# Current and Emerging Techniques in Neuroimaging of Sport-Related Concussion

**Carrie Esopenko, PhD**[1], **Nico Sollmann, MD, PhD**[2,3,4,5], **Elena M. Bonke, MSc**[2,6], **Tim L. T. Wiegand**[2], **Felicitas Heinen, BSc**[2], **Nicola L. de Souza, MSc**[7], **Katherine M. Breedlove, PhD**[8,9], **Martha E. Shenton, PhD**[5,9,10], **Alexander P. Lin, PhD**[5,8,9], **Inga K. Koerte, MD**[2,5]

[1] Department of Rehabilitation and Movement Sciences, Rutgers Biomedical and Health Sciences, Newark, NJ, USA

[2] cBRAIN, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Ludwig-Maximilians-Universität, Munich, Germany

[3] Department of Diagnostic and Interventional Neuroradiology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

[4] TUM-Neuroimaging Center, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

[5] Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[6] Graduate School of Systemic Neurosciences, Ludwig-Maximilians-Universität, Munich, Germany

[7] School of Graduate Studies, Biomedical Sciences, Rutgers Biomedical and Health Sciences, Newark, NJ, USA

[8] Center for Clinical Spectroscopy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[9] Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[10] VA Boston Healthcare System, Brockton Division, Brockton, MA, USA

## Abstract

Sport-related concussion (SRC) affects an estimated 1.6 to 3.8 million Americans each year. SRC results from biomechanical forces to the head or neck that lead to a broad range of neurological symptoms and impaired cognitive function. While most individuals recover within weeks, some develop chronic symptoms. The heterogeneity of both the clinical presentation and the underlying brain injury profile, make SRC a challenging condition. Adding to this challenge, there is also a lack of objective and reliable biomarkers to support diagnosis, to inform clinical decision making, and to monitor recovery following SRC.

**Address for correspondence:** Inga K. Koerte, MD, cBRAIN, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital, Ludwig-Maximilians-Universität, Waltherstr. 23, 80337 Munich. Phone: +49 4400 56903, ikoerte@med.lmu.de.

In this review, we provide an overview of advanced neuroimaging techniques that provide the sensitivity needed to capture subtle changes in brain structure, metabolism, function, and perfusion following SRC. This is followed by a discussion of emerging neuroimaging techniques, as well as current efforts of international research consortia committed to the study of SRC. Finally, we emphasize the need for advanced multimodal neuroimaging to develop objective biomarkers that will inform targeted treatment strategies following SRC.

**Keywords**

brain injury; sport-related concussion; magnetic resonance imaging; neuroimaging; diffusion imaging; personalized medicine

## 1. Introduction

An estimated 1.6 to 3.8 million athletes experience a sport-related concussion (SRC) annually in the United States alone [1]. Although SRC occurs in most sports, the incidence rates are highest in contact sports such as American football, soccer, and ice hockey [2, 3]. SRC results from biomechanical forces to the head or neck that lead to a broad range of neurological symptoms (e.g., headache, visual disturbances) and impaired cognitive function (e.g., post-traumatic amnesia). SRC-related symptoms are typically transient, resolving within days to weeks in adults, and within a month in children and adolescents [2, 4–7]. However, approximately 15% of athletes who sustain an SRC will go on to develop persistent symptoms [8]. The clinical presentation of SRC is also heterogeneous, and diagnosis is based on subjective symptom reporting, making it a challenging injury for both medical professionals and athletic staff alike. Yet, currently there are no established biomarkers for objective diagnosis, prognosis, or monitoring of recovery. Thus, much more research is needed that is focused on identifying objective and reliable measures for the diagnosis of SRC as well as more efficacious prognosis. Advanced neuroimaging techniques hold promise as they offer such objective and reliable measures.

Current clinical practice guidelines do not include routine neuroimaging following SRC [7, 9, 10]. Computed tomography (CT) or conventional magnetic resonance imaging (MRI) may be obtained to rule out, for example, intracranial hemorrhage in athletes who have experienced loss of consciousness, posttraumatic amnesia, persistently altered mental status (Glasgow Coma Scale <15 points), focal neurologic deficits, evidence of skull fracture on examination, or signs of clinical deterioration [10, 11].

Of note, these neuroimaging techniques lack sensitivity in detecting alterations of tissue microstructure, cerebral blood flow (CBF), and brain metabolism that, in fact, represent the most common manifestations of brain injury following SRC. Advanced neuroimaging techniques, however, provide the necessary sensitivity to capture even subtle brain alterations following SRC and have therefore been in the focus of SRC research aimed at developing objective biomarkers for the purpose of diagnosis as well as prognosis of SRC [12, 13].

In this review, we first provide a brief description of the neuroimaging techniques currently used to study SRC, followed by a brief summary of the main findings obtained with each technique, where we emphasize both strengths and limitations. We then discuss emerging neuroimaging techniques as well as current efforts of international research consortia committed to the study of SRC. Finally, we emphasize the need for advanced multimodal neuroimaging to inform targeted treatment strategies following SRC.

## 2. Magnetic Resonance Imaging

### 2.1 High-Resolution Structural Imaging

High-resolution, three-dimensional T1-weighted MRI is widely used to evaluate morphometric characteristics such as total brain volume, brain regional volume, and cortical thickness [14, 15]. Ready-to-use automated techniques have been developed to allow for easy segmentation of the brain's gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) space. Brain atlases can be used to segment the brain further into specific regions of interest (ROIs) and into subcortical structures (Fig. 1).

