Written Testimony

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Summary of Major Points from Written Testimony

- The Purdue Neurotrauma Group (PNG) proposes to achieve safer participation in youth sports by ***(i)*** education of athletes, parents, coaches, and healthcare providers, ***(ii)*** improved protective equipment, ***(iii)*** automated monitoring of exposure to head accelerations, and ***(iv)*** improved training of athletes.
- The PNG study, initiated in 2009, represents the largest and most comprehensive study of youth athletes exposed to repetitive head blows to-date in high school-aged girls *and* boys, playing soccer and football.
- A substantial number of statistically-significant short-term effects of repetitive head blows have been observed in the PNG study:
    - Decreases in functional MRI activation contrasts associated with working-memory task completion.
    - Decreases in MR spectroscopy-detected concentrations of neural metabolites.
    - Decreases in functional MRI measures of resting-state connectivity.
    - Decreases in functional MRI measures of regulation of neurovascular coupling.
    - Increases in white matter fractional anisotropy as assessed using diffusion-weighted MR imaging.
- Longer-term effects observed in the PNG study, by comparison of *pre-participation* assessments of soccer and football athletes with peers who do not participate in collision-based sports, provide evidence of neuroprotective/repair mechanisms that persist for at least several months after participation.
- These short- and long-term alterations, and their associations with exposure to head collision events, strongly suggest that limitation of exposure to head accelerations will reduce short-term consequences of participation and likely contribute to a reduction in the observation of concussion.
- Achievement of reduction in head acceleration event exposure *is technically feasible*, and should enable more youth to participate in more activities without increased risk of head injury.

Executive Summary

The Purdue Neurotrauma Group (PNG) has studied head injuries and the related changes in neurophysiology for seven years and our data set represents the largest and most comprehensive study of young male and female athletes exposed to repetitive head impacts to date. Our results demonstrate that the number of head impacts per week and their magnitude must be limited and that this monitoring is technically feasible. To achieve the goal of wider and safer participation, the PNG proposes the following four steps be taken. These are ***(i)*** improved education of stakeholders regarding what may be regarded as "safer" levels of head acceleration events and how to avoid inducing such events during practices, ***(ii)*** improved protective equipment, with emphasis on preventing energy transmission to the skull and brain, ***(iii)*** automated monitoring of athletes for exposure to head accelerations that are likely to contribute to brain injury, and ***(iv)*** improved training of athletes to minimize head acceleration (i.e., collision and whiplash) events.

The Study of Repetitive Subconcussive Injury in Youth Athletes

Since 2009, the PNG has conducted a longitudinal (within-season) and cross-sectional (across-season) evaluation of the effects of repetitive subconcussive exposure to head acceleration events in high school-aged athletes participating in contact sports. This study, comprising over 420 athlete-seasons of cognitive and advanced neuroimaging assessment in high school-aged girls playing soccer and boys playing football, represents the largest study to-date of the effects repeated subconcussive exposure and the linkage to traumatic brain injury in youth athletes.

Traumatic brain injury results from head accelerations that cause damage to the central nervous system. There are a variety of ways that this can happen and whiplash events may be just as dangerous as direct head impacts. Damage is ultimately caused by the dissipation of energy which, at the level of the brain, must occur through deformation of tissue (i.e., stretch and compression, typically quantified by strains), fluid movement, and mechanical disruption (e.g., cell rupture, myelin de-bonding, and synaptic derangement). While it is possible for a single large blow to the head to cause any or all of these effects and result in symptoms, it is fortunate that these types of head impacts are relatively rare (Daniel et al. 2012). It should be noted, however, that even small head accelerations can produce these consequences within a localized region and, if the rate of healing does not keep up with the rate of damage accumulation, the athlete would be expected to eventually experience symptoms, even in the absence of any particularly large hits. In fact, every head impact or whiplash event would be expected to produce a unique spatial pattern of strains, and repeated exposure to such events increases the chance that the locations of maximum strains will overlap, resulting in these locations being progressively damaged over time. Eventually, the local tissue will have its resistance to injury reduced, or the small tears will preclude normal operation of the cells, much the same way in which overuse injuries (e.g., running or marching with heavy packs) may lead to stress fractures.

