Sports-Related Subconcussive Head Trauma

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Introduction

Sports-related concussion (SRC) and subconcussive head trauma have received a lot of attention, not only in the scientific and medical communities, but in the public as well. Widespread media coverage and several high-profile cases have brought into question the damaging and long-term effects of sports-related traumatic brain injury (TBI) [1]. Specifically, there has been a broad range of neurodegenerative diseases and processes that include postconcussion syndrome, posttraumatic stress disorder, cognitive impairment, chronic traumatic encephalopathy (CTE), and *dementia pugilistica* that have been linked to repetitive sports-related head injury of any kind [2]. Research exploring the neuropsychological, neurophysiological, and biomechanical effects of SRC has increased dramatically over the past 20 years [3]. Although still in its infancy, research into the effects of subconcussive head trauma and repetitive head impacts has also begun to grow. The increased understanding of the damaging effects from SRC and subconcussive head trauma has led to changes in sport policy. Despite the growing research, there remain knowledge gaps and an incomplete understanding of the short-term and long-term effects of subconcussive head impacts. Continuous exposure to repetitive subconcussive head impacts sustained over a career has been linked to changes in behavior and neurodegenerative diseases [4]. Traumatic brain injury (TBI) is referred to as the "silent epidemic," as many of the physical, cognitive, behavioral, and emotional symptoms go unrecognized [5]. TBI is not only a major health concern in the United States but is also the leading cause of disability worldwide [6].

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There is growing concern in clinical practice regarding the immediate and long-term effects of multiple and frequent subconcussive blows in athletes participating in full contact sports. These effects, in terms of neurocognitive, behavioral, and underlying neural substrates, have not been sufficiently studied. In particular, concern is growing about the effect of subconcussive impacts on the head and how it may adversely affect cerebral functions [7–9]. Subconcussive blows are below the threshold to cause a concussion [10] and do not elicit any clinically identifiable concussion signs or symptoms [7–9]. Despite not producing any concussion-related signs and symptoms, subconcussive head impacts should not be overlooked. Animal and human studies have shown that even though these subconcussive blows do not result in apparent behavioral alterations, they can cause damage to the central nervous system [2, 11]. Moreover, subconcussive impacts still have the potential to transfer a high degree of linear and rotational acceleration forces to the brain [12]. Alterations in brain gray matter microstructure and neuropsychological deficits have been shown to correlate with the incidence of exposure to subconcussive head impacts during the participation in contact sports [3]. Unlike concussions, subconcussive blows go undiagnosed and are not assessed by medical professionals during a game or practice. Biomechanical research has revealed the staggering numbers of subconcussive head impacts athletes may receive over the course of a season and a career [1, 13]. Furthermore, postmortem studies have identified that repeated subconcussive impacts may have an accumulative effect [10]. It has been hypothesized that these frequent and repetitive subconcussive impacts exacerbate the cognitive aging process by reducing the cognitive reserve at an accelerated rate and lead to altered neuronal biology that may not present itself till later in life [14]. Recent neuroimaging studies have shown that brain injury does not only come from concussive episodes but exposure to subconcussive blows can also cause pathophysiological changes in the brain [15]. Similar to the research focused on concussion and mild traumatic brain injury (mTBI), the current literature on subconcussive head trauma is limited and study results are often mixed [16]. However, deeper investigations into SRC have revealed that subconcussive head trauma is a significant cause of acute and chronic functional and structural changes in the brain [17].

Animal Models of Subconcussive Head Trauma

It has been known since the late nineteenth century that repeated mild blows to the head in animal experiments could be lethal, even though there was no evidence of structural brain damage [18]. Initial animal models investigating the effects of subconcussive insults revealed that following a single subconcussive blow, there were no behavioral and histologic changes, yet repetitive subconcussive head trauma resulted in permanent injury [19]. Fujita et al. [20] reported that repetitive subthreshold head trauma did not cause axonal or vascular changes in the rat. In an early experiment looking at concussion in the rat, it was noted that following subconcussive blows, the animals showed signs of "posttraumatic amnesia" [21]. Additionally, Govons et al. [21] reported that subconcussive blows produced

convulsions in some of the rats, elicited altered activity for 24 h, and that the impact caused the animal to be momentarily stunned. Subconcussive head trauma has shown to decrease the polarizability of the cerebrum, although not to the extent of a full concussive blow [22]. Tedeschi [18] reported that repetitive subconcussive blows received over a short duration in a rat model elicited a higher incidence of ill effects. Furthermore, postmortem examination of these rats revealed widespread evidence of neuronal injury, myelin loss, and glial proliferation. Other studies of subconcussive head trauma have reported neuropsychological changes and ionic fluctuations which have been hypothesized to leave the brain more vulnerable to a repeated injury [23]. In another animal study investigating the effects of subconcussive head trauma induced by a mild lateral fluid percussion, Shultz et al. [10] found that such an injury caused acute neuroinflammation, despite any significant axonal injury, or cognitive, emotional, or sensorimotor alterations. Specifically, they documented a short-term increase in microglia, macrophages, and reactive astrogliosis which returned to normal at a 4-week follow-up. Acute neuroinflammation has also been documented in other animal and human studies of TBI. Repetitive mTBI, similar to neuroinflammation, may have cumulative effects leading to neurodegeneration [10] and has been linked to behavioral impairments after TBI [24]. Conversely, it has been thought that neuroinflammation may have a neuroprotective quality [25] and the brain may be better protected following an initial TBI [26]. Complementary to this notion of neuroprotection, it has also been reported that by gradually increasing the amount of brain injury, animals could tolerate trauma that would otherwise kill normal animals. This so-called trauma resistance was attributed to a stabilization of metabolic processes [27] and the idea of preconditioning has been well-documented for cerebral ischemia [28]. Although postmortem studies have identified that repeated subconcussive head trauma may have an accumulative effect and lead to neurodegenerative diseases [10], Slemmer and Weber [28], using a mechanical stretch to simulate mTBI in hippocampal cell cultures, found that when the tissue was preconditioned they observed a significant decrease in S-100B, indicating a positive effect of glial preconditioning. Moreover, Allen et al. [26] reported a rat model of repetitive mTBI preconditioning served to preserve motor function following a severe TBI and also elicited activation of secondary sites in the brain that may aid in recovery. More recently, utilizing an experimental mouse model of subconcussive head trauma, Tagge et al. [29] demonstrated neuropathological changes in the form of axonopathy, disruption of the blood-brain barrier, astrocytosis, and microgliosis. They also reported that the presence of focal phosphorylated tauopathy was detected in the acute phase of injury. These animal studies give evidence that subconcussive blows to the head are enough to cause injury to the brain.

