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REVIEW ARTICLE - BRAIN TRAUMA

Management of concussion in soccer

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Abstract

Background When participating in contact sports, (mild) head trauma is a common incident—observed in both professional and amateur sports. When head trauma results in transient neurological impairment, a sports-related concussion has occurred. Acute concussion, repetitive concussions, as well as cumulative "sub-concussive" head impacts may increase the risk of developing cognitive and behavioral deficits for athletes, as well as accelerated cerebral degeneration. While this concept has been well established for classic contact sports like American Football, Rugby, or Boxing, there is still an awareness gap for the role of sports-related concussion in the context of the world's most popular sport—Soccer.

Methods Here, we review the relevance of sport-related concussion for Soccer as well as its diagnosis and management. Finally, we provide insight into future directions for research in this field.

Results Soccer fulfills the criteria of a contact sport and is characterized by a high incidence of concussion. There is ample evidence that these events cause functional and structural cerebral disorders. Furthermore, heading, as a repeat sub-concussive impact, has been linked to structural brain changes and neurocognitive impairment. As a consequence, recommendations for the diagnosis and management of concussion in soccer have been formulated by consensus groups. In order to minimize the risk of repetitive concussion in soccer the rapid and reliable side-line diagnosis of concussion with adoption of a strict remove-from-play protocol is essential, followed by a supervised, graduated return-to-play protocol. Recent studies, however, demonstrate that adherence to these recommendations by players, coaches, clubs, and officials is insufficient, calling for stricter enforcement. In addition, future research to solidify the pathophysiological relevance of concussion for soccer athletes seems to be needed. Advanced neuroimaging and neurochemical biomarker analyses (e.g. S100β, tau and neurofilament light (NfL)) may assist in detecting concussion-related structural brain changes and selecting athletes at risk for irreversible damage.

Conclusion Sports-related concussion represents a genuine neurosurgical field of interest. Given the high socioeconomic relevance, neurosurgeons should get involved in prevention and management of concussion in soccer.

Keywords Brain imaging · Chronic traumatic encephalopathy · Concussion · Concussion biomarkers · Functional brain imaging · Post-concussion syndrome · Repetitive head trauma · Return to sport · Soccer · Standard concussion assessment tool · Sports-related concussion · Tau · Traumatic brain injury

Abbreviations

CISG	Concussion in Sports Group
CSF	Cerebrospinal fluid
CT	Computed tomography
CTE	Chronic traumatic encephalopathy
DMN	Default mode network
DTI	Diffusion tensor imaging
FIFA	Fédération Internationale de Football Association
fMRI	Functional magnetic resonance imaging
GFAP	Glial fibrillary acidic protein
MRI	Magnetic resonance imaging
MRP	Magnetic resonance perfusion
MRS	Magnetic resonance spectroscopy
NAA	N-acetylaspartate
NFL	National Football League
NfL	Neurofilament light
NSE	Neuron specific enolase
PCS	Post-concussion syndrome

This article is part of the Topical Collection on *Brain trauma*

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PET	Positron emission tomography
RTS	Return to sport
SCAT	Sport Concussion Assessment Tool
SIS	Second impact syndrome
SRC	Sports-related concussion
TBI	Traumatic brain injury
TMS	Transcranial magnetic stimulation

Sports-related concussion—the pathophysiological problem

In sports, head trauma is a common incident. It is often caused by a fall or a collision, while in some sports like full-contact martial arts or boxing, it is caused by intention. The risk of head trauma is not only limited to professional sports but is present in amateur and high school sports as well. When head trauma in sports results in transient neurological impairment, a sports-related concussion (SRC) has occurred. SRC is defined as a form of mild traumatic brain injury (TBI) by the 2017 Berlin Guidelines [65] and can be described as a complex pathophysiological state of the brain resulting from a direct force to the head or from indirect momentum transfer caused by a blow to the face, jaw, neck, or the rest of the body. Only in 8–19%, a short loss of consciousness occurs [65]. SRC is viewed as a pathophysiologic functional state of the brain going together with transient functional impairment, typically not including acute structural brain damage that can be detected on conventional brain imaging like computed tomography (CT) or magnetic resonance imaging (MRI) [65]. Typically, short-lived symptoms of mild TBI develop directly following the impact, including headache, confusion, memory impairment or dizziness, which can last for hours up to days and mostly resolve after around 2 weeks. In children and adolescents however, symptom durations up to 1 month are regarded as normal [61, 65, 69].

In up to 10–15% of affected athletes, symptoms last longer, for weeks up to months or even years. This condition is called the post-concussion syndrome (PCS). Before, PCS has been defined as lasting for more than a distinct period of time (DSM IV), while DSM V is rather calling it a post-traumatic cognitive disturbance and in ICD-10 no duration is mentioned [55, 94]. In certain sports like ice hockey, a PCS rate of up to 30% is reported [79, 93]. Risk factors for such a complicated outcome could be identified, including initially prolonged loss of consciousness, imminent coordination disorders, and coexisting epidemiological factors such as female sex or young age. Previous, repetitive concussions also play a distinct role in the development of PCS. The most important factor associated with the development of PCS was found to be the severity of early concussion symptoms following SRC [25, 44, 51, 54, 64, 65]. Comorbidities such as migraine or psychiatric disorders, if apparent prior to the SRC, may also increase the athlete's risk for developing PCS [52, 81, 95].