In the acute stage following SRC, gross macrostructural and morphological changes are typically absent [16]. However, studies have reported a decrease in total and regional brain volume, and cortical thickness in athletes with a history of SRC that occurred months to years before [17, 18]. More specifically, decreased total brain volume as well as decreased volume of the right posterior cingulate cortex, right anterior cingulate cortex, and hippocampus were reported in 10-14-year old athletes 1 month after SRC compared to healthy controls [19]. Reduced cortical thickness in the left dorsolateral prefrontal cortex and the right anterior and posterior inferior parietal lobes were reported in 10-14-year old athletes 3-8 months after sustaining an SRC; reduced cortical thickness was associated with slower reaction times in dual-task conditions [18]. Another study reported reduced cortical thickness in collegiate football athletes with a history of SRC (on average 10 months prior to testing) compared to healthy controls [17]. In this study, previously concussed football players had a significantly reduced cortical thickness in the left anterior cingulate cortex, orbital frontal cortex, and medial superior frontal cortex [17].

Taken together, these quantitative analysis techniques based on T1-weighted MRI used in research studies of SRC hold promise in identifying macrostructural brain alterations in parenchymal and subcortical volumes, as well as in cortical thickness. The findings, however, are non-specific, and alterations in brain regional volumes and cortical thickness are likely only occurring months to years following SRC. Future studies are thus needed to investigate the prognostic value of brain volumetric changes following SRC, earlier in the course of head injury.

### 2.2 Diffusion-Weighted Imaging

Diffusion-weighted imaging quantifies diffusion properties of water molecules detailing the magnitude (diffusivity) and the direction (anisotropy) of water molecule diffusion [20–23]. The diffusion of water molecules in brain tissue depends on properties such as cell size, cell density, membrane orientation and directionality of axons [20, 22, 24]. Therefore, characterizing

diffusion properties in a given brain area allows for the interpretation of structural properties of brain tissue [20, 22].

In the study of SRC, diffusion tensor imaging (DTI) has been the most commonly used diffusion MRI technique. DTI allows for the calculation of DTI scalar measures, e.g., fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). It can be applied to WM and GM regions and specific WM tracts (i.e., tractography) (Fig. 2). More specifically, FA describes the directionality of diffusion. It is a scalar measure ranging from 0 to 1. A value of 0 represents isotropic diffusion, meaning that water diffuses in all directions. Isotropic diffusion can be found in the CSF space. A value of 1 represents anisotropic diffusion, meaning that water diffuses along a single main axis. Anisotropic diffusion can be found in densely packed WM fiber tracts where water molecules are more likely to diffuse parallel to the main axis of the axons. MD describes the magnitude of the average diffusion along all three spatial axes. As such, MD represents the amount of diffusion in a given volume. AD describes the magnitude of diffusion along the main axis and is purported to be a measure of axonal integrity. RD describes the magnitude of diffusion perpendicular to the main axis (i.e., along the two radial/tangent axes). RD has been interpreted as a measure of the integrity of the myelin sheath. FA and MD are typically observed as being inversely related [12, 23, 25].

DTI has shown sensitivity in the detection and quantification of microstructural brain alterations following SRC. More specifically, several studies reported increased MD, RD, and AD as well as decreased FA 1 to 2 days following SRC, suggesting axonal injury or damage to myelin sheaths. Increases in MD and AD as well as decreases in FA have been associated with symptom severity and worse cognitive performance in collegiate athletes [26–28]. Increased RD and MD in anterior and posterior WM regions were shown at 2 days post-injury, whereas at 2 weeks post-injury, elevated RD and MD persisted solely in the prefrontal WM [26]. Even 2 months post-injury, most athletes' diffusivity values remained elevated relative to their individual baseline [26]. Other studies, however, report increased FA acutely following SRC, which may be a result of axonal swelling or cytotoxic edema [29–32]. Among the structures that seem to be most commonly affected by SRC are the corpus callosum, the corona radiata, the internal capsule, the uncinate fasciculus, the fronto-occipital fasciculus, and the inferior and superior longitudinal fascicles [33].

Importantly, the interpretation of diffusion measures is challenging because diffusion is measured in a voxel with a typical size of about $2x2x2mm^3$, which contains multiple different structures including axons, membranes, myelin sheaths, microtubules, and therefore likely a combination of co-occurring processes. As such, use of additional novel diffusion parameters, such as free-water imaging may increase the sensitivity and specificity of diffusion-weighted imaging [34]. Free-water imaging represents freely diffusing water molecules. It separately models the contribution of extracellular free water and water that is in the vicinity of cellular tissue. This is achieved by a bi-tensor model, with a diffusion tensor for modelling the tissue compartment, and a second isotropic compartment, with a fixed diffusion coefficient for modelling molecules in the extracellular space. Using free-water imaging increases the precision of conventional metrics such as FA and MD, and quantitatively estimates the degree of vasogenic edema and neuroinflammation [35, 36].

A study with university-level ice hockey players reported reduced free-water volume and reduced AD and RD following SRC. These alterations suggest decreased extracellular space and decreased diffusivity in the WM, possibly due to swelling and/or increased cellularity of glia cells [34].

Further novel diffusion sequences are currently under investigation, such as high angular resolution diffusion imaging, multi-shell imaging, diffusion kurtosis imaging (DKI), or neurite orientation dispersion and density imaging (NODDI) [37–39]. NODDI models diffusion signals by combining three tissue compartments: neurites, extra-neurites, and CSF. This allows for estimation of a neurite density index (NDI) and an orientation dispersion index (ODI), as well as a volume fraction of isotropic diffusion [40]. NODDI is best suited for estimating the microstructural complexity of dendrites and axons in-vivo, thus going beyond the assessment of standard diffusion measures [39]. A study directly comparing DTI to NODDI revealed that elevated FA and decreased MD along with increased intracellular volume fraction and reduced ODI indicate greater neurite density and coherence of neurite orientation within the brain's WM in collegiate athletes following SRC [41]. Additionally, decrease in FA and increase in AD and RD were associated with reduced intra-neurite water volume, at both the symptomatic phase following injury and at return to play [42].

