ASSESSING PRE-FRONTAL CORTEX OXYGENATION AFTER SPORT CONCUSSION WITH NEAR INFRARED SPECTROSCOPY

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Scott Allen Bishop, candidate for the degree of Master of Science in Kinesiology and Health Studies**,** has presented a thesis titled, ***Assessing Pre-Frontal Cortex Oxygenation After Sport Concussion With Near Infrared Spectroscopy,*** in an oral examination held on July 21, 2016. The following committee members have found the thesis acceptable in form and content, and that the candidate demonstrated satisfactory knowledge of the subject material.

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Abstract

Clinicians typically rely on neuropsychological and balance tests to track concussion recovery. These balance and neuropsychological tests only imply impairments that are based on performance – the tests do not directly measure (or reliably track) brain physiology throughout concussion recovery. Because of these issues, there has been a call to find an objective biomarker that can index both severity and the timeline for recovery. An additional problem is that, with the amount of concussions occurring at a recreational activity level, an effective biomarker must be cost effective, easily applied, and easily interpreted for lay people.

To address these issues, non-invasive near infrared spectroscopy (NIRS) was used to assess pre-frontal cortex oxygenation, by measuring relative changes in oxy- (HbO_2) and deoxy-hemoglobin (HHb), and the associated standard deviations. Resting hemoglobin, and hemoglobin changes in response to increases in CO_2 (induced by 20s breath-holds), were measured in all participants. Data were aggregated into healthy baselines (n = 115), and concussed participants on days 1-3 (n =14), 4-6 (n = 8), and 7-14 (n = 11). The data were statistically compared using 1 x 4 ANOVAs.

Results showed that resting HbO_2 values progressively lowered from days 1-3 to 7-14 (with no differences compared to controls). This is a similar statistical trend to a previous functional magnetic resonance imaging study that focused on concussions (Meier et al., 2015). The second major finding showed that hypercapnic HbO_2 standard deviation was lower than resting values in days 1-3 and 4-6, but reversed back towards the healthy control group as the injury abated. Monitoring pre-frontal cortex

oxygenation changes is a viable biomarker to assess the physiological state of the brain following concussion.

Keywords: concussion, pathophysiology, near-infrared spectroscopy, hypercapnia

Acknowledgments

I began this journey in 2011, when I was entering my 3rd year of undergraduate studies. At the time, all of my peers trod down the path towards medicine. And sadly, at that juncture I lost a friend to an overdose, and a high school classmate was murdered. Within the next year, a second friend was lost to overdose, a third was sent to rehab, and my grandfather died. All of this changed my life. It made me question my own morals. And it made me think that perhaps following the status quo, in regard to joining my pre-medicine friends on their quest, wasn't such a good idea. Life is short after all, so it seems that making your own decisions now, is better than questioning your own alternatives later.

And with these influences I chose my own path, in pursuit of objective truths. I had support from many people along the way, and if it not for them, I wouldn't be the person I am today. So, I send the most heart-felt, unpayable thank-you to my parents and brother, for the countless phone calls. Your support and love has been a rock when times were tough, and has provided me with fond memories throughout my successes. Thank you to Carmen Mezzadri for being with me throughout my journey - without your support and love I would not have made it to this point. To Drs Ashish and Aseem Grover, Sam Bryce, Justin Raine, Josh Thiessen, and Nav Dhaliwal - your support and friendship means the world to me. Friends are the family we choose for ourself. Finally, to Drs Patrick Neary, Paul Bruno, and Kim Dorsch - thank you for the guidance in my pursuit of knowledge, and to Dr Martin for serving as my external examiner. I appreciate everyone’s efforts on my behalf.

Scott Bishop
"Passion, Perseverance, Humility"

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List of Abbreviations, Symbols, and Nomenclature

ACA - Anterior Cerebral Artery

ACC - Anterior Cingulate Cortex

Ach – Acetylcholine neurotransmitter

ACTH – Adrenocorticotrophic Hormone

ApEn - Approximate Entropy

BC-CRP – British Columbia Concussion Recovery Protocol

BH - Breath-hold

BNST - Bed Nucleus of Stria Terminalis

BOLD fMRI – Blood Oxygen Level Dependant Functional Magnetic Resonance Imaging

CA – Cerebral Autoreguation

cAMP - Cyclic Adenosine Monophosphate

CBF – Cerebral Blood Flow

CDC – Center of Disease Control

CO_2 – Carbon Dioxide

CPP – Cerebral Perfusion Pressure

CTE - Chronic Traumatic Encephalopathy

CW – Continuous Wave

dCA – Dynamic Cerebral Autoregulation

dlPFC / DLPFC - Dorsolateral Prefrontal Cortex

DVMN - Dorsovagal motonucleus

ECG - Electrocardiography

fMRI - Functional Magnetic Resonance Imaging

fNIRS - Functional Near Infrared Spectroscopy

GABA – Gamma Amino Butaric Acid (Inhibitory Neurotransmitter)

GCS/S – Glasgow Coma Scale / Score

HHb - Deoxyhemoglobin

HbO_2 - Oxyhemoglobin

HR - Heart Rate

ICP – Intracranial pressure (mmHg)

ImPACT test – Immediate Post-Concussion Assessment and Cognitive Testing

LC - Locus Coeruleus

LED – Light Emitting Diode

M1 - Primary Motor Cortex

MAP - Mean Arterial Pressure (mmHg)

MCA - Middle Cerebral Artery

MCAV – Middle Cerebral Artery Velocity (cm/s)

MCAVmean – Middle Cerebral Artery Velocity Average (cm/s)

MCAVend /min / dias – Middle Cerebral Artery Velocity Diastolic (cm/s)

MCAVpeak / sys – Middle Cerebral Artery Velocity Systolic (cm/s)

mTBI - Mild Traumatic Brain Injury

Mx – Correlation between CPP and MCAVmean

NAA:Cr – N-Acetyl Aspartate:Creatine ratio

NHL – National Hockey League

NFL – National Football League

NIRS - Near Infrared Spectroscopy

NMDA Receptor – N-Methyl D-Aspartate Receptor (excitatory / glutamate receptor)

NO – Nitric Oxide

NTS - Nucleus of the Solitary Tract

NVC – Neurovascular Coupling

P300 – An electroencephalogram event-related-potential

PCO_2 – Pressure of Carbon Dioxide

$PETCO_2$ – End Tidal Carbon Dioxide Pressure (mmHg)

$PETO_2$ – End Tidal Oxyegn Pressure (mmHg)

PCA1- Posterior Cerebral Artery Section 1 (flow towards)

PCA2 - Posterior Cerebral Artery Section 2 (flow away)

PFC - Prefrontal Cortex

PKA/C - Protein Kinase ‘A’ and ‘C’

PM – Premotor Area

PO_2 – Pressure of O_2

PRx – Correlation between ICP and MAP

PVN - Paraventricular Nucleus

QCF - Quality Control Factor

RAS – Reticular Activating System

SCAT - Sport Concussion Assessment Tool

SED – Scaled Error Detection (control theory model)

SS - Squat-Stand

TBI - Traumatic Brain Injury

TCD - Transcranial Doppler Ultrasonography

TOI - Tissue Oxygenation Index

TSI - Tissue Saturation Index

V1 - Primary Visual Cortex

vmPFC / VMPFC - Ventromedial Prefrontal Cortex

1.0 - Introduction

Sport-related concussion rates of injury have steadily increased since the 1980's (Guerriero, Proctor, Mannix, & Meehan, 2012; Hootman, Dick, & Agel, 2007), but the management of this brain injury is without an objective biomarker for indexing concussion recovery. Despite the rise in injuries, even the exact definition of a concussion is difficult to state, as the injury exists on a continuum of brain injury severity, and has numerous misnomers which describe brain injuries with overlapping symptoms and required measurements (Fabbri et al., 2004; Gaetz, 2004; McCrory et al., 2009; Shaw, 2002).