If activity is resumed immediately after the trauma, the athlete is at risk of a second concussion within a brief period. Such repetitive mild traumatic brain injuries are associated with a condition named "second hit" phenomenon. Following trauma to the head, the injured brain tissue is believed to be in a vulnerable phase during which repetitive injury potentiates secondary injury cascade development [56, 90, 96]. SRC therefore must be regarded as an acute, progressive injury bearing the risk for exacerbated neurologic long-term consequences if an additional injury occurs during the brain's vulnerable phase. How long this vulnerable phase persists is a matter of debate—with several weeks or more being hypothesized [98]. In extreme, the very rare second impact syndrome (SIS) has been described, a diffuse cerebral swelling with delayed catastrophic deterioration or sudden death, which is believed to be caused by disturbed vasoreactivity resulting in rapid brain edema formation. In this extremely rare phenomenon, mortality rates of 50–100% have been described. This phenomenon is believed to occur when a second hit potentiates a first concussion, before concussion symptoms were about to develop [8, 60].

The topic of SRC recently gained public and media interest, as postmortem examinations of former professional American National Football League (NFL) athletes showed profound structural brain changes, called chronic traumatic encephalopathy (CTE), leading to numerous lawsuits by those affected against the NFL. However, the notion that repetitive head impacts result in chronic brain disorders are not novel per se. As early as in 1928, repetitive knock-outs in professional boxers were associated with a slowly developing condition of coordination disorders, psychiatric conditions, and advancing dementia, called "Punch Drunk" or "Dementia pugilistica" [58, 71]. Abovementioned neuropathological findings of retired NFL athletes with a history of repetitive concussions have shown profound structural changes in gray and white matter like cortical thinning, ventricle enlargement, cavum septum pellucidum as well as accumulation of hyperphosphorylated tau-protein (p-tau) [66, 67]. This condition called CTE contains symptoms of increased irritability, impulsiveness, aggression, depression, and progressive dementia [23, 24, 66, 67]. Reports also hint to an increased suicidal tendency, although there is lack of confirmation by distinct studies in the current literature to substantiate this assumption [33, 34]. The topic of CTE remains quite controversial. No distinct answers exist to the questions of correlation between pathological findings, clinical presentation, risk factors, and actual prevalence in a small, unilateral, and potentially biased population [10, 22, 35, 36].

Sports-related concussion—relevant for soccer?

In soccer—one of the most popular sports in the world with around 265 million people playing [43] and a large amount of children and adolescents participating—head injuries are mostly caused by head-to-head collisions and unanticipated ball contacts [25, 31, 46]. Though not publicly perceived as the classic risk discipline to suffer from head trauma and concussion, studies show a high rate of athletes affected by SRC, with SRC presenting 22% of soccer-related injuries [15, 25, 46, 82]. The relevance of SRC in soccer has been nicely reviewed in the past [53, 84]. Accordingly, 63% of soccer players have suffered a concussion during their playing careers, 82% of the athletes who had suffered a concussion had experienced two or more concussions over the course of their playing careers. Yet only 19% realized that these symptoms constituted a concussion. If exposed to repetitive concussions, soccer players are at risk of developing long-term neurologic impairment, PCS, and structural brain changes to be detected on functional brain imaging [7, 42, 48, 82, 91]. Furthermore, structural brain changes and neurocognitive impairment associated with heading are suggested, although the role of heading itself causing concussion is a topic of debate per se [19, 24, 40, 41, 47, 89]. As for CTE, this condition has been observed in a small cohort of soccer players, however, pathophysiological evidence for a causal link to SRC is missing [47].

Diagnosis and management of acute concussion in soccer

The potential complications and long-term consequences of repetitive SRC emphasize the importance to reliably diagnose and efficiently manage SRC to protect athletes from developing long-term neurologic and behavioral deficits. While this is evident in classic risk disciplines like American football or ice hockey, general awareness is only slowly shifting towards soccer too, despite the sport's popularity all over the world. With concussion symptoms being heterogenous and often mild, head trauma in soccer is frequently underdiagnosed, and potential consequences are neglected. The number of unknown cases of SRC in different disciplines is believed to be extremely high [70, 75]. Studies evaluating US high school and college athletes in different sports show that less than 50% report a SRC [14, 49, 75]. Indeed, competitors in amateur sports as well as athletes in junior and college leagues and children are at a higher risk to suffer from SRC, since their coordination and training skills are at a lower level than those of professional athletes [25, 31, 80]. The low level of awareness regarding SRC and its potential consequences among athletes, coaches, and in minors their legal guardians seems to be among the main reasons for this high number of unrecognized and thus unreported cases [14, 49].

The consensus statement from the 2012 and 2016 International Conference on Concussion in Sport, adopted by Fédération Internationale de Football Association (FIFA), indicates that players in doubt have to be immediately evaluated for any feature of concussion and should be withdrawn from play if a concussion has occured [25, 31, 80]. Measures to reliably diagnose a concussion on the field as well as implementing protective measures are prioritized to guarantee the athlete's safety.

