Cerebral Hemodynamic Influences in Task-Related Functional Magnetic Resonance Imaging and Near-Infrared Spectroscopy in Acute Sport-Related Concussion: A Review

Mario Forcione 1,2,*, Claudio Colonnese 3,4 and Antonio Belli 1,2

1 National Institute for Health Research Surgical Reconstruction and Microbiology Research Centre (NIHR SRMRC), University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital Birmingham (Heritage Building), Birmingham B15 2TH, UK; a.belli@bham.ac.uk
2 Neuroscience & Ophthalmology Research Group, Institute of Inflammation & Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, UK
3 Neuroradiology Section, Department of Human Neuroscience, Sapienza University of Rome, Rome 00185, Italy; claudio.colonnese@uniroma1.it
4 Mediterranean Neurological Institute “Neuromed” Scientific Institute of Hospitalization and Care (IRCCS), Pozzilli (IS) 86077, Italy
* Correspondence: mxf610@student.birmingham.ac.uk; Tel.: +44-012-137-14232

Received: 28 February 2018; Accepted: 13 April 2018; Published: 17 April 2018

Abstract: One of the challenges of managing athletes with sport-related concussion (SRC) is guiding them to a safe return to play. A potential biomarker for use in the clinical assessment of recovery is the analysis of brain activation patterns during task-related functional Magnetic Resonance Imaging (fMRI). However, fMRI studies have provided conflicting results regarding what is pathological. An element that can contribute to this disagreement are hemodynamic impairments of the brain that follow a concussion. A functional neuroimaging technique based on the optical properties of brain tissue—called functional near-infrared spectroscopy (fNIRS)—can be used to evaluate SRC athletes, partially taking into consideration these brain hemodynamic impairments. However, so far, fNIRS has not been extensively used in concussion. In this critical review, there is a description of the main fMRI results involving the neocortex in acutely concussed patients, the influences of hemodynamic impairments on fMRI and fNIRS and the advantages and disadvantages of fNIRS to limit this influence.

Keywords: task-related functional magnetic resonance imaging; BOLD signal; fMRI; near-infrared spectroscopy; NIRS; diffuse optical tomography; sport-related concussion; gradual return to play; brain hemodynamic; cerebral blood flow

1. Introduction

Sport-related concussion (SRC) is a mild traumatic brain injury (mTBI) characterized by functional impairment of the brain without structural abnormalities that can be detected with standard neuroimaging such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) [1].

Every year, in the United States of America, between 1.6 and 3.8 million contact-sport participants are affected by SRC with the highest number in American Football [2]. These numbers could be higher as concussion is often underreported, underreported or denied by players [3,4].

The pathogenesis of concussion is a violent shake of the brain inside the skull which causes a broad neuronal excitation and a subsequent neurometabolic cascade [5]. A second impact during...
this metabolic impairment can cause disproportionate damage to the brain [6,7]. One of the clinical challenges of SRC is managing a safe return to play, which would avoid a second impact during the window of brain vulnerability.

Currently, the return to play is based on symptomatic resolution [1,8]. However, this approach has been questioned as it may expose athletes to further head contact when not fully recovered. As a matter of fact, established neurocognitive tests (e.g., The Immediate Post-Concussion Assessment and Cognitive Testing ImPACT® Applications Inc.) have demonstrated reaction time and memory impairment in symptom-free concussed athletes [9–12]. Likewise, Slobounov et al. reported balance impairments in clinically symptom-free athletes following SRC [13,14]. Vagnozzi et al. using Magnetic Resonance Spectroscopy, reported the persistence of a pathological concentration of metabolites in the neurons (e.g., low levels of N-acetyl-aspartate) after symptom resolution [15]. In view of this and the phenomenon of athletes underreporting, return to play criteria based on symptoms may lead clinicians to overestimate the speed of recovery. Furthermore, the risk of further concussions is higher in formerly concussed players than in non-concussed players [16]. This may be due to the persistence of a slow reaction time that makes it difficult to quickly process the game and modify motor strategies to avoid or mitigate significant impacts.

Studies have been undertaken to find objective biomarkers to assess athletes with SRC [17,18]. One of the most tested neuroimaging techniques is task-related functional Magnetic Resonance Imaging (fMRI), used to analyse the memory system, which has demonstrated pathological brain activations that can be linked to concussion [19]. However, the analysis of these studies does not take into consideration the influence of brain hemodynamics over the blood oxygen level dependent signal (BOLD).

The objectives of this critical review are to compare the results from fMRI in acutely concussed patients with their brain hemodynamic impairment and describe the advantages and the disadvantages of using Near-Infrared Spectroscopy (NIRS) to detect the neurological activation factoring in this dysregulation.

This review is focused on acute sport-related and non-sport-related concussion occurring within one month prior to assessment. The fMRI results are restricted to those that show a different activation between healthy and concussed involving the neocortex. This limitation makes possible a comparison between the results from fMRI and NIRS as the latter can only analyse the superficial layers of the brain.

2. Hemodynamic Impairments in Acute Concussion

Alterations of cardiovascular autonomic regulation and cerebrovascular reactivity are reported in acutely concussed patients during physical tasks or stress (Table 1).

Overall, there are no differences between concussed and healthy volunteers at rest but in a percentage of the former there is the inability to answer to tasks with an appropriate increase of blood perfusion systemically and to the brain in particular. The decrease of cardiac output leads to an increase of heart rate (HR) as a compensatory mechanism. This impairment is highly related to the time since, and severity of, the injury. Nevertheless, it should be mentioned that signs of autonomic dysregulation have been reported during resting state as well as during the task [20,21].

