Abstract

As professional sports leagues have begun to recognize the detrimental short- and long-term impact of concussions, understanding the severity of concussions has taken on increasing importance. The ability to understand the microstructural and functional brain pathology of sports-related concussions (SRCs) has improved due to advances in neuroimaging. Advanced magnetic resonance imaging (MRI) techniques can now clearly show brain damage caused by concussions; however, little is known with respect to the link between brain damage and the long-term effects. This overview summarizes the potential association between advanced imaging findings and prognosis of SRCs. We found that diffusion tensor imaging, quantitative susceptibility mapping, neurite orientation dispersion and density imaging, perfusion weighted imaging, near-infrared spectroscopy, positron emission tomography, and functional MRI are promising technologies for providing objective prognostic information in patients with SRCs. Additional research is warranted to investigate the early imaging diagnosis of long-term effects, such as chronic traumatic encephalopathy and post-concussion syndrome.

Keywords: sports-related concussion, advanced imaging, neuroimaging, post-concussion syndrome, traumatic brain injury

1. INTRODUCTION

Athletes frequently experience mild brain injuries while taking part in contact sports. A sports-related concussion (SRC) occurs when a brain injury causes temporary neurologic impairment. According to the 2017 Berlin Guidelines, an SRC is a type of mild traumatic brain injury (mTBI) and is characterized as a complex pathophysiologic state of the brain brought on by either a direct force to the head or indirect momentum [1]. SRCs often include acute structural brain injuries, which appear on conventional imaging methods, such as magnetic resonance imaging (MRI) or computed tomography (CT) [1]. Between 10% and 15% of athletes with SRCs experience long-lasting effects that extend for weeks, months, or even years. Post-concussion syndrome (PCS) is characterized by symptoms that last longer than 4 weeks or by the emergence of new symptoms. Growing evidence has shown that SRCs may result in long-term deficits, including an increased risk of behavioral and cognitive issues. In addition to concussions, there is emerging concern that athletes who repeatedly experience head impact may also be at an increased risk for long-term neurologic issues [2].

Previous reports have suggested that persistent, subclinical neurophysiologic changes in youthful adults with a history of concussions are linked to significant clinical changes in cognitive function in late adulthood [3]. An early diagnosis or providing valuable risk assessment for developing long-term complications, such as PCS or chronic traumatic encephalopathy (CTE), is critical for athletes with an SRC. In such situations, banning the athlete from continued participation in sports could facilitate long-term neurologic regression and reduce the proportion of athletes who experience long-term deficits. Traditional neuroimaging cannot reveal structural abnormalities in classic SRCs [4, 5]. The focus of current research has been to investigate advanced neuroimaging techniques to identify typical alterations in brain structure and function. If athletes are exposed to the ongoing risk of repeated SRCs, one crucial issue is whether advanced neuroimaging can aid in detecting those who are at increased risk of long-term deficits.
Previous studies have demonstrated microstructural, functional, and neurometabolic alterations following SRCs for athletes by using advanced neuroimaging techniques [6]. It is unclear, however, if the links between these abnormalities and long-term outcomes, such as PCS, CTE, and long-term cognitive deficits, hinder evidence-based treatment for athletes with SRCs. Therefore, the aim of this overview is to describe the potential association between advanced imaging findings and prognosis for athletes with SRCs.

2. BRAIN WHITE MATTER DAMAGE

Diffuse axonal damage in the white matter of the brain is thought to be a primary pathophysiologic reaction to a concussion. White matter fibers have been reported to be especially susceptible to the rotating forces produced by closed-head injuries, which can shear and twist axon bundles and unfold over long periods of time [7].

2.1 Diffusion tensor imaging

Diffusion tensor imaging (DTI) is an advanced MRI method that can be used to investigate microstructural white matter damage through the diffusion properties of water in the brain [8]. Mounting evidence has demonstrated DTI-based white matter injuries following an SRC. Although some evidence indicates that even among athletes without concussions, DTI measures could also change after contact sports with repetitive, sub-concussive TBIs [9]. DTI metrics, such as reduced fractional anisotropy (FA), increased axial diffusivity (AD), and radial diffusivity (RD), are commonly used to demonstrate white matter damage. Several studies have investigated the links between these abnormalities and long-term cognitive deficits [10-12].

