Long-term effects of multiple concussions on prefrontal cortex oxygenation during neurovascular coupling activation in retired male contact sport athletes

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ABSTRACT

Purpose: This study aimed to investigate the long-term effects of multiple concussions on prefrontal cortex oxygenation during a neurovascular coupling activating task using near infrared spectroscopy (NIRS).

Methods: Self-reported physically active males who previously participated in contact team sports at various levels of competition and who previously had experienced at least 3 concussions (n = 29; mTBI) or had no history of concussions (n = 29; CTRL) were recruited. Participants completed a 5 min “Where’s Waldo” object identification protocol which consisted of participants closing their eyes for 20-s followed by 40-s (repeated 5 times over 5-min) of searching a computer screen for “Waldo” hidden in a field of distractors. NIRS (μM) was used to measure right and left prefrontal cortex cerebral oxygenation. Oxygenated (O2Hb), deoxygenated (HHb), total (tHb) haemoglobin, and haemoglobin difference (HbDiff) were analysed through the change in average maximal and minimal values (ΔMAX), Z-scores, and standard deviations.

Results: There were no significant differences in the relative change in cerebral oxygenation of the right prefrontal cortex between groups. In mTBI, left prefrontal cortex HHb ΔMAX (p = 0.031) and tHb ΔMAX (p = 0.044) were significantly lower than in the CTRL group. Within-group, right vs. left prefrontal cortex differences showed significantly lower values in left HbDiff Z-scores (p = 0.019) in only the mTBI group while the CTRL group showed significantly lower values in left HbDiff SD (p = 0.045).

Conclusion: This preliminary study suggests that there are changes in prefrontal cortex oxygenation in males who had a history of experiencing multiple concussions in their past during a neurovascular coupling activating task. These changes may represent potential long-term effects in the brain’s ability to adapt cerebral oxygenation during increased neural activity.

1. Introduction

Concussion has become one of the most prevalent medical conditions in individuals participating in sports over the last 15–20 years with a growing body of research observing changes in cognition and neuro-physiology. Previous research reports that approximately 20% of North American adolescents have sustained at least one concussion in their lifetime (Ilie et al., 2013; Veliz et al., 2017), and it is estimated that 54% of paediatric concussion cases in Canada are sport-related (Kazl and Torres, 2019). Whether these brain injuries sustained earlier in life will have a detrimental effect later in life is unknown. Although current medical treatment and preventative options are improving, many retired athletes would not have received the same standard of care for a concussion that is available today (Caron et al., 2013).

The immediate effects of concussions on physiological systems are well known, with research suggesting dysfunctions in static and dynamic cerebral autoregulation, cerebrovascular reactivity and neurovascular coupling (Bishop et al., 2017; Bishop and Neary, 2018; Len et al., 2011; Sharma et al., 2020; Wright et al., 2018). However, the long-term effects that multiple concussions can have over the course of an individual’s lifetime are just beginning to be understood. Sustaining multiple concussions has been suggested to increase the risk of...
neurodegenerative diseases, negatively impact cognition, and cause changes in behaviour later in life (Daneshvar et al., 2011; Guskiewicz et al., 2005; McKee et al., 2009; Montenigro et al., 2016). In studies of athletes with a history of 3 or more concussions, there were significant decreases in verbal memory scores and increases in the rates of self-reported impairments in memory, executive function, and information processing speed with these cognitive processes being studied 20–26 years after they had retired from competitive sports (Guskiewicz et al., 2005; Montenigro et al., 2016). These cognitive impairments have been reported in athletes retired from various sports including: boxers (Bailey et al., 2013; Di Virgilio et al., 2019; McKee et al., 2009; Tiberini et al., 2021), football (soccer) players (Rutherford et al., 2009; Straume-Naesheim et al., 2009), ice hockey players (Cantu and Register-Mihalik, 2011; Caron et al., 2013), American football players (Guskiewicz et al., 2005; McKee et al., 2009; Montenigro et al., 2016), and rugby players (Lewis et al., 2017; McMillan et al., 2017), all of whom had sustained multiple concussions prior to retirement. Additionally, it should be acknowledged that sub-concussive events may also play a role in long-term changes to cerebral physiology although these events do not typically present with overt concussion symptoms (Bulles et al., 2013; Dashaw et al., 2012; Smirl et al., 2020). While this will not be the focus of this current study, it is important to address this potential aspect of cerebral alteration as many athletes will experience sub-concussive events throughout their athletic careers.