Gall et al. found a lower HR response in the concussed group than in the healthy volunteers to physical tasks from a resting state [22]. The level of cardiovascular dysfunction is directly correlated with the time of return to play. Similar results have been found by La Fountaine et al. who showed an increase of HR and HR complexity from rest to task and a global reduction of stroke volume, which further decreased during a hand grip exercise [23,24]. Dobson et al. found an impediment in autonomic cardiovascular control, measuring HR and blood pressure during autonomic reflex tests (e.g., forced exhalation; orthostatic manoeuvres; Valsalva manoeuvre) [25]. Similarly, Middleton et al. described a case report of a concussed athlete diagnosed with autonomic dysfunction using autonomic reflex tests and successfully cured her by increasing the intravascular volume [26]. Len et al. measured the middle cerebral artery velocity through transcranial Doppler ultrasonography during changes of
the partial pressure of carbon dioxide [27]. The results showed slowed cerebrovascular reactivity and incapacity to return to resting-state values after breath-holding tasks and hyperventilation. In contrast to these results, Slobounov et al. did not find any HR alteration in SRC [28].

Table 1. Hemodynamic response to tasks or stress within 4 weeks from concussion.

| Author               | Year | Method                | Time of Assessment | N mTBI | Sport-Related Concussion | Main Findings                             |
|----------------------|------|-----------------------|--------------------|--------|--------------------------|-------------------------------------------|
| Gall et al.          | 2004 | ECG                   | 24 h               | 14     | Yes                      | Increase of HR                            |
| La Fountaine et al.  | 2009 | ECG                   | 48 h; 2 weeks      | 3      | Yes                      | Increase of HR complexity                 |
| Middleton et al.     | 2010 | Photoplethysmography  | 3 weeks            | 1      | Yes                      | Abnormal response to physical tasks       |
| Len et al.           | 2011 | Transcranial Doppler Ultrasound | 1 week          | 10     | Yes                      | Abnormal cerebrovascular reactivity       |
| Slobounov et al.     | 2011 | Photoplethysmography  | 12 days            | 17     | Yes                      | No abnormalities                          |
| La Fountaine et al.  | 2016 | Photoplethysmography  | 48 h; 1 week       | 10     | Yes                      | Reduction of stroke volume; increase of HR |
| Dobson et al.        | 2017 | Photoplethysmography  | 48 h; 72 h; 1 week; 2 weeks | 12     | Yes                      | Abnormal response to physical tasks       |

ECG: Electrocardiogram; HR: Heart Rate.

Cerebral blood flow (CBF) has been monitored after concussion. The results showed an uneven low perfusion to the neocortex with some parts—especially the frontal and temporal lobes—more affected than others in a percentage of the patients tested (Table 2).

Table 2. Regional cerebral blood flow within 4 weeks from concussion.

| Author               | Year | Method                | Time of Assessment | N mTBI | Sport-Related Concussion | Main Findings                             |
|----------------------|------|-----------------------|--------------------|--------|--------------------------|-------------------------------------------|
| Jacobs et al.        | 1994 | SPECT                 | 4 weeks            | 25     | No                       | Reduced rCBF                             |
| Lorberboym et al.    | 2001 | SPECT                 | 6 h                | 16     | No                       | Reduced rCBF                             |
| Agrawal et al.       | 2005 | SPECT                 | 10 days            | 30     | No                       | Reduced rCBF                             |
| Gowda et al.         | 2006 | SPECT                 | 72 h               | 92     | No                       | Reduced rCBF                             |
| Metting et al.       | 2009 | CT with contrast dye  | Mean time 3.9 h    | 76     | No                       | Reduced rCBF                             |
| Maugans et al.       | 2012 | MRI with contrast dye | 72 h; 2 weeks; 4 weeks or more | 12     | Yes                      | Reduced CBF                              |
| Meier et al.         | 2015 | MRI ASL               | 1 day; 1 week; 4 weeks | 17     | Yes                      | Reduced rCBF                             |
| Churchill et al.     | 2017 | MRI ASL               | 1–3 days; 5–7 days | 26     | Yes                      | Elevated rCBF and subsequently reduced rCBF |

ASL: Arterial Spin Labelling; CBF: Cerebral Blood Flow; CT: Computerized Tomography; MRI: Magnetic Resonance Imaging; rCBF: regional Cerebral Blood Flow; SPECT: Single Positive Emission Computerized Tomography.

The uneven distribution of CBF can be due to the mechanism of concussion and the shape of the skull, which exposes some areas of the brain more than others to impact with the skull vault. Jacob et al. described low regional CBF (rCBF) in one third of a mTBI population of adults and children [29]. The rCBF was still present in slightly less than half of them after three months. Gowda et al. showed similar results in more than half of a population with mTBI [30]. However, it should be noted that a proportion of patients with reduced rCBF had CT abnormalities and so would not be included in the current definition of SRC. Lorberboym et al. using SPECT on adults suffering amnesia after road traffic accidents, reported reduced rCBF in the frontal and temporal lobes in two thirds of the population examined [31]. Agrawal et al. tested rCBF in the temporal lobes on a paediatric population with mTBI [32]. They found reduced perfusion in slightly less than half of the population and that
this persisted after 3 months. Maugans et al. showed a reduction of total CBF in a paediatric SRC population [33]. Metting et al. using a non-ionic iodinated contrast agent on a CT scan reported a reduction of CBF in the frontal and occipital lobes in the mTBI population, with the lowest level for the most severe mTBI according to the Glasgow Coma Scale [34]. Meier et al. testing college football athletes, found an initial reduction of rCBF which resolved in combination with improvements in neurocognitive tests [35]. Churchill et al. tested two cohorts of concussed athletes at different points in time and found opposite levels of rCBF, especially in the temporal and frontal lobes [36].

It should be mentioned that the varying time of analysis in these studies makes it difficult to draw definite conclusions about brain hemodynamics.