To avoid this confusion in working definitions, a *sport concussion* will be defined in this project using the following criteria: 1) a brain injury acquired during a competitive sporting practice, or sanctioned sporting event; 2) a brain injury that is medically diagnosed; 3) a brain injury which is acquired through direct contact to the skull, or through a body blow which kinetically transfers forces and places the brain in motion within the skull (Gaetz, 2004; McCrory et al., 2009; Ommaya & Gennarelli, 1974); 4) a brain injury with a potential acute loss of consciousness, with symptoms spontaneously resolving within 7-10 days (Hou et al., 2012; McCrory et al., 2009; Shehata et al., 2009); and 5) a brain injury in which no skull fractures or brain structure deficits are present (Fabbri et al., 2004; McCrory et al., 2009). A non-sport concussion would thus be defined in this project, as an acquired brain injury that meets all of the above stipulations, minus the injury being acquired in a sport setting.

Moreover, the definitions of concussion and mild traumatic brain injury (mTBI) have some overlap in terms of symptoms and measured outcomes (see section 2.3 for

more detail), and are used interchangeably in the literature (Fabbri et al., 2004; McCrory et al., 2009). Thus, this project is susceptible to interpreting mTBI pathophysiology as the pathophysiology which would be expected in a concussion and/or a sport concussion. It is also worth noting that mTBI and concussion are both on the mild end of the brain injury spectrum. Traumatic brain injuries (TBIs) result in outcomes that do not spontaneously resolve, have structural deficits, and can be incurred through a kinetic transfer of forces, or through the absorbance of forces onto the skull (Gaetz, 2004; Ommaya & Gennarelli, 1974; Shaw, 2002; Wilberger, Ortega, & Slobounov, 2006).

Knowing that the definition of a concussion is somewhat convoluted, it is unsurprising that the clinical management of a concussion is also cumbersome. The Immediate Post-Concussion Assessment and Cognitive Testing protocol (henceforth referred to as the *ImPACT test*, Pittsburgh, PA, USA, 2015), is arguably the most widely used neuropsychological protocol for concussion assessment (Broglio, Ferrara, Macciocchi, Baumgartner, & Elliott, 2007; Cogstate Ltd, 2016; ImPACT Applications Inc., 2016). Thus, the use of the ImPACT test could be inferred as the test that neuropsychologists are referring to when they state that their own profession is the "cornerstone," (amongst a battery of other measures) (Aubry et al., 2002), that should be used when clinicians make return-to-play decisions (Aubry et al., 2002; Broglio et al., 2007; Collins, Iverson, Gaetz, Iii, & Lovell, 2012; Ritchie et al., 2015).

Early studies of the ImPACT test were lauded as being able to detect changes in cognition in the week following a diagnosed concussion (Iverson, Lovell, & Collins, 2003). However, more recent studies show that the test-retest reliability of the ImPACT assessment, and the environment in which the ImPACT test is taken, can both indicate

cognitive impairments in healthy participants - i.e., a false positive (Broglio et al., 2007; Resch, Macciocchi, & Ferrara, 2013; Resch, McCrea, & Cullum, 2013; Resch, Driscoll, et al., 2013; Schatz & Ferris, 2013; Schatz, Pardini, Lovell, Collins, & Podell, 2006). This is further compounded by athletes who consciously try and lower their baseline ImPACT test score, with some athletes being successful (Erdal, 2012). It is also noted that the Zurich Consensus on Concussion in Sport (McCrory et al., 2009) indicates that "*cognitive recovery largely overlaps with symptom recovery, [but,] it has been demonstrated that cognitive recovery may occasionally precede or more commonly follow clinical symptom resolution*." (McCrory et al., 2009, p.38).

In combing the above statement with research projects that indicate an inability of the ImPACT test to consistently align healthy asymptomic patients with no cognitive impairments (and vice versa), it seems that the ImPACT test should be questioned when returning athletes to sport. Alternatively, the ImPACT test results could, and likely must be considered in terms of physiological impairments (Bigler, 2015; Fox, 2011; Iverson, Echemendia, LaMarre, Brooks, & Gaetz, 2012; Kontos et al., 2014; Talavage et al., 2010). Moreover, there are other management practices which rely on balance testing pre- and post-injury (Guskiewicz, 2011). Once again, the reliability of these balance tests show that performance-based measurements without objectivity and physiological context, are unreliable (Buckley, Oldham, & Caccese, 2016; Finnoff, Peterson, Hollman, & Smith, 2009; Hunt, Ferrara, Bornstein, & Baumgartner, 2009; Onate, Beck, & Lunen, 2007; Starling, Leong, Bogle, & Vargas, 2015; Susco, Valovich McLeod, Gansneder, & Shultz, 2004; Wilkins, Valvovich Mcleod, Perrin, & Gansneder, 2004).

The current issue of poor concussion management is only compounded by epidemiological studies which further demonstrate why an objective biomarker is needed by the research and clinical fields. The Centre for Disease Control recently published an estimate that 1.7 million traumatic brain injuries occur each year in the US, with a conservative estimate of 1.6 – 3.8 million mild head injuries also being sustained (Daneshvar, Nowinski, McKee, & Cantu, 2011). More focused epidemiology studies have reported that concussions account for 8.9% of all high school athletic injuries, and 5.8% of all collegiate-level athletic injuries (Gessel, Fields, Collins, Dick, & Comstock, 2007). Within high school and collegiate athletics, American football produces the most concussions, with other contact sports such as ice hockey, and both men's and women's lacrosse, also producing high rates of concussion (Guerriero et al., 2012).

Given the magnitude of the problem it is imperative to develop objective indices and/or biomarkers that can index nervous system dysfunction, and better facilitate concussion management. Ideally these biomarkers would be difficult for participants to consciously alter, would have high inter- and intraclass correlations, and these biomarkers would also be easy for civilians to interpret.

