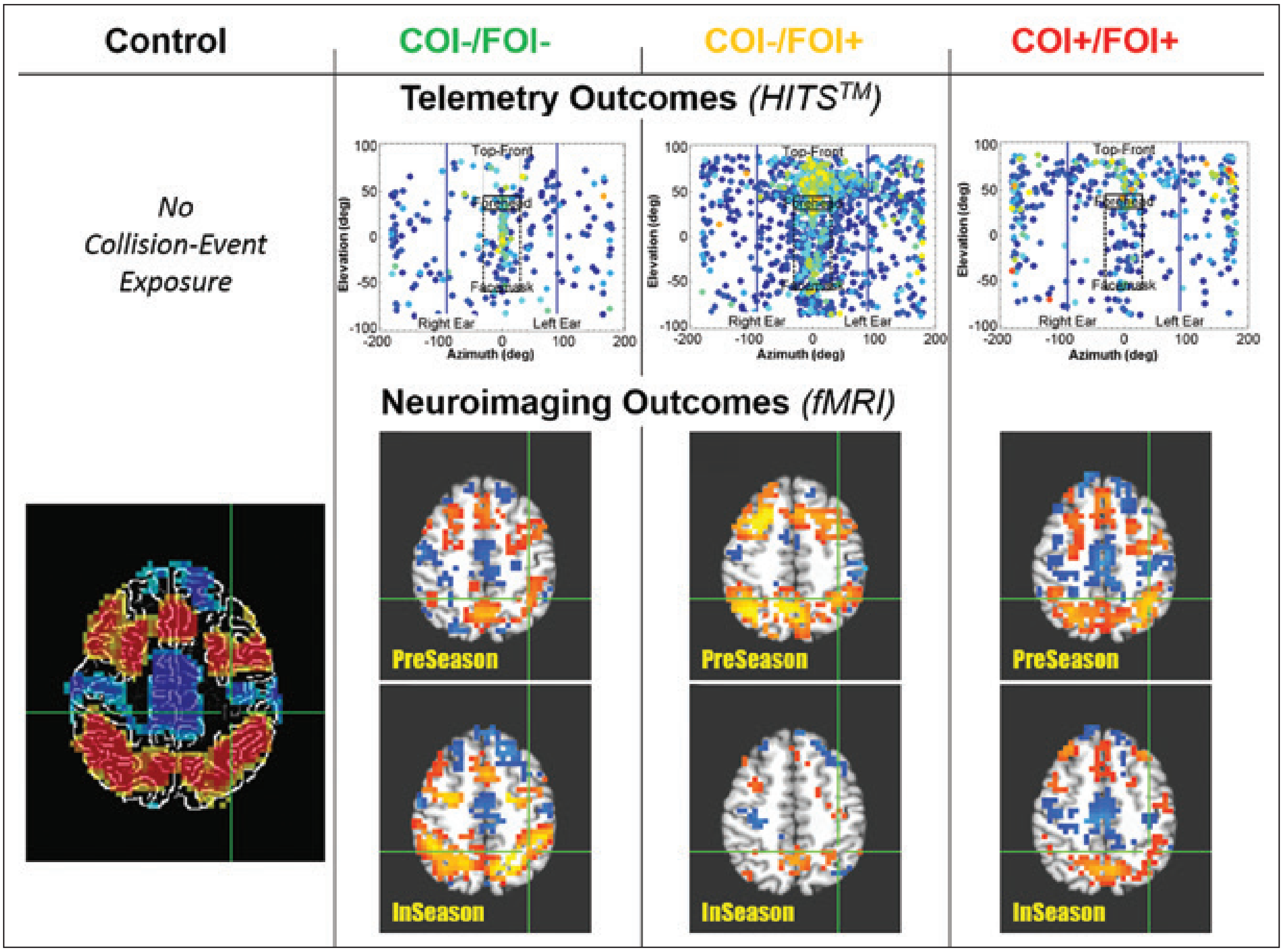

FIGURE 1 Head Impact Telemetry System (HITS) and functional magnetic resonance imaging (fMRI) scans for three high school football athletes before and during the playing season (plus control, left). COI−/FOI− denotes an arguably healthy brain; COI−/FOI+ indicates neurophysiologic changes without symptoms; COI+/FOI+ designates a symptomatic athlete diagnosed with concussion. See text for discussion. COI = clinically observed impairment; FOI = functionally observed impairment.

designates symptomatic athletes diagnosed with concussion. FOI+ classification was based on flagged scores obtained with Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) (Collins et al. 1999; Lovell and Collins 1998), the most commonly used tool at the collegiate and professional level to confirm diagnosis of concussion.