3. Task-Related Functional Magnetic Resonance Imaging in Acute Concussion

The fMRI is based on the BOLD weighting and gives information about cerebral tissue activation [37,38]. Moreover, the BOLD signal is based on the change of the ratio of deoxyhaemoglobin (HbH) to the sum of oxyhaemoglobin (HbO) and deoxyhaemoglobin (HbH) inside the voxels over time. These molecules have different magnetic properties and their relative concentrations change the voxels’ magnetic field. The rise of cerebral blood flow (CBF), due to neuronal activation, causes a higher concentration of HbO than HbH in the brain areas activated, producing changes in their magnetic properties. A comparison of the magnetic fields’ changes between voxels makes it possible to detect where the brain was activated due to the neurovascular coupling.

The neuroimaging and behaviour results of the studies that used fMRI in acutely concussed patients are conflicting. It should be noted that the time of assessment from injury and the samples, in both size and quality, differ greatly between studies which makes a direct comparison between them difficult.

Results can be divided into two groups according to the level of neuronal activation and the area covered: hyperactivation and hypoactivation (Table 3).

| Author             | Year | Task                                      | Time of Assessment | N mTBI | Sport-Related Concussion | Main Findings       |
|--------------------|------|-------------------------------------------|--------------------|--------|--------------------------|---------------------|
| McAllister et al.  | 1999 | N-back                                    | 4 weeks            | 12     | Yes                      | Hyperactivation     |
| McAllister et al.  | 2000 | N-back                                    | 4 weeks            | 18     | Yes                      | No abnormalities    |
| Jantzen et al.     | 2004 | Calculation; Digit span                   | 1 week             | 4      | Yes                      | Hyperactivation     |
| Lovell et al.      | 2007 | N-back                                    | 1 week             | 28     | Yes                      | Hyperactivation     |
| Smit et al.        | 2009 | N-back; Stroop; Finger sequence           | 4 weeks and more   | 21     | No                       | Hyperactivation     |
| Mayer et al.       | 2009 | Auditory orienting                        | 3 weeks            | 16     | No                       | Hyperactivation     |
| Pardini et al.     | 2010 | N-back                                    | 2 weeks            | 16     | Yes                      | Hyperactivation     |
| Slobounov et al.   | 2010 | Virtual reality                           | 4 weeks            | 15     | Yes                      | Hyperactivation     |
| Stulemeijejer et al.| 2010| N-back                                    | 6 weeks            | 43     | No                       | Hyperactivation     |
| Witt et al.        | 2010 | Auditory oddball                          | 13–200 days        | 31     | No                       | Hyperactivation     |
| Yang et al.        | 2012 | Auditory orienting                        | 3 weeks or more    | 14     | No                       | Hyperactivation     |
| Hammeke et al.     | 2013 | Sternberg                                 | 48 h               | 12     | Yes                      | Hypoactivation      |
| Kightley et al.    | 2014 | Visual memory                             | 90 days            | 15     | Yes                      | Hypoactivation      |
| Talavage et al.    | 2014 | N-back                                    | 72 h               | 4      | Yes                      | Hyperactivation     |

3.1. Hyperactivation

McAllister et al. were the first to use fMRI during an N-back task in a population of civilians and athletes [39]. They reported hyperactivation of the frontal lobes in a moderate working memory task. A follow-up study from the same group did not detect a significant increase from moderate to higher memory task [40]. Considering that the performances of the concussed and control groups were similar, a possible explanation of the fMRI results is the necessity for the concussed group to increase the neuronal activation in the easiest tasks to maintain the same level of performance as the controls. As such, they would reach the same level of neuronal activation that is reached by the controls in the
most difficult tasks. It can be noted that a similar test on children did not measure an activation of the neocortex but of the cerebellum [41]. Talavage et al. reported a pathological activation pattern in young concussed athletes compared with their baseline [42]. Jantzen et al. compared the results in a battery of tests with the patients’ baseline [43]. They reported neuronal hyperactivation after concussion and similar performance in the neurocognitive results before and after the injury. This is explained as a compensatory mechanism that allows patients to maintain the same level of performance with an increase of activation. Lovell et al. tested acutely concussed athletes within one week and subsequently within six weeks of concussion [44]. The authors described hyperactivation in the supplementary motor area, which had a direct correlation with the time of returning to play. It should be mentioned that the level of activation in the posterior parietal cortex was correlated with the severity of symptoms so that the lower it is the more severe the symptoms and vice versa. By contrast, Smits et al. described a direct link between an increased activation in bigger areas than controls and the severity of symptoms in SRC athletes approximately a month after injury [45]. It should be noted that a proportion of these observations occurred more than one month following the injury and so potentially they cannot be classified as acute. Similarly, Pardini et al. found hyperactivation was directly correlated with the severity of symptoms a week from injury [46]. Slobounov et al. reported a wider activation of the neuronal cortex in concussed athletes within a month of concussion during a spatial memory test [47]. Using diffusion tensor imaging, the authors ruled out white matter abnormalities, which could have explained this abnormal activation pattern [48]. However, it should be mentioned that compensation mechanisms have been linked to diffuse axonal injury in other studies on TBI patients [49,50].

3.2. Hypoactivation

Hammeke et al. scanned athletes with SRC during a memory task [51]. The authors reported that hypoactivation was associated with lower performance in the acute phase. In the chronic phase, they reported hyperactivation with a normalization of the performance, which might suggest a compensatory cognitive process. Mayer et al. reported hypoactivation associated with lower performance possibly due to an attention deficit [52]. Stulemeijer et al. found a correlation between hypoactivation of the temporal lobes and the severity of injury [53]. Although the average time of assessment was 24.6 days after injury, the measurements happened within 6 weeks of injury and, therefore, a percentage of these patients cannot be considered in acute. Witt et al. measured hypoactivation without changes in performance [54]. However, only a small percentage of the patients studied were in the acute setting as the range of assessment was between 13 and 200 days with an average of two months. In a paediatric population, Yang et al. found a reduced activation with a similar score in the test between concussed and controls [55]. In children between 9 and 90 days from the injury, Keightley detected hypoactivation related to poorer performance [56]. However, as in other studies, many of the subjects tested were not in acute timeframe.

