Functional Magnetic Resonance Imaging in Sport-Related Concussions

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Introduction

Sport-related concussion (SRC) remains a poorly understood clinical phenomenon, despite the numerous cases in athletics. This can primarily be attributed to the variable and inconsistent definition of concussion (also referred to as mild traumatic brain injury; mTBI), as well as the heterogeneity of the clinical manifestation and prognosis [1, 2]. Spontaneous recovery following a SRC is currently determined by clinical observations and self-reported symptoms rather than objective markers [3]. Findings from standard clinical neuroimaging techniques (computerized tomography [CT] scans; T_1- and T_2-weighted images) are typically negative for the majority of cases [1, 4, 5]. Specifically, two large recent studies of SRC reported positive findings of less than 1% on typical magnetic resonance imaging (MRI) sequences [6, 7].

These null findings on standard neuroimaging initially helped to propagate the view that SRC did not lead to frank neuronal pathology. However, an accumulating body of literature indicates that SRC may result in lingering impairments [for reviews see 8–11], with evidence of neuronal pathology remaining present long after the traditional clinical outcome measures (e.g., balance and cognitive testing)

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have returned to normal [12]. This has resulted in a proliferation of studies that have attempted to define more objective imaging biomarkers of SRC [13, 14]. Given functional MRI's ability to non-invasively perform in vivo measurements during demanding cognitive tasks [15] and to characterize intrinsic neuronal activity [16, 17], dozens of studies have subsequently used this imaging technique to better understand the pathophysiology of concussion.

This chapter first describes the physiological underpinnings of the blood oxygen level-dependent (BOLD) response measured by fMRI and how it can be altered by a concussive insult as well as various analytic considerations. Next, it provides a review of research using evoked fMRI paradigms, functional connectivity (fcMRI), and multimodal imaging studies that included BOLD imaging component to investigate the cognitive and psychological sequelae of SRC. The general benefits and drawbacks of both evoked fMRI and fcMRI studies are then discussed in the context of the SRC literature, including clinical heterogeneity in participant selection criteria, presence of symptoms, variations in scan time post-injury, history of multiple SRC, and sub-concussive head impacts exposure.

fMRI Physiology and Putative Effects of SRC

The ability of fMRI to dynamically measure brain function during higher order cognitive and emotional tasks represents a clear advantage relative to other imaging techniques that are only capable of measuring structural integrity such as susceptibility-weighted imaging (SWI) and diffusion tensor imaging (DTI). Moreover, unlike other functional techniques (e.g., electrophysiological [EEG] and optical imaging), fMRI is capable of probing both superficial cortical and deep gray structures, a powerful advantage given that shear stresses are more likely to accumulate in these regions [18].

The relationship between neurotransmission and resultant hemodynamic activity, referred to as neurovascular coupling, remains an active area of investigation [19]. During intrinsic activity (i.e., at rest, in the absence of evoked activity), the cerebral metabolic rate of glucose (CMR_{glu}), cerebral metabolic rate of oxygen ($CMRO_2$), and cerebral blood flow (CBF) are tightly coupled to maintain homeostasis [20–22]. Following excitatory neuronal transmission, metabolic demands change and energy (glucose) is required to reverse ionic influx that results in depolarization while the excess glutamate needs to be rapidly removed from the synaptic cleft [23–25]. Astrocytes take up excess glutamate, convert it to glutamine, and release vasoactive agents [23], while neurons concurrently release nitric oxide. These events likely contribute to vasodilation and a concomitant increase in CBF. Importantly, there is a decoupling between CBF and oxidative metabolism following neurotransmission, which leads to an excess of oxygenated blood, a decrease in the ratio of deoxyhemoglobin relative to oxyhemoglobin, and a subsequent increase in MR signal due to the differences in magnetic properties between the two forms of hemoglobin [26]. As such, the BOLD response represents an

amalgamation of signals derived from the ratio of oxy-to-deoxyhemoglobin, with contributions of CBF, and cerebral blood volume (CBV) [16, 27, 28].

The shape of the BOLD response is also complex, with the canonical hemodynamic response function (HRF) consisting of two primary components: a positive signal change that peaks approximately 4–6 s post-stimulus onset, and a post-stimulus undershoot (PSU) that peaks 6–10 s after the stimulus ends [29, 30]. The positive phase of the BOLD response has been associated with an increase in CBF and a subsequent change in the ratio of oxy-to-deoxyhemoglobin [29]. The biophysiological origins of the PSU remain more controversial. An early model attributed the PSU to temporal delays between when CBF (earlier response) and CBV (delayed response) returned to baseline levels [29, 31]. More recent work suggests that the duration of the PSU extends beyond the CBV return to baseline [32, 33] and may be driven by increased metabolic demands ($CMRO_2$) following neurotransmission [34–36] or post-synaptic inhibitory activity [37].

SRC can affect the different components of the BOLD response through several individual mechanisms as well as combinatory effects. Foremost, the concussive injury can result in alterations in synchronous neuronal activity, causing downstream effects on BOLD activity by changing the amount of glutamate in the synaptic cleft and the energetic needs of cells following neurotransmission [23, 38]. Direct support for this hypothesis comes from reports of neuronal loss in animal models of fluid percussion injury [39] and abnormal cell signaling [40]. Indirect support comes from findings of altered concentrations of glutamate and glutamine in the semi-acute and chronic stages of concussion during magnetic resonance spectroscopy [41–48].