To solve this concussion biomarker issue, some brain injury researchers have been examining the frontal lobe's contribution to medullary function, which includes understanding how a loss of brain function exerts effects on healthy variance of other systems (Blake, McKay, Meeuwisse, & Emery, 2015; Kontos et al., 2014; Lang, Czosnyka, & Mehdorn, 2003; Len et al., 2013; Ryan, Thorson, Otero, Vu, & Proctor, 2011; Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012; Urban, Barlow, Jimenez, Goodyear, & Dunn, 2015; Zweifel et al., 2008, 2010). This is because the frontal lobe

can alter both the medulla's capacity to monitor the unconscious processes (such as cardiorespiratory status), and conscious processes such as reaction time (Goodale & Milner, 1992; Lovallo, 2005; Sakagami, Pan, & Uttl, 2006; Taylor, Goehler, Galper, & Innes, 2010). Moreover, the medulla is known to be affected when a brain injury of any severity occurs (as indicated by the presence of unconsciousness) (Bishop & Neary, 2015; Gaetz, 2004; Ommaya & Gennarelli, 1974; Shaw, 2002).

Knowing that the frontal lobe can influence medullary function, and that brain injuries occur in the cortical layers, it is not surprising that recent publications have successfully shown that unconscious brain blood flow is perturbed when metabolic demands (globally or regionally) are placed on the brain (Kontos et al., 2014; Len et al., 2011, 2013; Meier et al., 2015; Mutch et al., 2014; Urban et al., 2015). When healthy, the cardiorespiratory centres in the medulla (or in a brain region), initiate a vasodilator response to an increase in metabolism which increases cerebral blood flow. This healthy response has been measured using functional magnetic resonance imaging (Fabiani et al., 2014; MacIntosh, Klassen, & Menon, 2003), transcranial Doppler ultrasound (Vernieri et al., 2004), and with near infrared spectroscopy (NIRS) (Fabiani et al., 2014; Lee et al., 2009; Molinari, Liboni, Grippi, & Negri, 2006). Again, all of these different cerebrovascular measures have shown that concussions alter these vasodilator processes (Kontos et al., 2014; Len et al., 2011, 2013; Meier et al., 2015; Slobounov, Gay, Johnson, & Zhang, 2012; Slobounov et al., 2011; Urban et al., 2015).

To date, transcranial Doppler, and functional magnetic resonance imaging have been used more frequently to assess the physiological status of concussions and brain injury severities that are more life threatening, and are more prone to structural damage

(commonly cited as Traumatic Brain Injuries – TBIs) (Brady et al., 2009; Critchley et al., 2003; Czosnyka, Smielewski, Piechnik, Steiner, & Pickard, 2001; Johnson et al., 2012; Len et al., 2011, 2013; Meier et al., 2015; Militana et al., 2015; Slobounov et al., 2012; Zweifel et al., 2010, 2008). However, more recently, near infrared spectroscopy (NIRS) has been used as a non-invasive, relative measure of cerebral oxy- and deoxy-hemoglobin concentration following concussion (Kontos et al., 2014; Urban et al., 2015).

To this author's knowledge, only two publications have focused on relative cerebral oxy- and deoxy- hemoglobin measures in humans post-concussion (Kontos et al., 2014; Urban et al., 2015). Briefly, the first hemoglobin-concussion publication utilized functional NIRS (fNIRS) to measure relative hemoglobin changes in the frontal lobe, and assessed the coupling of cortical activity to metabolite delivery during the ImPACT test. In general, the results showed that concussed participants, (who were still exhibiting symptoms within 15-45 days post injury), had less changes in oxyhemoglobin (HbO_2) during the ImPACT test, and performed worse on the test outcomes when compared to controls (Kontos et al., 2014).

The second study assessed the coherence of the fNIRS signal across (and within) the motor cortex of patients who suffered a concussion. These patients experienced post-concussive symptoms ranging from 31 – 473 days after injury. This post-concussive group revealed decreased intra- and inter-hemispheric oxyhemoglobin and total hemoglobin coherence values during a simple finger tapping task when compared to healthy controls (Urban et al., 2015). It is also noted that the participants in this study (Urban et al., 2015), whom were experiencing symptoms 731 days post-injury do not actually qualify as concussed individuals, as the literature has indicated that any

concussion in which symptoms last longer than 90 days is considered to be a case of post concussion syndrome (Dean, O'Neill, & Sterr, 2012; Jotwani & Harmon, 2010; King, 2003; Willer & Leddy, 2006).

Having identified only two publications which focus on relative hemoglobin changes after concussion, this thesis seeks to add to that body of knowledge. This paper will first provide the reader with relevant background information. The background literature will review healthy neurophysiology, cerebrovascular physiology, the brain injury continuum, and NIRS applications. The last portion of the review will be a summary of previously discussed content, after which, the outcomes of this project will be stated, followed by the methods, results and project discussion.

2.0 – Background Literature: Healthy Neurophysiology, Cerebrovascular Physiology, and Brain Injury

Previous research has demonstrated that cellular disturbances accompany traumatic brain injury and concussion (Collins et al., 2012; Gardner et al., 2014). These cellular changes result in global manifestations that are observed in terms of altered healthy electrochemical variance in the brain, and altered cerebrovascular regulation. In humans, it is known that normal function of cerebral vascular responses is dependent on oxygen utilization that is occurring for a given metabolic stats of a neuron, and how much metabolic by-product is being generated. However, limited data are available which examines the effects of concussion on cerebral flow and metabolic status in humans. Hence, this review will focus on healthy neurophysiology from a cellular and neurocircuit level, and will be followed by overlaps in healthy cerebrovascular physiology. The cerebrovascular physiology will focus on enhanced blood flow that is

brought on by metabolic changes via chemodetection processes. After these topics, brain injury modelling and physiology will be discussed, and paired with research that focuses on cerebral oxygenation.

2.1 - Neurophysiology

2.1.1 – Cellular homeostasis. *Cellular homeostasis* is processes that can be used to identify and regulate healthy energy requirements, electrochemical variance, and synapse structure, and thus can be objectively examined after a concussion. The regulation of energy will be discussed in the next section of this thesis, as metabolite delivery is reliant on the electrochemical variance, which concomitantly activates blood flow increases (Fabiani et al., 2014).

In terms of electrochemical variance, the synapse can be directly or intrinsically modified which increases the variance of calcium influx into the neuronal cytoplasm. This is a sign of healthy electrochemical homeostasis (O'Leary & Wyllie, 2011). Direct modification of the synapse occurs when synaptic densities of glutamate receptors (known as NMDA receptors), are increased or decreased. The direct increase in NMDA density can be accomplished in a variety of ways, including: 1) increased second-messenger-induced gene expression, 2) enhanced (synapse specific) cellular targeting of synthesized receptors, and 3) increased golgi organelle receptor recycling back to the synapse (Mcpherson, Ritter, & Augustine, 2008; Turrigiano, 2008). The direct increase in receptor density via second messenger pathways can be accomplished by cyclic adenosine monophosphate (cAMP) which can activate cFos genes. The resultant proteins that are associated with the expression of these cFos genes, will ultimately lead to a persistent enhancement of proteins synthesis that result in long term changes to the cell's

environment (Vaynman & Gomez-Pinilla, 2005). This pathway is also independent of calcium, and is considered an intrinsic modifier (Cohen et al., 2011).