Biomechanical Studies of Subconcussive Head Trauma

Biomechanical studies focusing on subconcussive head trauma have allowed for the quantification of the number of subconcussive impacts athletes are exposed to. These studies have also shown that significant amounts of force are transmitted to

deep midbrain and brainstem structures, that does not result in concussion or loss of consciousness [30]. Characterizing repetitive head impacts by biomechanical properties of frequency, linear acceleration, rotational acceleration, jerk, force, impulse, and impact duration, Broglio et al. [31] found that many variables including player position, location of impact, and practice versus game all contribute to the inhomogeneity of subconcussive trauma. Miyashita et al. [32] reported a similar variation in the biomechanical characteristics of repetitive head impacts in collegiate lacrosse players due to player position and session type. Moreover, session type has been identified as an important variable in the frequency of subconcussive exposure on account of the intensity of games, compared to practice demonstrating a higher incidence of these impacts [33, 34]. Adding to the variability of the biomechanical properties of subconcussive head impacts, there are also differences based on the sport being played. Comparing peak accelerations between football, ice-hockey, and soccer, Nauheim et al. [35] reported that peak accelerations in ice-hockey were significantly higher than those in football and substantially higher than those measured in soccer players. Furthermore, biomechanical studies report that forces like momentum and energy transfer associated with heading the soccer ball are far less than those found in football, boxing, hockey, and other full contact sports [36]. With the advent of new technologies, like the Head Impact Telemetry System (HITS) and wearable sensors, tracking the number and quantification of forces at impact has become more feasible. In a recent study, Broglio et al. [12] used the HITS to measure and record head impacts in 95 high school football players over a 4-year period of time. The results of this study highlighted the number of blows to the head an athlete is exposed to over the course of a season as well as the high degree of linear and rotational acceleration forces sustained during these impacts. Probably, the most shocking data to come out of these studies are the sheer quantity of subconcussive impacts endured during the course of a season, let alone an athlete's career. This number can be in the thousands, with one study reporting players sustaining over 1400 subconcussive blows over the course of a single season [37]. Tracking 1208 high school and collegiate football players over the course of a season, Beckwith et al. [38] found that players sustaining a concussion received more impacts and impacts of higher force on days they were diagnosed with a SRC. Consequently, a recent laboratory study of football helmets found that current varsity helmets are less protective to their older leather helmet counterparts when it comes to subconcussive blows [39].

Subconcussive hits do not only occur in collision sports like football, ice-hockey, and rugby. Soccer is a contact sport and chronic traumatic brain injury (CTBI) has been well documented in the literature [40]. During an average game, a soccer player heads the ball 6–12 times, which is estimated to be over 5000 headers for a 15-year career [11, 36]. However, most of the documented cases of concussion in soccer occur due to the players head contacting another player's head, the ground, or the goal post, not from purposeful heading [41]. The repeated subconcussive blows that are incurred from heading the soccer ball account for many clinical symptoms that span the spectrum from headache to brain damage and can also lead to alterations in acute and chronic cognitive functions [11]. It has long been known

that heading of the soccer ball could produce "footballer's migraine" [42]. Analyzing the blood levels of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) of 17 male soccer players before and after a bout of heading training, Bamac et al. [43] measured significant changes in both NGF and BDNF concentrations. Measuring blood levels of the neuroprotein S-100B, which is used as a biomarker to indicate brain damage, Mussack et al. [44] reported transient elevations following a dedicated training session of controlled heading in 61 soccer players. The S-100B levels did return to baseline levels 6 h after the heading session. Increases in S-100B concentrations have also been reported from pregame to postgame in football players [45]. Furthermore, biomechanical studies of full-blown concussive episodes have gone to great lengths to quantify and identify a threshold of concussion to no avail [46], as this is very difficult given the fact that each SRC is different [47]. These biomechanical studies illustrate the sheer volume and potential harmful effects from subconcussive head impacts.