Concussion has also been shown to directly reduce both CBF and metabolism in pediatric and adult athletes, which could affect the BOLD response [49–52]. Metabolic failure following concussion occurs even in the presence of normal perfusion [53], with an initial decoupling between CBF and CMR_{glu}, followed by a generally reduced cerebral metabolism [54]. Animal models suggest that alterations in CBF and CMR_{glu} may be the longest-lasting physiological deficits of concussion [55], with a handful of studies of athletes suggesting that resolution of CBF abnormalities closely mirrors previous reports from preclinical studies [50–52]. However, one study of adolescents with SRC showed increased CBF in the left insula and left dorsal anterior cingulate cortex (ACC) at 2 weeks post-injury relative to controls, with the elevation in the latter persisting up to 6 weeks post-injury. This increase was associated with more persistent post-concussive physical symptoms [56]. Future research investigating CBF following SRC is needed to better understand its role in recovery and vulnerability of the brain to a second concussive impact.

Brain trauma may also directly affect the structural integrity of the microvasculature. Animal models indicate a semi-acute reduction in capillary number and diameter both at the injury site and distally [57–59], with other studies suggesting that experimental TBI results in alterations to the reactivity of microvessel smooth muscle [60]. This latter effect has been confirmed in studies using fMRI and transcranial Doppler ultrasound to measure cerebral vascular reactivity in the acute phase of SRC in collegiate athletes [61–63].

To complement evoked studies of BOLD activity, researchers are increasingly turning to measures of fcMRI to examine neuronal health following SRC using resting-state scans. Connectivity studies are based on intrinsic neuronal fluctuations that synchronously occur over spatially distributed networks in both animals and humans [16, 64]. The majority (60–80%) of the brain's energy resources is expended to maintain homeostasis and intrinsic neuronal activity likely contributes to this heavy metabolic load [65, 66]. These intrinsic fluctuations in neuronal activity tend to alias to low-frequency fluctuations (0.01–0.10 Hz) in the BOLD signal, and therefore can be measured on any MRI scanner with a conventional echo-planar sequence. Several different properties of intrinsic activity can be examined including, but not limited to, static connectivity, dynamic connectivity, regional homogeneity, and the amplitude of low-frequency fluctuations [67]. Previous research indicates changes in baseline metabolism following a concussive injury [54] as well as an abnormal slow-wave electrophysiological activity during passive mental activity [68, 69], providing the biological relevance for fcMRI as a biomarker of concussion.

fcMRI has several advantages over more traditional evoked fMRI studies. Foremost, using a relatively simple task (i.e., passively maintaining fixation), it is possible to probe the neuronal integrity of the multiple sensory, motor, and cognitive networks that exist in the human brain. This can occur without concerns about practice effects or decreased novelty associated with multiple administrations of a task, potentially confounding the results. Specifically, a now seminal study from Smith and colleagues indicated that intrinsic neuronal activity measured from 36 participants was organized into distinct networks that mirror activity evoked across a variety (30,000 archival data sets) of cognitive challenges [70]. Further, fcMRI eliminates the complex requirements for presenting sensory stimuli and monitoring motor responses (e.g., interfacing with a computer, projecting stimuli, special nonferrous motor response devices), rendering it more feasible for performing clinical scans.

Several limitations need to be considered when analyzing fcMRI data. During resting-state scans, participants are simply asked to either fixate on a visual stimulus or close their eyes for a relatively brief period (~5–10 min). As such, resting-state paradigms have been criticized based on the general lack of control over participants' mental activities and the inability to specify what cognitive tasks participants performed in the scanner [71]. Similarly, athletes with SRC do not perform difficult cognitive tasks during resting-state scans, which may be of greater clinical relevance given that patients tend to report more cognitive problems during difficult tasks in everyday life [15, 72, 73]. Another critique of fcMRI studies is that the various analytic approaches (e.g., seed-based analysis vs. independent component analysis vs. graph theory metrics) that are used to parse network activation can result in different findings during data analyses of the same subjects [67]. Finally, noise has a more direct influence on the correlation coefficient in fcMRI relative to evoked signals [74], which can further complicate the interpretation of group-wise results.

Analytic Considerations for fMRI Studies

Several analytic considerations should be taken into account when performing fMRI research in SRC. Foremost, investigators have traditionally used region of interest (ROI) or voxel-wise analyses to compare the BOLD response between concussed and control athletes. However, these analytic methods assume that the heterogeneous initial injury conditions (e.g., a blow to the left temple, a blow to the jaw with rotational acceleration, a force transmitted to the occipital cortex following an indirect impact), result in a homogeneous pattern of gray matter abnormalities that would survive group-wise statistics [75]. Indeed, to survive group-wise statistics, ROI and voxel-wise analyses assume that there is a high degree of spatial overlap in disruptions to BOLD functioning. Although lesions tend to be more common in the diencephalon, midbrain, limbic circuit, and prefrontal cortex [13, 76], the premise of the spatial overlap assumption is likely to be flawed.