While much of the relevant literature has focused on the reported cognitive changes in these retired athletes, there is limited research available that explores the long-term effects on physiological mechanisms. One mechanism that is known to be disrupted following a single concussion during the acute phase (days, weeks) is the neurovascular coupling (NVC) mechanism (Wright et al., 2017). The NVC mechanism provides the brain with the ability to adapt to increased neural activity and metabolic demand by increasing cerebral blood flow to supply oxygen and nutrients to meet this demand (Tan et al., 2014). In healthy individuals, increased neural activity in the brain causes an increase in oxygenated haemoglobin (O$_2$Hb). The concomitant decrease in deoxy-haemoglobin (HHb) reflects an increase in local arteriolar vasodilatation (a result of the increased neural activity), which increases local cerebral blood flow and cerebral blood volume (Ferrari and Quaresima, 2012). Evidence suggests that immediately following a concussion, NVC becomes uncoupled resulting in an impaired ability to meet the metabolic demands of the injured brain. A reduction in cerebral blood flow is seen immediately following a concussion and the NVC mechanism is thought to overcompensate in an attempt to meet the increased metabolic demands (Smirl et al., 2015; Wright et al., 2017, 2018). This disruption in NVC is believed to be one of the factors that contribute to concussion patients having difficulties concentrating on cognitive tasks (Smirl et al., 2016). While the immediate acute effects of concussions on NVC have been studied (Smirl et al., 2016; Wright et al., 2017, 2018), there is currently only one study of how NVC is affected long-term following multiple concussions (Sharma et al., 2020). However, emerging research suggests that a history of multiple concussions is linked to long-term impairments in NVC. For example, Sharma et al. (2020) used functional near-infrared spectroscopy (fNIRS) to measure cerebral oxygenation variables and found that measures of cerebral O$_2$Hb, HHb, and the difference between oxygenated and deoxygenated haemoglobin (HbDiff) was significantly lower in a group of elite retired rugby players, with $\geq$3 prior concussions, compared to an age-matched control group with no concussion (Sharma et al., 2020).

Near infrared spectroscopy (NIRS) is a non-invasive, optical imaging technique that can be used to monitor relative changes in haemodynamic properties (Bishop and Neary, 2018; Ferrari and Quaresima, 2012). NIRS is a valid technology for measuring cerebrovascular health (Fabiani et al., 2014a; Tan et al., 2017), bedside monitoring following moderate to severe brain injury (Gomez et al., 2020), and recovery in concussion patients (Bishop and Neary, 2018; Forcione et al., 2018; Hocke et al., 2018).

The aforementioned work by Sharma et al. (2020) provided initial evidence that post-concussion impairments in NVC may persist in the long-term. However, more research is needed to fully grasp the potential long-term effects that concussions can have on cerebral autoregulatory mechanisms. Therefore, the purpose of this study was to use cerebral oxygenation parameters to explore potential long-term physiological changes due to concussions, and to confirm the findings of Sharma and colleagues. The primary aim of this study was to explore the effects that a history of multiple concussions (mTBI) on cerebral oxygenation parameters during an NVC-eliciting task later in life in retired contact sport athletes compared to retired control athletes with no history of previous concussions. A second aim was to determine if any differences between right and left prefrontal cortex cerebral hemodynamics exist within both the mTBI group and control group. We hypothesized that cerebral oxygenation variables (O$_2$Hb, HHb, tHb, HbDiff) will be significantly lower in the mTBI group when compared to CTRL group. Additionally, based on the findings of Sharma et al. (2020), we hypothesized that there would be significant differences between the right and left prefrontal cortex oxygenation variables within our study groups.