4. Limits of the Task-Related Functional Magnetic Resonance Imaging in Acutely Concussed Patients

In the elderly, Gauthier et al. showed that brain-hemodynamic impairments can influence the BOLD signal [57]. They compared MRI Arterial Spin Labelling (ASL) and BOLD results to demonstrate that the baseline concentration of deoxy-haemoglobin and vascular reactivity may cause an underestimation of the neuronal activation in fMRI of patients with impaired hemodynamics. These results called into question the ability to detect brain activation pattern in BOLD analysis in patients with cardiovascular impairments as SRC athletes are. Jantzen describes the importance of baseline scanning to eliminate hemodynamic influence and identify the neuronal activation related to tasks in the fMRI [19]. In other words, the comparison of the data between a resting-state baseline and a task makes it possible to isolate the signal from the neuronal activation. According to this principle, it is possible to compare the results of patients with different baselines. However, this analysis does not take into consideration two key elements of the hemodynamic in concussed patients. The first is that
the cardiovascular response in these patients changes from a resting state to a task. As a consequence, in the comparison between concussed participants and healthy volunteers, changes between baseline and task can be related to changes in the cerebral hemodynamic rather than neuronal activation, or at least the latter can be influenced by the former. That is to say, differences of BOLD signal between SRC and healthy volunteers can be explained as incapacity of the former to increase the CBF in response to a task as much as the healthy volunteers do, rather than a lack of neuronal activation.

The second is that in concussed patients, the CBF may be lower in some regions of the brain than others during the baseline. This may alter the fMRI because the areas affected would start from a different “starting point” than the surrounding ones. In other words, if the fMRI results are a comparison of the magnetic properties due to HbO and HbH between the baseline and the task, then a different baseline in one area due to cerebrovascular impairment can be read as different level of activation during the task compared to the surrounding voxels, even though the signal at this time is similar. For example, a similar distribution of CBF during the task may be seen as a hyperactivation in a formerly hypoperfused brain region and vice versa.

The importance of these factors is heightened upon taking into consideration that there is also a high inter-individual variability of the cerebral hemodynamic after concussion and in the following days. In general, this makes it impossible to standardize the level of cardiovascular impairment and the identification of which regions are impaired. Under these conditions, it is difficult to interpret fMRI results without first performing an assessment of the hemodynamic condition of the patients.

5. Near-Infrared Spectroscopy in Acutely Concussed Patients

The near-infrared spectroscopy (NIRS) is a functional imaging technique which uses near-infrared light at two or more wavelengths to assess the tissue oxygenation [58]. Near-infrared light is emitted towards the brain and is collected by a detector. The most likely pathway the photons travel in the tissue can be estimated using a Monte Carlo simulation, which is a computational technique to simulate stochastic physical processes. This simulation takes into consideration the probabilities of each photon being scattered or absorbed. According to this simulation the photon pathway can be described as a “photon banana” that connects the source and the detector (Figure 1).

**Figure 1.** Representation of the photon banana: On the left, an emitter and a detector of near-infrared light are represented placed on the scalp. On the right: A coronal section of the cranium shows the photon banana between the probes. The light emitted passes through the extra-cranial tissue, the bone, the cerebral-spinal fluid and the surface of the brain. It should be noted that the amount of light scattered increases with the depth of the photon banana.
One of the biggest limitations with the usage of NIRS is the interference of the extra-cranial tissue over the signal from the brain [59]. The best distance between the source and detector to obtain the optimum depth and signal-to-noise ratio is estimated to be between 30 and 35 mm [60]. At this distance, the signal from the intracranial tissue is mainly due to the surface of the brain which corresponds to the neocortex.

The modified Beer-Lambert law links the quantity of light absorbed at multiple wavelengths to the changes of concentration of chromophores, in this case HbO and HbH [61]. The absolute concentration of HbO and HbH can be detected using the optical properties of the tissues [62–64]. Although using this method the NIRS data can be influenced by the saturation of extra-cranial tissue, overall, they are highly indicative of the brain oxygen saturation [65]. NIRS data can be analysed according to the channels' spatial positions using a functional-neuroimaging technique called diffuse optical tomography (DOT). The analyses of the layers illuminated by near-infrared light result in a better reconstruction of the signal from the brain [61,66,67]. Using this technique on a structural neuroimaging (e.g., MRI) or an atlas, it is also possible to localize which brain areas are activated [68].

Comparison of the results between functional NIRS (fNIRS) and fMRI shows similar activation patterns as both techniques detect neuronal activation through the neurovascular coupling [69,70]. The validity of the neurovascular coupling remains intact in concussed patients and this is true for fMRI as for fNIRS. This is highlighted by Jantzen who focused on the fact that there is an alteration of BOLD signal in only some tasks rather than in all [19]. This suggests that the results are influenced, either completely or partially, by neuronal activation. This element validates the usage of techniques that measure the neuronal activation in concussed patients as the neurovascular coupling is at least somewhat maintained despite the hemodynamic impairments. However, one of the differences between the signal detected by fMRI and by fNIRS is that the former is a comparison between two moments in time, that is the changing of magnetic field, while the latter can be based on the absolute parameters at the time of the measurement, independent of the initial values. As a matter of fact, unlike fMRI, NIRS is able to measure levels of HbO and HbH during the baseline and the task separately. This makes it possible to compare levels of brain oxygenation between areas in the baseline and the task independently. This property allows fNIRS to overcome the second issue described in the previous paragraph related to the uneven distribution of CBF: the level of brain saturation in the different parts of the brain can be compared with each other regarding their baseline. Citing the example previously described, a low perfused region in the baseline would not be considered any more activated than the surrounding areas if they have similar level of tissue saturation during the task.