DTI considers diffusivity as a Gaussian distribution, i.e., a normally distributed process. However, due to diffusion hindrance, brain tissue is characterized by non-Gaussian diffusion. DKI is an extension of the DTI method that quantifies the non-Gaussian distribution of water diffusion [43]. It is considered to better reflect diffusion in brain areas with high tissue heterogeneity. In a study on high school and collegiate athletes, DTI detected a widespread decrease in MD and, to a lesser extent, decreased AD and RD at 24 hours post-injury. DKI detected increased axial kurtosis. Eight days post-injury, abnormalities in all diffusion metrics were even more widespread in the SRC athletes, despite improvement of symptoms and cognitive performance [31]. A follow-up examination 6 months later revealed continued widespread decreased MD and AD compared to controls. However, kurtosis metrics, which were significantly higher in concussed athletes in the acute phase, had normalized [44]. Another study found increased axial kurtosis in the SRC group <48 hours post-injury. These differences increased in extent and magnitude at 8 days, receded at 15 days, and returned to normal levels 45 days post-injury. Kurtosis FA exhibited a delayed response, with a consistent increase by days 15 and 45 [45]. Differences between diffusion and kurtosis properties thus indicate complementary roles of diffusion tensor metrics and diffusion kurtosis metrics in understanding the underlying pathophysiology in SRC [46].

Although diffusion-weighted MRI is one of the most promising techniques in the study of SRC, most studies to date are limited to group effects only. However, on a patient-specific level, the sensitivity for identifying specific changes, and how they may relate to trajectories of recovery, as well as to outcome, are still not known. Future studies need to develop further individual profiles of injury related to clinical outcome [47]. Additionally, the specificity of DTI will likely be increased by combining this approach with other neuroimaging techniques such as magnetic resonance spectroscopy (MRS).

### 2.3    Susceptibility-Weighted Imaging

Susceptibility-weighted imaging (SWI) is sensitive to para- or diamagnetic properties, which make possible the identification of even subtle accumulations of hemosiderin and/or blood products due to, for example, microhemorrhages [21, 48, 49]. SWI can either be evaluated visually by identifying and counting microhemorrhages (Fig. 3) or be analyzed using semi-automated quantitative techniques such as hypointensity burden (HIB) or quantitative susceptibility mapping (QSM), which estimate the isometric magnetic susceptibility of tissue. A significant increase in HIB has been described in ice hockey players 2 weeks following SRC [50]. A recent study using QSM in football athletes, who sustained an SRC, showed increased WM susceptibility at 24 hours and 8 days post-injury relative to football athletes without SRC, but no differences at 6 months post-injury [51]. Increased WM susceptibility was associated with longer return to play duration, and susceptibility changes were still noted even when athletes had recovered clinically.

Although the use of SWI is promising particularly when analyzed using quantitative algorithms, the detection of injury following SRC is limited to microhemorrhages and lacks sensitivity to more common tissue damage such as diffuse axonal injury. Thus, SWI is likely only capturing the tip of the iceberg of brain injury following SRC. Nonetheless, in combination with other neuroimaging techniques, it adds to what we know about brain injury in SRC.

### 2.4    Magnetic Resonance Spectroscopy

MRS allows for the assessment of brain metabolism by obtaining signal of metabolites [52, 53]. Metabolic information from either the whole brain or preselected voxels of interest within the brain (e.g., in the anterior cingulate cortex and posterior cingulate cortex for SRC) is collected [52–54]. The most commonly measured metabolites in the study of SRC include lactate, N-acetyl-aspartate (NAA, a measure of neuronal viability), choline (Cho, a measure of axonal injury and inflammation), myo-inositol (mI, a measure of glia cell activation and inflammation), and glutamate and glutamine (Glx, a measure of excitatory neurotransmission) [53]. Creatine (Cr, a marker of cerebral energetics) is typically collected as an internal reference for the measurement of other metabolite signal peaks, with metabolites often being reported as ratios with Cr as the denominator [53] (Fig. 4).

In athletes in the acute/subacute phase of SRC, reductions in NAA or the NAA/Cr ratio in the genu of the corpus callosum [55, 56], the dorsolateral prefrontal cortex [57], the prefrontal and primary motor cortices [57, 58], and adjacent to the cortical-subcortical junction [55, 57–60], along with decreased Glu/Cr ratio in the primary motor cortex [57], have been reported. Two studies have reported a return to baseline of the NAA/Cr ratio after 30 days and after 45 days following SRC [59, 60]. A second injury, however, may result in prolonged NAA normalization [59]. Interestingly, a study on repeated SRC reported an increase of NAA/Cho and NAA/Cr instead of a decrease [55]. The authors interpreted this finding as a possible indicator of neuroplasticity. Recent studies also report increased mI that was correlated with DTI and functional MRI (fMRI) parameters 1 month following SRC [61]. Another recent study reported an increase in mI following SRC, which was associated with gait disturbances [62].

Information about metabolic alterations in the brains of athletes post-injury may provide valuable insight into the pathogenesis underlying structural and functional brain abnormalities. Taken together, MRS is an important technique in the study of SRC, particularly when combined with other neuroimaging techniques.