Cognitive Assessment of Subconcussive Head Trauma

Exposure to subconcussive impacts that do not result in any clinically identifiable concussion signs or symptoms is a controversial topic, as researchers and clinicians are divided on their true effects. Some research has shown that subconcussive head trauma may have minimal impact on cognitive functions [48], although there is mounting evidence that subconcussive blows have detrimental effects on cognitive and cerebral functions [7, 15]. It has been hypothesized that exposure to repeated and multiple subconcussive blows throughout an athlete's career may compromise cognitive function [49]. It is becoming more apparent that brain injury does not only come from concussive episodes, but that the accumulation of these subconcussive blows may be detrimental [50]. A history of multiple concussions and subconcussive blows has been linked to depression, cognitive deficits, and progressive neuropathologies that include neurofibrillary tangles and deposits of amyloid plaques seen in Alzheimer's disease [51].

A majority of the literature that exists on acute and chronic sports-related subconcussive head trauma has been focused on soccer, as purposeful heading represents a form of repetitive subthreshold mild brain injury [36]. In a preliminary study, it was found that out of 77 retired Norwegian professional soccer players, 50% reported symptoms linked to heading and 75% suffered from disorientation, headache, and nausea [52]. Further studies by Tysvaer et al. used electroencephalograph (EEG) to evaluate professional soccer players. They found that 35% of the participants had abnormal EEGs and 70% displayed some form of neurological impairment [52, 53]. In addition to these findings, neuropsychological testing (Wechsler Adult Intelligence Scale) of the same soccer players revealed significant differences, compared to controls with one-third of participants' scores low enough to suggest evidence of organic brain damage [54]. Matser et al. [55] reported significant deficits in a neuropsychological assessment of amateur soccer players associated with heading. Specifically, they reported impaired performance in memory,

planning, and visual perception processing that was exacerbated by the number of previous concussions a player had sustained. Downs and Abwender [56] reported that subjects with a long history of soccer heading demonstrated slower patterns of motor speed and reaction time. Another study looking at purposeful heading by Witol and Webbe [9] revealed that players with the most reported number of headers had the lowest attention, concentration, and IQ scores. Decreased reaction time and reduced speed performing a motor task have been documented, when assessing the effects of concussive and subconcussive head trauma in soccer [49, 56, 57]. Although there is evidence that a long career, which accounts for many instances of heading the soccer ball, can lead to impaired brain function, it is not clear whether or not this increased likelihood is caused by numerous subconcussive blows or from full-blown concussive episodes [41]. Jordan et al. [58] found that there was a correlation between a history of concussion with increased symptoms in the United States national soccer team players and may suggest that full-blown concussions, as compared to repetitive subconcussive impacts, may be the cause of encephalopathic changes. But it seems evident in the literature that a long soccer career, which amounts to a higher frequency of heading and accumulation of subconcussive blows, contributes to impairments in cognitive function [41, 59]. However, in a review by Rutherford et al. [16] on neuropsychological testing and purposeful heading in soccer literature, they raise certain methodological concerns with a majority of the studies. They conclude that there is preliminary evidence that full-blown concussive episodes can have deleterious effects based upon neuropsychological examination, whereas the effects of subconcussive impacts on neuropsychological tests await more supporting evidence. Not all studies on heading in soccer have reported neuropsychological deficits [42]. In a recent study, Kontos and colleagues [60] used computerized testing in the form of Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) to test 63 adolescent soccer players. All subjects under study had no current (less than 3 months) history of concussion and were placed into one of the three groups based upon the number of documented headers as observed by the researchers over the course of two practices and games. Their results showed no significant differences between the low-, moderate-, and high-frequency heading groups on computerized neuropsychological assessment. However, the authors did note that the males showed lower scores on verbal memory, visual memory, and motor processing, compared to female participants. This decreased performance was attributed to differences based upon sex, even though males headed the ball more often than females.

Similar to the studies looking at the chronic effects of repetitive subconcussive head trauma, initial research looking at the acute effects has produced mixed results. Schmitt et al. [41] tested postural control and recorded subjects' self-reported symptoms immediately and at 24 h following a controlled session of intentional soccer ball heading. They found that prior to, immediately following, and at 24 h after the 40-min session of heading, there were no differences in postural control between the heading group and a control kicking group. Despite not finding any significant difference in postural control, there was an increase in concussion-related symptoms reported by the heading group immediately following the session which

resolved before the 24-h follow-up. The main complaints were headache, dizziness, and feeling lethargic. This reported finding was similar to that of Tysvaer [61] who found that 10 min following a session of purposeful heading, all subjects reported suffering from a headache. Consistent with these findings, Mangus et al. [62] and Broglio et al. [63] found no significant acute changes in balance following a session of purposeful heading. In a recent study by Rieder and Jansen [64], they took subjects and divided them into three groups to investigate the effects that a bout of acute heading would have on neuropsychological examination. The three groups consisted of subjects exposed to aerobic training and purposeful heading drills, the second group consisted of subjects only doing the aerobic training, and the third group did not exert themselves physically before neuropsychological testing. Neuropsychological testing was performed 1 week prior to training session and immediately after. The results showed no differences between groups and/or any deficits caused by heading drills. However, there was a higher incidence of headache during and after in the heading cohort, which the authors attributed to the most minor form of head trauma, cranial contusion, which is associated with local or diffuse transient headache. However, Putukian et al. [65] did not report any differences in self-reported symptoms and cognitive function in a pilot study after a soccer training session that included heading. Therefore, symptoms from subconcussive blows may be shorter lived and only detectable immediately after insult. Investigating the role of concussion history on the neurocognitive effects of subconcussive impacts using the Automated Neuropsychological Assessment Metrics, Forbes et al. [66] found no significant differences between the experimental and control group of female high school soccer players. Although the number of headers recorded for both groups was almost identical (24.9 and 24.3), it was far less than the incidence of subconcussive blows documented in other contact sports. Several other studies looking at the effects of heading in soccer report no significant changes in neuropsychological testing following exposure to repetitive head impacts [65, 67–69]. Employing the use of a computerized tablet, Zhang et al. [70] devised a variant of common eye tracking research, prosaccade, and antisaccade by having participants point toward a target (Pro-Point) or point to the opposite target (Anti-Point). Eye tracking research has been shown to be more sensitive in picking up cognitive and functional deficits, compared to standard neuropsychological testing [71–73]. In their study, Zhang et al. [70] tested 12 female high school soccer players following practice that included heading of the soccer ball. No difference was seen between the soccer group, compared to sex and age-matched control group on the Pro-Point task. Although the Anti-Point task, like the antisaccade task used in eye tracking studies, showed that subjects in the soccer group who were exposed to heading demonstrated significantly slower response times, compared to the control group. Following head injury, oculomotor deficits are common and impaired eye movements have been documented in concussion and postconcussion syndrome [71]. Although deficits in eye movement have been documented in concussion, little work has been done to study oculomotor function in subconcussive head impacts. Using a cohort of 12 high school football players, Zonner et al. reported oculomotor dysfunction in the form of increased near point of convergence (NPC) during the