Over the past seven years, PNG has been the first to document statistically significant changes in brain structure, function, and chemistry in living football and soccer players who were not diagnosed with a concussion (Poole et al. 2014; Talavage et al. 2014; Abbas et al. 2015b; Svaldi et al. 2016). Two important features of these observed changes should be noted. First, they have been observed to affect a large fraction (30-60%) of players on the teams studied to date (Breedlove et al. 2014; Nauman et al. 2015; Talavage et al. 2016). Second, they have repeatedly been observed to be best-correlated with the measures of cumulative acceleration exposure, be they the number of head collisions experienced or the aggregate energy incident on the head (Breedlove et al. 2012; Svaldi et al. 2016). Taken together, it is clear that head accelerations (a more general term to encompass both direct blows to the head or whiplash events associated with blows to other locations on the body) that *do not* result in a near-term diagnosis of concussion can still cause cellular-level injuries that accumulate over time.

It is critical to note that the neuroimaging literature strongly suggests that some level of injury can be sustained without immediate presentation of symptoms. Damage or alterations in functional capacity at a single location in the brain need not produce corresponding changes in behavior (Viswanathan et al. 2015). Such injury could range from ionic imbalance (Hovda 2014) to neuronal membrane damage (e.g., widening of the Nodes of Ranvier) that has not yet precluded delivery of information in the brain (Ouyang et al. 2010).

The potential for hidden/covert damage is what makes repetitive brain injury so insidious, and is hypothesized to have confounded past investigations into the causes and consequences of concussion. A critical concept for understanding "concussion" and the difficulty in quantifying its causes, is that an individual should not be expected to 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. Rather, provided that the flow of information through the brain is not wholly impeded, behavior should be expected to be within normal performance limits, albeit possibly being considered more strenuous. Even if a location within the brain has been impaired such that information cannot pass through it, the presence of multiple pathways by which information may reach the intended destination within a necessary time frame may preclude any symptoms being evidenced by the individual. Therefore, it is likely that the entire communication process must be interrupted or significantly delayed for a failure of the system (i.e., a concussion) to be observed.

Overview of the Purdue Neurotrauma Group Study

The PNG study uses structural health monitoring (Talavage et al. 2015) as a framework in which to detect disordered conditions in brain behavior before symptoms arise: while there is obvious value in improving treatment and return-to-learn/play protocols, the greatest benefit is to be gained from preventing the underlying injury. Once the biochemical cascades are initiated, it may be possible to intervene and mitigate subsequent damage (Shi 2015), but the most effective "treatment" is prevention of those cascades in the first place.

Our study thus has initially been directed at characterization of brain changes associated with repeated exposure to subconcussive events (i.e., head accelerations that *do not* produce clinical observation of symptoms) in youth athletes, particularly those exposed to repeated head acceleration collisions from sports such as football and soccer.

Combining cognitive testing, advanced neuroimaging, and daily monitoring of head acceleration events, the PNG study (Figure 1) 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 cognitive assessments. Partnering with multiple institutions (Bailes et al. 2015) conducting similar research via the Concussion Neuroimaging Consortium (http://www.concussionimaging.org), our goal is to evaluate biomarkers derived from these varied assessments to better characterize the risk that an individual who has been exposed to subconcussive events will exhibit abnormal brain behavior, and how elevated their risk might be for subsequent diagnosis of concussion.

Before discussing key findings of this study, it is critical to observe that a key component of the PNG study has not been widely replicated in any of the large, multi-institutional efforts currently being funded by federal sources. Specifically, the PNG study derives much of its benefit from the within-season longitudinal nature of its cognitive and neuroimaging assessments—the acquisition of a within-subject baseline, before participation/exposure, has proven to be critical to our understanding of both short- and long-term alterations in brain behavior and health. The value of a pre-participation assessment comes from the fact that most measures of brain function/physiology and cognitive performance used to study concussion exhibit appreciable population variance, complicating interpretation of differences between subjects. Within-subject changes in measurements, as a function of exposure, have frequently proven to exhibit greater variance than are exhibited across the source population prior to exposure. The ability, therefore, to recognize that a late-in-the-season individual no longer resembles the pre-participation population makes it straightforward to interpret changes in cognitive or neuroimaging biomarkers as meaningfully-related to the independent variable of exposure. Given work by our group and others (McAllister et al. 2014; Johnson et al. 2014), the comparisons made in the large multi-institutional 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.

