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The effect of repetitive subconcussive collisions on brain integrity in collegiate football players over a single football season: A multi-modal neuroimaging study

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A B S T R A C T

The cumulative effect of repetitive subconcussive collisions on the structural and functional integrity of the brain remains largely unknown. Athletes in collision sports, like football, experience a large number of impacts across a single season of play. The majority of these impacts, however, are generally overlooked, and their long-term consequences remain poorly understood. This study sought to examine the effects of repetitive collisions across a single competitive season in NCAA Football Bowl Subdivision athletes using advanced neuroimaging approaches. Players were evaluated before and after the season using multiple MRI sequences, including T_1-weighted imaging, diffusion tensor imaging (DTI), arterial spin labeling (ASL), resting-state functional MRI (rs-fMRI), and susceptibility weighted imaging (SWI). While no significant differences were found between pre- and post-season for DTI metrics or cortical volumes, seed-based analysis of rs-fMRI revealed significant ($p < 0.05$) changes in functional connections to right isthmus of the cingulate cortex (ICC), left ICC, and left hippocampus. ASL data revealed significant ($p < 0.05$) increases in global cerebral blood flow (CBF), with a specific regional increase in right postcentral gyrus. SWI data revealed that 44% of the players exhibited outlier rates ($p < 0.05$) of regional decreases in SWI signal. Of key interest, athletes in whom changes in rs-fMRI, CBF and SWI were observed were more likely to have experienced high G impacts on a daily basis. These findings are indicative of potential pathophysiological changes in brain integrity arising from only a single season of participation in the NCAA Football Bowl Subdivision, even in the absence of clinical symptoms or a diagnosis of concussion. Whether these changes reflect compensatory adaptation to cumulative head impacts or more lasting alteration of brain integrity remains to be further explored.

1. Introduction

There has been a growing concern over sports-related brain injuries and possible long-term consequences; however, there has been less of a focus on the cumulative effects of repetitive subconcussive impacts. Subconcussive impacts are defined as events similar to those giving rise to a concussion, or mild traumatic brain injury (mTBI), but apparently involving insufficient impact forces or accelerations to produce symptoms associated with mTBI (Shuttleworth-Edwards et al., 2008). Many contact sports, including American football, soccer, rugby, boxing, wrestling, and lacrosse, result in rather high numbers of repetitive head impacts throughout a season and career, with football having been observed to lead possibly to thousands of subconcussive impacts for a single player over the course of one season (Merchant-Borna et al.,

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2016; Talavage et al., 2014).

The cumulative effects of multiple mild TBI incidents or accumulation of subconcussive impacts remain understudied and poorly understood. Many studies have demonstrated that multiple TBI events lead to greater functional impairments than are associated with only a single TBI (Longhi et al., 2005; Prins et al., 2013), suggesting that longer-term structural changes occur, possibly with each such incident (Giza and Kutcher, 2014). Further, there appear to be various long-term cognitive, motor, and psychiatric deficits associated with repeated injuries (Guskiewicz et al., 2000; Riemann and Guskiewicz, 2000) and likely with greater cumulative exposure to subconcussive impacts (Bailes et al., 2013; Montenigro et al., 2016). Animal and human research have demonstrated that repetitive impacts can cause pathophysiological changes in the brain and central nervous system without the presence of acute behavioral changes (Bauer et al., 2001; Talavage et al., 2014). However, since subconcussive impacts typically go undiagnosed or unmanaged (Baugh et al., 2012; McKee et al., 2009), the means by which accumulation of impacts over the course of a season (or career) can lead to altered neurobiology later in life remains inferred (Broglio et al., 2012). Nonetheless, many recent case studies have demonstrated gross and microscopic pathology changes that are best attributed to repeated mTBI and exposure to subconcussive impacts (McKee et al., 2009; Omalu et al., 2005).

Within American football, studies have shown that specific positions may have a differential risk of concussion and exposure to subconcussive impacts, and, therefore, neurodegenerative diseases (Lehman, 2013). It is thought that "speed" players (quarterback, running back, wide receiver, defensive back, safety, linebacker, etc.) and "non-speed" players (offensive and defensive line) are at differing risks, due to the nature of their positions. "Speed" players often build up momentum prior to tackling or being tackled, whereas "non-speed" players typically engage in hits immediately after the ball is snapped (Broglio et al., 2012; Pellman et al., 2004). However, there is still great debate regarding whether greater risk of mTBI exists for players exposed to the higher-magnitude impacts (i.e., speed players) or those exposed to the repetitive immediate head impacts (i.e., non-speed players). Of interest here, several studies have shown that linemen receive more cumulative impacts (especially at the front of the head) and develop more post-impact symptoms than other positions (Baugh et al., 2015; Crisco et al., 2010).