## 2.5 Functional Magnetic Resonance Imaging

fMRI detects changes in blood oxygenation thereby measuring CBF to and from a given brain area. The measurement of change in blood oxygenation is called blood oxygen level-dependent (BOLD) imaging [63, 64]. Studies examining alterations in brain function following SRC either use task-based fMRI or resting-state fMRI (rsfMRI). In this section, we first provide a summary of studies using task-based fMRI followed by a summary of studies using rsfMRI to examine alterations in brain function following SRC.

**Task-based fMRI:** Task-based fMRI assesses brain function while participants complete a series of tasks targeting different cognitive domains (e.g., working memory, executive functioning) or motor movements (e.g., finger tapping). Early studies using fMRI have shown alterations in brain function using cognitive and motor tasks following SRC [65–67]. Further, alterations in fMRI signal could be observed in athletes who sustained an SRC even in the absence of differences in cognitive performance compared to controls. This result suggests that fMRI may be sensitive to functional alterations of brain regions that last beyond recovery of cognitive functioning [65–67]. Serial fMRI in collegiate athletes following SRC have also shown greater activation on a more cognitively demanding 2-back working memory task in the acute and subacute stages compared to healthy comparison participants; again even in the absence of differences in behavioral performance [68].

Another study reported chronic abnormalities in brain function in athletes who report persistent symptoms 1-month post-injury compared to those who did not show any symptoms [66]. Reduced activation has also been shown in children in the subacute and chronic stages following SRC using verbal and non-verbal working memory tasks as compared to healthy children [69]. However, others have shown that hyperactivation in the prefrontal and parietal cortices during working memory tasks is associated with severity of SRC symptoms [70].

**rsfMRI:** rsfMRI assesses intrinsic brain function in the absence of cognitive or motor tasks and is therefore also referred to as task-negative fMRI. Intra- and inter-network connectivity between brain regions that are anatomically separated but functionally connected (i.e., temporally correlated) have been investigated using rsfMRI following SRC [71, 72]. Studies have shown reductions in functional connectivity between the medial regions of the default mode network (DMN) acutely following SRC [73], as well as a reduction in the number and strength of connections within regions of the DMN in asymptomatic athletes in the subacute phase (~10 days) following SRC [74].

Aside from the DMN, increased functional connectivity has been shown in the executive control and ventral attention networks in adolescents in the subacute phase ( 2 months) following SRC [75]. Furthermore, there is evidence that alterations in functional connectivity

may persist beyond symptom recovery, with athletes showing increased functional connectivity between frontal brain regions months post-injury [76].

In addition to changes in network connectivity after SRC, differences in regional homogeneity have also been noted. Specifically, a recent study reports increased regional homogeneity in the sensorimotor, visual, and temporal cortices, as well as reduced regional homogeneity in the frontal cortex in athletes 1 month following SRC [77]. Further, increased global connectivity has been shown in athletes who were examined within 1-3 days following SRC, decreased global connectivity was found in athletes who were examined 5-7 days following SRC [78]. Importantly, these results suggest that timing of rsfMRI, even in the acute stage following SRC, may impact both the variability in findings and their interpretation.

Taken together, previous studies emphasize the potential of task-based and rsfMRI studies of SRC. Functional MRI holds promise in determining the timeline of recovery, even when symptoms have resolved, while rsfMRI may prove useful in the assessment of functional connectivity in the acute stage following SRC, as it does not require cognitive exertion. There are, however, limitations of both task-based and rsfMRI that need to be considered. The most important limitation may be that the BOLD signal is highly susceptible to noise and artifact (e.g., movement, head motion, WM signal), which need to be addressed during quantitative analyses and may impact the interpretation of results. Additionally, given the high susceptibility to noise, both task-based and rsfMRI may only be interpreted at a group level, and thus currently cannot be used to develop individual injury profiles of injury or to predict prognosis following SRC.

### 2.6   Arterial Spin Labeling

Arterial spin labeling (ASL) measures blood perfusion by labeling the arterial blood flowing to the brain. ASL sequences can provide CBF quantification in the brain without the need for intravenous contrast agent administration, contrary to dynamic susceptibility contrast perfusion imaging that is more frequently used in the clinical routine setting [79, 80]. Currently, primarily pseudo-continuous ASL (pCASL) is applied, which offers a higher signal-to-noise ratio with less sensitivity to tag dispersion compared to previously used pulsed ASL [80, 81] (Fig. 5).

Recent studies have shown reduced CBF in the first 24-48 hours following SRC, predominantly in frontoparietal cortices and thalamus compared to healthy controls [82]. These alterations in CBF were also associated with measures of balance, using the balance error scoring system (BESS), memory and impulse control on computerized tests, as well as symptom duration[82]. Furthermore, a longitudinal imaging study identified reduced CBF in the right superior temporal sulcus and right dorsal mid-insular cortex at day 1 following SRC, and increased CBF 1 month post-injury suggesting recovery [83]. Of note, individuals with poor clinical outcome at 1 month post-injury showed decreased CBF in the right dorsal mid-insular cortex.

Another study reported reduced CBF one week after injury [84]. Interestingly, neurocognitive performance had returned to baseline by that time, suggesting that alterations in CBF

continued even when cognitive impairment had subsided. Still another study reported an association between symptom severity and increased CBF in the posterior cortices [85]. Specifically, athletes with greater cognitive symptoms showed reduced CBF in the subcortical and frontal regions compared to athletes with greater somatic symptoms. Further, CBF was lower in the cognitive symptom subgroup, but higher in the somatic symptom subgroup compared to healthy controls.