Findings of the Purdue Neurotrauma Group Study

Several key short-term findings in high school-aged athletes have been obtained from the PNG study as a consequence of the longitudinal nature of the study within each of the seven seasons of study to-date.

a) The initial finding of the PNG study—in boys playing football—was the presence of statistically-significant decreases in functional MRI activation contrasts associated with completion of a rather simple working-memory task. While such a finding might not be remarkable on its own, these decreases were observed when the subjects (a) did not exhibit alterations in task success, and (b) did not exhibit outward symptoms associated with a diagnosis of concussion—i.e., were asymptomatic. Critically, these findings (Figure 2) proved to be best-correlated with recent exposure to head acceleration events (Breedlove et al. 2012; Talavage et al. 2014; Robinson et al. 2015), and the persistence of these decreases (Figure 3) appears to be related to average weekly exposure to head acceleration events experienced by the athletes (Breedlove et al. 2014; Nauman et al. 2015).

b) A second finding in male football players was the presence of statistically-significant alterations in MR spectroscopic assessments of metabolite concentrations—in dorsolateral prefrontal cortex (DLPFC; a region associated with planning and executive function) and primary motor cortex (M1)—arising at the beginning of the period of exposure to collisions, and persisting throughout the competition season and beyond (Poole et al. 2014; Poole et al. 2015).

c) An additional observation from male athletes participating in football (Abbas et al. 2015b; Abbas et al. 2015c) was that measures of the network connectivity, as assessed using functional MRI, exhibited statistically significant drops in the periods following increases in the average weekly exposure to head acceleration events—e.g., at the commencement of practices (typically associated with two contact activities per day), and late in the season (when activities intensify due to post-season tournaments).

d) These findings were extended beyond male athletes to female athletes, with observation in functional MRI of decreased regulation of cerebrovascular reactivity (a measure of the coupling between brain activity and the vascular delivery of metabolites) in *both* male football and female soccer athletes (Figure 4) at the high school level, with the degree of this decrease in regulation linked to the number and aggregate energy associated with the history of head acceleration events as of the time of the assessment (Svaldi et al. 2015; Svaldi et al. 2016).

e) Finally, recent preliminary analyses further suggest that male athletes who are exposed to the highest levels of head acceleration events also exhibit the greatest *increases* in the directionality of the diffusion of water molecules in axonal tracts (i.e., increases in fractional anisotropy) as measured by diffusion-weighted MR imaging (Chun et al. 2015; Jang et al. 2016). This increase in the directionality of the diffusion of water (Figure 5) suggests that extracellular spaces—which normally do not restrict the diffusion of water—have been decreased, potentially through chronic inflammation of the brain.

In addition to these short-term observations, the cross-sectional nature of the study across seasons and associated comparison to peer controls (of like gender, and from the same high schools) who have not previously participated in contact sports, has highlighted population-level differences at the pre-participation assessment that suggest the presence of longer-term—possibly even persistent—alterations in brain behavior and health, that are likely to be undesirable for periods exceeding a few months (or even weeks) out of the year:

a) Statistically-significant decreases in MR spectroscopy-assessed neural metabolites *during* the season, were found to represent drops from elevated concentrations *prior* to the season (Poole et al. 2014).

b) Resting-state measures of brain connectivity, as obtained using functional MRI, were found to be elevated (relative to noncollision-sport peers) prior to the season, and to recover to these high levels once head acceleration levels stabilized during the season (Abbas et al. 2015b; Abbas et al. 2015c).

c) Further analyses of brain networking using graph theoretic approaches (Bullmore and Sporns 2009) has revealed a meaningful dependence of pre-participation connectivity on *both* the (self-reported) history of concussion and the history of participation in sports involving repetitive exposure to head acceleration events, with a continuum appearing to exist from healthy noncollision-sport athletes without a history of concussion to collision-sport athletes having a history of concussion, with collision-sport athletes without a history of concussion lying at an intermediate location (Abbas et al. 2015a).