Several previous studies have found a linkage between the degree (quantified by number or average magnitude) of exposure to repetitive subconcussive impacts and the degree of pathophysiological change in the brains of collision-sport athletes. These changes have been observed in asymptomatic athletes through evaluation of measures derived from: cognitive testing (Breedlove et al., 2012; Talavage et al., 2014; Breedlove et al., 2014; Nauman et al., 2015); task-driven and resting-state brain behavior (Abbas et al., 2015c; Breedlove et al., 2012; Talavage et al., 2014; Robinson et al., 2015); neurovascular coupling (Svaldi et al., 2015; Svaldi et al., 2016); white matter health (Davenport et al., 2014; Mayer et al., 2015; Obler et al., 2010; Chun et al., 2015); and gray matter (Bazarian et al., 2014; Mayer et al., 2015) volume, including hippocampal-specific assessment (Singh et al., 2014). Additionally, the biochemistry of athletes has been observed to vary over the course of exposure to repetitive impacts (Poole et al., 2014; Poole et al., 2015). Further, the differential response to impacts appears to be markedly dependent on previous concussive history (Johnson et al., 2014).

In this multimodal MRI study, the cumulative effects of subconcussive impacts were examined on NCAA Football Bowl Subdivision players over the course of a single intervarsity athletic season. Athletes were evaluated using MRI measures before (pre-) and immediately after (post-) their competition season, and monitored during the majority of activities using helmet-based accelerometers (BodiTrak) to quantify impact exposure. The explicit MRI sequences included T_1-weighted imaging, diffusion tensor imaging (DTI), arterial spin labeling (ASL), resting-state functional MRI (rs-fMRI), and susceptibility weighted imaging (SWI). We predicted that greater accumulation of high intensity impacts would jeopardize functional/structural and vascular integrity of the brain, as assessed in the manner we have previously documented in clinically *asymptomatic* athletes (Slobounov et al., 2010; Talavage et al., 2016; Zhu et al., 2015). Based on prior reports, we also predicted that offensive and defensive linemen would have the greatest number of cumulative impacts (at any threshold level), and that this group would be most likely to evidence neural changes, as observed via MRI. Our specific hypotheses were that a differential sensitivity related to accelerometer measures would be observed for the MRI modalities likely to be associated with cumulative subconcussive exposure over the entire athletic season. Specifically, we expected ASL and SWI abnormalities would be related to rs-fMRI measures and accelerometer measures in clinically *asymptomatic* athletes studied before and after the football season.

2. Methods

2.1. Subjects

Twenty-three (23) male collegiate student football athletes participated in this study. Twenty (20) players completed both MRI scans: within one week before the athletic season began (before any contact practices began during preseason and the regular season) and within one week after the last game of the season (post-season). All subjects provided informed consent, as approved by the Penn State University Institutional Review Board. Image quality assurance measures resulted in exclusion of data from two subjects, resulting in a pool of 18 subjects (21.6 ± 1.28 years old) for subsequent analyses. Our MRI analyses relied on accurate segmentation of 3D MPRAGE volumetric images based on FreeSurfer (Fischl et al., 2002). One subject failed on segmentation due to severe motion artifacts. The other failed on segmentation due to inappropriate image acquisition. Of these 18 subjects, previous concussion history includes no (n = 10), one (n = 6), or two (n = 2) prior diagnosed injuries. However, none of the athletes were recovering from, or were diagnosed with, a concussion during the period of study, or in the nine months prior to the pre-season evaluation.

2.2. Impact history assessment

Impacts to the head for all 23 participating athletes were monitored using the BodiTrak system from HeadHealth Network. These helmet-based sensors comprise elastic fabric with pressure monitors and impact sensors, and provide estimates of both linear acceleration (in units of G) and location of incident impact. The sensors were to be fitted and placed into the athlete's helmet during practices (53 possible sessions; see Table 1), but were not worn during games. Sensor data were collected and, over the course of the season, counts of accumulated (practice) events were assessed using thresholds of ≥ 25G and ≥ 80G, attempting to quantify the majority, if not all, impacts that are likely to be relevant to brain health (McCuen et al., 2015), as well as the count of hits traditionally expected to be associated with concussion (Broglio et al., 2010).

2.3. MRI acquisition

MRI data were collected on a Siemens 3T Prisma MR scanner (Siemens, Erlangen, Germany) with a 32-channel head coil. Images were obtained for each subject prior to participation (*Pre*) and after the football season had ended (*Post*) using the following acquisitions: (1) high-resolution 3D T_1-weighted; (2) a resting-state functional MRI (rs-fMRI) acquisition; (3) 3D pulsed arterial spin labeling (ASL); (4) diffusion-weighed images from which diffusion tensors could be computed (DTI); and (5) susceptibility-weighted imaging (SWI).