The first step in protecting the athlete from potential negative consequences is a reliable concussion diagnosis. In 2016, the Concussion in Sports Group has formulated a standardized evaluation protocol which has to be applied following head trauma in competition or training not to miss a concussion [64]. Accordingly, athletes should be forced to stop activity at once to undergo a standardized diagnostic assessment. This standardized "side-line evaluation" should assess state of consciousness, orientation, cranial nerve function, balance as well as detect warning symptoms for severe injury [64, 65, 99]. For standardization, different diagnostic tools have been established, with the "Sport Concussion Assessment Tool" (SCAT) being the most frequently used one, first established in 2004 [9, 62]. Just recently, this tool has been updated to SCAT-5, comprising different assessment stages (Table 1) [16, 99]. It is clear that performing a side-line assessment immediately following head trauma provides the best chance for detecting SRC real-time [61, 65]. If according to SCAT-5 a SRC cannot definitely be ruled out, the athlete should be removed from play and not be allowed to continue activity on the same day [65]. The British Football Association's updated guidelines include this rule: "If in doubt, sit them out". Ideally, SCAT-5 side-line evaluations should be complemented by a SCAT-5 baseline evaluation at the beginning of the season. This aims at the possibility to compare the individual baseline performance with performance post-injury, thus further improving the reliability of the individual assessment [65].

It is detrimental not to miss the so-called "red flags" during side-line evaluation, to differentiate concussion from a more serious injury like structural brain damage or traumatic spinal cord injury. Such "red flags" include neck stiffness, vomiting, double vision, motor, or sensory deficits of the extremities and in the extreme seizures, leading to the assumption of a serious condition. In this case, the athlete should be immediately immobilized and taken to hospital for further diagnostics including radiological evaluation using standard CT and/or MRI, depending on the presumed injury [65].

When a concussion is probable by the result of the side-line evaluation and following the athlete's removal from play, a

Table 1 The five steps of on-field assessment of the concussed athlete, using the Sport Concussion Assessment Tool—SCAT (5th edition) (modified from Davis, 2017)

1	Red flags: warning signs to evaluate for serious injury
2	Observable signs: including loss of consciousness, motion or coordination disorders, disorientation or confusion, facial injury
3	Standardized memory assessment: Maddocks questions
4	Glasgow Coma Scale
5	Cervical spine assessment: neck pain, pain free movement, limb strength, and sensation

detailed follow-up examination performed by a medical expert should follow. This examination should consist of a detailed assessment of concussion history and a thorough neurological examination. Importantly, potential deterioration following head trauma must not be missed. Therefore it is recommended to include eyewitnesses', coaches', and legal guardians' statements [65]. Although neuropsychological assessment by a trained, accredited neuropsychologist in the return to sports decision has been recommended [4, 6, 11, 12, 50, 63], there is no current consensus for inclusion in the standard assessment following SRC [65].

Although the recommendations and tools for proper concussion diagnosis and management have considerably advanced over the last years, a recent assessment of head collision events during the 2014 FIFA World Cup Tournament has drawn a quite sobering picture [15]. The authors could show that concussion assessment protocols, adopted by FIFA in 2014, were not followed in 63% of events when players involved in head collisions were not assessed by side-line health care personnel. Of 81 identified head collisions with two or more concussion signs, only 19 were officially reported. Eighty-six percent of the players who displayed three or more concussion signs returned to play during the same game although they should have been removed from play. In addition, neither a baseline neurologic assessment nor a standardized assessment to reliably rule out concussion following head trauma are routinely performed in soccer up to date. One problem with SCAT-5, which may explain its low compliance rate, is the need to isolate the affected athlete for about 10 min in a distinct area away from the side-line for assessment. This might be feasible in American football, as game time can be paused. In soccer, however, game time is running and therefore a standardized neurologic assessment is not routinely performed, increasing the risk for missing SRC and thus not adhering to a strict removal from play protocol [15]. Not only in professional but especially in amateur sports or high school/college leagues, it is indispensable for liable organizations to take responsibility for the athlete's security and to enforce standards to reduce the risk of long-term consequences [68, 78]. Especially in soccer, adherence to the recommended concussion guidelines is complicated since a thorough evaluation of a potentially concussed athlete is hardly possible without creating disadvantages for the affected player's team. Strict guidelines on how to manage the concussed athlete and protect him/her from repetitive head trauma should be enforced not only in individual local or regional soccer organizations but in the official game rules applied in national and international tournaments.

The graduated return to sports protocol

There is no specific treatment for SRC. After removal from play and medical and neurological clearance, a resting phase should follow. The athlete should be shielded from external visual and acoustic influences and should not take part in strenuous physical or intellectual activity for at least 24–48 h while symptomatic. In the case of children and adolescents, this also implies absence from school. If symptoms like headache, vertigo, dizziness, or concentration deficits occur when limited activity is reassumed, the first resting phase should be prolonged. Following this first resting phase, a graduated "return to sport" or in children and adolescents a preceding "return to school" strategy should be pursued. In the latter case, "return to school" should always precede "return to sports" [21, 38, 39, 65]. This graduated "return to sports" includes designated time periods with increasing activity levels which the athlete must complete without worsening symptoms before moving on (Table 2) [65]. First, the athlete is allowed minimal activity following the initial resting phase. Subsequently, training intensity increases until full performance. All these stages endure for 24 h, with downgrading to previous stage if symptoms occur. In school children, an analogous "return to school" strategy is recommended, with children only allowed to participate in learning activities when completely restored and symptom-free [17, 29, 65]. These graduated programs to resume activity aim to ensure the concussed athlete can only participate in sports when restored from concussion symptoms [13, 45, 65]. In the advanced rehabilitation phases of the "return to sport" protocol, a "push through symptoms" is possible, if symptoms are prolonged. Ensuring a sufficient period of absence from sports participation protects the athlete from the aggravating consequences of repetitive concussions.