The tendency for both short- and long-term alterations to be associated with higher levels of exposure to head acceleration events strongly suggests that a key aspect to the prevention of subconcussive, and likely also concussive, injury is the limitation of exposure to such events. Approaches such as hit counts will not represent an ideal solution, when applied in a one-size-fits-all manner, but do represent an excellent first step in reducing the risks to youth athletes in regard to short- and long-term alterations in brain health. Enhanced modeling of individual athletes and continued exploration of the features of head accelerations that most contribute to subsequent alterations in cognitive and neuroimaging biomarkers can provide greater refinement in the future with regard to which events "matter" and are, therefore, appropriate to be "counted". More critically, the potential that there does exist some axis (dimension) along which there is a minimum threshold above which head acceleration events are increasingly likely to contribute to short- and/or long-term alterations in brain health would argue that enhancements in protective measures and training could both contribute to an ultimate solution that reduces the risk of brain injury in youth athletes.

The Path to Prevention

Based on the findings above we propose the keys to safer participation include ***(i)*** improved education of coaches, officials, and parents regarding what may be regarded as "safer" levels of head acceleration events and how to control the incidence rate of these events during practices, ***(ii)*** improved protective equipment, increasing the efficacy in preventing energy transmission to the skull and brain, ***(iii)*** automated monitoring of athletes for exposure to those head acceleration events that are most likely to contribute to brain injury, and ***(iv)*** improved training of athletes to minimize head accelerations associated with collision and whiplash events. As detailed in Talavage et al. (2015), the PNG study provides not only a means to detect and characterize changes as a function of acceleration event exposure, but also provides a framework in which prevention and intervention may be evaluated.

(i) Educating athletes, coaches, athletic directors, officials, parents, and even healthcare providers so that they understand the mechanisms by which athletes expose themselves to large head accelerations, is an important step forward. Eliminating tackling from practice (as per the recent Ivy League mandate) was found in our study (Talavage et al. 2015) to appreciably decrease the average number of head impacts and concomitant alterations in observed biomarkers. Even if contact activities are not eliminated, altering participation schedules to provide more days off between such activities is likely to be beneficial due to the potential for natural repair processes to mitigate the cumulative damage.

(ii) Beyond using some form of hit count to reduce the total number of head impacts, it is practical to improve safety equipment, including designing padding and helmets that absorb more energy and reduce the total energy delivered to the brain. While this is, in fact, not a difficult problem to solve, efforts have been slowed by the fact that equipment certification has focused on mitigating skull fractures and other major trauma, as opposed to concussion. Current helmet designs therefore prevent massive trauma (largely by spreading the force out over a larger area), but do little to reduce the energy transferred to the brain. Once the limits of energy transfer beyond which brain injury occurs are identified, it will be readily feasible to develop new design criteria for helmets and standards that, when combined with current testing protocols, will both eliminate massive trauma *and* dramatically decrease the energy transferred through the helmet to the brain.

(iii) The PNG study has demonstrated that substantial changes in brain behavior can arise in the absence of (obvious) symptoms, and that these changes may accumulate over time. Consequently, improvement of diagnostic protocols—including both (a) telemetry-based monitoring of the number and magnitude of head accelerations, and (b) clinical follow-up evaluations possibly including an array (e.g., blood and neuroimaging) of biomarkers and cognitive testing—should be expected, in the near future, to dramatically increase sensitivity and specificity of clinical assessments.

(iv) Continued educational protocols (akin to “Heads Up”) in conjunction with the telemetry argued for in *(iii)*, have significant potential for rapidly enhancing player skill level, leading to improved techniques that decrease player risk of head injury. For example, low-cost sensors that monitor the number, magnitude, and location of head impacts can provide feedback to athletes and coaches, allowing them to encourage less-risky play and game techniques in real-time. Rapid and appropriate correction of poor tackling, heading, etc. will permit athletes to participate more frequently and more safely.

Concluding Thoughts

The search for neuroimaging biomarkers has yielded potentially powerful insights into the mechanisms of brain injury while also redefining what we should consider “injury” to be. Based on the PNG study findings that decreased exposure corresponds to fewer and smaller changes in brain function, it is critical that research efforts be put in place to enhance preventative approaches to brain injury, rather than solely focusing on post-injury recovery. Effecting these preventative approaches will require participation from multiple stakeholders, including parents, coaches, officials, and healthcare providers. All must advocate for measures that will further the *prevention* of brain injury, including reduction of exposure to head impacts, introduction of adequate rest periods between contact activities, and appropriate education of all participants in the sporting enterprise. In conjunction with the further advancement of the science, this joint effort has the greatest potential for improving the overall safety of youth, with long-term positive consequences for this vulnerable population.