A recent study showed that football players with a history of concussions had olomotor deficits suggestive of slower processing speed and less flexibility in cognitive function. These deficits are associated with decreased white matter integrity on DTI of areas projecting to critical cognitive oculomotor structures [12]. These findings offer a new understanding that might account for the mechanisms underlying long-term cognitive deficits in athletes who had concussions [12]. de Souza et al. [11] focused on the long-term relationships following SRC between cognition and white matter structure; however, no difference in DTI indices was detected between athletes with and without a history of SRC. de Souza et al. [11] reported that among athletes with a history of SRC, decreased FA and increased MD and RD in several white matter bundles are associated with worse memory, processing speed, and executive capacity. Despite diversity in the domains revealing connections, the findings suggested that athletes with a history of SRC had a stronger correlation between cognitive performance and white matter organization. Bartnik-Olson et al. [10] also reported decreased FA and increased RD in pediatric athletes with SRCs and cognitive symptoms compared to pediatric athletes without cognitive symptoms and controls, suggesting that white matter/glial involvement is linked to PCS [10]. In general, these findings demonstrated the importance of examining white matter organization to better estimate cognition for several years after an SRC and provided evidence of imaging metrics related to these long-term effects. These studies did not investigate the predictive power of imaging metrics acquired following the last SRC for long-term deficits, which may serve to provide useful information for clinical decision-making in patients with SRCs.

A recent study provided a longitudinal evaluation (1 week after an SRC, at the time of return-to-play [RTP], and 1 year following the time of RTP) and found that diverse stages of recovery over time were related to different aspects of brain physiology [13]. Specifically, it was found that FA showed no significant effects 1 year following the time of RTP, whereas MD showed lasting long-term effects [13]. Moreover, the MRI metrics were also related to the time of RTP and acute symptom severity (Figure 1) [13]. Taken together, these findings significantly enhanced our comprehension of how the brain recovers naturally from trauma. Other DTI evidence also showed the presence of significant microstructural alterations in the white matter of athletes with a prolonged clinical recovery from a SRC compared to a non-concussed control group [14]. In addition, Wilde et al. [14] concluded that DTI is sensitive to changes in white matter in the chronic and early phases of an SRC; this evidence preliminarily indicated the prognostic utility of DTI. Notably, Wilde et al. [14] did not directly compare the difference in white matter diffusivity between athletes sustaining an SRC with and without a prolonged recovery. The conformance of these findings over longer post-injury periods should be investigated further.

In addition, it has been demonstrated that serum neurofilament light is correlated with DTI estimates of backscatter tensor imaging (BTI) [15]. Therefore, combining advanced neuroimaging and concussion biomarkers, such as neurofilament light and tau, could potentially improve SRC diagnosis and provide crucial information for prognosis. Such information is essential for preserving an athlete’s health and may help with improving the RTP protocols [16].

2.2 Quantitative susceptibility mapping

As a quantitative extension of susceptibility-weighted imaging, quantitative susceptibility mapping (QSM) calculates an isotropic magnetic susceptibility tensor for each tissue voxel using off-resonance data collected from multi-echo MRI datasets [17]. Among complicated mTBIs, QSM has been used to locate focal tissue damage in military members [18]. A preliminary investigation analyzed longitudinal QSM metrics at 24 h, 8 days, and 6 months post-injury for concussed and control football athletes. It was found that the concussed athlete group had significant increases in white
matter susceptibility during the acute (24 h) and subacute (8 days) periods, but these effects had recovered by the 6-month visit [19]. At the group level, the identified susceptibility alterations following a concussion appeared to last longer than self-reported clinical recovery indicators. Susceptibility increased within the white matter revealed a strong correlation with RTP duration at the level of individual participants [19], suggesting that QSM can detect physiologic changes of white matter induced by SRCs, and the observed tissue alterations (increased susceptibility) appear to continue beyond the clinical outcome estimate and are connected to the RTP duration following an SRC [19]. This preliminary study did not reveal how the QSM metrics are relevant to RTP, thus additional studies are needed to determine the prognostic utility of QSM for SRC.

2.3 Neurite orientation dispersion and density imaging

Neurite orientation dispersion and density imaging (NODDI) is a diffusion MRI model that can acquire data with multiple different diffusion weightings to calculate the water contributions of various tissue types inside each voxel [20]. In areas with complicated neurite geometry, the NODDI model also computes the orientation dispersion index (ODI), which measures the angular deviation among neurites and is a more accurate way to measure neurite dispersion than FA (e.g., crossing or fanning fibers). With evidence that it was sensitive to the effects of reiterant brain strikes, the NODDI model demonstrated potential as a tool to study mTBI [21]. The long-term effects of concussion have recently been studied using NODDI, which revealed that a history of concussion is linked to increased neurite water volume and decreased ODI [22]. Churchill et al. [23] showed that increased neurite dispersion is present in concussed athletes who had more symptoms and took longer to recover. The Churchill et al. [23] study provided a longitudinal investigation of SRC from acute injury to RTP utilizing NODDI, which increased our understanding of how SRC affects the microstructure of white matter [23]. NODDI is a relatively new and developing method that was shown to be of value for learning more about how brain tissue changes during concussion recovery. Future research should examine the NODDI at SRC and over a longer timeline post-SRC to estimate the possible changes.