Table 2 Graded return to sport (RTS), modified by McCrory et al. (McCrory et al. 2017). In advanced activity stages, a "push through symptoms" is allowed, if symptoms are prolonged

Level	Graduated return to sport (RTS)	Aspects
0	Initial resting phase (24–48 h)	Bed rest, shielded from visual/acoustic influences
1	Symptom-limited activity (≥ 24 h)	Reduced daily activity, ascend if symptom-free
2	Light aerobic exercise (≥ 24 h)	e.g., walking, jogging; ascend if symptom-free - Non-contact training - Full-contact training
3	Sport-specific exercise (≥ 24 h)	Light-specific training with reduced intensity, e.g., running, passing the ball, no match-situations; ascend if symptom-free
4	Non-contact training (≥ 24 h)	Full sport-specific exercise with increasing intensity, without match-situations; ascend if symptom-free
5	Full-contact training (≥ 24 h)	Full sport-specific exercise with full intensity, match-situations in training; ascend if symptom-free
6	Return to sport	Normal game play

Future research directions in concussion in soccer

As an early diagnosis of SRC is essential, and as conventional neuroimaging like MRI or CT fail to show structural changes in classic SRC [28, 72], research in neuroimaging is focusing on advanced imaging techniques to detect characteristic changes in brain structure and function leading to early diagnosis or to provide valuable information about the athlete's risk to develop complications like post-concussion syndrome or CTE. Advanced neuroimaging can show microstructural changes even in asymptomatic soccer athletes with a history of (repetitive) SRC [2, 42, 48]. To objectify the structural damage as well as the brain tissue's functional changes caused by SRC is one goal of advanced neuroimaging. One important question is whether advanced neuroimaging may help in identifying individuals at risk for developing PCS or neurologic long-term deficits like CTE if exposed to the ongoing risk of repeated SRC. In this case, a permanent banishment from participation could prevent long-term neurologic deterioration and limit the number of individuals developing PCS or CTE.

Advanced neuroimaging modalities are becoming widespread—including task-based functional MRI (fMRI), resting-state fMRI, diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), magnetic resonance perfusion (MRP), and transcranial magnetic stimulation (TMS) as well as tau-positron emission tomography (Tau-PET) as only some of the methods in current use [97]. For example, in studies using MRS, a decrease of protein N-Acetylaspartate (NAA) predominantly in white matter tracts could be detected, in the acute phase and enduring up to 30 days post injury [32, 37, 59, 98]. Studies using DTI report profound white matter changes such as a decrease in mean diffusivity, an increase in fractional anisotropy in white matter and a reduction in radial diffusivity, up to 6 months post injury [97]. Task-fMRI studies show highly varying results, showing either an increase or decrease in activity in task-related networks, while resting-state fMRI show varying altered default mode network (DMN) connectivity as well.

Advanced neuroimaging methods can also show the influence of SRC on brain perfusion, metabolism, and connectivity. However, due to differing methodology and lack of controlled randomized trials, practicability to predict the athlete's risk of developing long-term neurologic consequences when exposed to the risk of repeated concussions is still in question with advanced functional brain imaging remaining at a rather experimental state for the time being.

Another approach in concussion research to provide diagnostic, prognostic, and monitoring information is the focus on neurochemical biomarkers. In the last decade, tremendous research has been conducted in this field, with a multitude of biomarkers taken into consideration, including S100β, glial fibrillary acidic protein (GFAP), neuron specific enolase (NSE), neurofilament light (NfL), brain-derived neurotropic factor, amyloid beta and tau protein, examined either in CSF, serum, or both [77].

So far, S100β is the most prominent TBI biomarker in the literature. This major low-affinity calcium binding protein located in astrocytes [3, 20, 57] is significantly elevated not only in trauma patients with structural brain damage proven in CT but also in athletes showing signs of concussion and even in asymptomatic soccer headers [48, 73, 77, 97]. Brain specificity of S100β has been questioned though, with rising levels demonstrated in athletes participating in soccer and in other disciplines like running, swimming or even in critically ill patients without head injury [30, 83, 92], with S100β believed to be released from cells such as adipocytes or chondrocytes during physical exertion [18, 27, 76].

As it has been hypothesized that diffuse axonal white matter injury is the main type of damage following mild TBI leading to neurologic and neuropsychologic deficits, axonal proteins NfL, and tau are promising biomarkers aiming to rate the amount of axonal injury [5, 40, 48, 87]. Various studies show elevated serum tau within the first hours following SRC

[1, 26, 85, 87]. Also, prolonged elevation up to 72 h post injury is apparent in athletes with prolonged RTS [26, 88]. Though brain-specific, it is in question how trauma-specific these findings are, as serum tau is elevated following sole physical exertion in the absence of head trauma as well [26, 74, 100]. Elevated serum tau is also shown to be associated with prolonged RTP, though with less prognostic value then elevated serum NfL [88]. Serum NfL, significantly elevated following SRC in different sports [86, 89], shows high prognostic value in predicting prolonged RTS, overshadowing serum tau or S100β [88].

One problem with integrating those serum biomarkers into daily routine in detecting concussion could be their low specificity in the acute phase, as abovementioned studies show. Therefore, on-side blood examinations in the acute state post injury would lead to a high number of false-positive results. More promising, if well-designed future studies show positive results, could be the examination of serum biomarkers like serum NfL over a full season. In a prolonged return to sports decision for example, when slight symptoms remain and a "push through symptoms" rehabilitation phase could be started, increased biomarker concentration could hint to a higher risk for developing complications. Another thought for possible use, if future studies show reproducible results, could be to ascertain a baseline of relevant serum biomarkers before and at the end of each season, with the preventive exclusion of potentially endangered athletes in the presence of prolonged or persistent critical serum biomarker concentrations until the next season.