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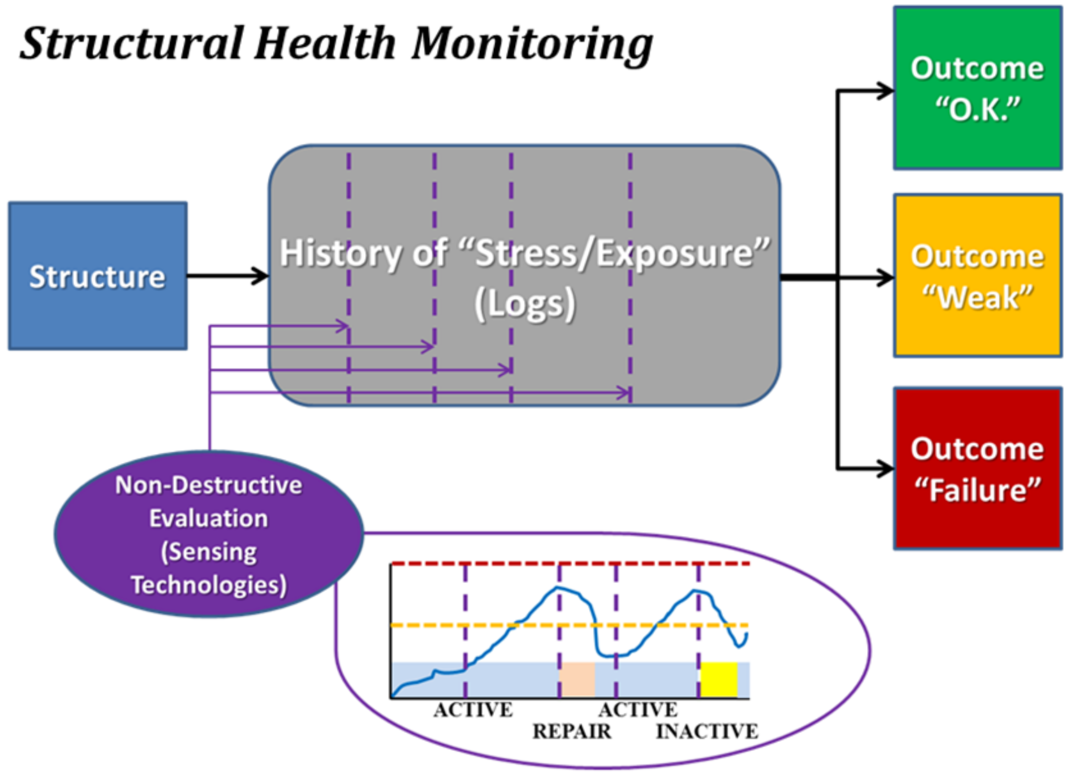

Figure 1: Block diagram illustrating the concept of Structural Health Monitoring (SHM). The structure of interest is monitored for usage over time, and periodically assessed using non-destructive evaluation methodologies. Each such assessment permits categorization of the structure as being healthy ("O.K."), altered ("Weak") or severely damaged ("Failure"). Note that depicted images are intended only as schematic representations of data and/or associated analyses. *From Talavage et al. (2016).*