Taken together, there is evidence for alterations in ASL-derived CBF, which are associated with neurocognitive performance and symptom pattern and severity. Moreover, these studies suggest that alterations in CBF may extend beyond symptom resolution. However, the number of studies using ASL to investigate alterations in CBF following SRC is small, and future studies are needed to assess the reliability of ASL in predicting recovery. Multimodal approaches may help to understand better CBF changes over time in SRC and could potentially link such changes to findings of structural and functional imaging.

## 3   Perspectives and Future Directions

### 3.1   New Techniques and Approaches

Recent research demonstrates the potential of advanced neuroimaging in the study of SRC. Specifically, advanced neuroimaging techniques hold promise for identifying alterations in brain structure and function that may be used for the diagnosis and prognosis of SRC. Further, novel techniques such as free-water imaging, NODDI, and DKI have recently been applied to SRC and show great promise in elucidating underlying pathophysiological processes in SRC.

Still, the interpretation of neuroimaging measures can be challenging. For example, structural imaging using T1-weighted MRI and diffusion MRI may not allow to pinpoint the underlying cellular or neurophysiological alterations. Similar problems have been noted for fMRI, specifically regarding the interpretation of subject-specific changes in the MRI signal. Multimodal neuroimaging, defined as the combination of neuroimaging data collected using different modalities such as structural imaging (e.g., T1-weighted MRI, DTI, SWI), neurochemistry (MRS), functional imaging (fMRI), and perfusion imaging (ASL) [86] may, however, advance our understanding of the underlying pathophysiological processes. Nonetheless, further research is needed to determine whether or not, and how, specific alterations in brain structure, metabolism, function, and perfusion relate to one another and to trajectories of recovery following SRC.

In addition, studies that employ advanced neuroimaging techniques with multiple neuroimaging modalities targeting brain structure and function may provide better understanding of brain structural and functional alterations that may persist even after symptom resolution or in the absence of cognitive dysfunction. Imaging may potentially be more sensitive to subtle alterations while it is likely that the cognitive tests used in the acute setting may not be sufficiently sensitive to subtle alterations in brain structure or function. Alternatively, these persistent alterations in brain structure and function may be evidence of compensatory processes. However, use of more sophisticated and multimodal neuroimaging

techniques in longitudinal study design will provide more granular information to answer these questions.

Artificial intelligence (AI) has shown great promise in detecting abnormalities in different types of data such as patients' medical history and demographic information, neuropsychological assessment scores, and neuroimaging measures. Retrospective clustering analyses have been performed on balance and vestibular diagnostic data of patients with mild traumatic brain injury (mTBI) [87]. By integrating diffusion measures with MRS and volumetric measures, as well as neurobehavioral data and genetic markers, SRC classification models achieved up to 93% sensitivity and 87% specificity [88]. However, the more subtle the data abnormalities in individuals with SRC, the more advanced AI models and the more data is required to achieve high performance. Together with the continuous improvement of AI algorithms (particularly deep learning model architectures) and computational power, big-data approaches from research consortia may go hand in hand with the further application of AI to understand better the neurophysiologic underpinnings of SRC.

### 3.2 Multi-Site Consortium Studies and Mega-/Meta-Analysis of Data

The majority of neuroimaging studies in SRC lack generalizability due to small sample sizes, the inclusion of subjects with limited age ranges (e.g., college-age athletes), and a focus on male athletes participating in contact sports (e.g., American football players). Additional shortcomings include a lack of appropriate control groups and potential bias due to a lack of sufficient preinjury assessments.

Large-scale multi-site studies are emerging worldwide in the field of SRC where all sites complete the same pre-injury, post-injury, and long-term assessment to determine the acute, chronic, and long-term changes associated with SRC. One such study, the Concussion, Assessment, Research and Education (CARE) consortium, funded by the National Collegiate Athletic Association (NCAA) and the US Department of Defense (DoD) [89, 90], has a research core focused on using multimodal neuroimaging to determine the acute and chronic effects of SRC on brain structure, function, and metabolism in a large sample of male and female collegiate athletes.

Another big-data approach, Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA), is leveraging already existing data from multiple international sites, allowing for in-depth meta- and mega-analyses [91, 92]. The ENIGMA Brain Injury working group aims to investigate brain trauma occurring across different sub-populations [93, 94], with one of the groups focusing particularly on sport-related brain injury [95].

The collection of prospectively or retrospectively harmonized measures across multiple sites is a significant strength of consortium studies. However, a significant challenge of these studies is the interpretation of neuroimaging data from multiple locations. For example, investigators must correct for the effect of noise produced by different MRI scanners when collecting data across sites, as well as account for differences in testing protocols and variability in participant groups (e.g., collegiate versus recreational athletes).

### 3.3. Towards Personalized Medicine

To date, most neuroimaging studies in SRC are based on group effect findings. To move towards personalized medicine with information relevant to individual profiles of injury, individual baseline neuroimaging and neuropsychological assessments of athletes before they experience an SRC is needed. This approach allows for pre-injury/post-injury comparisons at the individual patient level. In addition, more sophisticated analysis techniques such as normative atlases, based on data from healthy controls, have shown to be promising. One of the first of such studies compared FA measures of patients experiencing chronic symptoms following mTBI, using a normative atlas to detect individual profiles of injury. This approach allows for the quantification and mapping of injury patterns, thereby providing important new information to the treating physician [47].