beginning of the season that was associated with exposure to subconcussive head impacts [74]. This study supported the previous findings of Kawata et al. [75] that also reported increases in NPC, following the completion of a competitive collegiate football season.

In an early study of boxers, Heilbronner and colleagues [76] were the first to demonstrate changes in cognitive function immediately following a fight when compared to a prefight assessment. Specifically, they noted a decline in verbal and incidental memory, and noted that numerous subconcussive blows may be more deleterious than less frequent full-blown concussions, as the number of rounds a boxer fights better predicts the development of encephalopathy, compared to the number of knockouts. In a study by Ravdin et al. [68] investigating the effects of subconcussive blows, boxers were administered neuropsychological examinations before a fight, after the fight, and at a 1-month follow-up session. They noted that at 1-month postfight, neuropsychological performance had increased beyond baseline assessment taken prior to the fight, which was attributed to pre-bout training that included sparring and weight loss. Repetitive subconcussive head trauma has been hypothesized to be the main cause of neurocognitive dysfunction in boxers and that the accumulation of subconcussive blows may lead to cognitive deterioration of brain function [77].

Shuttleworth-Edwards and Radloff [78] investigated the differences between rugby players and athletes involved in noncontact sports and found that rugby players had a poorer performance on visuomotor processing speed. Additionally, they subdivided the rugby players into two groups, based upon the frequency of the positions to be exposed to subconcussive head trauma. This within-group analysis revealed that the group that regularly receives more subconcussive impacts displayed lower scores on the digit symbol substitution visuomotor task. Interestingly enough, it has been reported that despite a five times greater frequency of head injuries, rugby players outperform soccer players in neuropsychological testing [79]. Additionally, Parker et al. [49] found that the subjects exposed to repeated subconcussive blows in football, rugby, and lacrosse showed increased medial–lateral sway in their gaits. In a study by Killam et al. [80] examining athletes with and without a history of concussion and athletes recovering from concussion to a control group without any history of head trauma, researchers concluded that subconcussive head trauma seen in contact sports produces subclinical cognitive impairments. Similarly, Stephens et al. [69] performed neuropsychological testing on adolescent soccer and rugby players. They reported no evidence of neurological dysfunction in both the soccer and rugby players, when compared to their noncontact counterparts. Although no individual had suffered a recent (within the past 3 years) head injury, those with a previous concussion showed poorer performance on attention measures. Looking at several quality-of-life measures including: executive function, anxiety, depression, emotional and behavior dyscontrol, fatigue, and sleep disturbances, Meehan III et al. [81] found no association of previous concussion in athletes aged 40–70 who had participated in collegiate collision sports.

In a recent study by Miller et al. [48], a neuropsychological assessment of collegiate football players via the Standardized Assessment of Concussion (SAC) and

the ImPACT was performed at three time intervals: preseason, midseason, and postseason. No subjects under study received a clinically diagnosed concussion, yet they were exposed to numerous subconcussive blows throughout the season. There were no significant decreases in the overall SAC and ImPACT scores reported, yet significant improvements in visual memory and reaction time were noted. Recently, Talavage et al. [15] reported changes in cerebral functions attributed to multiple subconcussive impacts, as evidenced by declines in the visual working memory in high school football players in the absence of clinical signs of concussion. Although it is common for football players to report headaches following practice, it is not yet known whether this is a posttraumatic phenomenon or caused from subconcussive impacts [82]. However, when looking at 282 high school athletes competing in high-contact sports like football and low-contact sports like soccer, Tsushima et al. [83] found significantly worse performance in processing speed and reaction time in the high-contact group, compared to the low-contact group. Jennings et al. [84] found no significant effects of repetitive head impacts on Child-SCAT3 (Sport Concussion Assessment Tool) scores for youth football players. Similarly using ImPACT and SAC neurocognitive tests, Miller et al. [48] reported no significant changes in scores for 58 collegiate football players exposed to subconcussive impacts during preseason, midseason, and postseason testing. While neurocognitive testing is an important part of the return-to-play process, it may not be specific enough to detect the smaller changes in neurocognition that can be caused by subconcussive head impacts.