2. Methods

Testing for this study was obtained at the University of Regina and the University of Victoria in Canada. Ethical approval from both institutional human research ethics boards was obtained prior to collection of data (REB#2017-032; REB#17–128). All procedures were conducted in accordance with the Declaration of Helsinki for the ethical testing of human subjects.

2.1. Participants

Male volunteer participants ($n = 84$; 40–75 yrs) were recruited in Victoria, BC, Canada, and Regina, SK, Canada, from December 2018 to March 2020. Out of these 84 participants, 55 were retired contact sport athletes who had sustained 3 or more concussions (Sharma et al., 2020) in their playing careers (mTBI), and the remaining 29 were concussion naïve controls with no history of concussions (CTRL). The mTBI group included rugby, soccer, American football, and ice hockey players, with some athletes playing at the elite international and national level, and community/recreational level, in their chosen sport. CTRL participants also competed in high level sports with concussion naïve athletes competing in soccer, water sports, tennis, golf, running and cycling. All volunteers were briefed on the testing protocol and purpose before signing an informed consent form. To meet the inclusion criteria, participants in both groups were required to have had played sports throughout their youth and continued to play during their adult life until they “retired” from their chosen sport. Additionally, all participants reported that they maintained an active lifestyle up to the time of testing. Demographic information and physical characteristics were collected at the time of testing (Table 1). In addition to height (cm) and body mass (kg), a brief medical history, including concussion history, was collected as well as details on sleep, meals, medication, caffeine and alcohol consumption, and exercise for the 24 h prior to testing. Subjects also completed the 5th edition of the Sport Concussion Assessment Tool (SCAT5) symptom scale (McCray et al., 2017) to assess if they were currently experiencing ongoing concussion symptoms. Exclusion criteria included any caffeine intake within 6 h, exercise within 4 h, and alcohol within 12 h, and any active concussions.

2.2. Procedure

Participants were given a simple explanation of the equipment functionality and then were properly fitted with the equipment. For most participants, two PortalLite devices (Artinis Medical Systems, Einsteinweg, Netherlands) were used to monitor both the right and left prefrontal cortex hemispheres of the brain. For 10 of the participants,
the left side was monitored with an Oxymon NIRS device which has identical functionality as the PortaLite devices (Artinis Medical Systems, Einsteinweg, Netherlands), and uses the same data collection and analysis software. Seven participants in the mTBI group were monitored with the Oxymon NIRS device while 3 participants in the CTRL group were monitored with the PortaLite and Oxymon use continuous-wave near infrared light to assess cerebral oxygenation (micro-molar, \( \mu M \)) parameters. These include: oxygenated haemoglobin (\( O_2Hb \)), deoxygenated haemoglobin (\( HHb \)), total haemoglobin (\( Hb \); \( O2Hb + HHb \)), and haemoglobin difference (\( HBdDiff \); \( O2Hb - HHb \)). \( Hb \) has been suggested to be proportional to cerebral blood volume, while \( HBdDiff \) reflects an increase in arteriolar vasodilation and subsequent increases in local cerebral blood flow and cerebral blood volume, due to the NVC mechanism (Ferrari and Quaresima, 2012). Absolute haemoglobin concentrations were determined by using spatially-resolved spectroscopy (SRS). The probe on the devices uses one receiver and 3 pairs of light emitting diodes (LED). The first pair of LEDs (760 and 843 nm) is located 30 mm from the receiver with the second pair (761 and 845 nm) located 35 mm from the receiver, and the third pair (762 and 848 nm) located 40 mm from the receiver. The probes were placed 1 cm above the participant’s eyebrows over the right and left prefrontal cortex on the lateral side of the supraorbital ridge to avoid the frontal sinus (Bishop and Neary, 2018). Both probes were covered by a black headband to secure its position on the participant and to avoid external infrared light interfering with the signal. The Quality Control Factor (QCF) built into the software indicates the quality of the optical signal and was always 99.5–100%. The devices were connected to separate Oxysoft 3.0.97.1 software using Bluetooth connection for data collection.