Second, despite the known complexity of the hemodynamic response function (HRF), previous studies have typically estimated a single parameter (typically a beta coefficient) by convolving a canonical HRF, such as a gamma variate or a double-gamma variate function, with known experimental conditions (e.g., onset of a particular trial) to derive a predictor function (e.g., regressor). Importantly, this assumes that the different components of the HRF (positive phase and PSU) and their relationship to each other are unaffected by concussion. Animal models suggest that the acute and sub-acute phases of injury are associated with significant disruptions to metabolism and microvasculature, both of which could impact the HRF [57, 77, 78]. Although basic visual stimuli were associated with an increased volume of activation within the visual cortex in individuals with mild-to-severe TBI, there were no differences in the basic shape of the HRF when compared to controls. Others reported an earlier time-to-peak, a positive magnitude shift in the estimated HRF, and a reduced PSU within the visual cortex and medial temporal cortex for semiacute concussed participants relative to healthy controls [79]. Additional fMRI studies modeling the full time course of a deconvolved HRF are needed to explicitly compare the different components of the HRF as well as their individual sensitivity and specificity to provide additional information about underlying neuropathology that is not available with more standard fMRI analyses (Fig. 11.1).

Third, as previously stated, the BOLD signal is temporally sluggish and represents an indirect measure of neuronal activity, resulting from a complex mixture of many underlying physiological processes. As most of these physiological processes may be affected by trauma, it is unfeasible to "isolate" a single biological mechanism that underlies an abnormal BOLD response when fMRI is collected alone [80]. This, along with the heterogeneity of SRC, makes the use of multimodal imaging beneficial to understand biological processes, potential covariates, and changes over time indexed with imaging techniques through the confirmation of multiple sources of information [81]. Indeed, defining recovery based on any single variable (i.e., symptom-free) or a single imaging modality potentially risks a premature

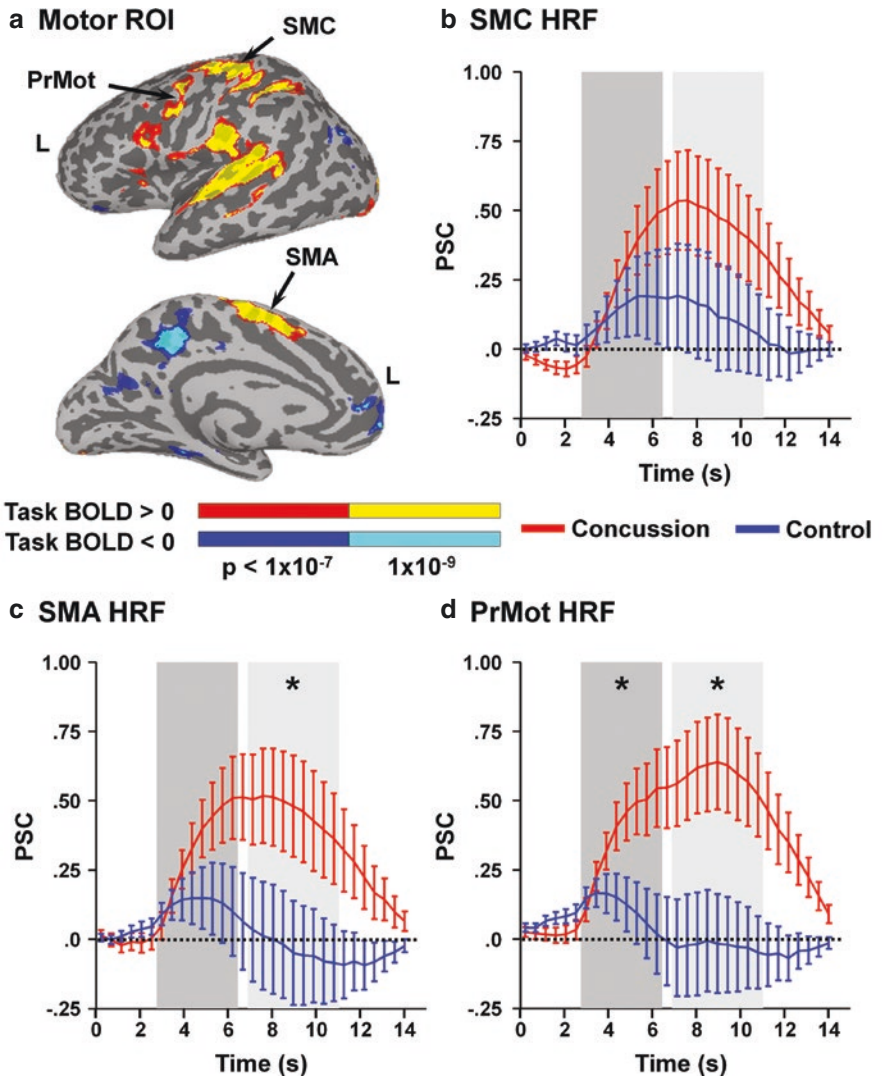

Fig. 11.1 Evoked BOLD during a multisensory cognitive control task demonstrating the importance of examining the entire hemodynamic response function (HRF) for abnormalities. Panel (**a**) depicts a priori regions of interest (ROI) within motor circuitry including the left sensorimotor cortex (SMC), bilateral supplementary motor area (SMA), and left premotor area (PrMot). ROI were derived from a contrast comparing the active trials relative to baseline, collapsing across both concussion and control groups. Inflated views of increased activation relative to baseline are denoted in warm colors for the lateral medial portions of the left (L) hemisphere, whereas decreased activation is denoted in cool colors. Panels (**b**), (**c**), and (**d**) present the percent signal change (PSC) values for the entire BOLD HRF within these ROI. Shaded bars indicate the expected peak (dark gray; 2.76–6.44 s) and inhibitory (light gray; 9.90–11.04 s) phases of the HRF during a stimulus cue presentation, with asterisks denoting significant group differences (concussion group [red line] > control group [blue line]) within a phase. Error bars represent the standard error to the mean. (Data adapted from Mayer et al. [209])

return-to-play decision that may put athletes at risk for worse outcomes, should a repeat, temporally proximate SRC occur.