Combined with advanced neuroimaging, concussion biomarkers like NfL could potentially advance SRC diagnosis as well as lend important prognostic information, leading to a more secure identification of athletes endangered to suffer from aggravated symptoms, PCS, or even CTE following repetitive head trauma. Such information is important in increasing the athlete's security and could aid in improving return to sport protocols.

Conclusion

To effectively protect the soccer athlete from the risks of repetitive concussions while competing in sports is essential to reduce the risk of developing neurological and behavioral long-term consequences. Although refined protocols and algorithms for immediate diagnosis and management of athletes with concussion have been developed the compliance of athletes, teams, and officials with these measures is still unsatisfying. It is of key importance that public focus shifts to the risks of soccer players sustaining repetitive concussions and their potential consequences, since millions of people of all ages, including a high number of children and adolescents, participate in this sport. The responsible organizations should find strategies to make this popular sport safer, adhering to concussion guidelines more strictly as a first step. This also includes further research devoted to a more detailed assessment of the athlete. Taking care of these athletes with head injuries should be of genuine interest to neurosurgeons, both clinically and academically. Thus, neurosurgeons should take the responsibility for this important and exciting field of clinical neuroscience.

Compliance with ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

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References

1. Alosco M, Kasimis A, Stamm J et al (2017) Age of first exposure to American football and long-term neuropsychiatric and cognitive outcomes. Transl Psychiatry. https://doi.org/10.1038/tp.2017.197
2. Bahrami N, Sharma D, Rosenthal S et al (2016) Subconcussive head impact exposure and white matter tract changes over a single season of youth football. Radiology 281(3):919–926
3. Barger SW, Van Eldik LJ (1992) S100 beta stimulates calcium fluxes in glial and neuronal cells. J Biol Chem 267(14):9689–9694
4. Bleiberg J, Cernich AN, Cameron K, Sun W, Peck K, Ecklund PJ, Reeves D, Uhorchak J, Sparling MB, Warden DL (2004) Duration of cognitive impairment after sports concussion. Neurosurgery 54(5):1073–1078 discussion 1078-80
5. Blennow K, Brody DL, Kochanek PM, Levin H, McKee A, Ribbers GM, Yaffe K, Zetterberg H (2016) Traumatic brain injuries. Nat Rev Dis Prim 2:16084
6. Broglio SP, Macciocchi SN, Ferrara MS (2007) Neurocognitive performance of concussed athletes when symptom free. J Athl Train 42(4):504–508
7. Caccese JB, Kaminski TW (2016) Minimizing head acceleration in soccer: a review of the literature. Sports Med 46(11):1591–1604
8. Cantu RC (1998) Second-impact syndrome. Clin Sports Med 17(1):37–44
9. Cantu RC (2006) An overview of concussion consensus statements since 2000. Neurosurg Focus 21(4):1–6
10. Castellani RJ, Perry G, Iverson GL (2015) Chronic effects of mild neurotrauma: putting the cart before the horse? J Neuropathol Exp Neurol 74(6):493–500
11. Collie A, Darby D, Maruv P (2001) Computerised cognitive assessment of athletes with sports related head injury. Br J Sports Med 35:297–302
12. Collie A, Maruff P (2003) Computerised neuropsychological testing. Br J Sports Med. https://doi.org/10.1136/bjsm.37.1.2
13. Collins MW, Grindel SH, Lovell MR et al (1999) Relationship between concussion and neuropsychological performance in college football players. JAMA 282(10):964–970