The Neary Protocol (Neary et al., 2019) was used to assess physiological difference between the two groups. For this study, data was gathered from the 5-min rest period and the 5-min object identification portion of the Neary Protocol. As environmental standardization is important when utilizing NIRS (Juliana et al., 2022; Wang et al., 2022), each participant was set up in a similar room with minimal external light, the same computer monitor, and minimal external distractions to avoid interference with the NIRS devices. Participants were seated 50 cm away from a 76 cm computer monitor and asked to remain still for a 5-min resting phase to establish resting physiology. Following the resting phase, an online object identification protocol was conducted to stimulate an increase in NVC. During the NVC protocol, consisting of 5-min (5 cycles of 20 s eyes closed: 40 s eyes opened and searching), participants were engaged in a complicated visual search paradigm that involves searching on a computer monitor for an object character of specific shape and colour (“Waldo”) that is hidden in a field of distractors of similar colour and shape. The “Where’s Waldo” protocol has been used and validated in previous research to elicit a NVC response with a within-subject coefficient of variance of 2–3% (Smirl et al., 2016). If the participant found “Waldo” within the 40 s of searching, then another “Where’s Waldo” novel picture was immediately presented, ensuring that the participant would continue searching until the entire 40 s segment was completed. Fig. 1 displays a representative graph of the NIRS response to the visual task of one representative participants in the mTBI group.

2.3. Data analysis

All NIRS data for each participant were filtered using a low-pass filter to remove excess noise (Bishop and Neary, 2018) prior to being exported at 10 Hz into a custom-made Microsoft Excel spreadsheet template. Variables were analysed using the computed change between the average of the maximal and minimal values (\( \Delta \text{MAX} \)) of the five, 60 s trials for each NIRS variable during the “Where’s Waldo” object identification protocol. Z-scores and standard deviations (SD) were also calculated and analysed. When examined in isolation, the raw NIRS data are relative values that are difficult to average between participants. The addition of Z-scores allows for normalization of these values and increases the signal-to-noise ratio to provide a stronger insight when comparing between participants. These analysis methods have been utilized and described effectively in previous research (Chen et al., 2019; Ichikawa et al., 2010). A required sample size of 76 participants was determined using GPower v3.1.9.2, with an accepted alpha risk of 0.05, effect size of 0.70, and power of 80%. Statistical analysis was performed (IBM SPSS v.25, Chicago, IL) with tests for homogeneity of variance (Levene’s Test). Effect size was calculated and included in all tables. Data was collected from December 2018 to March 2020. Independent student t-tests were used to compare each NIRS variable between the two groups. Paired sample t-tests were used to compare within-group right and left prefrontal cortex differences. Statistical significance was set to \( p \leq 0.05 \).

| Table 1 |
|-------------------|-------------------|-------------------|
| Group             | mTBI (n=55)        | CTRL (n=29)       |
| Mean Age (SD) (yrs) | 59 (8)*            | 64 (8)*            |
| Mean Height (SD) (cm) | 177.4 (5.5)        | 175.8 (6.7)        |
| Mean Body Mass (SD) (kg) | 91.0 (13.9)        | 84.6 (12.5)        |
| Median number of previous concussions (IQR) | 3 (1.5-5)*        | 0 (0)*             |
| Mean SCAT5 Score (SD) | 3.2 (2.0)          | 0.5 (1.0)          |

* Significant between group differences
† Effect size was measured with Cohen’s D.
3. Results

3.1. Participant characteristics

There was a significant difference in the mean age of the groups (p = 0.01), with the CTRL (mean = 64 ± 8 yrs) being older than the mTBI (mean = 59 ± 8 yrs). Mean height (p = 0.26) and body mass (p = 0.051) were not significantly different between the two groups. As per the research design, mean number of concussions were significantly different (P < 0.001), with mTBI having a minimum of 3 previous concussions, while the CTRL experienced none (Table 1). Reported SCAT5 values were not significantly different between groups (p = 0.084). No adverse events occurred during testing.