In the top row of figure 1 are plots of the site and magnitude (intensity) of blows (called "events") reported over the entire season by the Head Impact Telemetry System (HITS; Simbex, LLC). The center of each plot represents the face, with facemask and forehead regions denoted by dashed boxes. Each dot is colored (heat map) to indicate the severity of the reported acceleration: dark blue represents the lowest recorded accelerations ("coldest"; HITS recording threshold = 10 g), bright red the highest ("hottest"; roughly 120 g), and yellow-orange an intermediate range of 40–80 g. Note that most of the accelerations are under 30 g (darker blues), with slightly over 60 g (i.e., orange dots) corresponding to the 95th percentile of the accelerations observed in our high school football athlete population.

Below are six functional magnetic resonance imaging (fMRI) contrast maps associated with an n-back working memory task (Ragland et al. 2002) in which subjects view a sequence of letters and press a button if the currently presented letter matches that shown one presentation prior (1-back task) or two (2-back). The imaging sessions were conducted on football players before (PreSeason) and during (InSeason) the competition schedule.

Preferential brain responses are shown using a heat map. Orange indicates brain regions exhibiting greater metabolic activity during performance of the 2-back task, and blue indicates regions more active during the 1-back task. Areas with no coloration represent regions of the brain that are equivalently active or inactive in the two tasks. We are generally interested in the stability or instability of the spatial pattern of activation valence (i.e., orange, no coloration, blue) more than the absolute level, as changes in metabolic demand typically reflect underlying alterations in neuronal recruitment or health.

Concussed vs. Asymptomatic Athletes

Perhaps the most important observation to make is that some athletes are able to participate in football and remain arguably healthy (COI−/FOI−; figure 1, 2nd column). The depicted athlete was observed to have excellent tackling technique (e.g., kept his head clear from contact, wrapped and rolled with the ball carrier) and played the entire season with just over 200 reported events, of which only one exceeded 60 g. This athlete also exhibited fMRI contrast patterns that were quite consistent with the control population (figure 1, far left column) both before and during competition activities.

In contrast, athletes diagnosed as concussed (COI+/FOI+; figure 1, far right column) exhibit changes in biomarkers consistent with the literature (Lovell et al. 2003; Mayer et al. 2015a,b; Meier et al. 2015; Yeo et al. 2011). Mechanically, the athlete depicted here differs from the arguably healthy (COI−/FOI−) athlete by having experienced a number of large magnitude (above 60 g) events at multiple locations around the head. Although this athlete missed three weeks of the season because of his diagnosed concussion, he still accumulated more than 800 events. Obtained approximately 72 hours after diagnosis of concussion, this athlete's InSeason fMRI shows relatively focal reductions in contrast (Lovell et al. 2003), consistent with the local changes in neuronal metabolic activity expected with injury—either the simpler (1-back) task becomes harder and the two tasks look more similar (i.e., move toward "no coloration" or even "blue" if the 2-back task can no longer be performed), or inputs to the given area are disrupted and it is no longer recruited during either task, resulting in more equivalent nonactivation (again, moving toward "no coloration").

Critically, some athletes exhibit appreciable changes in biomarkers in the absence of symptoms (COI−/FOI+; figure 1, 3rd column). The athlete shown here accumulated over 1,800 events during the season, largely concentrated at the top front of his helmet, as a result of lowering and leading with his head. Obtained after a week in which HITS reported more than 240 events exceeding 10 g, this athlete's InSeason fMRI exhibits more substantial changes in contrast than did the concussed (COI+/FOI+) athlete, with the bulk of the brain now apparently working equally hard to perform the 1- and 2-back tasks. It is important to reiterate that this athlete was asymptomatic, giving no cause to be examined by the team's medical staff.

Variability and Duration of Effects

Taking our 7 years of study as a whole, changes in the neurophysiologic behavior of asymptomatic athletes such as those evidenced in figure 1 are fairly common (Abbas et al. 2015a,b; Breedlove et al. 2012; Chun et al. 2015; Poole et al. 2014, 2015; Robinson et al. 2015; Shenk et al. 2015; Svaldi et al. 2015, 2016; Talavage et al. 2014). This statement is corroborated by work from other research groups evaluating asymptomatic brain health with diffusion-weighted imaging (Bazarian et al. 2014; McAllister et al. 2014) and resting-state fMRI (Johnson et al. 2014).