Neuroimaging of Subconcussive Head Trauma

Few reports in the literature have found any gross structural differences in the brain following concussive or subconcussive head trauma, as evaluated by computed tomography (CT) and standard magnetic resonance imaging (MRI). CT and conventional MRI for the most part are usually found to be normal following concussion, as it is more of a metabolic reaction to trauma than a structural injury [85]. Although, their use can be invaluable in ruling out more serious injuries like skull fractures and hemorrhages. However, one study that looked at boxers longitudinally saw evidence in 13% of the boxers of progressive brain injury, as well as several boxers presenting with cortical atrophy and *cavum septum pellucidum* (Fig. 12.1) [86]. Another CT study evaluating soccer players saw an increase in cerebral atrophy and ventriculomegaly in 27% and 18% of the professional soccer players, respectively [52, 53]. With the advent of newer MRI techniques, there is hope they will have a higher sensitivity and specificity for detecting brain injury caused by subconcussive trauma. These more advanced MRI techniques (Fig. 12.2) like functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), and susceptibility-weighted imaging (SWI) may offer promise in providing some insight into the injured brain, due to concussion and subconcussive head trauma [2]. Experiments utilizing fMRI to study the short-term and long-term effects of subconcussive repetitive head trauma are

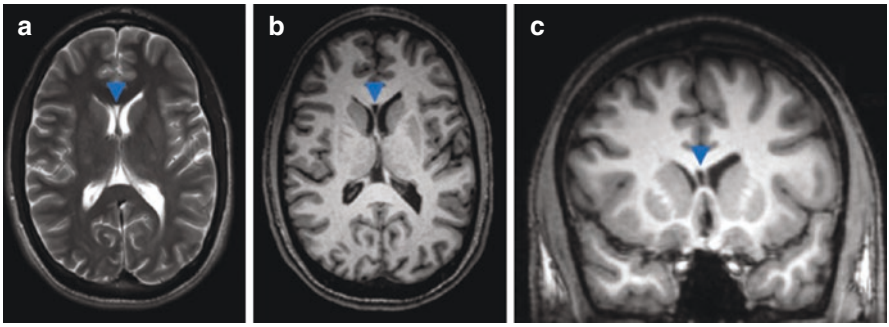

Fig. 12.1 Example of *cavum septum pellucidum* on (**a**) axial T2-weighted, (**b**) axial T1-weighted, and (**c**) coronal T1-weighted MRI

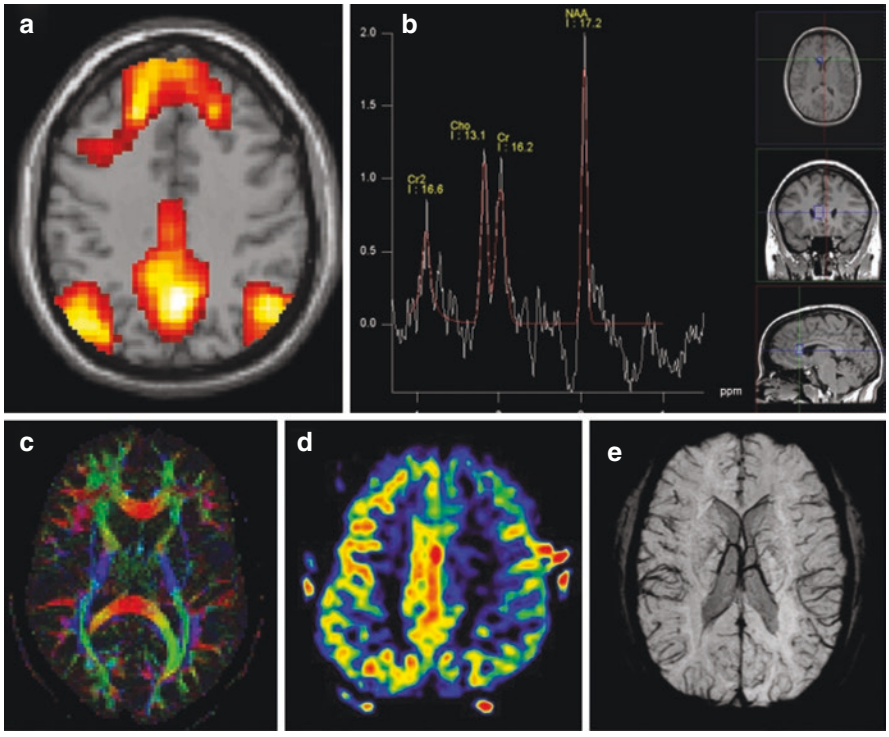

Fig. 12.2 Example of (**a**) fMRI, (**b**) MRS, (**c**) DTI, (**d**) ASL, and (**e**) SWI neuroimaging techniques

growing. Talavage et al. [15] took 11 high school football players and performed an fMRI visual working memory paradigm and baseline neuropsychological testing. They found that the number of collisions was significantly correlated to changes in the subject's fMRI activation. Using resting state functional magnetic resonance imaging (rs-fMRI), Abbas et al. [87] reported functional connectivity differences in

the default mode network (DMN) between football players sustaining repetitive head impacts over the course of the season, compared to noncollision athlete controls. Furthermore, differences in functional connectivity were seen between preseason and postseason rs-fMRI scans, indicating the presence of long-term brain changes from these impacts. Looking into the effects of acute exposure to subconcussive head impacts in rugby, Johnson and colleagues [88] reported differences in resting state functional connectivity between pregame and postgame scans (Fig. 12.3). Specifically, they observed increased connectivity from the left supramarginal gyrus to bilateral orbitofrontal cortex and decreased connectivity from the retrosplenial cortex and dorsal posterior cingulate cortex. Furthermore, an analysis based on concussion history revealed that players with a prior history of concussion exhibited only decreased functional connectivity following exposure to subconcussive head trauma, while those with no history showed increased connectivity. Similarly, work by Abbas et al. [87, 89] has shown short-term changes in brain activity following exposure to subconcussive head impacts. These changes observed with fMRI and rs-fMRI show a trend that as the number of subconcussive head impacts increases, there are larger changes in brain activation patterns [90, 91]. Using seed-based connectivity analysis of rs-fMRI, Slobounov et al. [92] revealed changes in functional connectivity to right and left isthmus of the cingulate cortex and left hippocampus in collegiate football players over the course of a single season.