Fourth, fMRI signals are critically linked to CBF and the dysregulation of autonomic control of neurovascular coupling. Therefore, investigators may calibrate the BOLD signal with arterial spin labeling (ASL) measures of CBF [76, 82–85]. Hypercapnic normalization is another frequently used technique that is achieved through the administration of CO_2, a voluntary breath-hold scan, or more regularized breathing [86, 87]. This method assumes that hypercapnia has a limited effect on neural activity and oxygen metabolism and, thus, primarily measures CBF and/or CVR [88, 89]. Previous results suggest that the hypercapnia method accounts for variability in subject vasculature and physiology differences during task performance, as well as changes in magnetic field strength [63, 90–92]. In recent years, several studies of concussions have observed perturbations in CVR in acute and chronic phases of injury [85, 93–96], providing support for calibrating the BOLD signal. SRC has also been associated with greater reductions in BOLD activity during the early phase of a respiratory challenge task, primarily in frontal and prefrontal areas, whereas no significant effects on resting global CBF were observed [61]. Collectively, these results highlight the importance of examining neurovascular response to physiological stressors after a SRC in conjunction with standard BOLD measurements.

Review of the Current Literature on Functional Imaging and SRC

Review of Evoked fMRI Studies

SRC has been associated with acute and chronic impairments in executive functions/working memory, attention, and memory [8, 97]. fMRI can be useful in examining the integrity of brain regions or networks underlying these cognitive changes. Abnormal brain activation patterns during working memory tasks have been consistently reported in the SRC literature. Seminal studies using the N-back task suggested a complex relationship between cognitive load and functional activation at 1 month post-injury, with hyperactivation observed within the dorsolateral prefrontal cortex (DLPFC) and lateral parietal cortex during moderate load, whereas hypoactivation was observed during low and high loads compared to healthy controls [98, 99]. More recently, a longitudinal study of university athletes has indicated that hyperactivation of the inferior parietal lobe in concussed when compared to the control group persisted 2 months post-injury, despite no differences in neurobehavioral performance [100]. Hypoactivation of different brain regions was also observed in two studies using similar working memory tasks. Specifically, hypoactivation was observed within the DLPFC of athletes with persistent post-concussion symptoms [101], and within the ventral ACC, medial temporal gyri, and the occipital cortex of both recovered and symptomatic athletes [85]. Overall, these studies

provide support for changes in neuronal activity of brain regions implicated in working memory following SRC.

Hyperactivation has been reported during other cognitive and motor tasks. Specifically, it has been observed within the DLPFC, parietal cortex, and hippocampus during a virtual reality spatial memory task in recently concussed, yet asymptomatic athletes, relative to non-concussed controls [102]. Similarly, using a sensorimotor coordination and memory task, hyperactivation of frontoparietal regions was observed in recently concussed intercollegiate football players, even in the absence of differences in neurobehavioral performance [103]. Additionally, the increased BOLD response has been documented in several brain regions during oculomotor tasks, ranging from the acute to the chronic phase of SRC, even in the absence of cognitive alterations [104–106]. The degree of hyperactivation may be indicative of a prolonged recovery profile in athletes, particularly when accompanied with sparse and diffuse activation patterns [107], and suggests the presence of compensatory neural mechanisms following SRC [103].

Associations between self-reported symptom intensity and differential activation patterns within several regions, including the working memory and attention networks, have been shown in athletes following SRC [101, 108, 109]. Specifically, symptom intensity in concussed athletes was associated with hyperactivation of frontal and parietal cortical regions within the first week of injury [109]. In contrast, a series of studies from Chen and colleagues found an association between persistent post-concussion symptoms and hypoactivation of prefrontal regions during visual and verbal working memory tasks [101, 108]. They also reported more diffuse activation patterns in the symptomatic athletes relative to controls [101], with activation peaks outside the ROIs [108]. Together, these results indicate that persistent symptoms may be predictors of changes in frontal and parietal brain activation in the chronic phase of injury.

The possible effects of a history of multiple SRC and repetitive sub-concussive impacts on BOLD response are still not well described, with a few published studies yielding variable results. Evidence of hypoactivation of left hemispheric language regions during a verbal learning memory task was observed in former high school athletes with a history of multiple SRC when compared to former athletes who never sustained a concussion [110]. Yet, null results have also been reported in active high school and college athletes with a history of SRC [111, 112]. Thus, more work is needed to fully understand the contribution of multiple concussive injuries on the BOLD response. A single study have examined the effect of head impact exposure to the BOLD response. High school football athletes with embedded sensors in the helmet to tally the number of head hits throughout the season were scanned pre- and post-season. Results indicated that, in the absence of a SRC, athletes with higher numbers of head collision events to the top front of the head, directly above the DLPFC, showed hypoactivation within the DLPFC, accompanied by cognitive impairments on an N-back task [113].