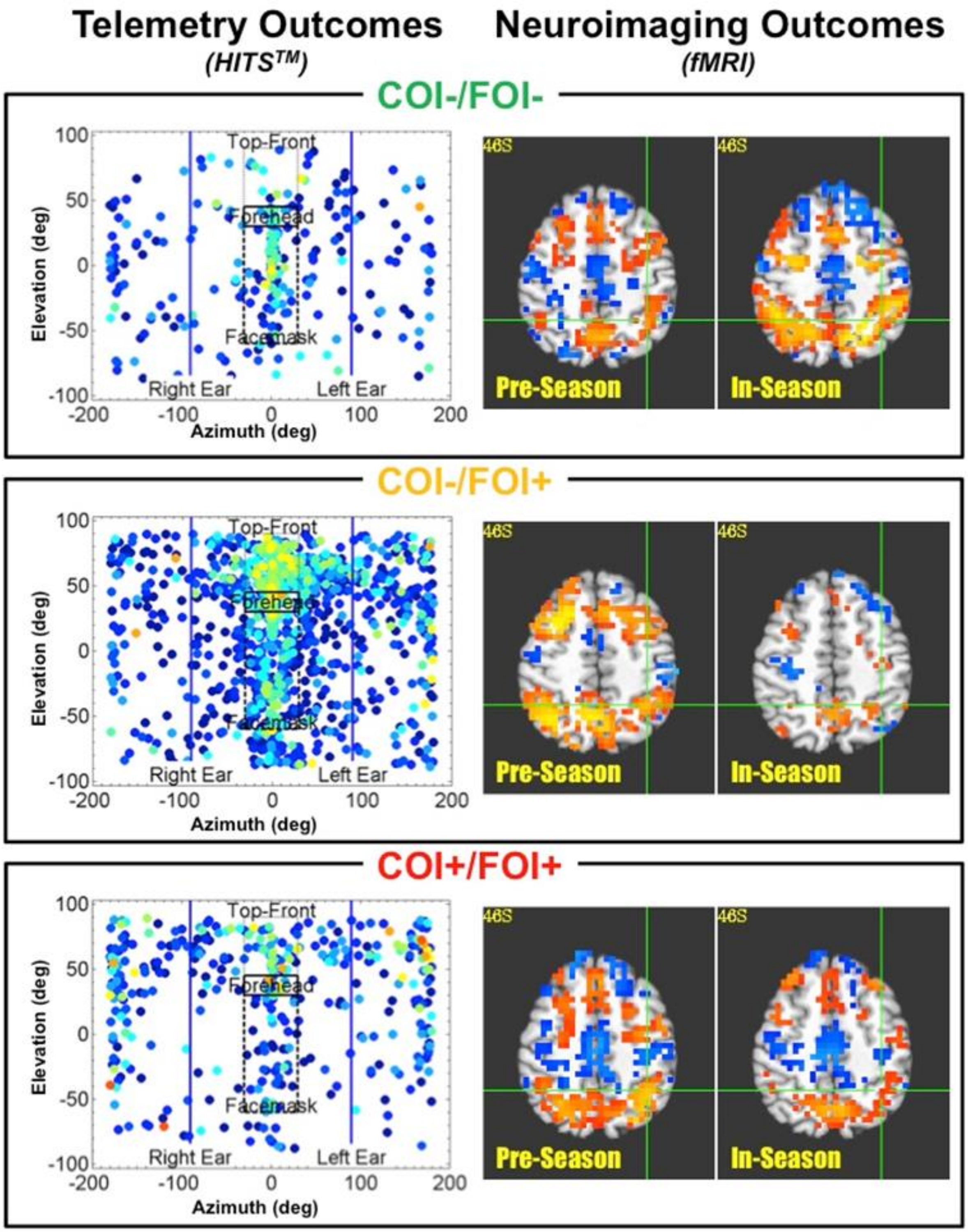

Figure 2: Comparison of (*left column*) head impact maps and (*right column*) fMRI measurements of "verbal" (letter-based) N-back working memory task for three high school athletes in the pre-season and subsequent to exposure to repeated head acceleration events. One athlete (*top row*) experienced a relatively low number of small magnitude hits and did not exhibit significant changes between pre-season and in-season scans. A second

athlete (*middle row*) exhibited a large number of hits primarily to the top front of the helmet and, although not diagnosed with a concussion, exhibited statistically significant changes in neurophysiology. This athlete was representative of a new category of impairment observed in 30-60% of high school football players studied. A third athlete (*bottom row*) who was diagnosed with a concussion took a number of large hits (orange and red circles) and exhibited substantial changes in neurophysiology. Activation is depicted for a 2-back vs. 1-back working memory contrast, with preferential activation for the 2-back task indicated by orange-red coloration, and for the 1-back task by blue-cyan coloration.