Because the highest incidence of SRC occurs in male-dominated contact sports, our understanding is largely based on studies of male American football players [96]. However, differences between sports, training, medical care, and lifestyle, as well as biological differences such as biological sex remain largely unknown. In this context, an underrepresented cohort in the study of SRC are female athletes, even though evidence suggests that female athletes are at a higher risk of SRC compared to males competing in sex comparable sports [97–99]. Research also suggests that female athletes may be particularly vulnerable to brain alterations following SRC [100]. These sex differences in SRC risk and outcomes could be due to physiological or hormonal differences between males and females [101–103]. For instance, sex dimorphisms in axonal development have been noted, with axons of females showing greater vulnerability to shear injury [104]. Moreover, increased glucose metabolism and CBF in females may contribute to sex differences in brain function following SRC [105, 106]. There is also evidence that SRC outcomes in females may be linked to the hormonal profile at time of injury (i.e., follicular vs. luteal phase of the menstrual cycle) [107]. Thus, current studies should include a measurement of hormonal profiles with the aim of associating hormone levels at time of injury with clinical outcome.

## 4. SUMMARY

Advanced neuroimaging techniques have the potential of capturing microstructural, metabolic, functional, and perfusion changes that occur acutely and chronically following SRC. To date, the main findings in SRC are regional and whole-brain volumetric alterations as well as reduced cortical thickness, WM microstructural alterations, alterations in neurochemical concentrations, and altered brain function and connectivity. The integration of imaging measures in multimodal approaches, big-data analyses, and steps towards personalized medicine are currently being conducted with the aim to improve our understanding of the nature of SRC, which, in turn, will pave the way toward targeted treatment and prognosis based on individual profiles of injury.