Tachtsidis et al. described the necessity to assess the brain activation in a control condition to eliminate the systemic signal in a NIRS analysis [71]. Although the regression of the signal from baseline to task allows important steps towards the elimination of systemic influences, this may be insufficient in concussed patients as the systemic influence may not be consistent switching from task to baseline. Therefore, as in the fMRI, the incapacity of the concussed group to hemodynamically answer to a task as much as the healthy volunteers can cause an underestimation of the neuronal activation. Consequently, the experimental design of NIRS in concussion should take into consideration that there may be a pathological, non-linear hemodynamic response from rest to task in some patients. A possible solution is to gradually increase the difficulty of the task so that the hemodynamic response can be tracked. To our knowledge, the only study conducted with NIRS on SRC is from Kontos et al. who tested concussed patients from 15 to 45 days after injury during the ImPACT® [72]. They matched the NIRS signal with an atlas to identify the brain regions activated and they found a hypoactivation during memory tasks. One of the limitations of this study is that the test used was not tailored for fNIRS measurements as described above. However, it should be mentioned that the authors recorded a baseline to subtract out the systemic signal from the neuronal activation.

Worthy of note is the fact that recent studies proposed new analysis of the NIRS data that would allow measurements of the cerebrovascular health [73,74]. These NIRS analyses can be included in
the assessment of brain activation to achieve a clearer picture of the influence of the hemodynamic on the results.

6. Conclusions

The hemodynamic impairment that follows an episode of concussion can affect the BOLD signal and can partially explain the differences in fMRI results seen in SRC. fNIRS would be able to partially address this problem due to its capacity to quantify the level of tissue saturation as an independent measurement rather than a relative parameter. The experimental design of NIRS should take into consideration the autonomic dysfunction that may follow concussion in order to reduce maximally its effects on the signal due to neuronal activation. Currently, only limited studies of NIRS in SRC have been undertaken and the advantages of NIRS in SRC still have to be appropriately tested.

Due to the high variability of the clinical presentation and evolution of concussion, no single neurocognitive imaging modality is currently able to completely address this pathology. NIRS should be included in studied alongside existing neurocognitive tests in clinical practice to assess its value in guiding the recovery and safe return to play of athletes with SRC.

Author Contributions: Mario Forcione conceived and wrote the paper; Claudio Colonnese reviewed the paper and added critical contributions to the text; Prof Antonio Belli reviewed the paper and added critical contributions to the text. Mario Forcione is a PhD student of the University of Birmingham who is working in the project “Brain Injury and Trauma Monitoring Using Advanced Photonics” financed by the European Union Horizon 2020 Research and Innovation Program under grant agreement 675332. This article presents independent research funded by the National Institute for Health Research Surgical Reconstruction and Microbiology Research Centre (NIHR SRMRC), partnership between University Hospitals Birmingham NHS Foundation Trust, the University of Birmingham, and the Royal Centre for Defence Medicine. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. McCrory, P.; Meeuwisse, W.; Dvorak, J.; Aubry, M.; Bailes, J.; Broglio, S.; Cantu, R.C.; Cassidy, D.; Echemendia, R.J.; Castellani, R.J.; et al. Consensus statement on concussion in sport—the 5th international conference on concussion in sport held in Berlin, October 2016. Br. J. Sports Med. 2017. [CrossRef] [PubMed]
2. Daneshvar, D.H.; Nowinski, C.J.; McKee, A.C.; Cantu, R.C. The epidemiology of sport-related concussion. Clin. Sports Med. 2011, 30, 1–17. [CrossRef] [PubMed]
3. McCrea, M.; Hammeke, T.; Olsen, G.; Leo, P.; Guskeiwicz, K. Unreported concussion in high school football players: Implications for prevention. Clin. J. Sport Med. 2004, 14, 13–17. [CrossRef] [PubMed]
4. Lovell, M.R.; Collins, M.W.; Maroon, J.C.; Cantu, R.; Hawn, M.A.; Burke, C.J.; Fu, F. Inaccuracy of symptom reporting following concussion in athletes. Med. Sci. Sports Exerc. 2002, 34, S298. [CrossRef]
5. Giza, C.C.; Hovda, D.A. The new neurometabolic cascade of concussion. Neurosurgery 2014, 75 (Suppl. 4), S24–S33. [CrossRef] [PubMed]
6. Vagnozzi, R.; Tavazzi, B.; Signoretti, S.; Amorini, A.M.; Belli, A.; Cimatti, M.; Delfini, R.; Di Pietro, V.; Finocchiaro, A.; Lazzarino, G. Temporal window of metabolic brain vulnerability to concussions: Mitochondrial-related impairment—Part I. Neurosurgery 2007, 61, 379–389. [CrossRef] [PubMed]
7. Tavazzi, B.; Vagnozzi, R.; Signoretti, S.; Amorini, A.M.; Belli, A.; Cimatti, M.; Delfini, R.; Di Pietro, V.; Finocchiaro, A.; Lazzarino, G. Temporal window of metabolic brain vulnerability to concussions: Oxidative and nitrosative stresses—Part II. Neurosurgery 2007, 61, 390–396. [CrossRef] [PubMed]
8. Echemendia, R.J.; Giza, C.C.; Kuter, J.S. Developing guidelines for return to play: Consensus and evidence-based approaches. Brain Inj. 2015, 29, 185–194. [CrossRef] [PubMed]
9. Echemendia, R.J.; Putukian, M.; Mackin, R.S.; Julian, L.; Shoss, N. Neuropsychological test performance prior to and following sports-related mild traumatic brain injury. Clin. J. Sport Med. 2001, 11, 23–31. [CrossRef] [PubMed]
10. Lovell, M.R.; Collins, M.W.; Iverson, G.L.; Field, M.; Maroon, J.C.; Cantu, R.; Podell, K.; Powell, J.W.; Belza, M.; Fu, F.H. Recovery from mild concussion in high school athletes. J. Neurosurg. 2003, 98, 296–301. [CrossRef] [PubMed]
11. Broglio, S.P.; Macciochi, S.N.; Ferrara, M.S. Neurocognitive performance of concussed athletes when symptom free. *J. Athletic Train.* 2007, 42, 504–508.