3. BRAIN CORTEX THICKNESS OR VOLUME REDUCTION

Cortical thickness dynamically correlates with age in the developing brain. Abnormal cortical development may result in adverse outcomes in behavior, emotion, and

Figure 1 | Visual exhibition of different neuroimaging from Churchill NW et al. [13]: significant effects of SRC in brain areas at SYM, medical clearance to RTP, and 1 year after RTP.

Parameters include global functional connectivity (Gconn) by functional MRI, cerebral blood flow (CBF) by arterial spin labeling (ASL), fractional anisotropy (FA), and mean diffusivity (MD) by diffusion tensor imaging (DTI). Slices are shown as maximum-intensity projections in axial and sagittal planes (Montreal Neurological Institute coordinates: x = −4, z = +14). RTP = return to play; SYM = early symptomatic injury.
cognition [24, 25]. Cortical thickness can be measured with high-resolution MRI using FreeSurfer pipeline. Urban et al. [26] compared pediatric athletes with concussions 3–8 months post-injury to athletes without a concussion history. The pediatric athletes with concussions had thinner cortices in the left dorsolateral prefrontal cortex and the right anterior and posterior inferior parietal lobes, which were related to a longer reaction time when completing dual tasks [26]. Although more studies are needed, these results suggested that persistent PCS or worse cognitive efficiency in more difficult tasks may be associated with a decreased cortical thickness in the chronic phase of recovery after a pediatric SRC. Another investigation showed an increased symptom reporting rate (using the parent-rated Post-Concussion Symptom Inventory) in the pediatric mTBI group that was linked to decreased cortical thickness in the left temporal, lateral temporal lobe, interior frontal pole, and the right temporal pole [25].

Several studies have investigated how cortical thickness in adults changes after an SRC. A recent study reported no significant difference in cortical metrics (thickness or volume) in the amygdala between acute and an early long-term duration of time (6 months) after an SRC among collegiate athletes [27]. It was suggested that the association between macroscopic gray matter structure and SRC is nominal between the acute and early long-term phases post-injury (i.e., 6 months). Current results have largely pointed to a limited relationship between classic SRC and gray matter structure during an interval of 6 months [25, 27, 28]. We cannot, however, completely exclude the possibility that the long-term effects for gray matter after SRC could be found when followed for a sufficient length of time. Therefore, longitudinal investigations across multiple years should be conducted on athletes who have been injured.

4. CEREBRAL BLOOD FLOW ALTERATION

It has been reported that recurrent mTBIs may increase the risk of dementia and neurodegeneration [29-31]. Although the mechanism underlying this observed association is unclear, there are some possible explanations. According to animal studies, mild brain injury alters the ion and neurotransmitter flux, microstructure of axons, metabolism, inflammatory processes, and cerebral blood flow (CBF), but may not result in structural damage that can be seen by traditional imaging techniques [32-34]. To reduce secondary injuries, RTP strategies in SRC rely on clinical symptom relief. The relief of clinical symptoms following an mTBI may, however, not always coincide with physiologic recovery, leaving a concealed window of cerebral susceptibility that is more susceptible to further injuries [30, 35]. Therefore, there is an urgent need to confirm the cumulative effects that might develop post-injury. Arterial spin labeling (ASL) is a neuroimaging method that quantifies relative or absolute CBF, which is then used as an indicator of cerebral blood vessels. ASL has identified integral decreases of CBF in patients with moderate or severe brain injuries. There are few studies, however, that have focused on CBF in SPC participants, and the results vary widely.

Bartnik-Olson et al. [10] evaluated pediatric SPC subjects with persistent PCS using PWI. Their results showed that SRC patients had reduced CBF and relative cerebral blood volume (CBV) in the bilateral thalami compared to healthy controls. The thalamus is a core brain structure that contains nuclei groups and white matter bundles linked to distant regions of the pallium. It has been reported that decreased thalamic CBF caused by sudden deceleration or acceleration movements may lead to development of persistent PCS [36-38].