3.2. Data used for physiological analyses

Of the 55 previously concussed athletes, right-side data of 2 participants and left-side data of 9 participants were lost due to signal and equipment issues, while the left-side data of 1 CTRL participant were lost. This resulted in the analysis of the right prefrontal cortex using 53 mTBI and 29 CTRL subjects, and the left analysis using 46 mTBI and 28 CTRL subjects. Prefrontal cortex differences between the mTBI and CTRL groups are summarized in Table 2. Within-group right vs. left prefrontal cortex differences are summarized in Table 3.

No between-group differences in any haemodynamic ΔMAX, Z-scores, or standard deviations were found in the right prefrontal cortex.

Left prefrontal cortex measures showed a significantly lower HHb ΔMAX and tHb ΔMAX in the mTBI when compared to CTRL.

As provided in Table 3, within-group differences between right and left prefrontal cortex showed both the mTBI and CTRL had significantly higher left HHb ΔMAX and left tHb ΔMAX when compared to the right side. The mTBI group also showed significantly lower left HbDiff Z-scores compared to the right side which was not observed in the CTRL group. The CTRL group uniquely showed a significantly lower HbDiff SD in the left side compared to the right side.

4. Discussion

This study explored the potential long-term effects of multiple concussions on cerebral oxygenation parameters during an object identification protocol (“Where’s Waldo”). This protocol has been used in previous research in both healthy and sport concussion participants (Sharma et al., 2020; Smirl et al., 2016), and elicits the greatest NVC response when compared to other methods (Smirl et al., 2016; Wright et al., 2017). To the authors’ knowledge, only Sharma et al. (2020) used NIRS to explore the long-term effects of multiple concussions on NVC on retired contact sport athletes with a history of multiple concussions. The main findings of our study were the statistically significant differences in cerebral oxygenation between the mTBI and CTRL groups, and within-group right and left prefrontal cortex variance. These results, reflected in the changes in cerebral oxygenation parameters, provide preliminary evidence that there are potential long-term, prolonged, and minimal values (ΔMAX) of the five, 60 s trials for each NIRS variable.

![Fig. 1. Normalized Representative Graph of Left O₂Hb and HHb NIRS Response to Visual Stimulation Task. Variables were analysed using the average of the maximal and minimal values (ΔMAX) of the five, 60 s trials for each NIRS variable.](image-url)

Table 2

| NIRS (μM)     | Right Side | Left Side |
|---------------|------------|-----------|
|               | mTBI n = 53| CTRL n = 29| Levene’s Test | P-value* | Effect Size | mTBI n = 28 | CTRL n = 28| Levene’s Test | P-value* | Effect Size |
| O₂Hb ΔMAX     | 2.77 (1.12)| 2.21 (0.94)| 0.92          | 0.679     | 0.54      | 2.08 (0.64)| 2.71 (0.19)| 0          | 0.151     | 0.38      |
| O₂Hb Z        | 4.09 (2.77)| 4.19 (3.31)| 0.22          | 0.887     | 0.03      | 3.30 (1.99)| 4.52 (4.11)| 0.04       | 0.095     | 1.33      |
| O₂Hb SD       | 0.72 (0.47)| 0.90 (0.61)| 0.52          | 0.158     | 0.33      | 0.57 (0.35)| 0.97 (1.08)| 0.01       | 0.068     | 0.50      |
| HHb ΔMAX      | 0.73 (0.47)| 0.80 (0.52)| 0.26          | 0.559     | 0.14      | 0.78 (0.45)| 1.33 (1.24)| 0          | 0.031     | 0.59      |
| HHb Z         | 5.88 (3.53)| 7.09 (5.03)| 0.02          | 0.258     | 0.28      | 5.26 (2.56)| 5.59 (3.65)| 0.13       | 0.653     | 0.10      |
| HHb SD        | 0.24 (0.22)| 0.23 (0.25)| 0.78          | 0.806     | 0.04      | 0.22 (0.19)| 0.47 (0.85)| 0.01       | 0.142     | 0.41      |
| tHb ΔMAX      | 2.70 (1.51)| 2.72 (1.29)| 0.98          | 0.954     | 0.01      | 2.53 (0.95)| 3.79 (3.11)| 0          | 0.044     | 0.55      |
| tHb Z         | 5.12 (3.48)| 5.53 (3.35)| 0.08          | 0.633     | 0.12      | 4.61 (2.88)| 5.45 (4.48)| 0.07       | 0.328     | 0.22      |
| tHb SD        | 0.87 (0.66)| 1.06 (0.86)| 0.38          | 0.261     | 0.25      | 0.72 (0.49)| 1.39 (1.88)| 0.01       | 0.076     | 0.49      |
| HbDiff ΔMAX   | 3.11 (2.01)| 3.14 (2.84)| 0.35          | 0.95      | 0.01      | 3.15 (1.74)| 3.18 (2.65)| 0.04       | 0.075     | 0.46      |
| HbDiff Z      | 6.55 (0.34)| 7.77 (0.46)| 0.26          | 0.183     | 0.30      | 0.50 (0.29)| 0.63 (0.38)| 0.27       | 0.108     | 0.38      |