Research using DTI to assess white matter integrity in the brain following exposure to subconcussive head impacts has also increased (Fig. 12.4). Much of the DTI research that has been done to date has focused mainly on measuring changes in DTI metrics from preseason to postseason in males participating in high school and collegiate football. These studies have yielded mixed results in detecting significant changes in fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). Bazarian et al. [93] took a cohort of nine high school student athletes and performed DTI preseason and postseason at an interval of 3 months apart and, using accelerometers, showed that the subjects sustained between 26 and 399 subconcussive impacts. One subject received a concussion during the season and demonstrated the highest number of voxels in the white matter with significant change in FA and MD from pre- to postseason. The subconcussive group showed the next highest number of voxels with significant FA and MD changes, with most subjects displaying an increase in FA and a decrease in MD. In contrast, Chappell et al. [94] reported an increase in apparent diffusion coefficient (ADC) and a decrease in FA in the deep white matter of 81 professional boxers. They inferred that these abnormalities reported may reflect the cumulative effects of repetitive subconcussive head trauma. Similarly, using DTI, Koerte et al. [95] reported widespread differences in white matter integrity between a small cohort of soccer players with no previous concussive episode, compared to swimmers. Specifically, they observed significantly increased RD in several major white matter tracts including the corpus callosum. Using the Head Impact Telemetry System (HITS™), Davenport et al. [96] monitored 24 male high school football players over the course of a season. In addition, the subjects underwent preseason and postseason assessment via ImPACT and DTI. Correlation analysis revealed a significant

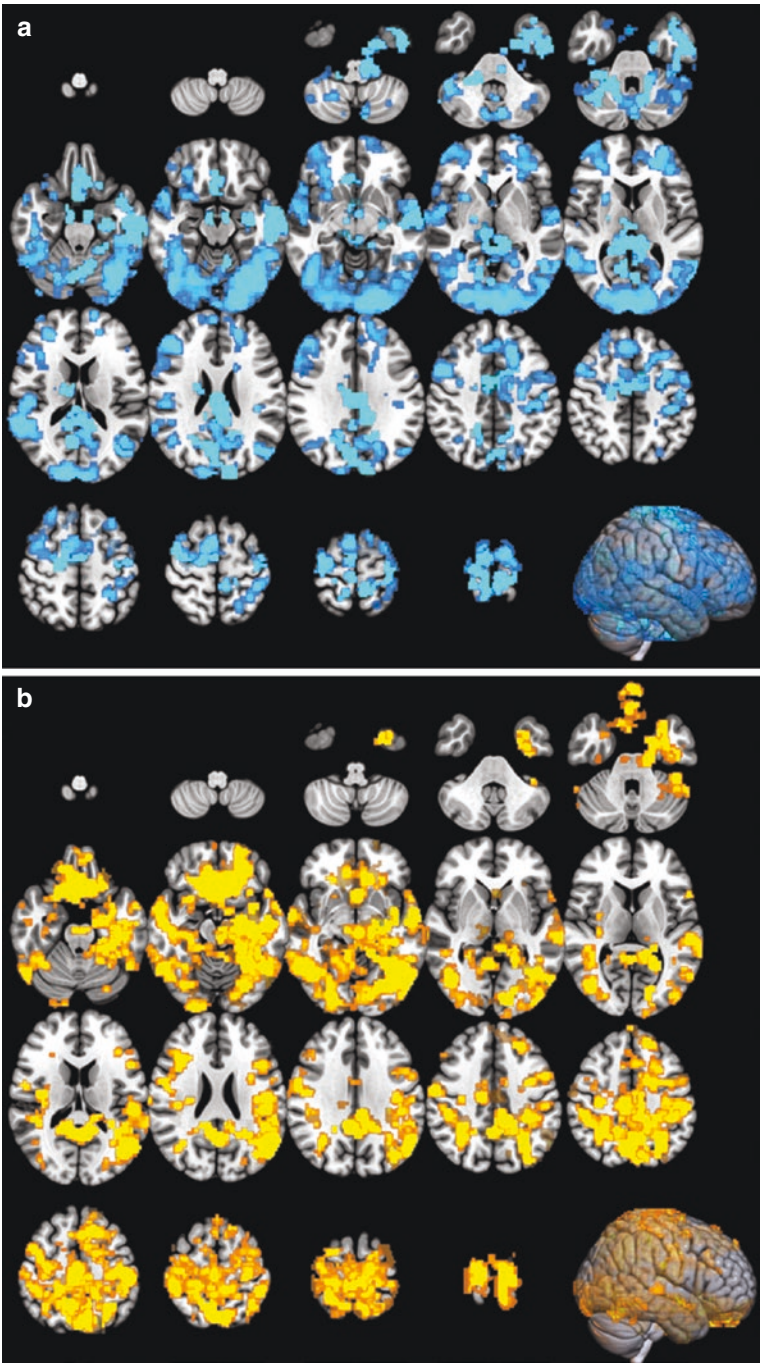

Fig. 12.3 Differences in functional connectivity between rugby players with no history of concussion (**a**) and history of previous concussion (**b**) showing areas of increased functional connectivity (cool colors) and decreased functional connectivity (warm colors). (From Johnson et al. [88])