Another study using ASL showed that the CBF in the left dorsal anterior cingulate cortex in athletes with physical symptoms 2-6 weeks post-injury persisted longer than asymptomatic athletes and controls [39]. These areas are recognized as functionally-linked nodes of the salience network [40]. Stephens et al. [39] evaluated how SRC-related symptoms were related to relative CBF perfusion, although the findings disagreed with several reports of decreased CBF following an mTBI [41, 42]. The sample size (15+15) and follow-up time (2-6 weeks) in the Stephens et al. study [39] were both small, which may result in insufficient statistical power to estimate the relationship between CBF and symptoms.

The direction of CBF alteration following an mTBI has not been consistently observed. The relationships between CBF perfusion alterations, symptoms, and recovery after an mTBI should be further evaluated.

5. TAU AGGREGATION AND INCREASED NEUROINFLAMMATION

Chronic traumatic encephalopathy (CTE), a neurodegenerative tauopathy marked by tau protein aggregation, has been increasingly diagnosed in athletes with a repeated SRC history at the time of autopsy [43]. Most patients with CTE are older, while only a small number of observations of tau aggregation in youth at autopsy have been reported [44]. The pathogenesis of CTE is still unclear, even though axonal pathology and neuroinflammation may play a role [45, 46]. Severe TBI, as a chronic illness process, causes progressive white matter stunting, which is connected to ongoing neuroinflammation [47] and a higher risk of neurodegenerative diseases [45]. Positron emission tomography (PET) has been extensively used in TBI research for decades [48]. Tau aggregation was recently discovered in older athletes or in athletes who sustained a severe TBI, thus utilizing PET tau-tracers [49-51].

Using a combined PET/MR scanner and dual PET tracers ([11C]PK11195 for neuroinflammation or microglial activation and [18F]THK5317 for tau aggregation), Marklund et al. [52] found that youth with SRCs and
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athletes with symptomatic recurrent SRCs had higher neuroinflammation and tau aggregation at prolonged post-injury time points \[52\]. The imaging was done at 6 months-to-several years after the latest SRC, suggested that pathology was ongoing at prolonged post-injury intervals, and supported by the elevated serum NF-L and CSF levels. These results implied that a persistent pathogenic mechanism might be involved in the elevated risk of neurodegeneration linked to TBI and repeated SRC; however, this cause-and-effect interactions needs to be demonstrated in future research.

6. NEAR-INFRARED SPECTROSCOPY

The non-invasive optical imaging technique known as near-infrared spectroscopy (NIRS) has great temporal resolution and can be used to track relative alterations in cerebral hemodynamics \[53\]. NIRS has been confirmed by several researches to be a precise metric of cerebrovascular health \[54, 55\], and a reliable technique for tracking the recovery of concussion patients \[56, 57\]. Hemodynamic dysfunction in the prefrontal cortex has been reported in adults with persistent PCS using NIRS \[56\]. A recent study using NIRS explored the long-term effects of repeated SRC history on prefrontal cortex oxygenation in retired athletes during squat-stand exercises \[58\]. The hemodynamic responses to the squat-stand intervention between the mTBI and control (no history of concussions) groups were significantly different. The findings provided preliminary evidence that NIRS can detect the long-term deleterious effect of repeated concussions on dynamic cerebral autoregulation in contact sport athletes \[58\]. Although the findings indicated that athletes with concussion histories have impairment in the prefrontal brain oxygenation, no clinically relevant conclusion can be made about this information now. The severity of cerebral hemodynamic defects that develop over time in athletes needs to be confirmed by additional studies.

Wu et al. \[59\] utilized task-based functional NIRS to study the neurophysiologic bases of the inattention component generated by SRC in young athletes \[59\]. Wu et al. \[59\] found that during visual sustained attention processing, post-SRC athletes exhibited considerably more regional activation in the middle lobe and regional hyper-communication among bilateral occipital areas compared to normal controls, that was forcefully linked with increased hyperactive/impulsive symptoms. The results suggested that abnormal left middle frontal gyrus activation and hyper-communications between the right inferior occipital cortex and bilateral calcarine gyri during visual attention processing could lead to attention deficiencies in SRC patients. These results offered a crucial understanding of the mechanisms underlying inattention caused by a TBI, thus emphasizing the role of changed neuronal activities and mutual effects in the occipital and middle frontal regions \[59\].

7. QUANTITATIVE ELECTROENCEPHALOGRAPHY

Quantitative electroencephalography (qEEG), a computer-assisted method of analyzing and interpreting EEG data, enables identification of subtle changes in the patterns and types of EEG activities and links to activities of the brain \[60\]. A persistent decrease in the mean alpha frequency in the resting qEEG was the most consistent finding for athletes who had suffered concussions \[61\]. A decrease in the sustained mean alpha frequency was found in a previous study with concussed athletes examined up to 12 months after a concussion \[62\]. There is evidence that alpha frequency reduction is also strongly linked to memory and attention deficits \[63\]. These results have revealed consistent neurophysiologic changes following SRCs that tend to worsen with additional injuries \[3\].