* Significance between group differences (If Levene’s test was significant, p values were used to reflect unequal variance).
* Z-scores are unitless values.
* Effect size was measured with Cohen’s D.
effects on NVC in former contact sport athletes with a history of multiple concussions.

The prefrontal cortex plays a major role in executive functioning, task focusing, and personality. By using two optical probes, each monitoring one side of the prefrontal cortex, this study explored differences in NVC in former contact sport athletes with a history of multiple concussions. Both cells are part of the neural network involved in executive functioning and cognitive decline, and their function can have an impact on the neural networks in the brain which can lead to behavioural and cognitive declines that are often reported in individuals with a history of multiple concussions (Guskiewicz et al., 2005; Iverson et al., 2012; Montenigro et al., 2016).

It is important to note that there are some major differences between these studies, as Sharma and colleagues used an 8-channel functional NIRS device that was able to explore regional differences of the prefrontal cortex, while the current study was limited to a single channel and a single region on which to explore each side. However, our study also had double the sample size in mTBI participants which could account for some of the differences. Another major difference between studies was that Sharma et al. (2020) used mainly ex-professional and elite amateur rugby players, while the mTBI participants in the current study included a range of elite international, national and community-level former athletes from different sports (soccer and rugby).

Another study by Hocke et al. (2018) again supports the use of NIRS to potentially help identify biomarkers in concussion recovery. Hocke et al. (2018) used NIRS to examine cortical communication patterns in prefrontal and motor areas in adults with persistent post-concussion syndrome (PPCS). While there are differences between the studies, mainly being that their study population was still endorsing a high volume of concussion symptoms, it is interesting to note that they found significant differences in functional connectivity between different regions of the prefrontal cortex as assessed across by using utilizing NIRS (Hocke et al., 2018). These limited studies suggest that there might be a role for NIRS in the diagnosis, monitoring, and management of individuals not only suffering from active concussion symptoms, but who might have lingering impairments later in life.

NVC is thought to be regulated by astrocytes and microglial cells (Muoio et al., 2014), and prolonged disruptions in the proper function of these cells may explain why there are potential long-term impairments in individuals with a history of multiple concussions. Both cells are part of the neurovascular unit that acts as part of the blood brain barrier to respond to changes in cerebral homeostasis (Muoio et al., 2014). They do so by influencing blood vessel control (Muoio et al., 2014), and act as mediators for cerebral blood flow control (Muoio et al., 2014). It is known that the biomechanical forces experienced during a concussion can have an impact on the neural networks in the brain which can lead to difficulties with cognition (Giza and Hova, 2014). Although these impairments usually resolve over time, being exposed to repeated sub-concussive forces or sustaining multiple concussions, often experienced by contact athletes, may lead to these systems being affected later into life. These long-term changes have been observed in retired boxers (Bailey et al., 2013; Di Virgilio et al., 2019), American football players (McKee et al., 2013), military personnel (Mac Donald et al., 2011), and individuals with post-concussion syndrome (Di Virgilio et al., 2016; Pearce et al., 2019). Long-term impact to the neurovascular unit may be one reason why there are observed differences in measured HHb and tHb.
in the mTBI group of this study compared to CTRLs. It is possible that these impairments to the neurovascular unit, negatively impact the physiological mechanisms which control NVC leading to the delayed response as would normally happen in healthy, concussion naïve individuals.