Review of Functional Connectivity Studies

Several fcMRI studies have focused on the default-mode network (DMN), which typically includes medial and lateral parietal, medial prefrontal, and medial and lateral temporal cortices [17]. The DMN is believed to mediate a variety of mental activities such as episodic memory recall and future-oriented thought processes that occur during periods of unconstrained mental activity and therefore is typically associated with deactivation during evoked tasks [114, 115]. SRC studies of the DMN connectivity in the acute and sub-acute phases of injury have shown inconsistent results, with one study showing hyperconnectivity [116], while another study did not find differences between concussed and controls unless participants underwent a physical stress challenge [117]. There is also evidence of changes in resting-state networks from playing a single season of football in children and adolescents [118], with the delta power spectrum of the DMN providing a good classification accuracy between youth athletes in the low and the high head impacts exposure group [119].

Multiple fcMRI studies using whole-brain analysis have documented acute [120], sub-acute [121, 122], and persistent [123–125] differences between concussed athletes and controls following SRC in additional networks outside the DMN, including areas underlying memory, attention, and executive functions. Differences in regional homogeneity (ReHo), a metric of local connectivity, have also been observed at 1 month post-concussion, but not at more acute time points in a large cohort of collegiate athletes relative to healthy contact sports athletes [126]. Similar results were found in a study of network-based statistics and average nodal strength [127]. In contrast, alterations of ReHo in the middle and superior frontal gyri, areas associated with the DMN, have been observed in concussed athletes 24 h post-injury [128]. A recent study indicated acute elevations in ReHo in frontal regions that are typically associated with the DMN, whereas other resting-state metrics, such as average nodal strength, and the relative amplitude of slow oscillations of resting-state fMRI (fractional amplitude of low-frequency fluctuations; fALFF), did not show differences between concussed athletes and controls [67]. Moreover, a history of multiple SRC and exposure to repetitive, yet sub-concussive head impacts from contact sports participation has been associated with fcMRI. For instance, increased connectivity between the areas in frontal cortices, hippocampus, and cingulate cortices was observed in football players with a history of multiple SRC relative to healthy controls without football or concussion history [129].

All of these studies analyzed fcMRI from a static connectivity perspective that computes the average functional coupling among the brain regions across a scan length. More recent studies have used dynamic functional analysis, where the focus is on the dynamic evolution of fcMRI during the entire scan [130, 131]. Such an approach enables the extraction of additional information regarding abnormalities in neural network communication, which may be complementary to findings from static connectivity analyses (Fig. 11.2). This approach was used in two studies of SRC. One study showed that at time of return to play, concussed athletes with both higher symptom intensity and prolonged recovery had altered scale-free dynamics