The use of cAMP also activates protein kinase A and C (PKA/C), which can extrinsically modulate NMDA-receptor-mediated calcium currents. When an NMDA receptor is phosphorylated the result is an increased amount of calcium fluxing into the cytosol (Rebola, Srikumar, & Mulle, 2010). These intrinsic and extrinsic cAMP pathways can directly or indirectly modify the synapse, which again, leads to healthy electrophysiological homeostasis (Heusner & Martin, 2008; O'Leary & Wyllie, 2011).

To further the topic of cellular homeostasis and healthy electrochemical variance, it has been reported that cultured neurons that are depraved of external stimuli gain the ability to independently depolarize, but when the external inputs are restored, this ability is lost. This provides evidence for neuronal homeostasis where regulating intracellular calcium is achieved with and without external inputs.

From a fundamental biology standpoint, the presence of homeostasis requires both feed-forward and feedback mechanisms. Feed-forward mechanisms are thought of as synaptic neuromodulators as these mechanisms typically rely on altering the amount of calcium influx, without any regard for the present state of intracellular calcium (O'Leary & Wyllie, 2011). A feed-forward example is the previously mentioned extrinsic cAMP-PKA/PKC pathway. In this feed-forward scenario, NMDA receptors can be phosphorylated and increase the amount of fluxing calcium, irrespective of the current intracellular level of calcium (Gallagher, Orozco-Cabal, Liu, & Shinnick-Gallagher, 2008). Feedback mechanisms are likely a far more intricate process for

monitoring intracellular calcium with relation to external input (Turrigiano, Abbott, & Marder, 1994).

Despite not fully knowing how feedback and feed-forward mechanisms regulate internal ion concentrations, one idea put forth from a control theory perspective is the combination of scaled error detection (SED) and bang-bang models. Specifically, SED describes a neuron's constant attempt to correct the over- or under-shoot of intracellular calcium during stimulation. Over time, the constant corrections for over- or under-shooting can lead to a net of zero error, but this is only if a constant calcium input is present (which neurons do not have). Conversely, the bang-bang model dictates that no corrections are made below a set point, but once surpassed, 'bang', the mechanism is active until corrected, then 'bang' it is off (O'Leary & Wyllie, 2011). Again, both of these are potential control theory paradigms that can be used to describe how neuronal feedback works. What is known is that electrochemical homeostasis is indirectly monitored, and that both feedback (SED or bang-bang) and feed-forward (bang-bang) can utilize many different cellular pathways. This includes processes like manipulating the number of synthesized proteins for synaptic influxes (feedback), and the phosphorylating of NMDA receptors (feed-forward). However, it must also be noted that these feedback mechanisms have been over-simplified, and likely rely on integration of other intrinsic/indirect signals which determines the direction and strength of response (O'Leary & Wyllie, 2011; Tymianski & Tator, 1996).

Having touched on the homeostasis of metabolite and electrochemical variance, the last topic is the structural maintenance of the cell. Microtubules are thought to play a prominent role in structural plasticity and cytoarchitectural homeostasis. Experiments

with embryogenic Drosphila neurons have been used as models to understand synaptic regulation, as cells during this life stage only use one neurotransmitter - acetylcholine (Ach). One experiment used these cells and genetically manipulated them to target for both Ach over-expression and suppression. The results from this showed that over-expression in Ach resulted in a decreased postsynaptic dendritic arbor; whereas Ach suppression significantly increased the postsynaptic arbor (Tripodi, Evers, Mauss, Bate, & Landgraf, 2008). The overall conclusions from this study were that structural plasticity and/or homeostasis can operate on a localized scale. The authors of this experiment also explicitly noted that, manipulating gene expression only leads to altered presynaptic vesicle density changes, and does not guarantee voltage differences across the cleft. Thus, the integrated role of electrophysiology (and the second messenger system) must be further studied to understand how electrical stimulation can act as a stop or start growth signal for dendritic arbors (Avila, Lucas, Perez, & Hernandez, 2004; Tripodi et al., 2008; Turrigiano, 1999). In lay-terms, Turrigiano's (1999) article title is an excellent summary of the interactions between electrical and structural interaction – "the more things [intrinsic and extrinsic electrophysiology] change, the more they [dendrite structure] stay the same."

To briefly put these paragraphs back into the context of this thesis, when a brain injury is sustained the ability to maintain cellular homeostasis from a metabolite, cytoarchitectural, and electrochemical perspective is disturbed (Barkhoudarian, Hovda, & Giza, 2011; Giza & Hovda, 2001). The above paragraphs were an overview of some of the physiology processes which need to recover. The cellular pathophysiology will be discussed in the brain injury section of this thesis.

2.1.2 – Neurophysiology summary. This section discussed the stability of the nervous system, by highlighting how feed-forward and feedback mechanisms can maintain electrochemical and cytoarchitectural homeostasis under healthy conditions. These feed-forward and feedback processes typically use receptor modification and gene expressions to try to indirectly monitor intracellular calcium by both integrated scaled error detection, and bang-bang theories of control (O'Leary & Wyllie, 2011). Furthermore, the variance in electrophysiology interacts with dendritic arbors to maintain cytoarchitectural homeostasis. Research for this concept suggests that arbors are stabilized with higher amounts of electrophysiological input, which are partially due to feed-forward cAMP-PKA/C, and partially due to increased receptor density brought on cAMP-NMDA receptor synthesis. Both of these mechanisms also affect the stop and start growth signals and microtubule-associated proteins (Hanus & Ehlers, 2008; Turrigiano, 2008).

The inherent properties of electrophysiological and cytoarchitectural homeostasis have implications on a neurocircuit level, and global nervous system level (Turrigiano, 1999, 2008). The first implication is that cellular electrochemical and cytoarchitecture regulation will further stabilize neurocircuits, but will still allow for new synapses to be formed by the myriad efferent and afferent signals. This leads to a top-down and bottom-up psychophysiological view, where various brain structures are being stimulated by all forms of stimuli, and are constantly shaping the input and output of the stimuli (Chang et al., 2013; Lovallo, 2005; O'Leary & Wyllie, 2011; Taylor et al., 2010). Said differently, healthy regulation of electrochemical variance and cytoarchitecture is important for neuroplasticity.

The second implication is that this top-down and bottom-up system has the collective ability to maintain electrochemical variance, and can be leveraged to index health. Specifically, a healthy range of ion variance within a brain region is associated with healthy variance in other systems; as the inverse would lead to nervous systems in which the capacity to respond to various stimulations (environmental or visceral) would be hindered (Thayer et al., 2012). Thus, some researchers have turned to transforming their acquired signals (visceral or motor outputs) into different measures of variance, which include standard deviations, approximate entropy, detrended fluctuation analysis, etc (Blake et al., 2015; Cao & Slobounov, 2011; Cavanaugh et al., 2006; Costa, Goldberger, & Peng, 2005; Pincus, 1991; Thayer et al., 2012).

Understanding healthy neurophysiology gives credence to the idea that an injury to the frontal lobe can have implications for cell physiology, neurocircuit and autonomic physiology, and global nervous system output. These include detecting and responding to various stimuli, which ranges from chemodetection processes to psychological tests (Iverson, Brooks, Collins, & Lovell, 2006; Iverson et al., 2003). These concepts will be further discussed in the brain injury section of this thesis.