14. Cusimano MD (2009) Canadian minor hockey participants' knowledge about concussion. Can J Neurol Sci 36(3):315–320
15. Cusimano MD, Casey J, Jing R, Mishra A, Solarski M, Techar K, Zhang S (2017) Assessment of head collision events during the 2014 FIFA world cup tournament. JAMA 317(24):2548–2549
16. Davis G (2017) Sport concussion assessment tool - 5th edition. Br J Sports Med. https://doi.org/10.1136/bjsports-2017-097506SCAT5
17. Davis GA, Anderson V, Babl FE et al (2017) What is the difference in concussion management in children as compared with adults? A systematic review. Br J Sports Med 51(12):949–957
18. Dietrich MO, Tort AB, Schaf DV, Farina M, Gonçalves CA, Souza DO, Portela LV (2003) Increase in serum S100B protein level after a swimming race. Can J Appl Physiol 28(5):710–716
19. DiVirgilio TG, Hunter A, Wilson L, Stewart W, Goodall S, Howatson G, Donaldson DI, Ietswaart M (2016) Evidence for acute electrophysiological and cognitive changes following routine soccer heading. EBioMedicine 13:66–71
20. Donato R (1999) Functional roles of S100 proteins, calcium-binding proteins of the EF-hand type. Biochim Biophys Acta 1450(3):191–231
21. Echemendia RJ, Giza CC, Kutcher JS (2015) Developing guidelines for return to play: consensus and evidence-based approaches. Brain Inj 29(2):185–194
22. Gardner A, Iverson G, McCrory P (2014) Chronic traumatic encephalopathy in sport: a systematic review. Br J Sports Med 48:84–90
23. Gavett BE, Cantu RC, Shenton M, Lin AP, Nowinski CJ, McKee AC, Stern RA (2011) Clinical appraisal of chronic traumatic encephalopathy. Curr Opin Neurol 24(6):525–531
24. Gavett BE, Stern RA, Mckee AC (2011) Chronic traumatic encephalopathy: a potential late effect of sport-related concussive and subconcussive head trauma 1. Clin Sports Med. https://doi.org/10.1016/j.csm.2010.09.007
25. Gessel LM, Fields SK, Collins CL, Dick RW, Dawn Comstock R (2007) Concussions among United States high school and collegiate athletes. J Athl Train 42(4):495–503
26. Gill J, Merchant-Borna K, Jeromin MA, Livingston W, Bazarian J (2017) Acute plasma tau relates to prolonged return to play after concussion. Neurology 88:595–602
27. Haimoto H, Hosoda S, Kato K (1987) Differential distribution of immunoreactive S100-alpha and S100-beta proteins in normal nonnervous human tissues. Lab Investig 57(5):489–498
28. Haller S (2017) Advance MR imaging in sports-related concussion and mild traumatic brain injury - ready for clinical use? Eur J Neurosci 46:1954–1955
29. Harmon KG, Drezner JA, Gammons M, Guskiewicz KM, Halstead M, Herring SA, Kutcher JS, Pana A, Putukian M, Roberts WO (2013) American Medical Society for Sports Medicine position statement: concussion in sport. Br J Sports Med 4747:15–2615
30. Hasselblatt M, Mooren FC, von Ahsen N, Keyvani K, Fromme A, Schwarze-Eicker K, Senner V, Paulus W (2004) Serum S100beta increases in marathon runners reflect extracranial release rather than glial damage. Neurology 62(9):1634–1636
31. Helmich I (2018) Game-specific characteristics of sport-related concussions. J Sports Med Phys Fitness 58(1–2):172–179
32. Henry LC, Tremblay S, Boulanger Y, Ellemberg D, Lassonde M (2010) Neurometabolic changes in the acute phase after sports concussions correlate with symptom severity. J Neurotrauma 27(1):65–76
33. Iverson GL (2014) Chronic traumatic encephalopathy and risk of suicide in former athletes. Br J Sports Med 48(2):162–165
34. Iverson GL (2016) Suicide and chronic traumatic encephalopathy. J Neuropsychiatr Clin Neurosci 28(1):9–16
35. Iverson GL, Gardner A, McCrory P, Zafronte R, Castellano R (2015) A critical review of chronic traumatic encephalopathy. Neurosci Biobehav Rev 56:276–293
36. Iverson GL, Keene C, Perry G, Castellani R (2018) The need to separate chronic traumatic encephalopathy neuropathology from clinical features. J Alzheimers Dis 61:17–28
37. Johnston KM, Bloom GA, Ramsay J, Kissick J, Montgomery D, Foley D, Chen J-K, Ptito A (2004) Current concepts in concussion rehabilitation. Curr Sports Med Rep 3:316–323
38. Kamins J, Bigler E, Covassin T et al (2017) What is the physiological time to recovery after concussion? A systematic review. Br J Sports Med 51(12):935–940
39. Kerr ZY, Zuckerman SL, Wasserman EB, Covassin T, Djoko A, Dompier TP (2016) Concussion symptoms and return to play time in youth, high school, and college American football athletes. JAMA Pediatr 170(7):647
40. Kinnunen KM, Greenwood R, Powell JH, Leech R, Hawkins PC, Bonnelle V, Patel MC, Counsell SJ, Sharp DJ, Sharp DJ (2011) White matter damage and cognitive impairment after traumatic brain injury. Brain 134:449–463
41. Kirkendall DT, Jordan SE, Garrett WE (2001) Heading and head injuries in soccer. Sports Med 31(5):369–386
42. Koerte IK, Ertl-Wagner B, Reiser M, Zafonte R, Shenton ME (2012) White matter integrity in the brains of professional soccer players without a symptomatic concussion. JAMA 308(18):1859–1861
43. Kunz M (2007) 265 million playing football. Fifa Mag:10–15
44. Lee YM, Odom MJ, Zuckerman SL, Solomon GS, Sills AK (2013) Does age affect symptom recovery after sports-related concussion? A study of high school and college athletes. J Neurosurg Pediatr J Neurosurg Pediatr 12(12):537–544
45. Leininger BE, Gramling SE, Farrell AD, Kreutzer JS, Peck Iii EA (1991) Neuropsychological deficits in symptomatic minor head injury patients after concussion and mild concussion. J Neurol Neurosurg Psychiatry 54:846–847
46. Levy ML, Kasasbeh AS, Baird LC, Amene C, Skeen J, Marshall L (2012) Concussions in soccer: a current understanding. World Neurosurg 78:535–544
47. Ling H, Morris HR, Neal JW, Lees AJ, Hardy J, Holton JL, Revesz T, Williams DDR (2017) Mixed pathologies including chronic traumatic encephalopathy account for dementia in retired association football (soccer) players. Acta Neuropathol 133:337–352
48. Lipton ML, Kim N, Zimmerman ME, Kim M, Stewart WF, Branch CA, Lipton RB (2013) Soccer heading is associated with white matter microstructural and cognitive abnormalities. Radiology 268(3):850–857
49. Llewellyn T, Burdette GT, Joyner AB, Buckley TA (2014) Concussion reporting rates at the conclusion of an intercollegiate athletic career. Clin J Sport Med 24(1):76–79
50. Lovell MR (2002) The relevance of neuropsychologic testing for sports-related head injuries. Curr Sports Med Rep 1(1):7–11
51. Lovell MR, Iverson GL, Collins MW, McKeag D, Maroon JC (1999) Does loss of consciousness predict neuropsychological decrements after concussion? Clin J Sport Med 9(4):193–198
52. Lovell MR, Iverson GL, Collins MW, Podell K, Johnston KM, Pardini D, Pardini J, Norwig J, Maroon JC (2006) Measurement of symptoms following sports-related concussion: reliability and normative data for the post-concussion scale. Appl Neuropsychol 13(3):166–174
53. Maher ME, Hutchison M, Cusimano M, Comper P, Schweizer TA (2014) Concussions and heading in soccer: a review of the evidence of incidence, mechanisms, biomarkers and neurocognitive outcomes. Brain Inj 28(3):271–285
54. Makdissi M, Cantu RC, Johnston KM, McCrory P, Meeuwisse WH (2013) The difficult concussion patient: what is the best