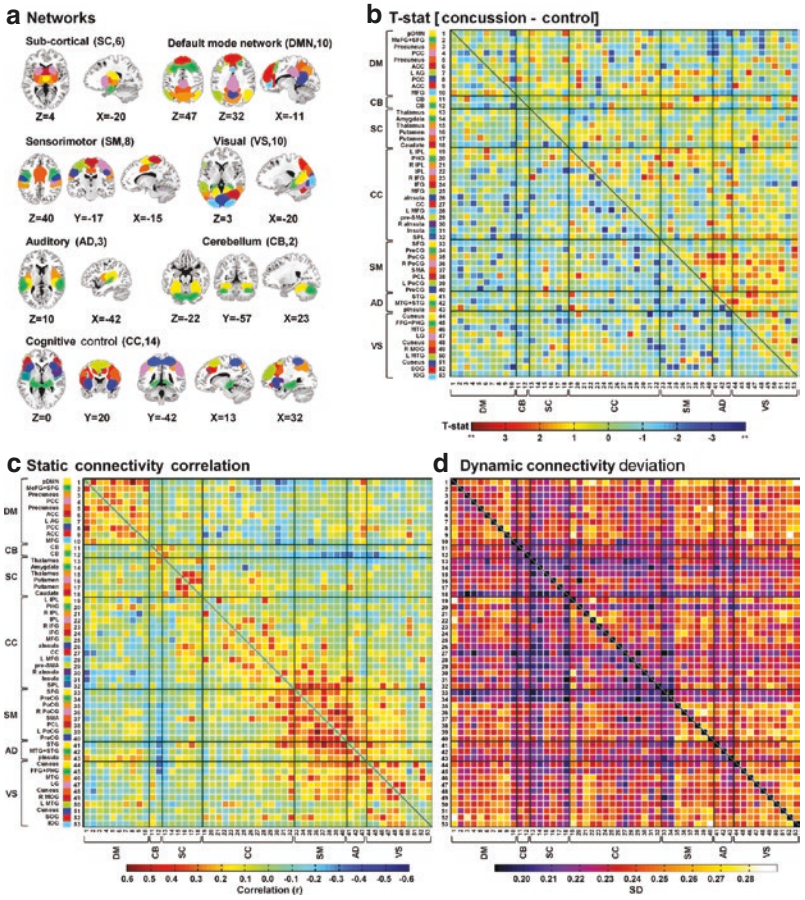

Fig. 11.2 Exemplar data depicting both static and dynamic functional connectivity in cohorts of adult mTBI patients and matched healthy controls. Panel (**a**) depicts the 53 intrinsic connectivity networks (ICN) derived across both mTBI and control participants following group independent component analysis. Individual ICN are clustered into seven overarching networks: subcortical (SC; 6 ICN); default mode network (DMN; 10 ICN); sensorimotor (SM; 8 ICN); visual (VS; 10 ICN); auditory (AD; 3 ICN); cerebellum (CB; 2 ICN); and cognitive control (CC; 14 ICN). Sagittal (X), coronal (Y), and axial (Z) slice locations are presented according to the Montreal Neurological Institute system. The color-coding for each ICN within each of the seven major networks is presented within Panel (**b**), as well as t-statistics representing independent sample comparisons of static (above diagonal) and dynamic (below diagonal) functional connectivity (fcMRI) across the two groups. Individual labels include: L, left; R, right; pDMN, posterior default mode network; MeFG, medial frontal gyrus; SFG, superior frontal gyrus; PCC, posterior cingulate cortex; ACC, anterior cingulate cortex; AG, angular gyrus; MFG, middle frontal gyrus; IPL, inferior parietal lobule; PHG, parahippocampal gyrus; IFG, inferior frontal gyrus; aInsula, anterior insula; CC, cingulate cortex; pre-SMA, pre-supplementary motor area; SPL, superior parietal lobule; PreCG, precentral gyrus; PoCG, postcentral gyrus; SMA, supplementary motor area; PCL, paracentral lobule; STG, superior temporal gyrus; MTG, middle temporal gyrus; pInsula, posterior insula; FFG, fusiform gyrus; LG, lingual gyrus; MOG, middle occipital gyrus; SOG, superior occipital gyrus; IOG, inferior occipital gyrus. ** indicates different upper/lower t-limits (3.7 for static; 3.9 for dynamic). Panel (**c**) presents the pair-wise Pearson correlation values (r), while panel (**d**) presents the standard deviation (SD) of the pair-wise Pearson correlation values across the 126 sliding windows, for concussion (under diagonal) and control groups (above diagonal). (Data adapted from Mayer et al. [210])

relative to control athletes [132]. Further, differences in dwell times for multiple connectivity states were also observed between former athletes with a history of multiple SRC and healthy controls that did not report a SRC [133]. Thus, this dynamic connectivity may provide an additional avenue to study changes related to SRC and additional studies are needed.

In summary, multiple fcMRI metrics have shown sensitivity to SRC, with studies reporting abnormalities in static and dynamic functional connectivity at various time points post-concussion, such as acutely and at time of return to play, with conflicting evidence of prolonged abnormalities that may be explained by the use of different connectivity metrics. Based on these studies, fcMRI appears to be well poised for interrogating connectivity within all major structures and networks of the brain following SRC.

Added Value of Multimodal Imaging

Multimodal MRI studies have indicated concomitant alterations of perfusion, function, chemistry, and brain microstructure at various time points after SRC [134–138]. Recent studies in SRC suggested that group-based differences in BOLD activity may be driven by a mixed effect from vascular and metabolic origins, providing support for the use of multimodal MRI imaging [85, 139]. Specifically, concomitant alterations of DMN connectivity and increased cerebrovascular reactivity (CVR) (Fig. 11.3), a measure of vasculature integrity, have been observed in college athletes a few months post-concussion when compared to healthy controls [139]. Further, a recent study using a working memory paradigm found both reduced BOLD activation and reduced CVR in the ventral ACC and the medial temporal gyri in concussed athletes 4 months post-concussion relative to the control group, supporting the idea that concussion is associated with both vascular and neural dysfunction [85]. The combination of evoked fMRI and event-related potentials (ERPs) can also add valuable information on brain function, as it can afford both high spatial resolution and temporal fidelity. Following a concussion, the decreased BOLD signal has been associated with abnormal ERPs [140, 141], again supporting that alterations in vascular and neuronal response may be simultaneous.

Finally, a series of multimodal studies of SRC by Churchill and colleagues have highlighted the variability among imaging indices that is consistent with the heterogeneous nature of SRC [134, 142, 143], with time-varying changes in diffusion, function, and CBF being observed. Interestingly, the changes were more prominent when the symptoms are most severe, and the recovery was slow [134, 142].

Psychiatric Sequelae of SRC and fMRI

Functional MRI can also help better understand the underlying neural correlates of the development and recovery of psychiatric symptoms in concussed athletes [144]. The relationship between SRC and psychiatric sequelae has been well documented