12. Van Kampen, D.A.; Lovell, M.R.; Pardini, J.E.; Collins, M.W.; Fu, F.H. The “value added” of neurocognitive testing after sports-related concussion. *Am. J. Sports Med.* 2006, 34, 1630–1635. [CrossRef] [PubMed]

13. Slobounov, S.; Tutwiler, R.; Sebastianelli, W.; Slobounov, E. Alteration of postural responses to visual field motion in mild traumatic brain injury. *Neurosurgery* 2006, 59, 134–193. [CrossRef] [PubMed]

14. Slobounov, S.; Slobounov, E.; Sebastianelli, W.; Cao, C.; Newell, K. Differential rate of recovery in athletes after first and second concussion episodes. *Neurosurgery* 2007, 61, 338–344. [CrossRef] [PubMed]

15. Vagnozzi, R.; Signoretti, S.; Cristofori, L.; Alessandrini, F.; Floris, R.; Isgro, E.; Ria, A.; Marziali, S.; Zoccatelli, G.; Tavazzi, B.; et al. Assessment of metabolic brain damage and recovery following mild traumatic brain injury: A multicentre, proton magnetic resonance spectroscopic study in concussed patients. *Brain* 2010, 133, 3232–3242. [CrossRef] [PubMed]

16. McCrea, M.; Guskiewicz, K.; Randolph, C.; Barr, W.B.; Hammeke, T.A.; Marshall, S.W.; Kelly, J.P. Effects of a symptom-free waiting period on clinical outcome and risk of reinjury after sport-related concussion. *Neurosurgery* 2009, 65, 876–883. [CrossRef] [PubMed]

17. Eierud, C.; Craddock, R.C.; Fletcher, S.; Aulakh, M.; King-Casas, B.; Kuehl, D.; LaConte, S.M. Neuroimaging after mild traumatic brain injury: Review and meta-analysis. *Neuroimage Clin.* 2014, 4, 283–294. [CrossRef] [PubMed]

18. Yuh, E.L.; Hawryluk, G.W.; Manley, G.T. Imaging concussion: A review. *Neurosurgery* 2014, 75 (Suppl. 4), S50–S63. [CrossRef] [PubMed]

19. Jantzen, K.J. Functional magnetic resonance imaging of mild traumatic brain injury. *J. Head Trauma Rehabil.* 2010, 25, 256–266. [CrossRef] [PubMed]

20. La Fountaine, M.F.; Toda, M.; Testa, A.; Bauman, W.A. Cardioautonomic instability following a sports-related concussion in a 20-year-old male. *Int. J. Cardiol.* 2014, 172, e511–e512. [CrossRef] [PubMed]

21. La Fountaine, M.F.; Gossett, J.D.; De Meersman, R.E.; Bauman, W.A. Increased QT interval variability in 3 recently concussed athletes: An exploratory observation. *J. Athletic Train.* 2011, 46, 230–233. [CrossRef] [PubMed]

22. Gall, B.; Parkhouse, W.; Goodman, D. Heart rate variability of recently concussed athletes at rest and exercise. *Med. Sci. Sports Exerc.* 2004, 36, 1269–1274. [CrossRef] [PubMed]

23. La Fountaine, M.F.; Heffernan, K.S.; Gossett, J.D.; Bauman, W.A.; De Meersman, R.E. Transient suppression of heart rate complexity in concussed athletes. *Auton. Neurosci. Basic Clin.* 2009, 148, 101–103. [CrossRef] [PubMed]

24. La Fountaine, M.F.; Toda, M.; De Meersman, R.E.; Bauman, W.A. Cardiovascular autonomic dysfunction. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2010, 35, 310–313. [CrossRef] [PubMed]

