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Review

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

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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, underestimated 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 Ultrasonography	1 week	10	Yes	Abnormal cerebrovascular reactivity
Slobounov et al.	2011	Photoplethysmography	12 days	17	Yes	No abnormalities
La Fountaine et al.	2016	ECG; 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 rCRF
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; CRB: 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).

Table 3. Task-related functional Magnetic Resonance Imaging (fMRI) within 4 weeks from concussion.

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	Finger sequences; 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	Hypoactivation
Pardini et al.	2010	N-back	2 weeks	16	Yes	Hyperactivation
Slobounov et al.	2010	Virtual reality	4 weeks	15	Yes	Hyperactivation
Stulemeijer et al.	2010	N-back	6 weeks	43	No	Hypoactivation
Witt et al.	2010	Auditory oddball	13–200 days	31	No	Hypoactivation
Yang et al.	2012	Auditory orienting	3 weeks or more	14	No	Hypoactivation
Hammeke et al.	2013	Sternberg	48 h	12	Yes	Hypoactivation
Keightley 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).

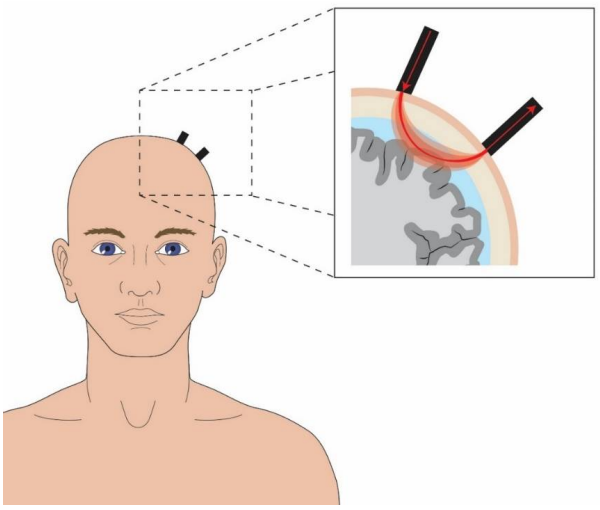

Figure 1. Representation of the photon banana: On the left, an emitter and a detector of near-infrared light are represented placed on the scalp. On the right: A coronal section of the cranium shows the photon banana between the probes. The light emitted passes through the extra-cranial tissue, the bone, 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.

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