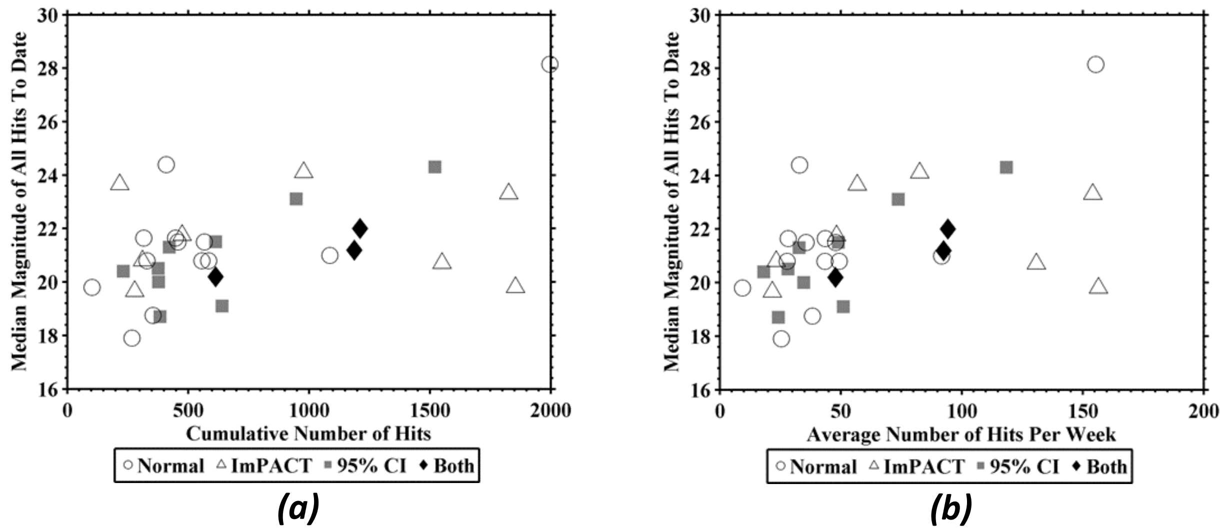

Figure 3: Relation of flagging category (ImPACT™ or fMRI or none) of players during post-season assessments, as related to the median magnitude of the blows taken over the course of the season and (a) the number of cumulative hits, or (b) average hits per week over the entire season. Open circles indicate that the subject's ImPACT™ and fMRI measures were within the normal range. Open triangles indicate that the subject's ImPACT™ test was flagged. Gray squares were used to denote those instances when at least 11 ROIs of a subject's fMRI scan exceeded the 95% confidence interval. Finally, black diamonds indicated those sessions where the subject's ImPACT™ and fMRI were flagged. A gap in our data occurred between 600 and 900 cumulative hits. Players who sustained more than 900 cumulative hits had a 75% chance of being flagged, whereas players who sustained fewer than 600 cumulative hits had only a 36% chance of being flagged. Similarly, a gap occurred in our data between 60 and 80 average hits per week. *Adapted from Nauman et al. (2015).*