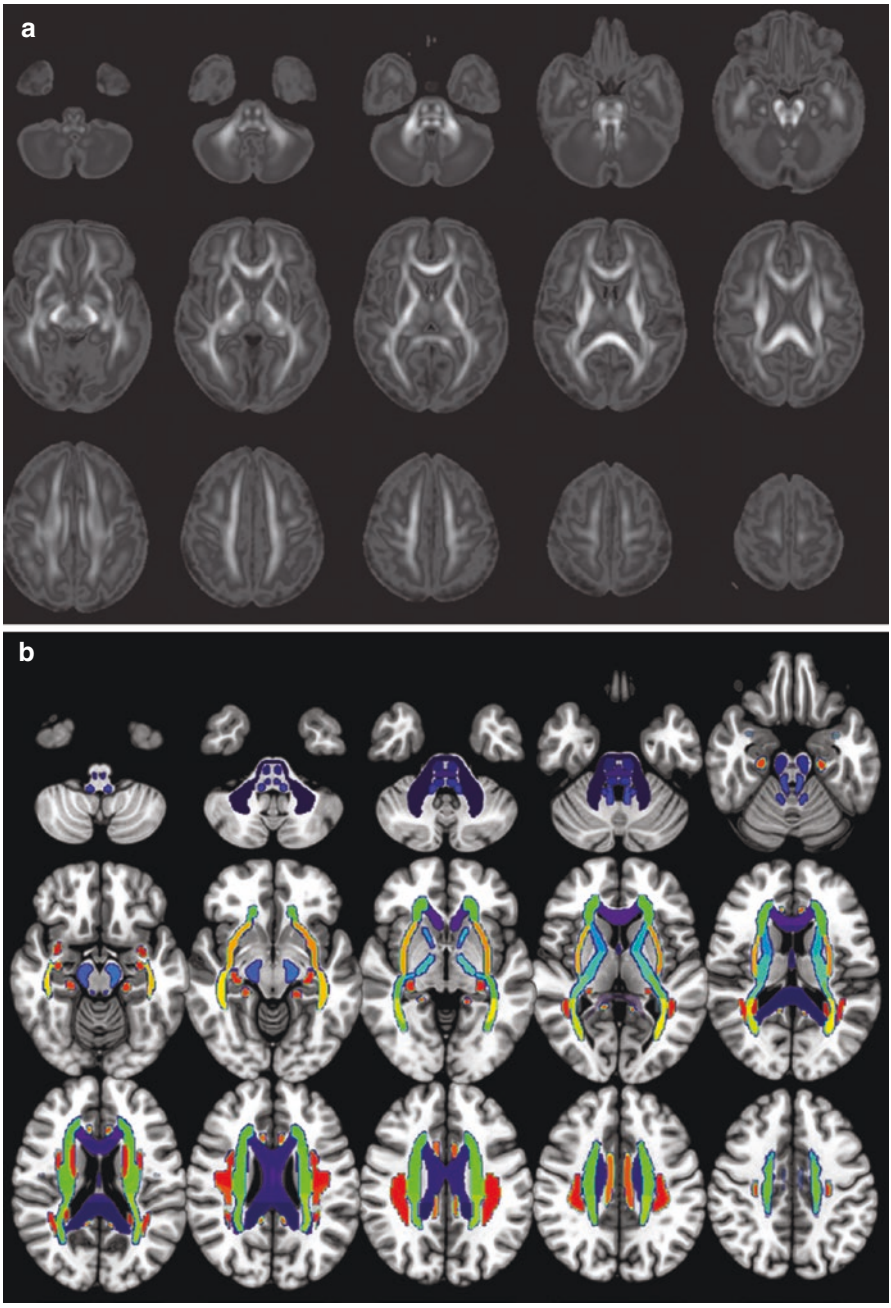

Fig. 12.4 Examples of DTI analysis with whole-brain normalized white matter tracts (**a**) and region of interest white matter tracts (**b**)

linear relationship between changes in fractional anisotropy and the combined components of the risk-weighted cumulative exposure to subconcussive head impacts. Decreases in FA have been reported in the inferior longitudinal fasciculus, forceps minor, forceps major, cingulum, corpus callosum as well as whole-brain white matter [97–101]. Increase in FA have also been observed in the parietal lobe, prefrontal white matter, and whole-brain white matter [99, 102, 103]. This variety of findings is also seen in studies reporting MD, RD, and AD DTI metrics [95, 104–110]. Confounding the literature even more, some studies report no significant differences in DTI metrics [92, 106, 111].