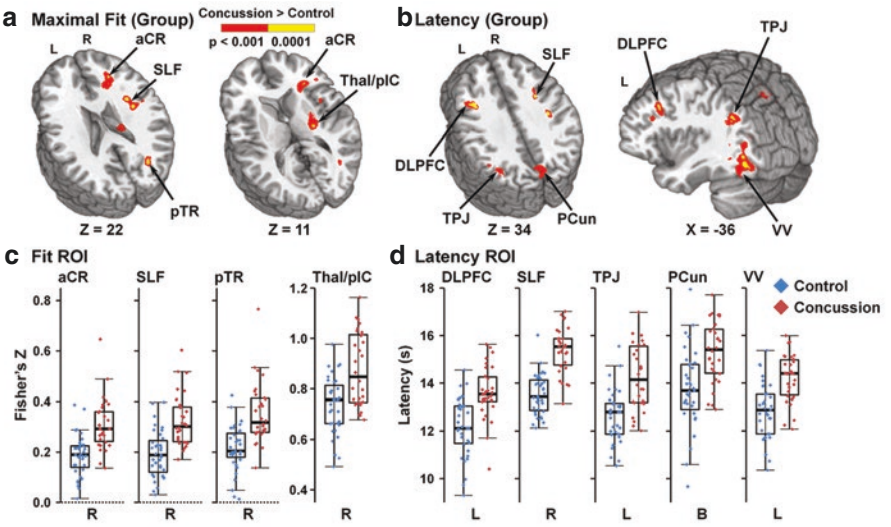

Fig. 11.3 Data depicting the use of BOLD imaging to detect changes in cerebral vascular reactivity (CVR) in a cohort of pediatric concussion patients and controls. Panel (**a**) depicts a main effect of group for increased maximal voxel-wise fit to a subject-specific, variably time-delayed $ETCO_2$ regressor matrix (red: $p < 0.001$; yellow: $p < 0.0001$) for concussed participants relative to healthy controls during a hypercapnia challenge. Displayed regions of interest (ROI) include the right (R) anterior corona radiata (aCR), R superior longitudinal fasciculus (SLF), posterior thalamic radiation (pTR), and R thalamus and posterior internal capsule (Thal/pIC). Similarly, Panel (**b**) depicts a main effect of group for increased latency to maximal voxel-wise fit in the $ETCO_2$ matrix in RBOI that include the left (L) dorsolateral prefrontal cortex (DLPFC), R SLF, L temporoparietal junction (TPJ), bilateral (B) precuneus (PCun), and L ventral visual stream (VV). Coordinates for select axial (Z) and sagittal (X) slices are given according to the Talairach atlas. Panels (**c**) and (**d**) display box and scatter plots of the Fisher's Z (maximal fit; **c**) and latency (**d**) for select ROI region in each group (concussion: red; controls; blue). (Data adapted from Dodd et al. [94])

[128, 145–147], showing elevated symptoms acutely, with partial recovery of psychiatric symptoms within a month of the injury [148, 149]. The potential for long-term psychiatric consequences of SRC remains an important area of study, as a higher incidence of psychiatric symptoms has been shown in retired, professional athletes with a history of SRC compared to those with no reported concussion [150–154]. However, prospective, longitudinal studies are needed to better understand potential moderators and mediators of this relationship.

While premorbid psychopathology and psychosocial changes related to SRC (e.g., loss of position, lack of support from the team) can result in prolonged psychiatric symptoms [2, 144, 145, 155], biologically based disruptions of the emotional processing neural networks can also contribute [148]. Mesocorticolimbic and frontal-subcortical networks and/or their white matter connections may be directly or indirectly affected through shearing forces or inflammation [13, 156]. Additionally, the stress response as a result of SRC engages the sympathetic nervous system and

the hypothalamic-pituitary-adrenal (HPA) axis [82, 83, 157–159], resulting in further dysregulation of emotional processing networks [160–162].

fMRI studies of SRC have elucidated brain regions and networks that may be implicated in psychiatric disturbance [128, 148, 163, 164]. Specifically, a longitudinal study showed decreased fcMRI between the DMN and attention regions was observed at 1 day post-injury in collegiate athletes, with improvement at 1 month post-injury above levels in the non-injured, control group, suggesting the presence of compensatory neural response to injury [148]. In the more chronic phase of injury, whole-brain analysis revealed that concussed athletes with depressive symptoms showed less activation of the prefrontal and limbic regions during a working memory task relative to non-depressed concussed athletes and controls [163].

Overall, these fMRI studies have shown that prefrontal regions, limbic regions, and the DMN are some of the most susceptible regions to SRC, areas that are also implicated in increased psychological symptoms [128, 148, 163, 164]. DMN abnormalities have been theorized to be associated with rumination and self-referential thinking, which may link DMN alterations to psychological symptoms [128, 148]. However, causal relationships remain unclear and are likely multifactorial [164].

Overarching Issues in fMRI Research in SRC

As alluded to in the preceding sections, several potential confounds need to be carefully considered when performing and evaluating fMRI studies of SRC. Some common clinical confounds include injury-related pain (orthopedic), fatigue, poor effort, other comorbid medical and psychiatric conditions, and the presence of prescribed medications (e.g., narcotics or sedatives) that may alter neurovascular coupling or complicate the interpretation of BOLD response [165–167]. Some non-specific somatic (e.g., pain and fatigue) or medication confounds can be reduced or eliminated by recruiting orthopedically injured patients as control participants [168–170]. Some psychosocial factors may be specific to athletes [171], thus including healthy athletes as the control group may be a better comparison than community controls. Additionally, it is impossible to disambiguate whether differences in BOLD response result from trauma-induced alterations in neurophysiology, from task-performance differences (e.g., accuracy or reaction time), or a combination of these effects. Interpretation of data from task-based studies is also frequently complicated by learning and/or practice effects, which are minimal during passive rest, providing support for the usage of fcMRI [172–174].

Developing methods for improving the nosology of SRC and understanding of symptom trajectory will be critical for coalescing disparate neuroimaging findings. Currently, there is no single definition or set of diagnostic criteria for SRC [2, 175] or clinical recovery [176]. For example, an athlete who was only dazed following a blow to the head and an athlete who was unconscious for 20 min with a large subdural hematoma can both be classified as having suffered from SRC under current nosology [1, 177]. Additionally, differences between SRC and non-SRC may exist,

which can complicate the interpretation of results of studies with mixed samples. While the acute clinical presentation is similar [97, 178], a recent fcMRI study revealed reduced connectivity in the anterior cingulate cortex and posterior cingulate cortex hubs of the DMN in athletes when compared to non-athletes following a concussion [179]. Other groups have observed a decreased fcMRI in athletes that could result from a history of multiple SRC or high exposure to repetitive, subconcussive head impacts [118, 180, 181]. Based on these studies, athletes appear to be a different population because of the inherent risks associated with sports participation.