Of greater concern, many PreSeason measures for the collision-sport athletes in our study suggest that some level of injury is present before they ever take the field (Abbas et al. 2015a,b; Poole et al. 2014). As such, it is possible that imaging them during their collision-sport participation in middle school may be warranted.

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Moreover, athletes who have experienced many subconcussive events require an exposure-dependent time period before biomarkers recover to more closely resemble those of noncollision-sport peers—i.e., those exposed to more events take longer to recover. As we have shown (Breedlove et al. 2014; Nauman et al.

2015), athletes exhibit higher rates of deviant neurocognitive and neurophysiologic measures during the season than afterward, but even postseason measurements—obtained 3–5 months after participation—reveal a high likelihood of injury for athletes who experienced more than 60–70 events per week (exceeding 10 g, as reported by HITS). This finding is unsurprising, as it may take several days, or even weeks, after injury before repair and a complete return to normal physiology—even if the individual takes time off from activity (Ghaffar et al. 2006).

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Appreciable changes in neurophysiology in asymptomatic athletes demonstrate that symptoms are a subset of injury, where the concept of injury must encompass nonstructural alterations (e.g., changes in ionic balance; Hovda 2014). Note that changes in fMRI contrast (figure 1, bottom) are generally concomitant with a high number of HITS-reported acceleration events *even when this number is not coupled to diagnosis of a concussion*. This observation argues in favor of the hypothesis that exposure to subconcussive events plays a critical role in the accumulation of injury (McKee et al. 2009).

Our study suggests that there is a very direct link between changes in the brain and an individual's subconcussive exposure, comprising factors including technique, number of physical head blows experienced, and net occurrence of whiplash-like stresses on the brain from other blows (e.g., tackles not involving a blow to the head).

Current and Future Research

According to the findings reviewed here, evidence exists that some level of subconcussive injury can be sustained without immediate presentation of symptoms. Such injury could range from ionic imbalance (Hovda 2014) to neuronal damage that has not yet precluded delivery of information in the brain. This last is a critical concept for understanding concussion—an individual will not exhibit symptoms until information flow is interrupted or at least sufficiently disrupted so as to reduce the reliability of neuronal summation in place and/or time.

Investigations of the Purdue Neurotrauma Group

Our study seeks to detect these disordered conditions before symptoms arise: while there is obvious value in improving treatment and return-to-life protocols, the greatest benefit is to be gained from preventing the underlying injury. Our study thus has initially been directed at characterization of brain changes associated with subconcussive injury in youth athletes, particularly those exposed to repeated head acceleration events.

Combining neurocognitive testing, advanced neuroimaging, and daily monitoring of head acceleration events, our study tracks athletes before, during, and after exposure to events that are likely to contribute to brain injury. We now have data from football and women's soccer teams at three high schools and one college, comprising 420 athlete-seasons, more than 1,300 MRI sessions, and roughly 1,400 neurocognitive assessments. Partnering with multiple institutions conducting similar research (Bailes et al. 2015), our intention is to evaluate biomarkers derived from these varied assessments to draw conclusions about how impaired individuals are likely to be, based on their exposure to acceleration events.

A key component to all of the findings reported above is the acquisition of a within-subject baseline, either before participation or before an exposure of interest. Most neurophysiologic and neurocognitive measures used to study concussion exhibit appreciable population variance, complicating interpretation of differences between subjects. However, when within-subject changes become larger than the variation in a population, it is straightforward to interpret changes as meaningful.

Needed Research

It is critical to recognize—particularly when assessing outcomes from studies in which only postinjury scans are available—that concussed and asymptomatic athletes with similar histories of head acceleration events can exhibit similar biomarkers, and that both generally exhibit appreciable differences relative to noncollision-sport peers (Abbas et al. 2015a,b; Poole et al. 2014; Svaldi et al. 2015, 2016). Unfortunately, the current well-funded studies into concussion do not incorporate such a model—their focus is on tracking recovery from symptoms, rather than on understanding how to prevent those symptoms from occurring. Given work by our group and others (Johnson et al. 2014; McAllister et al. 2014), the comparisons made in these large studies are at risk of revealing few differences between concussed and asymptomatic athletes. Lack of biomarker alteration due to concussion must not be misinterpreted to downplay the serious potential for long-term damage associated with this clinically recognized injury.

In conclusion, the structural health monitoring model should be effective in the study of concussion, as it provides a mechanism to quantify both injury and recovery. Assessment of individual athletes before, during, and after exposure to potentially deleterious events will provide the best opportunity to characterize injury and to guide mitigation of these consequences, whether through improved prevention, intervention, and/or therapy.

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