Fewer imaging studies have utilized magnetic resonance spectroscopy (MRS) to investigate neurometabolite changes in the brain following exposure to subconcussive head impacts (Fig. 12.5). Results from these studies also show mixed results. Koerte et al. [112] used MRS to evaluate the long-term effects of repetitive head impacts by scanning 11 retired professional soccer players and reported significant increases in choline (cho) and myo-inositol (mI) which are markers for cell membrane metabolism and glial health. An MRS pilot study of retired professional athletes with a known exposure to concussions and subconcussive head trauma revealed a significant increase in choline (Cho) and glutamate/glutamine (Glx) concentrations [113]. Bari et al. [114] reported significant decreases in Glx metabolites in both male football players and female soccer players. However, Chamard et al. [115] reported no significant changes in neurometabolite concentrations from

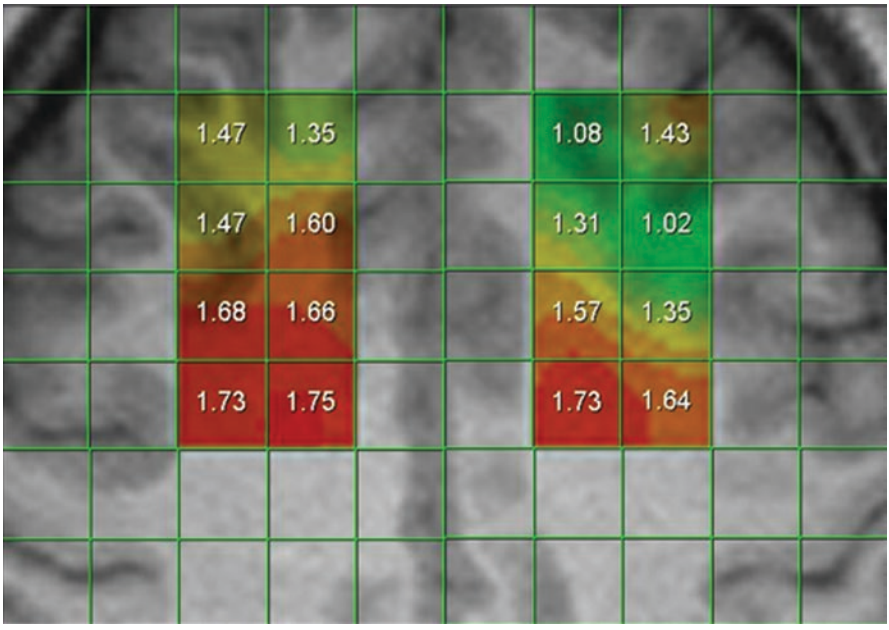

Fig. 12.5 Examples of MRS metabolite maps for NAA/Cho in a concussed athlete showing differences in NAA/Cho homogeneity between the right and left frontal white matter regions

pre- to postseason in male ice-hockey players, but a significant decrease in NAA/Cr in female ice-hockey players. This highlights the importance of gender as an important confound when looking at the SRC and subconcussive literature.

Looking at CTBI in boxers, Bailey and colleagues [116] used transcranial Doppler ultrasound to assess cerebral hemodynamic function. Specifically, the authors looked at dynamic cerebral autoregulation, cerebrovascular reactivity to changes in carbon dioxide (CVR CO_2), and orthostatic tolerance in 12 current professional male boxers, compared to 12 male nonboxers matched for age and physical fitness levels. Results of this study revealed neurocognitive dysfunction and impaired cerebral hemodynamic function, compared to the control group. The CVR CO_2 metric was also correlated with the amount of sparring training the boxers had undergone, not the number of competitive bouts. This study was the first to demonstrate that cerebral hemodynamic function is compromised in CTBI. The authors contributed this hemodynamic and neurocognitive impairment to the mechanical trauma, mostly in the form of subconcussive impacts, experienced from sparring during a career in boxing. Measuring cerebrovascular reactivity in 26 female high school soccer players revealed significant changes in the frontotemporal region of the brain that did not return back to baseline levels till 8 months after the end of the season [117]. Similarly, Champagne et al. documented decreases in cerebral blood flow (CBF) and impaired cerebrovascular reactivity in the DMN [118]. Slobounov et al. [92] utilizing a multimodal imaging approach showed significant increases in global CBF measured by arterial spin labeling (ASL). They also reported that 44% of the players exhibited outlier rates of regional decreases in SWI signal. These changes measured by rs-fMRI, ASL, and SWI were associated with players receiving more high G force impacts. Use of advanced neuroimaging techniques, especially when combined in a multimodal approach, has the potential to characterize the neuropathology of subconcussive head trauma and offer valuable insight into its acute and chronic effects.

Conclusion

Impacts to the head in collision sports are unavoidable, and as serious as concussion is, subconcussive impacts happen much more often. These subconcussive head impacts are now being implicated as a source for the deterioration of cerebral structures and function later in life [12]. Despite being labeled as subconcussive, subthreshold, or subclinical, it is apparent that athletes in contact sports are subjected to an alarming number of these impacts. Contradictory to what the "subconcussive" moniker may imply, subconcussive impacts have shown the ability to cause brain injury [11]. Although the full effect of subconcussive blows on the brain is not known, there is a research focus to understand the immediate and long-term effects they may have [50]. It is important for future research to focus not only on concussive blows, but on varying degrees of head trauma that include subconcussive impacts, as well as time intervals between repetitive sports-related head trauma [2]. Furthermore, empirical evidence suggests that a history of concussion leads to an

increased susceptibility to sustain recurrent concussions [119, 120] and further study is needed to explore the effects that subconcussive head trauma may have on those with a history of prior concussion and those without [121]. It appears that like the current SRC literature the research around subconcussive head impacts remains inconsistent with mixed findings. However, it is not hard to believe, despite the overall lack of agreement based on neuropsychological and neuroimaging measures, that subconcussive impacts can cause microstructural and biochemical changes in the brain [37]. Nonetheless, as the research on subconcussive head impacts continues to evolve, so do the policies related to player safety.

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