2.2 – Cerebrovascular Physiology

While the last section discussed neuronal ion and cytoarchitecture homeostasis, this section addresses another crucial process that can be affected by brain injury - metabolite delivery regulation. It is known that the central nervous system acts as the global detection-response system for the entire body (Taylor et al., 2010). Hence, to perform such grand-scale monitoring approximately 20% of glucose is sent to the brain (Willie et al., 2011).

In trying to regulate glucose delivery to meet the metabolic demands of neurons (which need to constantly reverse polarity), elaborate mechanisms for maintaining blood flow have been documented (Ainslie & Duffin, 2009; Filosa & Blanco, 2007; Forstermann & Sessa, 2012; Kim et al., 2015; Kostoglou, Debert, Poulin, & Mitsis, 2014; Russo et al., 2004; Smirl, Hoffman, Tzeng, Hansen, & Ainslie, 2015). Generally speaking, blood volume and blood pressure, and both craniospinal volume and craniospinal pressure, need to be monitored by the brain to ensure metabolite delivery. It is well documented that the regulation of metabolites is accomplished by manipulating the previously mentioned variables. Collectively, the volume-pressure metrics previously identified are used to define cerebral perfusion pressure (CPP), which is the positive pressure gradient by which metabolite exchange is achieved. Mathematically, CPP is defined as the arterial blood pressure at the Circle of Willis, minus intracranial pressure (ICP). ICP is a function of venous diastolic pressure and cerebrospinal fluid pressure (Willie, Eller, & Ainslie, 2009).

In understanding the main variables that physiologically govern CPP, two things must be considered: 1) that the majority of this physiology is linked between the periphery and the medulla, and 2) that the medulla is linked to limbic and cortical areas of the brain, which means that brain injuries can affect chemodetection processes (Bishop & Neary, 2015; Gardner et al., 2014; Tan, Iverson, & Taylor, 2014). Thus, the following sub-section will address the mechanisms by which chemodetection maintains CPP and ensures metabolite delivery. These mechanisms are important for the reader to understand because concussion pathophysiology publications typically do not discuss healthy regulation.

2.2.1 – Chemodetection physiology. Metabolic status is monitored by central and peripheral chemodetection mechanisms. Specifically, central CO_2 (and pH) are monitored by the caudal and rostral ventral respiratory groups, the retrotrapezoid nucleus, and the Botzinger Complex (Spyer & Gourine, 2009). Peripheral chemodetection is monitored by chemoreceptors that are found on the carotid artery, which feed into the carotid sinus nerve (which is a branch of the glossopharyngeal nerve). A secondary source of peripheral chemodetection stems from chemoreceptors found on the aortic arch, which feeds into the vagus nerve. The glossopharyngeal nerve feeds into the nucleus of the solitary tract, and the vagus nerve originates in the dorsal vagal motonucleus (Spyer & Gourine, 2009; Taylor et al., 2010; Wilson-Pauwels, Akesson, & Stewart, 1988). Furthermore, both of these nuclei are located immediately inferior to the locus coeruleus (Counts & Mufson, 2011; Spyer & Gourine, 2009; Wilson-Pauwels et al., 1988). Because of the anatomical location of these detection sites, it has been proposed that peripheral chemodetection identifies the metabolic state of blood flowing toward the brain, and electrochemically stimulates the central detection site. Thus, peripheral chemodetection allows for sampling of the metabolic state of the body after external respiration, which is crucial for integrating responses with central chemodetection (Ainslie & Duffin, 2009).

As seen in **Figure 1** research indicates that a diffuse chemodetection network exists within the medulla, which includes the locus coeruleus, raphe nucleus, nucleus of the solitary tract, ventral regions of the medulla, etc. An important aspect for the mechanisms of chemodetection is that blood flow to the medulla must be inversely related to CO_2 detection and respiration (Aaslid, 1992; Ainslie & Duffin, 2009). This is

partially due to the fact that needless increases in blood flow (with no change in metabolite activity) can decrease CO_2 detection, and give a false reading of metabolic status. Hence, as the central and peripheral signals are integrated, a steady amount of blood flow becomes crucial so as to not alter cellular respiration needlessly. For example, as central and peripheral integration occurs, a lowered blood volume will likely cause the neural threshold to be surpassed as the amount of CO_2 being absorbed in the blood stream increases. This will activate medullary-monitored mechanisms such as ventilation and heart rate (Ainslie & Duffin, 2009).

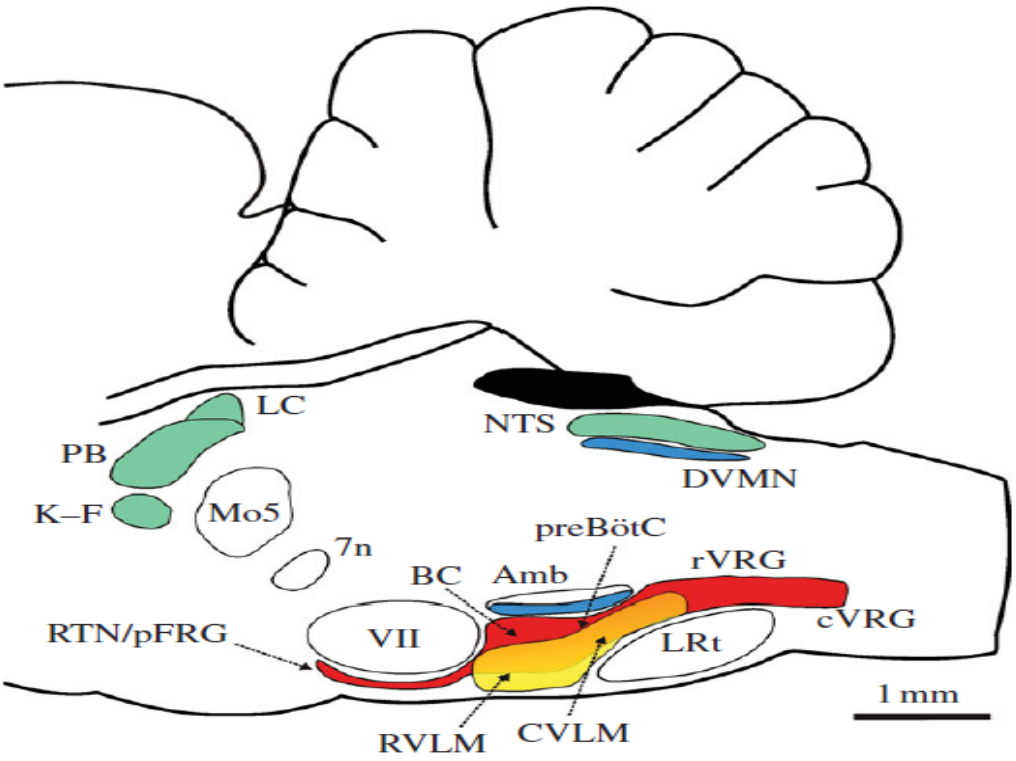

Figure 1 - Sagittal view of central chemodetection nuclei found within the medulla. **VII**, facial nucleus; **Amb**, nucleus ambiguus; **BC**, Botzinger complex; **cVRG**, caudalventral respiratory group; **CVLM**, caudal ventrolateralmedulla; **DVMN**, dorsal vagal motonucleus; **K – F**, Kolliker – Fuse nucleus; **LC**, locus ceruleus; **LRt**, lateral reticular nucleus; **Mo5**, motor trigeminal nucleus; **NTS**, nucleus of the solitary tract; **PB**, parabrachial nucleus; **preBotC**, pre-Botzinger complex; **RTN/pFRG**, retro-trapezoid nucleus/parafacial respiratory group; **r/cVRG**, rostral ventral respiratory group; **RVLM**, rostral ventrolateral medulla. Adopted from Spyer & Gourine (2009). Copyright permission has been granted to use this figure.