The inability to focus or concentrate immediately after a concussion is a common symptom that has been reported (Chen et al., 2007; King et al., 1995). Although concussion patients are usually able to overcome these impairments, many retired contact sport athletes observe that their ability to focus and concentrate decreases as they age (Guskiewicz et al., 2005; Montenigro et al., 2016). The majority of the mTBI participants in our study complained of challenges to their general ability to focus and concentrate during daily activities. This is potentially reflected in the differences in SCAT5 scores between the mTBI and CTRL groups as the mTBI group did have a higher starting baseline score. Although not statistically significant, there was a large effect size between the two groups. Future studies should explore this further to determine whether these complaints are expected, age-related decline or if they could be explained, at least in part, by potential impairments to the NVC mechanism.

Additionally, although not statistically significant, there were several measures in this study that showed a trend toward physiological differences in oxygenation parameters. Notably, many of the left-side standard deviation (SD) variables had large differences (20–52% greater values) between the mTBI group and the CTRL group and although not statistically significant, shows to be potential variables to explore in future research. Variance and randomness are associated with healthy physiological function in many systems (Bishop et al., 2017; Pincus, 1991), therefore it is important to observe the response of NIRS SD values that occurred in the different groups. It has been suggested that disease or injury may suppress the usually observed variance in a physiological system (Bishop and Neary, 2018; Pincus, 1991; Thayer et al., 2012). The trending differences in SD values in this study may provide clues that there are long-term dysfunction to the physiological processes in individuals with a history of concussions.

Both the mTBI and CTRL groups demonstrated significant bilateral prefrontal cortex differences in HHb ΔMAX and tHb ΔMAX. Other studies have shown similar differences between the right and left hemispheres during NVC eliciting tasks in healthy subjects (Phillips et al., 2016; Sharma et al., 2020). As mentioned previously, larger variances in physiological processes is associated with healthier physiological function (Bishop et al., 2017; Pincus, 1991). While the CTRL group did show significant differences in HbDiff SD between right and left prefrontal cortices, the mTBI group did not. The supressed variance in HbDiff SD of the mTBI group may indicate that this group is more likely to be experiencing an impaired state (Bishop and Neary, 2018; Pincus, 1991; Thayer et al., 2012).

It is important to note that the normal aging process does influence NVC in both human and mice models with reduced maximal activation and larger variability in O2Hb in older adults (Balbi et al., 2015; Fabiani et al., 2014b; Zaletel et al., 2005). There are many factors that contribute to an aging related uncoupling including increases in oxidative stresses, endothelial dysfunction, and astrocyte dysfunction (Sorond et al., 2013; Taranantini et al., 2017; Toth et al., 2013). There were significant differences between the ages of the participants in the two groups. While the wide age range is a limitation, it is inherent in a population of retired athletes. This is a real-world scenario and directly represents what would be seen when studying retired athletes. However, since the CTRL group was older and still showed significant difference between cerebral oxygenation variables, it may be possible that these differences are occurring regardless of any potential effect of aging.