approach to investigation and management of persistent (> 10 days) postconcussive symptoms? Br J Sports Med 47(5):308–313
55. Manley G, Gardner AJ, Schneider KJ et al (2017) A systematic review of potential long-term effects of sport-related concussion. Br J Sports Med 51:969–977
56. Manville J, Laurer HL, Steudel W-I, Mautes AEM (2007) Changes in cortical and subcortical energy metabolism after repetitive and single controlled cortical impact injury in the mouse. J Mol Neurosci 31(2):95–100
57. Marshak DR (1990) S100 beta as a neurotrophic factor. Prog Brain Res 86:169–181
58. Martland H (1928) Punch Drunk J Am Med Assoc 91(15):1103
59. McCrea M, Meier T, Huber D et al (2017) Role of advanced neuroimaging, fluid biomarkers and genetic testing in the assessment of sport-related concussion: a systematic review. Br J Sports Med 51:919–929
60. McCrory PR, Berkovic SF (1998) Second impact syndrome. Neurology 50(3):677–683
61. McCrory P, Feddermann-Demont N (2017) What is the definition of sports-relted concussion: a systematic review. Zurich Open Repos Arch Univ Zurich. https://doi.org/10.1136/bjsports-2016-097393
62. McCrory P, Johnston K, Meeuwisse W, Aubry M, Cantu R, Dvorak J, Graf-Baumann T, Kelly J, Lovell M, Schamasch P (2005) Summary and agreement statement of the 2nd International Conference on Concussion in port, Prague 2004. Br J Sports Med 39:196–204
63. McCrory P, Makdissi M, Davis G, Collie A (2005) Value of neuropsychological testing after head injuries in football. Br J Sports Med 39:58–63
64. McCrory P, Meeuwisse WH, Aubry M et al (2013) Consensus statement on concussion in sport: the 4th International Conference on Concussion in sport, Zurich, November 2012. J Athl Train 48(4):554–575
65. McCrory P, Meeuwisse W, Dvorak J et al (2017) Consensus statement on concussion in sport—the 5th international conference on concussion in sport held in Berlin, October 2016. Br J Sports Med. https://doi.org/10.1136/bjsports-2017-097699
66. McKee AC, Cantu RC, Nowinski CJ, Tessa Hedley-Whyte E, Gavett BE, Budson AE, Santini VE, Lee H-S, Kubilus CA, Stern RA (2009) Chronic traumatic encephalopathy in athletes: progressive tauopathy following repetitive head injury. J Neuropathol Exp Neurol 68(7):709–735
67. McKee AC, Stein TD, Nowinski CJ et al (2013) The Spectrum of disease in chronic traumatic encephalopathy. Brain 136:43–64
68. McNamee MJ, Partridge B, Anderson L (2016) Concussion ethics and sports medicine. Clin Sports Med 35(2):257–267
69. Meaney DF, Smith DH (2011) Biomechanics of concussion. Clin Sports Med. https://doi.org/10.1016/j.csm.2010.08.009
70. Mez J, Daneshvar DH, Kiernan PT et al (2017) Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. JAMA 318(4):360–370
71. Millspaugh JA (1937) Dementia pugilistica. US Nav Med Bull 35: 297–303
72. Morgan CD, Zuckerman SL, King LE, Beaird SE, Sills AK, Solomon GS (2015) Post-concussion syndrome (PCS) in a youth population: defining the diagnostic value and cost-utility of brain imaging. Childs Nerv Syst 31(12):2305–2309
73. Mussack T, Dvorak J, Graf-Baumann T, Jochum M (2003) Serum S-100B protein levels in young amateur soccer players after controlled heading and normal exercise. Eur J Med Res 8(10):457–464
74. Neselius S, Zetterberg H, Blennow K, Randall J, Wilson D, Marcusson J, Brisby H (2013) Olympic boxing is associated with elevated levels of the neuronal protein tau in plasma. Brain Inj 27(4):425–433
75. O'Connor KL, Baker MM, Dalton SL, Dompier TP, Broglio SP, Kerr ZY (2017) Epidemiology of sport-related concussions in high school athletes: National Athletic Treatment, Injury and Outcomes Network (NATION), 2011–2012 through 2013–2014. J Athl Train 52(3):175–185
76. Otto M, Holthusen S, Bahn E, Söhnchen N, Wiltfang J, Geese R, Fischer A, Reimers CD (2000) Boxing and running lead to a rise in serum levels of S-100B protein. Int J Sports Med 21(8):551–555
77. Papa L, Ramia MM, Edwards D, Johnson BD, Slobounov SM (2015) Systematic review of clinical studies examining biomarkers of brain injury in athletes after sports-related concussion. J Neurotrauma 32:661–673
78. Partridge B (2014) Dazed and confused: sports medicine, conflicts of interest, and concussion management. J Bioeth Inq 11(1):65–74
79. Pauelsen M, Nyberg G, Tegner C, Tegner Y (2017) Concussion in ice hockey—a cohort study across 29 seasons. Clin J Sport Med 27(3):283–287
80. Pfister T, Pfister K, Hagel B, Ghali WA, Ronksley PE (2016) The incidence of concussion in youth sports: a systematic review and meta-analysis. Br J Sports Med 50:292–297
81. Reid MW, Cooper DB, Lu LH, Iverson GL, Kennedy JE (2018) Adversity and resilience are associated with outcome after mild traumatic brain injury in military service members. J Neurotrauma 35:1146–1155
82. Reynolds BB, Patrie J, Henry EJ, Goodkin HP, Broshek DK, Wintermark M, Druzgal TJ (2017) Comparative analysis of head impact in contact and collision sports. J Neurotrauma 34:38–49
83. Routsi C, Stamataki E, Nanas S, Psachoulia C, Stathopoulos A, Koroneos A, Zervou M, Jullien G, Roussos C (2006) Increased levels of serum S100B protein in critically ill patients without brain injury. Shock 26(1):20–24
84. Rutherford A, Stephens R, Potter D (2003) The neuropsychology of heading and head trauma in association football (soccer): a review. Neuropsychol Rev 13(3):153–179
85. Shahim P, Gren M, Liman V et al (2016) Serum neurofilament light protein predicts clinical outcome in traumatic brain injury. Nat Publ Gr. https://doi.org/10.1038/srep36791
86. Shahim P, Linemann T, Inekci D, Karsdal MA, Blennow K, Tegner Y, Zetterberg H, Henriksen K (2016) Serum tau fragments predict return to play in concussed professional ice hockey players. J Neurotrauma 33(22):1995–1999
87. Shahim P, Tegner Y, Gustafsson B et al (2016) Neurochemical aftermath of repetitive mild traumatic brain injury. JAMA Neurol 73(11):1308
88. Shahim P, Tegner Y, Marklund N, Blennow K, Zetterberg H, Shahim C (2018) Neurofilament light and tau as blood biomarkers for sports-related concussion. Neurology. https://doi.org/10.1212/WNL.0000000000005518
89. Shahim P, Tegner Y, Wilson DH, Randall J, Skillbäck T, Pazooki D, Kallberg B, Blennow K, Zetterberg H (2014) Blood Biomarkers for brain injury in concussed professional ice hockey players. JAMA Neurol 71(6):684
90. Shitaka Y, Tran HT, Bennett RE, Sanchez L, Levy MA, Dikranian K, Brody DL (2011) Repetitive closed-skull traumatic brain injury in mice causes persistent multifocal axonal injury and microglial reactivity. J Neuropathol Exp Neurol 70(7):551–567
91. Spiotta AM, Bartsch AJ, Benzel EC (2012) Heading in soccer. Neurosurgery 70(1):1–11
92. Stalnacke B-M, Ohlsson A, Tegner Y, Sojka P (2006) Serum concentrations of two biochemical markers of brain tissue damage S-100B and neurone specific enolase are increased in elite female soccer players after a competitive game. Br J Sports Med 40(4): 313–316
93. Tator C, Davis H (2014) The postconcussion syndrome in sports and recreation. Neurosurgery 75(suppl_4):S106–S112