Research has indicated that CO_2 changes between 35-55mmHg is the range of detection sensitivity. This sensitivity is thought to have the greatest vasomotor effect on arterioles and pre-capillary sphincter radius. Specifically, increased amounts of CO_2 (i.e., hypercapnia) causes the smooth muscle of smaller blood vessels to relax, whereas hypocapnia causes constriction across a much wider range of vessels and diameters (Willie et al., 2009; Willie, Cowan, et al., 2011). Moreover, hypercapnia's association to increased vessel radius and higher metabolism has also led to research that indicates that increased CO_2 levels are associated with sympathetic nervous system shifts and increased aerobic respiration.

Having stated some of the broad anatomy and physiology of chemodetection, the following paragraphs will review the cellular mechanisms which promote changes in flow to metabolically active tissue. These mechanisms are closely related to the previous section's discussion of ion homeostasis regulation, and, can be altered after concussion.

When tissue is metabolically active, CO_2 and lactate create a regional pH decrement which will activate ATP-K+ and voltage-gated K+ channels (Harris, Reynell, & Attwell, 2011). Remembering that cells have higher intracellular concentrations of potassium, a further influx from a now-active potassium channel will cause a hyperpolarization of the smooth muscle cell. This hyperpolarization will cause intracellular calcium channels to deactivate, which will limit smooth muscle actin-myosin cross bridge formations (Ainslie & Duffin, 2009; Faraci & Sobey, 1996; Forstermann & Sessa, 2012; Golding, 2002; Jackson, 2005; Kaneko-Kawano et al., 2012). This mechanism may also be associated with other unknown events that characterize endothelium-derived hyperpolarization factor (Golding, 2002). Again,

despite observing these changes in the presence of altered CO_2 levels, the mechanisms by which this occurs are still not clear.

An additional mechanism that also has an effect on hypercapnia is nitric oxide (NO), as previous research has indicated that arterio-venous differences which measured surrogates for NO have increased with increased CO_2 (Ainslie, Celi, McGrattan, Peebles, & Ogoh, 2008; Peebles et al., 2008). However, unlike CO_2, NO is a not a flow signal that is generated as a metabolic by-product. On the contrary, NO is generated through nitric oxide synthase activity, which can be directly enhanced through PKA/C activity (Russo et al., 2004). Nitric oxide synthase can also be enhanced through increased calcium-calmodulin binding (Forstermann & Sessa, 2012). This calcium-calmodulin binding occurs through either activation of calcium release into the cytosol from the endoplasmic reticulum, or through glutamate receptor stimulation – both of these calcium fluxing scenarios are possible through either spontaneous neuronal activity, or through enhanced neural activation.

Once NO is generated, it diffuses into the smooth muscle cells that are associated with cerebrovascular vessels. Through the interaction between cyclic guanosine monophosphate and protein kinase G, myosin light chain kinase is inhibited and cannot promote vasoconstriction (when calcium is present) (Gao et al., 2013). It is at this juncture where the aforementioned CO_2 – potassium fluxes play a role in further promoting vasodilation, as the amount of potassium will alter how much calcium in the smooth muscle is fluxing into the smooth muscle cytosol. As a last note, the source of influxing calcium in vascular smooth muscle is likely from astrocytes that have been stimulated from neurons, and not directly from neurons (Filosa & Blanco, 2007). That

said (and as previously alluded), this vasodilation process can occur regionally, or globally (Huckstepp & Dale, 2011; Iceman, Richerson, & Harris, 2013; Ott, Nuding, Segers, Lindsey, & Morris, 2011).

The importance of these vasodilatory mechanisms cannot be under estimated when considering the effects on the injured brain. The following section will address how the injured brain disrupts these processes.

2.3 – Brain Injury

As a foreword on this section, it is understood that neuronal cellular homeostasis and brain blood flow are regulated by medullary and regional neurovascular coupling mechanisms. Thus, the pathophysiology of brain injury is based on the severity of the injury, and this regulates cerebrovascular function. For human research, non-invasive techniques must be used to measure the dysregulated state of the brain. This section will also describe other aspects of brain injury modelling, including the physiology of why some outcomes (such as decreased reaction times) are occurring.

2.3.1 – Initial Assessment. Although medical professionals have successfully used the Glasgow Coma Scale (GCS) to stratify severe brain injuries, there are few neurophysiology and/or cerebrovascular metrics (aside from intracranial pressure and cerebral perfusion pressure), that are consistently used to also infer traumatic brain injury (TBI) severity. The GCS is useful for traumatic brain injuries, but mild traumatic brain injuries (mTBI) are a grey area for diagnosing. This is evidenced by the mixed statements from the Zurich Consensus (McCrory et al., 2009), and the Neurotraumatology Committee's model for mild head injury (see **Table 1**) (Fabbri et al., 2004). Specifically, the Neurotraumatology Committee's mild brain injury

stratifications seem to indicate that low- and medium-risk head injuries overlap with some concussion symptoms that are stated in the Zurich Consensus (Fabbri et al., 2004; McCrory et al., 2009; Povlishock & Bullock, 2007).

To compare these two statements it is noted that both documents share similarities around the loss of consciousness, amnesia, and headaches. However, the Zurich Consensus position on cognitive impairments (i.e., slowed reaction time), was not reflected within the Neurotraumatology Committee's stratification of neurodeficits in the low and medium risk injuries. Moreover, vomiting was associated with a medium-risk injury in the Neurotraumatology Committee, but was not listed as a symptom in the Consensus on Concussion.

Conversely, these two consensus statements agree on what a concussion is not, which is best described by the Neurotraumatology Committee as a high risk mild traumatic brain injury. This injury, generally speaking, represents an injury or accident that might have caused a TBI if conditions were slightly less favourable (Fabbri et al., 2004; McCrory et al., 2009; Nortje & Menon, 2004).

Table 1

Neurotraumatology Committee of the World Federation of Neurosurgical Societies for Mild Head Injury. Adapted from Fabbri et al. (2004).