25. Lobreroym, M.; Lampl, Y.; Gerzon, I.; Sadeh, M. Brain SPECT evaluation of amnestic ED patients after mild head trauma. *Am. J. Emerg. Med.* 2002, 20, 310–313. [CrossRef] [PubMed]
32. Agrawal, D.; Gowda, N.K.; Bal, C.S.; Pant, M.; Mahapatra, A.K. Is medial temporal injury responsible for pediatric postconcussion syndrome? A prospective controlled study with single-photon emission computerized tomography. *J. Neurosurg.* 2005, 102, 167–171. [CrossRef] [PubMed]
33. Mauğans, T.A.; Farley, C.; Altaye, M.; Leach, J.; Cecil, K.M. Pediatric sports-related concussion produces cerebral blood flow alterations. *Pediatrics* 2012, 129, 28–37. [CrossRef] [PubMed]
34. Metting, Z.; Rodiger, L.A.; Stewart, R.E.; Oudkerk, M.; De Keyser, J.; van der Naalt, J. Perfusion computed tomography in the acute phase of mild head injury: Regional dysfunction and prognostic value. *Ann. Neurol.* 2009, 66, 809–816. [CrossRef] [PubMed]
35. Meier, T.B.; Bellgowan, PS.; Singh, R.; Kuplicki, R.; Polanski, D.W.; Mayer, A.R. Recovery of cerebral blood flow following sports-related concussion. *JAMA Neurol.* 2015, 72, 530–538. [CrossRef] [PubMed]
36. Churchill, N.W.; Hutchison, M.G.; Richards, D.; Leung, G.; Graham, S.J.; Schweizer, T.A. The first week after concussion: Blood flow, brain function and white matter microstructure. *Neuroimage Clin.* 2017, 14, 480–489. [CrossRef] [PubMed]
37. Mark, C.I.; Mazerolle, E.L.; Chen, J.J. Metabolic and vascular origins of the bold effect: Implications for imaging pathology and resting-state brain function. *J. Magn. Reson. Imaging* 2015, 42, 231–246. [CrossRef] [PubMed]
38. Heeger, D.J.; Ress, D. What does fMRI tell us about neuronal activity? *Nat. Rev. Neurosci.* 2002, 3, 142–151. [CrossRef] [PubMed]
39. McAllister, T.W.; Saykin, A.J.; Flashman, L.A.; Sparling, M.B.; Johnson, S.C.; Guerin, S.J.; Mamourian, A.C.; Weaver, J.B.; Yanofsky, N. Brain activation during working memory 1 month after mild traumatic brain injury: A functional MRI study. *Neurology* 1999, 53, 1300–1308. [CrossRef] [PubMed]
40. McAllister, T.W.; Sparling, M.B.; Flashman, L.A.; Guerin, S.J.; Mamourian, A.C.; Saykin, A.J. Differential working memory load effects after mild traumatic brain injury. *Neuroimage* 2001, 14, 1004–1012. [CrossRef] [PubMed]
41. Krivitzky, L.S.; Roebuck-Spencer, T.M.; Roth, R.M.; Blackstone, K.; Johnson, C.P.; Gioia, G. Functional magnetic resonance imaging of working memory and response inhibition in children with mild traumatic brain injury. *J. Int. Neuropsychol. Soc.* 2011, 17, 1143–1152. [CrossRef] [PubMed]
42. Talavage, T.M.; Nauman, E.A.; Breedlove, E.L.; Yoruk, U.; Dye, A.E.; Morigaki, K.E.; Feuer, H.; Leverenz, L.J. Functionally-detected cognitive impairment in high school football players without clinically-diagnosed concussion. *J. Neurotrauma* 2014, 31, 327–338. [CrossRef] [PubMed]
43. Jantzen, K.J.; Anderson, B.; Steinberg, F.L.; Kelso, J.A. A prospective functional MR imaging study of mild traumatic brain injury in college football players. *Am. J. Neuroradiol.* 2004, 25, 738–745. [PubMed]
44. Lovell, M.R.; Pardini, J.E.; Welling, J.; Collins, M.W.; Bakal, J.; Lazar, N.; Roush, R.; Eddy, W.F.; Becker, J.T. Functional brain abnormalities are related to clinical recovery and time to return-to-play in athletes. *Neurosurgery* 2007, 61, 352–360. [CrossRef] [PubMed]
45. Smits, M.; Dippel, D.W.; Houston, G.C.; Wielopolski, P.A.; Koudstaal, P.J.; Hunink, M.G.; van der Lugt, A. Post concussion syndrome after minor head injury: Brain activation of working memory and attention. *Hum. Brain Mapp.* 2009, 30, 2789–2803. [CrossRef] [PubMed]
46. Pardini, J.E.; Pardini, D.A.; Becker, J.T.; Dunfee, K.L.; Eddy, W.F.; Lovell, M.R.; Welling, J.S. Postconcussive symptoms are associated with compensatory cortical recruitment during a working memory task. *Neurosurgery* 2010, 67, 1020–1028. [CrossRef] [PubMed]
47. Slobounov, S.M.; Zhang, K.; Pennell, D.; Ray, W.; Johnson, B.; Sebastianelli, W. Functional abnormalities in normally appearing athletes following mild traumatic brain injury: A functional MRI study. *Exp. Brain Res.* 2010, 202, 341–354. [CrossRef] [PubMed]
48. Zhang, K.; Johnson, B.; Pennell, D.; Ray, W.; Sebastianelli, W.; Slobounov, S. Are functional deficits in concussion individuals consistent with white matter structural alterations: Combined fMRI & DTI study. *Exp. Brain Res.* 2010, 204, 57–70. [PubMed]
49. Maruishi, M.; Miyatani, M.; Nakao, T.; Muranaka, H. Compensatory cortical activation during performance of an attention task by patients with diffuse axonal injury: A functional magnetic resonance imaging study. *J. Neurol. Neurosurg. Psychiatry* 2007, 78, 168–173. [CrossRef] [PubMed]
50. Turner, G.R.; Levine, B. Augmented neural activity during executive control processing following diffuse axonal injury. *Neurology* 2008, 71, 812–818. [CrossRef] [PubMed]
51. Hammeke, T.A.; McCrea, M.; Coats, S.M.; Verber, M.D.; Durgerian, S.; Flora, K.; Olsen, G.S.; Leo, P.D.; Gennarelli, T.A.; Rao, S.M. Acute and subacute changes in neural activation during the recovery from sport-related concussion. *J. Int. Neuropsychol. Soc.* 2013, 19, 863–872. [CrossRef] [PubMed]

52. Mayer, A.R.; Mannell, M.V.; Ling, J.; Elgie, R.; Gasparovic, C.; Phillips, J.P.; Doezema, D.; Yeo, R.A. Auditory orienting and inhibition of return in mild traumatic brain injury: A fMRI study. *Hum. Brain Mapp.* 2009, 30, 4152–4166. [CrossRef] [PubMed]

53. Stulemeijer, M.; Vos, P.E.; van der Werf, S.; van Dijk, G.; Rijpkema, M.; Fernandez, G. How mild traumatic brain injury may affect declarative memory performance in the post-acute stage. *J. Neurotrauma* 2010, 27, 1585–1595. [CrossRef] [PubMed]

54. Witt, S.T.; Lovejoy, D.W.; Pearlson, G.D.; Stevens, M.C. Decreased prefrontal cortex activity in mild traumatic brain injury during performance of an auditory oddball task. *Brain Imaging Behav.* 2010, 4, 232–247. [CrossRef] [PubMed]

55. Yang, Z.; Yeo, R.A.; Pena, A.; Ling, J.M.; Klimaj, S.; Campbell, R.; Doezema, D.; Mayer, A.R. An fMRI study of auditory orienting and inhibition of return in pediatric mild traumatic brain injury. *J. Neurotrauma* 2012, 29, 1214–1216. [CrossRef] [PubMed]

56. Keightley, M.L.; Saluja, R.S.; Chen, J.K.; Gagnon, I.; Leonard, G.; Petrides, M.; Pito, A. A functional magnetic resonance imaging study of working memory in youth after sports-related concussion: Is it still working? *J. Neurotrauma* 2014, 31, 437–451. [CrossRef] [PubMed]