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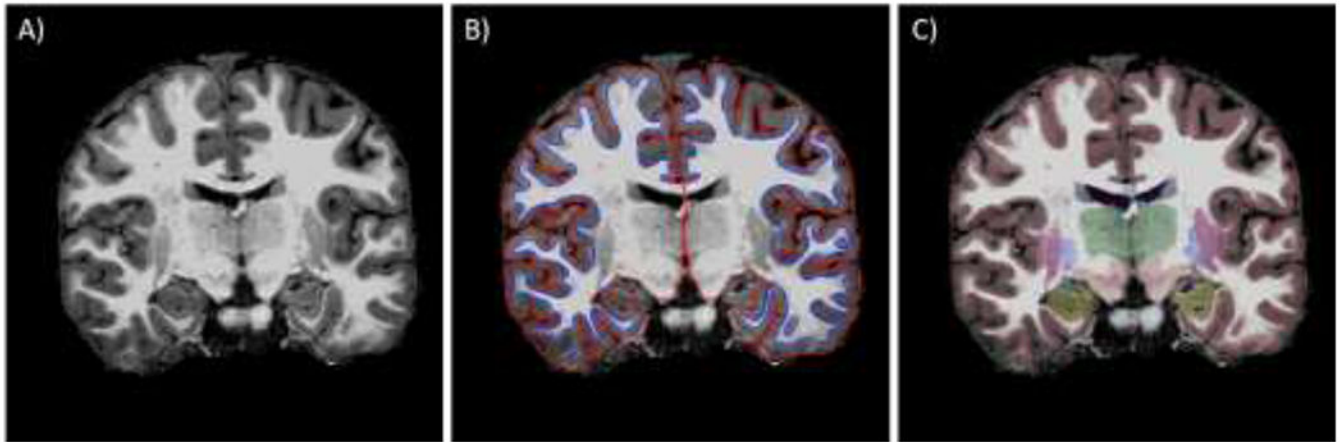
**Figure 1:**
T1-weighted magnetic resonance imaging (MRI): A) Coronal view of T1-weighted MR image of the brain. B) Segmentation using FreeSurfer 7.2: Surface of pial (red) and white matter boundary (blue) superimposed on T1-weighted image. The distance between the two surfaces can then be used to calculate cortical thickness. C) Segmentation using FreeSurfer 7.2: Label maps of subcortical gray matter volumes superimposed on T1-weighted image.
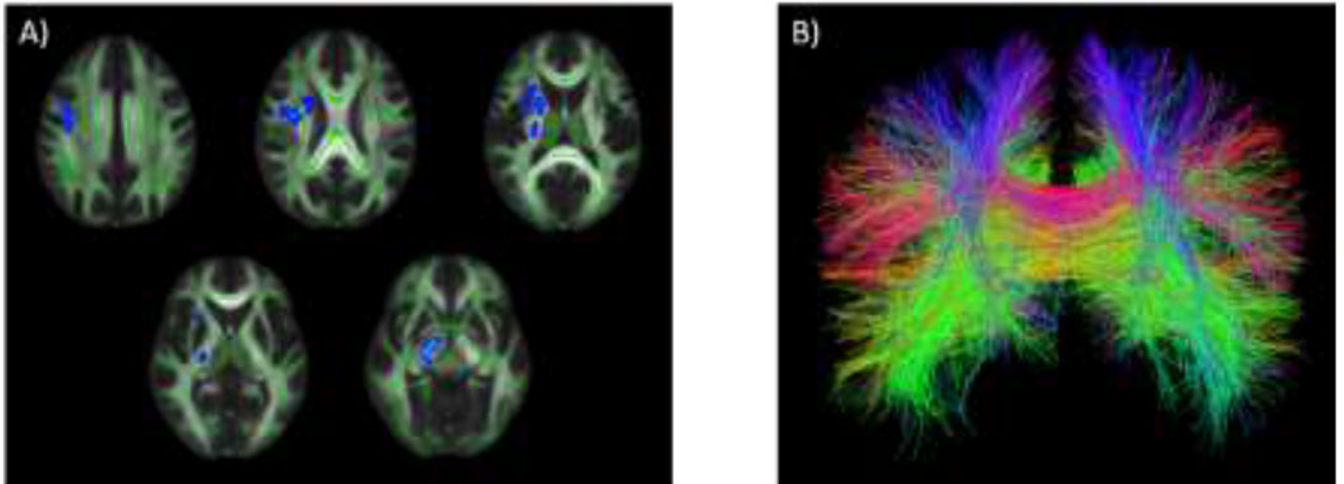
**Figure 2:**
Diffusion tensor imaging (DTI): A) Tract-based spatial statistics (TBSS) may reveal voxels with statistically significant differences in diffusion metrics between groups (blue areas) superimposed on white matter skeleton (green). B) Two-tensor tractography of an individual's white matter. DTI can be used to delineate white matter tracts and to evaluate diffusion metrics of specific white matter tracts (tractography).
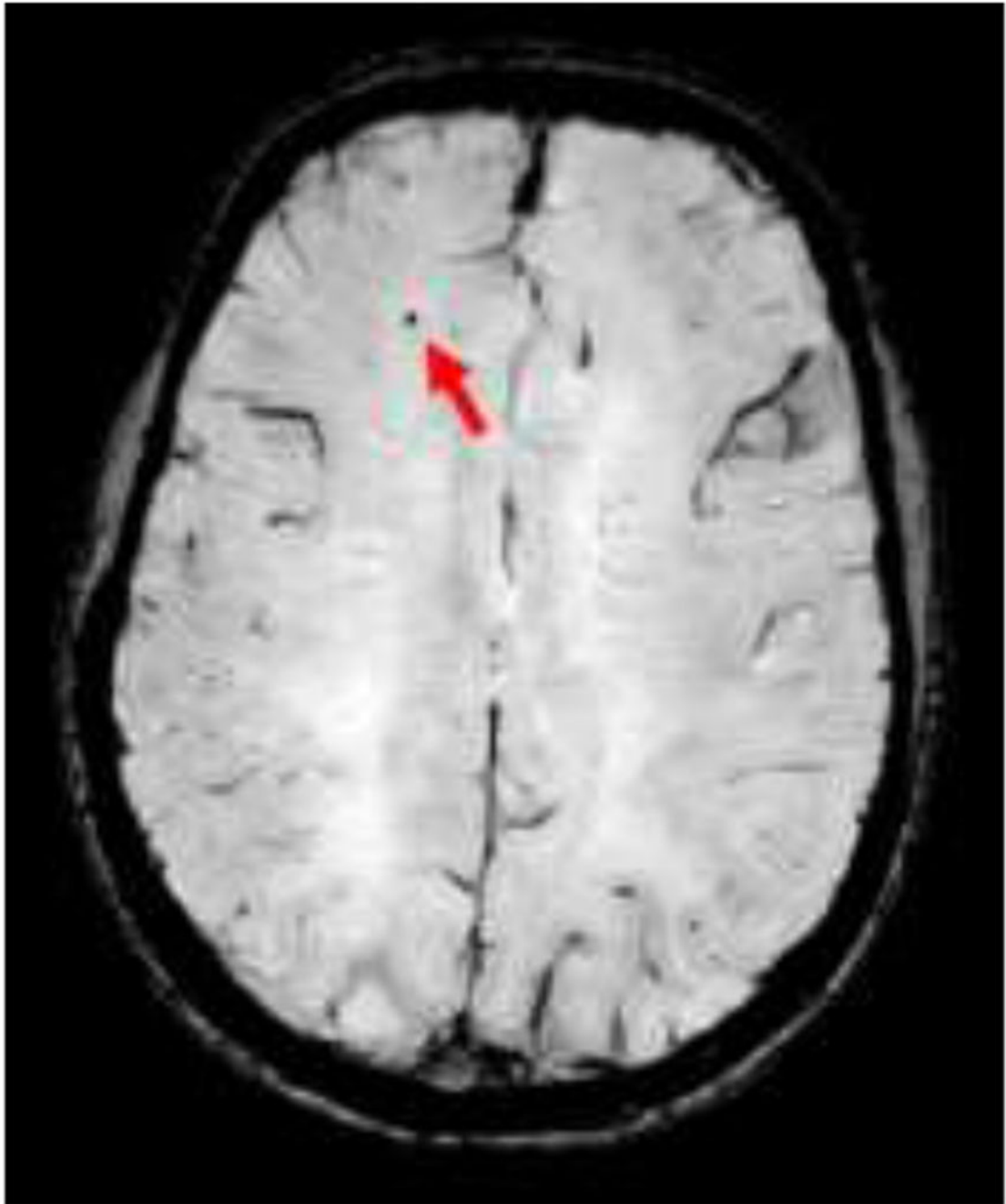
**Figure 3:**
Susceptibility-weighted imaging (SWI): SWI is sensitive to microhemorrhages following brain injury. Microhemorrhages appear as punctate regions of signal drop out with blooming artifact (red arrow).
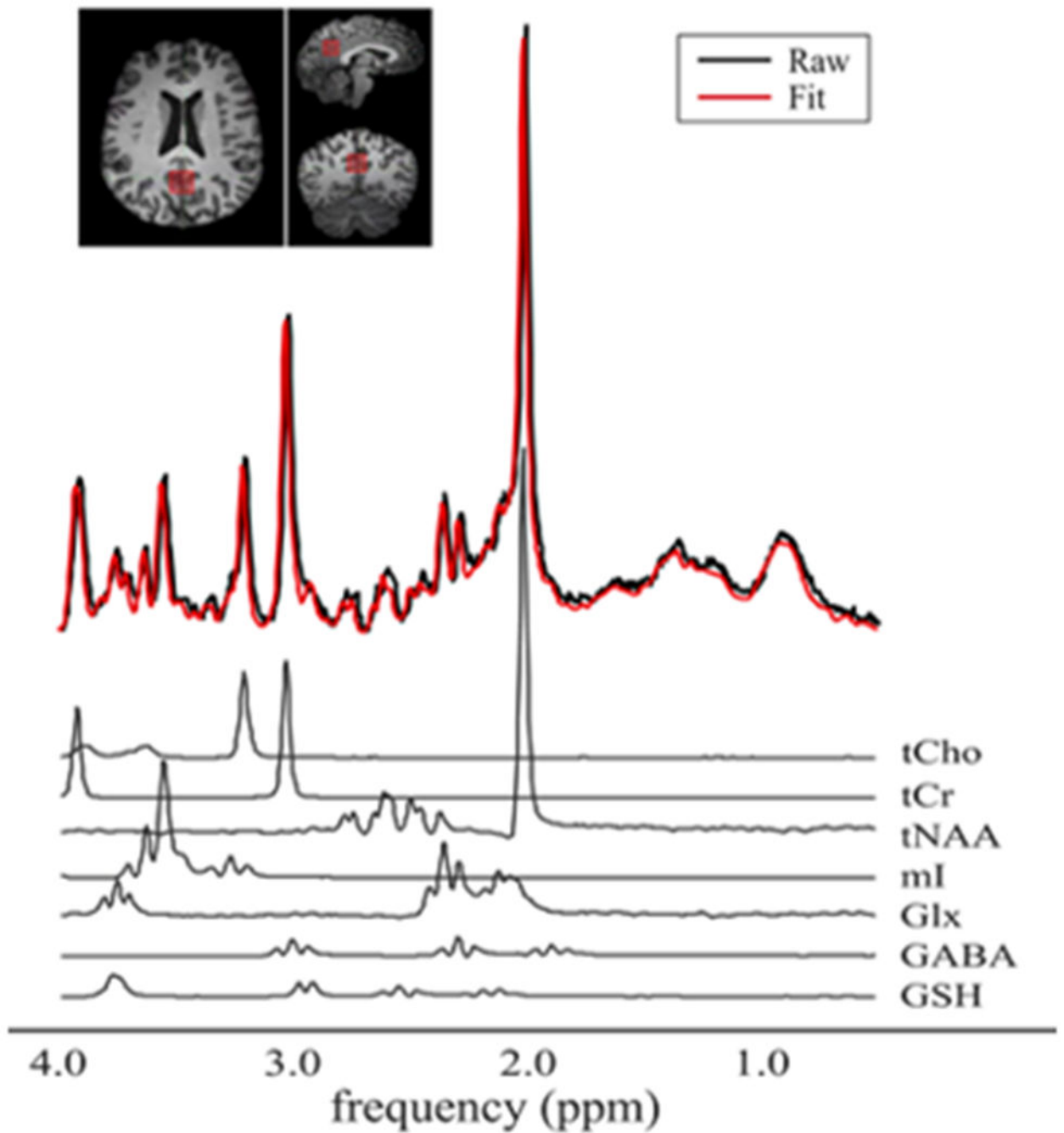
**Figure 4:**