	Low Risk	Medium Risk	High Risk
Glasgow Coma Scale (GCS)	15	15 with clinical findings	14 or 15 with neurodeficits or skull fracture or risk factors with/without clinical findings
Clinical findings	No	1) Amnesia 2) Diffuse headache 3) Vomiting 4) Loss of consciousness	1) Amnesia 2) Diffuse headache 3) Vomiting 4) Loss of consciousness
Neurodeficits	No	No	Yes
Skull fracture	No	No	Yes
Risk factors	No	No	1) Coagulopathy 2) Age >60years 3) Previous neurosurgery 4) Pre-trauma epilepsy 5) Alcohol and/or drug misuse
Imaging	No	CT scan or skull X-Ray	CT scan
Disposition	Home	In hospital (3-6 h after CT or 24 h after skull X-ray) followed by home observation	In hospital (24-48 h), followed by home observation

Given these reports, it can be stated that high-risk mild traumatic brain injuries are not to be treated as a concussion but as a medical emergency. Moreover, both low- and medium-risk mild brain injuries and concussions have some overlapping grey areas which may need clarification. This includes more thorough operational definitions, further research into the quantification of neurodeficits, and possibly stratifying both vomiting and nausea symptoms.

In terms of concussion management, the injured party must refrain from both cognitive and physical activities until concussion symptoms have returned to normal (as seen on the Sport Concussion Assessment Tool (SCAT) and the Zurich Consensus on Concussion in Sport (Kelly et al., 2005; McCrory et al., 2009; Shehata et al., 2009). Once symptoms have abated, a monitored gradual return to normal activity can be implemented (McCrory et al., 2009), including a neurocognitive test and sub-maximal exercise test. Despite the limits of the ImPACT test that were stated in the Introduction, using the ImPACT test and other measurements when asymptomatic (and prior to performing exercise), is an accepted approach to concussion management (Gaetz & Iverson, 2009; Guskiewicz, 2011; Jha et al., 2015). The aforementioned approach is ideal, as it can screen the athlete for resting cognitive, balance and/or physiological impairments prior to an exercise challenge, which may result in symptom exacerbation (Baker, Freitas, Leddy, Kozlowski, & Willer, 2012; Jotwani & Harmon, 2010; Slobounov et al., 2011; Tan et al., 2014; Zhang et al., 2012)

Said differently, allowing an athlete to perform exercise without attempting to first measure the athlete's balance performance, cognitive performance, and/or physiology is concerning, as an episode of exercise induced exacerbation may have been

avoided by simply noticing that multiple measures do not align with lack of symptoms. Even if these measurements prompt an explicit question to the athlete to confirm their lack of symptoms, or to perhaps prompt an exercise trial at a lower level of exercise intensity, the risk of harm is further mitigated when compared to the alternative scenario.

Moving forward with return-to-play, if no symptoms are exacerbated by the monitored sub-maximal exercise session the athlete can attempt non-contact drills. This includes activities such as warm-ups and some conditioning drills. If no symptoms are present within 24hrs, additional sport-specific drills can be incorporated into the exercise regime. Lastly, if no symptoms are present the athlete can attempt full contact. However, if symptoms persist at any of the aforementioned return-to-play stages, the athlete must wait for 24-48 hours until attempting the same level of activity again (Gaetz & Iverson, 2009; McCrory et al., 2009).

Having highlighted the management, and overlaps within the mild brain injury continuum, the following subsection will address the epidemiology of concussion, the brain injury acquisition model (and the relevant global manifestations of injury), and the pathophysiology of concussion.

2.3.2 - Concussion modelling: epidemiology, pathomechanics & outcomes, and pathophysiology. *2.3.2a – Concussion epidemiology.* It has been reported that 1.7 million incidents in the United States will result in a TBI, with an additional 1.6 – 3.8 million injuries resulting in concussion (Daneshvar et al., 2011). It is also noted that these figures are likely conservative values that do not adequately account for motor vehicle accidents (Carroll, Cochran, Guse, & Wang, 2012; Williamson & Goodman, 2006). Research has consistently shown that helmeted and/or contact sports, produce

high rates of concussion (Daneshvar et al., 2011; Fuller, Taylor, Raftery, et al., 2015; Grindel, 2003; Kerr, Hayden, Dompier, & Cohen, 2015; Kirkwood, Parekh, Ofori-Asenso, & Pollock, 2015; Roberts, 2011).

In regard to concussion in sport, data from a national high school and collegiate injury surveillance system were pooled to examine concussion rates (Gessel et al., 2007). To standardize this, athlete exposures and injuries were defined. An exposure was classified as one athlete's participation in a single practice or competition, and an injury was defined using the following criteria: 1) occurring during an organized practice or competition; 2) requiring medical attention by a team athletic therapist or physician; and 3) resulting in restriction of participation from practice or competition for one or more days (Gessel et al., 2007). Football had the highest overall rate of injury for practice and games combined, with 0.47 and 0.61 concussions per 1000 exposures at the high school and college level, respectively. Separately, 1.55 and 3.02 concussions were sustained during football competitions at the high school and collegiate level, respectively. The next highest combined rate of concussion was men's and women's soccer. The overall number high school and collegiate females sustaining a concussion was 0.36 and 0.63 per 1000 exposures, respectively. Comparatively, the combined sample of high school and collegiate males only sustained 0.22 and 0.49 concussions, respectively. Interestingly, both male and female participation in a sanctioned soccer competition produced a far higher rate of injury than practice, which was a similar finding to football. One downfall of this large pool of data is that ice hockey, another sport known to produce a high frequency of concussions, was not considered and therefore was a limitation in this population study (Gessel et al., 2007).

More recently, epidemiology researchers reported that football accrues between 64 and 76.8 concussions in 100,000 athlete exposures (Guerriero et al., 2012). Other contact sports such as ice hockey, and both men's and women's lacrosse, were also identified as sports with high rates of concussion. Specifically, the second highest concussion-inducing sport (next to football), was ice hockey, which was reported to accumulate between 54 and 61.9 injuries per 100,000 exposures. The third highest was men's lacrosse, with 40 to 46.6 concussions; with women's soccer (33 to 34 injuries) and women's lacrosse (31 to 35 injuries) rounding out the 4th and 5th sports with the highest rates of injury per 100,000 exposures. Generally speaking, these injury rates indicate that the aforementioned sports will have one or more concussions per team, per season (Guerriero et al., 2012).

While these aforementioned reviews are recent reports of various sports, they also confirm previous research which indicates that contact and/or helmeted sports have high rates of concussion (Grindel, 2003). Moreover, these reviews do not focus on rugby, which is a non-helmeted contact sport that is unique in the sense that the stoppage time for injury is limited (Fuller, Taylor, Raftery, et al., 2015). The outcomes for amateur rugby resulted in a range between 0.3% – 11.4% probability for concussion for the Rugby Union, and a range of 7.7% - 22.7% range for the probability of concussion in the Rugby League. This finding of higher injury rates in upper-tiered rugby was also consistent when comparing the injury rates in the professional Rugby 15's versus the Rugby 7's (Fuller, Taylor, & Raftery, 2015).

2.3.2b Pathomechanics & outcomes. Regarding the pathomechanics and pathophysiology of brain injury, traumatic brain injuries and concussion exist on a

continuum, and thus share some common injury features. One of the mechanistic overlaps between TBI and concussion is that both injuries can occur through changes in inertia (in multiple directions), which do not require a direct blow to the head. From a physics standpoint, this has been described as the transfer of sufficient kinetic energy. For example, a slow and sustained skull-crushing force will not induce a concussion, nor will a small high velocity projectile (as it will likely pierce the skin). Thus, a large force must be absorbed by the body or head to initiate the inertia (Shaw, 2002).