57. Gauthier, C.J.; Madjar, C.; Desjardins-Crepeau, L.; Bellec, P.; Bherer, L.; Hoge, R.D. Age dependence of hemodynamic response characteristics in human functional magnetic resonance imaging. *Neurobiol. Aging* 2013, 34, 1469–1485. [CrossRef] [PubMed]

58. Davies, D.J.; Su, Z.; Clancy, M.T.; Lucas, S.J.; Dehghani, H.; Logan, A.; Belli, A. Near-infrared spectroscopy in the monitoring of adult traumatic brain injury: A review. *J. Neurotrauma* 2015, 32, 933–941. [CrossRef] [PubMed]

59. Davie, S.N.; Grocott, H.P. Impact of extracranial contamination on regional cerebral oxygen saturation: A comparison of three cerebral oximetry technologies. *Anesthesiology* 2012, 116, 834–840. [CrossRef] [PubMed]

60. Strangman, G.E.; Li, Z.; Zhang, Q. Depth sensitivity and source-detector separations for near infrared spectroscopy based on the Colin27 brain template. *PLoS ONE* 2013, 8, e66319. [CrossRef] [PubMed]

61. Strangman, G.; Boas, D.A.; Sutton, J.P. Non-invasive neuroimaging using near-infrared light. *Biol. Psychiatry* 2002, 52, 679–693. [CrossRef]

62. Fantini, S.; Franceschini, M.-A.; Maier, J.S.; Walker, S.A.; Barbieri, B.B.; Gratton, E. Frequency-Domain Multichannel Optical Detector for Noninvasive Tissue Spectroscopy and Oximetry. *Opt. Eng.* 1995, 34, 32–43. [CrossRef]

63. Fantini, S.; Franceschini, M.A.; Gratton, E. Semi-infinite-geometry boundary problem for light migration in highly scattering media: A frequency-domain study in the diffusion approximation. *J. Opt. Soc. Am. B* 1994, 11, 2128–2138. [CrossRef]

64. Matcher, S.J.; Cooper, C.E. Absolute quantification of deoxyhaemoglobin concentration in tissue near infrared spectroscopy. *Phys. Med. Biol.* 1994, 39, 1295–1312. [CrossRef] [PubMed]

65. Clancy, M.; Belli, A.; Davies, D.; Lucas, S.J.E.; Su, Z.J.; Dehghani, H. Comparison of neurological NIRS signals during standing valsalva maneuvers, pre and post vasopressor injection. In *Diffuse Optical Imaging V*; Dehghani, H., Taroni, P., Eds.; SPIE-International Society for Optical Engineering: Bellingham, WA, USA, 2015; Volume 9538.

66. Clancy, M.; Belli, A.; Davies, D.; Lucas, S.J.E.; Su, Z.J.; Dehghani, H. Monitoring the injured brain—Registered, patient specific atlas models to improve accuracy of recovered brain saturation values. In *Diffuse Optical Imaging V*; Dehghani, H., Taroni, P., Eds.; SPIE-International Society for Optical Engineering: Bellingham, WA, USA, 2015; Volume 9538.

67. Boas, D.A.; Gaudette, T.; Strangman, G.; Cheng, X.; Marota, J.J.; Mandeville, J.B. The accuracy of near infrared spectroscopy and imaging during focal changes in cerebral hemodynamics. *NeuroImage* 2001, 13, 76–90. [CrossRef] [PubMed]

68. Chiarelli, A.M.; Maelin, E.L.; Low, K.A.; Fabiani, M.; Gratton, G. Comparison of procedures for co-registering scalp-recording locations to anatomical magnetic resonance images. *J. Biomed. Opt.* 2015, 20, 016009. [CrossRef] [PubMed]
69. Amyot, F.; Zimmermann, T.; Riley, J.; Kainerstorfer, J.M.; Chernomordik, V.; Mooshagian, E.; Najafizadeh, L.; Krueger, F.; Gandjbakhche, A.H.; Wassermann, E.M. Normative database of judgment of complexity task with functional near infrared spectroscopy—Application for TBI. *NeuroImage* 2012, 60, 879–883. [CrossRef] [PubMed]

70. Fantini, S.; Sassaroli, A.; Tgavalekos, K.T.; Kornbluth, J. Cerebral blood flow and autoregulation: Current measurement techniques and prospects for noninvasive optical methods. *Neurophotonics* 2016, 3, 031411. [CrossRef] [PubMed]

71. Tachtsidis, I.; Scholkmann, F. False positives and false negatives in functional near-infrared spectroscopy: Issues, challenges, and the way forward. *Neurophotonics* 2016, 3, 031405. [CrossRef] [PubMed]

72. Kontos, A.P.; Huppert, T.J.; Beluk, N.H.; Elbin, R.J.; Henry, L.C.; French, J.; Dakan, S.M.; Collins, M.W. Brain activation during neurocognitive testing using functional near-infrared spectroscopy in patients following concussion compared to healthy controls. *Brain Imaging Behav.* 2014, 8, 621–634. [CrossRef] [PubMed]

73. Fabiani, M.; Low, K.A.; Tan, C.H.; Zimmerman, B.; Fletcher, M.A.; Schneider-Garces, N.; Maclin, E.L.; Chiarelli, A.M.; Sutton, B.P.; Gratton, G. Taking the pulse of aging: Mapping pulse pressure and elasticity in cerebral arteries with optical methods. *Psychophysiology* 2014, 51, 1072–1088. [CrossRef] [PubMed]

74. Tan, C.H.; Low, K.A.; Kong, T.; Fletcher, M.A.; Zimmerman, B.; Maclin, E.L.; Chiarelli, A.M.; Gratton, G.; Fabiani, M. Mapping cerebral pulse pressure and arterial compliance over the adult lifespan with optical imaging. *PLoS ONE* 2017, 12, e0171305. [CrossRef] [PubMed]