The brain function index (BFI) that was independently validated in a prospective FDA trial is derived from EEG characteristics connected with brain injury (including measures of connectivity, EEG signal complexity, and alterations in the frequency spectra). The BFI is recorded from frontal and frontotemporal brain areas and best reflects the current understanding of the physiology of concussion \[64, 65\]. The BFI was demonstrated as a biomarker that could offer an indicatrix of functional brain injury after an mTBI. A previous study verified the potential clinical value of BFI in a longitudinal assessment of athletes after an SRC \[66\]. In addition, the enhanced BFI, which expands the BFI to incorporate multimodal input, including vestibular characteristics and select neurocognitive features, showed better sensitivity to changes following SRC and whole recovery \[67\]. Future research is needed to establish the long-term effects of BFI for athletes following SRC.

In summary, using EEG in SRC, especially event-related potentials, has provided several insights into the neurophysiologic changes that persist following mTBI and tended to get worse with subsequent injuries.

8. FUNCTIONAL MRI

Resting-state functional MRI (rs-fMRI) evaluates the inherent variations in the blood oxygen-level dependent (BOLD) signals and is specifically sensitive to alterations in brain function after concussion. Studies have shown that concussions change the brain’s inherent connectivity networks and the strength of the functional connections between various brain regions. After a brain injury, the default mode network (DMN) and salience network frequently exhibit impaired intra- and inter-network activities \[68, 69\]. A notable characteristic of concussion is the diffuse elevation in hyperconnectivity or functional connectivity \[42, 70, 71\]. Hyperconnectivity is considered to be a usual reaction of the brain to neurologic injuries with a known inflammatory element \[72\]. Hyperconnectivity has been demonstrated in some research at the acute, sub-acute, and chronic stages.

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Table 1 | Summary of main findings of different neuroimaging techniques related to long-term deficits of SRC.

<table>
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<td>At RTP</td>
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</table>

SRC = sport-related concussion, FA = fractional anisotropy, AD = axial diffusivity, RTP = return to play, CBF = cerebral blood flow, CBV = cerebral blood volume, NODDI = neurite orientation dispersion and density imaging, ODI = orientation dispersion index, PCS = post-concussion syndrome.
after a concussion and is linked to severe symptoms or slower recoveries [73-75].

Müller et al. [76] reported that the deficiency in dynamic flexibility of SRC patients is connected to stronger nodal strength in the left middle frontal gyrus, indicating restructuring in an area linked to attention. This rudimentary study showed that the inherent brain dynamics as well as structural organization are changed in networks associated with attention in adolescents who had concussions. Another study using rs-fMRI found that compared to concussed athletes without depressive symptoms, athletes with prior concussions who reported depressive symptoms at the day 1 visit had greater global connection [77]. These studies provided further support that hyperconnectivity is pathologic in athletes with a concussion history, which was demonstrated in the rs-fMRI BOLD signal connectivity and potential mood dysregulation.

With the exception of rs-fMRI, the cerebrovascular reactivity, which is evaluated by task-based fMRI (hypercapnic task), has been shown to be sensitive to alterations in brain after exposure to reduplicative brain acceleration in athletes [78]. Svaldi et al. [79] used this task-based fMRI to further observe that the alterations in cerebrovascular reactivity are connected with drawn-out cumulative to head acceleration events [79]; however, this connection disappeared after a prolonged period (1–2 months) of rest. Thus, there is still no direct evidence of a relationship between task-based fMRI and long-term deficits from SRCs.

9. CONCLUSION

The prediction of long-term deficits from SRCs remain challenges. Advanced neuroimaging has revealed subclinical alterations in electrophysiology, neurocognition, and neuroanatomy for athletes and retired athletes, though findings are varied (Table 1). Of the available neuroimaging modalities, DTI is the most studied, EEG is the most accurate, and fMRI is most promising, but lacks direct evidence related to long-term effects. It is yet unclear how or whether these alterations reach the clinical threshold. From a clinical standpoint, an important area of neuroimaging is to provide valuable information to confirm individuals who may be at risk of a drawn-out PCS, and aid in decisions with respect to when RTP should be considered. Beyond imaging markers, neurofilament light and tau are promising blood biomarkers aimed to evaluate the amount of axonal injury, and combining such biomarkers and neuroimaging metrics is promising.

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