94. Tator C, Davis H, Dufort P, Carmella Tartaglia M, Davis K, Ebraheem A, Hiploylee C (2016) Postconcussion syndrome: demographics and predictors in 221 patients. J Neurosurg 125: 1206–1216
95. Terry DP, Huebschmann N, Maxwell B, Cook N, Mannix R, Zafonte RD, Seifert T, Berkner PD, Iverson GL (2018) Pre-injury migraine history as a risk factor for prolonged return to school and sports following concussion. J Neurotrauma. https://doi.org/10.1089/neu.2017.5443
96. Terwilliger VK, Pratson L, Vaughan CG, Gioia GA (2016) Additional post-concussion impact exposure may affect recovery in adolescent athletes. J Neurotrauma 33:761–765
97. Turner RC, Lucke-Wold BP, Robson MJ, Omalu BI, Petraglia AL, Bailes JE, Hayes RL, Mondello S, Biomarkers B (2013) Repetitive traumatic brain injury and development of chronic traumatic encephalopathy: a potential role for biomarkers in diagnosis, prognosis, and treatment? Front Neurol. https://doi.org/10.3389/fneur.2012.00186
98. Vagnozzi R, Signoretti S, Cristofori L et al (2010) Assessment of metabolic brain damage and recovery following mild traumatic brain injury: a multicentre, proton magnetic resonance spectroscopic study in concussed patients. Brain 133(11):3232–3242
99. Yengo-Khan A, Hale A, Zalneraitis B, Zuckerman S, Sills A, Solomon G (2016) The sport concussion assessment tool: a systematic review. Neurosurg Focus. https://doi.org/10.3171/2016.1.FOCUS15611
100. Zetterberg H, Hietala MA, Jonsson M et al (2006) Neurochemical aftermath of amateur boxing. Arch Neurol 63(9):1277