Magnetic resonance spectroscopy (MRS): Representative spectrum obtained from the posterior cingulate gyrus (inset) of a collegiate athlete post-concussion. The spectrum (red) is shown whereby each of the metabolites are fitted to the raw data. The chemical shift indicated by frequency is used to identify each metabolite and quantified by the fitting to produce concentrations or ratios to creatine. tCho: total choline, tCr: total creatine, tNAA: total N-acetyl aspartate, mI: myoinositol, Glx: glutamate and glutamine, GABA: gamma amino butyric acid, GSH: glutathione, ppm: parts per million.
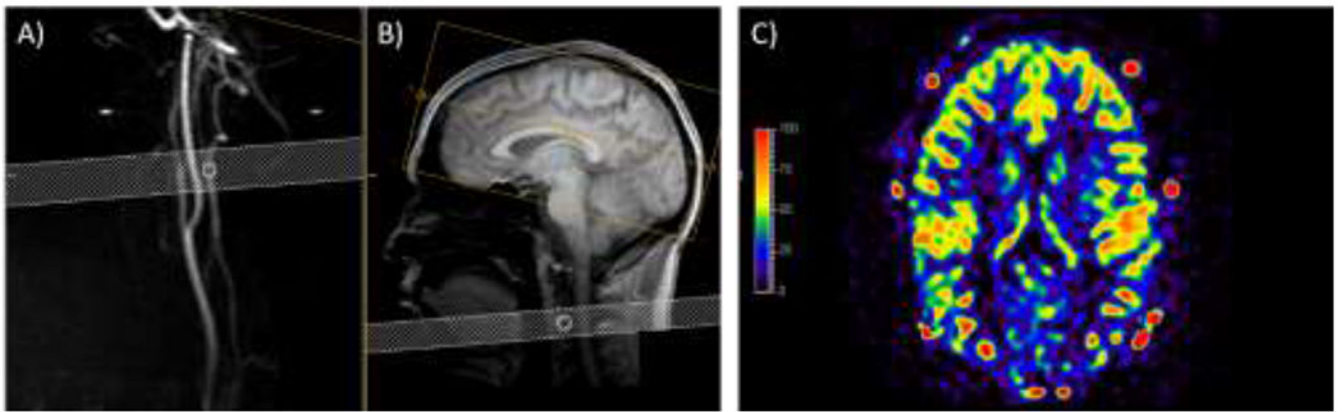
**Figure 5:**
Arterial spin labeling (ASL): A) and B) Labeling plane (hatched area) for labeling blood-water flowing to the brain in internal carotid arteries and vertebral arteries on both sides using radiofrequency inversion, and image acquisition volume (orange box). C) Cerebral blood flow (CBF) map of the brain. Image shown was obtained using pseudo-continuous ASL (pCASL).