Furthermore, the nature of SRC itself is heterogeneous, given the variety of clinical features, anatomical location, mechanism of injury, and recovery trajectories [81, 175, 182–184]. Heterogeneity can also arise in SRC as different sports, player positions, and skill levels can be associated with different injury characteristics [175] and, therefore, with potential differences in neuroimaging. For instance, football has been associated with translational forces while boxing has been associated with greater rotational forces which may put boxers at a greater risk for traumatic axonal injuries [175, 185]. Further, a recent study of cognitively unimpaired former collegiate and professional football players suggests that career duration and primary playing position seem to modify the effects of a history of multiple SRC on white matter structure and neural recruitment [186].

fMRI data collection is costly and recruitment of SRC patients who meet strict inclusion criteria (e.g., homogeneous in both injury severity and time since injury with no pre-existing neurological or psychiatric disorders) is challenging. The combination of these factors has resulted in another methodological challenge, namely the utilization of small sample sizes despite the inherently low signal-to-noise ratio of fMRI [38, 187]. Specifically, the majority of fMRI studies following SRC have been reported with sample sizes just at or below commonly accepted recommendations based on statistical power. As a result, these studies may likely be underpowered, suffering from low positive predictive power, and providing poor estimates of the true effect size [187, 188] and potentially contributing to conflicting findings. To combat the problem of small sample sizes, funding agencies have recently developed standard clinical definitions, common data elements, and informational platforms for creating community-wide data-sharing initiatives (e.g., Federal Interagency Traumatic Brain Injury Research; FITBIR). These efforts should accelerate research in this critical area by permitting the pooling of data for meta-analyses, such as recently occurred with the ENIGMA [189] and the NCAA-DoD CARE consortium [67] initiatives.

Finally, while fMRI itself can provide objective information about SRC, fMRI studies may still use self-report measures to establish a diagnosis and gain information on post-concussion symptoms. Importantly, symptom self-report may vary as a function of the sample with SRC populations being associated with the risk of under-reporting neurobehavioral symptoms to return to play faster [190–193], whereas other concussion samples may over-report symptoms [194, 195], especially in the presence of potential financial compensation [196]. Multiple sociological barriers may account for the under-reporting of symptoms ranging from lack of

education regarding the seriousness of SRC for parents, players, and coaches, hesitancy to report symptoms that do not result in significant pain, desire not to be removed from play, and stigmatization of concussion as an invisible, non-real injury [190, 193, 197, 198]. The peer pressure to continue to play and not report an injury is particularly important in vulnerable populations such as children who may not comprehend and underestimate the risks involved in continued participation, and in low socioeconomic areas where participation is perceived as a path to future benefit [199–201]. Additional pressures are on the coaching staff who may feel pressured to win and underestimate the risk of returning a player to the field prematurely [202–204].

Conclusion

Sport-related concussion presents diagnostic and prognostic challenges for many reasons, especially because of the heterogeneity of clinical presentation and mechanism of injury. The past two decades were marked by a collective scientific effort to identify and develop biomarkers of SRC, which propelled research using advanced imaging measures. fMRI provides researchers with the ability to non-invasively measure the functional integrity and modulation of neuronal circuitry following SRC at relatively high spatial resolution. Evidence of alterations of brain activation has been observed in the acute, sub-acute, and chronic phases of injury, with the intensity of post-concussion symptoms and the number of remote SRC being associated with more alterations. Further, research shows group differences in both evoked and resting-state activity were observed for concussed athletes who were asymptomatic and declared ready to return to play when compared to controls.

An important feature of SRC is the potential for repeated concussions over the course of an athletic event, a season, or a lifetime. Regardless of the sociological factors, under-reporting of symptoms can lead to premature return-to-play decisions and put players at risk for exacerbated outcomes related to the occurrence of multiple SRC [154, 205–207]. In athletes, the body of literature presented herein suggests that neuronal recovery may lag behind the recovery of behavioral and cognitive symptoms, emphasizing the need for objective biomarkers of when it is truly safe to return to play [12]. Although fMRI studies have provided insights into the brain dysfunctions stemming from SRC, the use of multiple metrics and multimodal imaging will be necessary to fully grasp the multifaceted and time-dependent pattern of neuropathology due to the neurometabolic cascade of concussion [54, 208]. This will be especially true as future studies may attempt to utilize fMRI to aid in the premortem diagnosis of chronic traumatic encephalopathy, a neurodegenerative disorder that has been associated with a history of multiple SRC and high exposure to sub-concussive insults (CTE).

In summary, SRC is associated with a complex, multifaceted, and time-dependent pattern of pathologies due to the neurometabolic cascade of concussion [2, 55]. Although advanced neuroimaging is still in its infancy for detecting pathophysiological markers of trauma, fMRI has helped to reshape our understanding of the

neuropathological effects associated with SRC. Given the heterogeneity inherently associated with concussion research [14, 175], well-powered studies with more homogeneous inclusion criteria (time post-injury, injury severity, symptomatic status, history of SRC, sports, and position) are critically needed for truly understanding the underlying pathophysiology and natural recovery course of the injury.

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