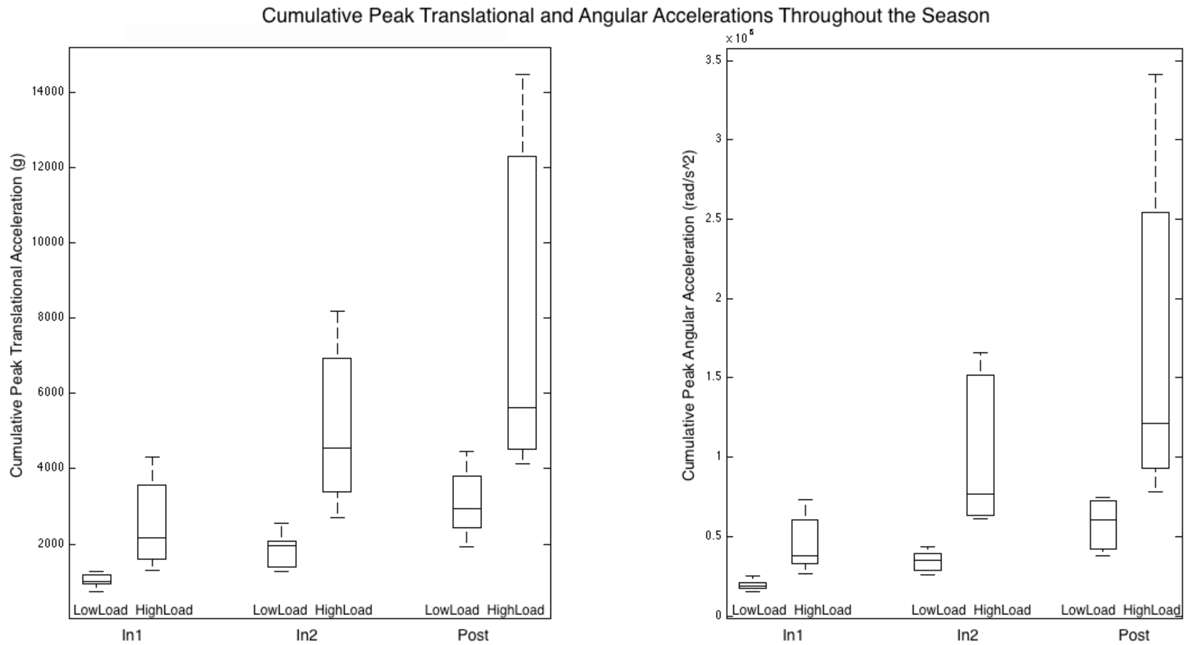

Figure 4: Box and whisker plots of cumulative peak translational acceleration (cPTA) and cumulative peak angular acceleration (cPAA) distributions for soccer athletes at each assessment session. Boundaries of boxes represent the 25th and 75th percentiles (1st and 3rd quartiles) and the line inside the boxes indicates the median (50th percentile) of the distribution. Assessment sessions *In1* and *In2* comprise intermediate measurements during first and second half of the competition season; and Post represents groupings based on end of season cumulative totals. Athletes are grouped by individual rank above (*HighLoad*; n = 7) or below (*LowLoad*; n = 7) the median Relative Cumulative Exposure (RCE; see text). Athletes in the *Top* group were observed to have experienced significantly greater cPTA and cPAA than athletes in the *Bottom* group at each session ($p_{FDR} < 0.05$, unpaired *t*-test). Note that the *HighLoad* and *LowLoad* groups are session specific—i.e., an athlete need not remain in the *HighLoad* or *LowLoad* group for all three assessment periods. *Adapted from Svaldi et al. (2016)*.

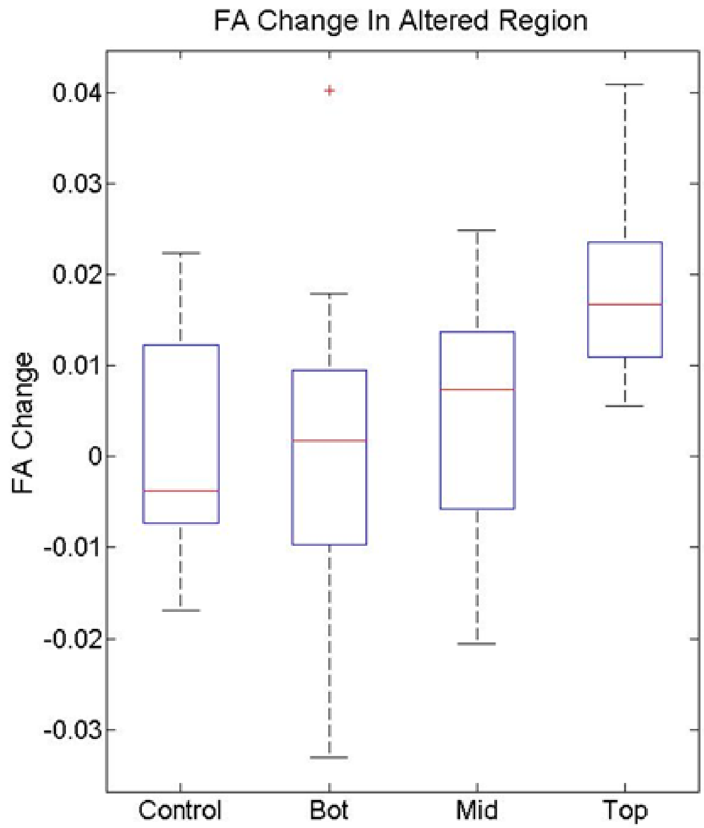

Figure 5: Distribution of fractional anisotropy (FA) changes in white matter regions of interest indicate that high school-aged male athletes participating in football who experience the highest levels of repeat exposure to head acceleration events (*Top*) exhibit statistically significant increases in FA relative to their pre-participation assessment. This elevation of FA suggests that these athletes are experiencing inflammation of the brain (Povlishock and Katz 2005). Test-retest contrasts are indicated for high school-aged male athletes participating in non-contact sports (*Control*; N=15) in addition to three groups of football players, divided into thirds (upper = *Top*, middle = *Mid*, lower = *Bot*; N=15 in each) based on accumulated counts of head acceleration events reported by the xPatch (X2 Biosystems, Inc.) to exceed 20 g (McCuen et al. 2015). *From Jang et al. (2016).*