There are several important limitations to acknowledge in this study. Due to equipment limitations, 10 subjects in this study had their left prefrontal cortex measurements using the Oxymon NIRS device instead of the Portalite NIRS devices, however, both devices are made by the same manufacturer and use the same software. Since both systems function in the same manner, the data gathered and analysed with one device would be consistent with the other. Additionally, due to the age of the participants the differential path-length factor (DPF) calculation of the NIRS devices was not able to be specific for each participant. DPF calculations consist of values up until the age of 50 (Kohl et al., 1998), and are used in the NIRS calculations to determine the thickness of the medium the light is travelling through. Since the majority of participants in this study were above the age of 50, the maximal DPF value of 6.26 was used for all participants (Duncan et al., 1996). As a consequence, this may have led to an underestimation of the NIRS variables. It is also important to consider the placement of the NIRS probe and although previous research has used the posterior and medial cerebral arteries to assess cerebral blood flow velocity to investigate NVC (Smirl et al., 2016; Wright et al., 2018), we elected to use the prefrontal cortex using NIRS because of the known executive function of the prefrontal cortex when performing activities that stimulate NVC activity (Bishop and Neary, 2018; Hocke et al., 2018; Sharma et al., 2020). Signal consistency over the 5-min object identification period was also a potential limitation for a number of participants. Participants were instructed on how to properly sit during the object identification protocol so as to optimize the NIRS signal by limiting as much head movement as possible. The data on concussions were self-reported by the participants and could have led to inaccuracies on the reported number of concussions experienced over the course of the participant’s life. Finally, specific demographic information on age of retirement from competitive sports, time since last concussion, hand dominance, and current physical activity level was not collected. Additionally, range of the number of concussions experienced by the mTBI group (3–15 reported concussion), range of ages (40–75 years), extent of physical activity later in life, and SCAT5 scores may be potential confounding variables. Future studies should explore these factors for any potential confounding effects that they might have on cerebral oxygenation parameters as well as attempt to age-match participants and control for the extent that participants participated in physical activity later in life as these could be factors that influence cerebral physiology.

In summary, this study provided preliminary evidence that there are potential long-term changes to cerebral oxygenation parameters during an NVC eliciting task in retired contact sport athletes who experienced multiple concussions and supports previous research by Sharma and colleagues who also showed altered oxygenated and deoxygenated hemodynamic activity at the prefrontal cortices. The significant differences observed in the left prefrontal cortex for HHb ΔMAX and tHb ΔMAX in the mTBI group compared to the CTRL group during the object identification protocol suggest that the mTBI group may have prolonged disruptions in their ability to adapt cerebral blood flow to increase neural demands. Additionally, the expected large variation in HbDiff SD between hemispheres was not observed in the mTBI group, providing further evidence of potential impairment. Although these data suggest the presence of impairments, clinical relevance currently remains to be fully elucidated. Understanding the changes that occur in the brains of previously concussed retired contact sport athletes can better guide development of novel post-concussion treatment options, and more effectively target impaired systems for intervention with treatment options that are currently available. Importantly, these would not only be for the older athlete but could also guide treatment and preventative options for younger athletes to avoid any potential long-term impairments to the NVC mechanism. However, our collective results support the findings by Hocke et al. (2018) that showed reduced functional connectivity, which reflect altered NVC, in adults with persistent post-concussion symptoms (Schumacher et al., 2019).

Future research is warranted to determine the severity of cerebral haemodynamic impairments that occur on a long-term basis in retired athletes. This could be accomplished by conducting longitudinal studies to follow athletes from their competitive playing careers, into their recreational careers and beyond. A focus should also be made to determine if any long-term effects of multiple concussions exist for
females. Finally, additional studies exploring an integrative physiology approach (e.g., cerebral blood flow response, blood pressure, and expired gas analysis) are needed to fully assess the impact of former concussions, and particularly multiple concussions, on long-term performance of physiological systems. Providing greater insight into how these systems are affected over time could lead to the development of potential solutions for retired athletes who are currently experiencing impairments and can better direct intervention strategies early in the concussion recovery process to minimize the effects that concussions can have for long-term.

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CRediT authorship contribution statement

Luke W. Sirant: Writing – original draft, Writing – review & editing. Methodology, Conceptualization, Formal analysis, Data curation. Jyotpal Singh: Writing – review & editing. Methodology, Conceptualization, Software, Formal analysis, Data curation. Steve Martin: Writing – review & editing, Conceptualization, Funding acquisition. Catherine A. Gaul: Writing – review & editing, Methodology, Conceptualization, Funding acquisition, Project administration. Lynneth Stuart-Hill: Writing – review & editing. Methodology, Conceptualization, Funding acquisition. Darren G. Candow: Writing – review & editing, Methodology. Cameron Mang: Writing – review & editing, Methodology. Patrick Neary: Writing – review & editing. Supervision, Funding acquisition, Conceptualization, Resources, Project administration.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Steve Martin reports financial support was provided by Canadian Academy of Sport and Exercise Medicine.

Data availability

The data that has been used is confidential.

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