A concussion does not need to result in a loss of consciousness (LOC), but when unconsciousness does occur, it can take on similar characteristic to a TBI (i.e., both brain injury severities can result in a loss of consciousness). From a brain injury model standpoint, explaining how a concussion and TBI can both exhibit the same symptom (albeit for different time periods), is difficult to conceive as severe infliction causes neuronal cell death. Conversely, a concussion typically shows no observable structural damage that could underpin a loss of consciousness (Bigler & Maxwell, 2012; Bigler, 2012; Gaetz, 2004; Shaw, 2002).

To address the discrepancies between brain injury severity, brain injury symptoms, and loss of consciousness, brain injury models have been developed that incorporate both the neuroanatomy and physiology of an acceleration-deceleration injury. The most prominent brain injury model to incorporate these transient changes in consciousness and concussion symptoms is the Ommaya-Gennarelli model (1974). In previous years, this model had received a great deal of attention but more recent pathophysiology publications fail to mention how their valuable work contributes. The main predictions from this model are: 1) when a trauma threshold is surpassed and loss

of consciousness is achieved, the cortical and subcortical areas will be far more affected than that of the brainstem; 2) damage to the brainstem cannot occur without more severe damage to the subcortical and cortical areas; and 3) cognitive symptoms can occur without loss of consciousness; however, the reverse cannot occur (i.e., if you lose consciousness, symptoms must be accompanied) (M. Gaetz, 2004; Ommaya & Gennarelli, 1974).

Furthermore, Ommaya and Gennarelli (1974) indicated that the rotational inertia induced from an oblique force transfer (that results in transverse and coronal plane vectors) will cause more harm than compressional injuries that occur in just the sagittal plane. More specifically, sagittal compression injuries resulted in good recovery, lateral injuries resulted in coma and/or severe disability, and the oblique injuries fell in between these two severities (Gaetz, 2004).

In addition to identifying the sagittal and/or transverse forces as those associated with concussion-inducing damage, the Ommaya-Gennarelli model (1974) also sought to address concussion symptoms and the transient loss of consciousness. Unfortunately, this model, in the era it was proposed, was limited by the lack of computer processing power. However, the since this brain injury model was first proposed, neuroscience has developed techniques that have refined and reinforced the potential mechanisms which underpin the transient signs and symptoms that this model sought to explain. To elaborate on the concussion pathology from an outcome perspective (i.e., increased or worsening reaction times), motor learning experts have revealed that the frontal lobe (where concussions are primarily sustained), is an area of the brain that is associated

with the extended dorsal and ventral neural circuits of visuo-spatial and visuo-motor processing (Sakagami et al., 2006).

As seen in **Figure 2**, the dorsal and ventral circuits branch out of the primary visual cortex (V1). The V1-dorsal circuit stimulates the parietal cortex (including the primary somatosensory area) which is linked to the primary motor cortex. Conversely, the V1-ventral pathway projects to the infero-temporal cortex. From the frontal lobe the dorsolateral prefrontal cortex (DLPFC) and the ventrolateral prefrontal cortex (VLPFC), can influence the pre-motor (PM) and primary motor (M1) areas of the brain, and can also be influenced by the inferotemporal cortex. Generally speaking, the dorsal stream is designated as the spatially oriented pathway and the ventral stream is known as the identification and interpretation pathway (Goodale & Milner, 1992; Sakagami et al., 2006). Moreover, visual processing through the posterior parietal cortex is used for immediate decision (i.e., action plans), and is excellent with visual-spatial tasks. The inferotemporal cortex is used more for identifying and inhibiting behaviours (Goodale & Milner, 1992).

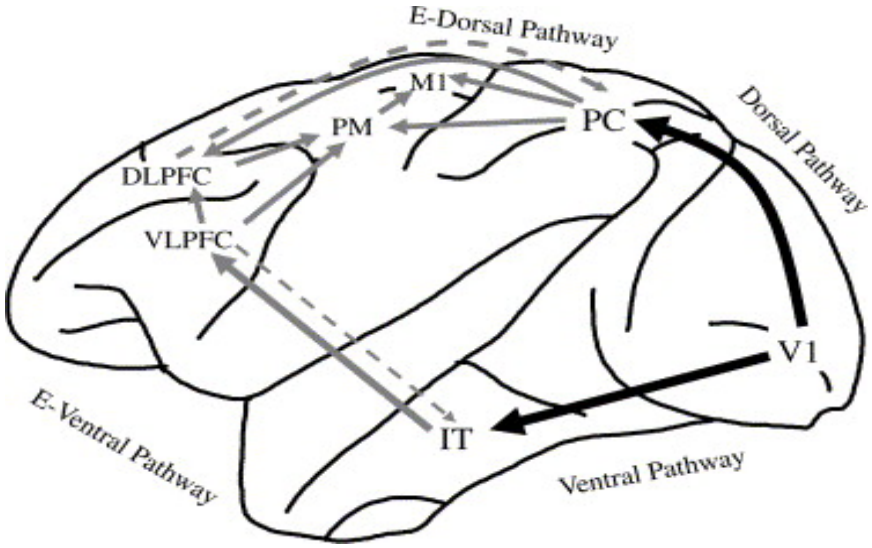

Figure 2 – Pathways of activation commonly seen in visuospatial and visuomotor tasks. V1 = primary visual cortex, IT= inferotemporal cortex, PC = posterior parietal cortex, M1 = primary motor cortex, PM = pre-motor cortex, VLPFC= ventrolateral pre frontal cortex, DLPFC = dorsolateral prefrontal cortex. Adopted from Sakagami et al., 2006. Copyright permission has been granted to use this figure.

In relation to brain injury, it is the obliquely generated transverse and coronal vectors that are kinetically transferred into the brain which will affect the DLPFC and VLPFC. Consequently, inputs to the extended dorsal and extended ventral pathways will be altered, which likely manifests as a suppressed action plans and inhibition processes. There is considerable evidence to support this as some of the initial concussion management strategies assessed executive function through a variety of visuospatial and motor tasks (Eckner, Lipps, Kim, Richardson, & Ashton-Miller, 2011; Howell, Osternig, Van Donkelaar, Mayr, & Chou, 2013; McCrory, Makdissi, Davis, & Collie, 2005; Randolph, McCrea, & Barr, 2005).

These cognitive paradigms involve both simple reaction times (which primarily involve the dorsal pathway), and choice reaction times, which require the identification of a stimulus and the decision to inhibit or proceed (thus requiring the ventral pathway). To further the notion of altered motor learning circuits, a recent review has reported that inter- and intra-hemispheric functional connections are lowered during resting state fMRI recordings (Johnson et al., 2012; Slobounov et al., 2012). As seen in **Figure 3**, the mTBI functional connections between the medial prefrontal cortex (MPFC) and the DPLFC (labelled ‘D’ in **Figure 3**) were still significantly altered 24 hours after the concussion subjects were symptom free and were medically cleared (Johnson et al., 2012).

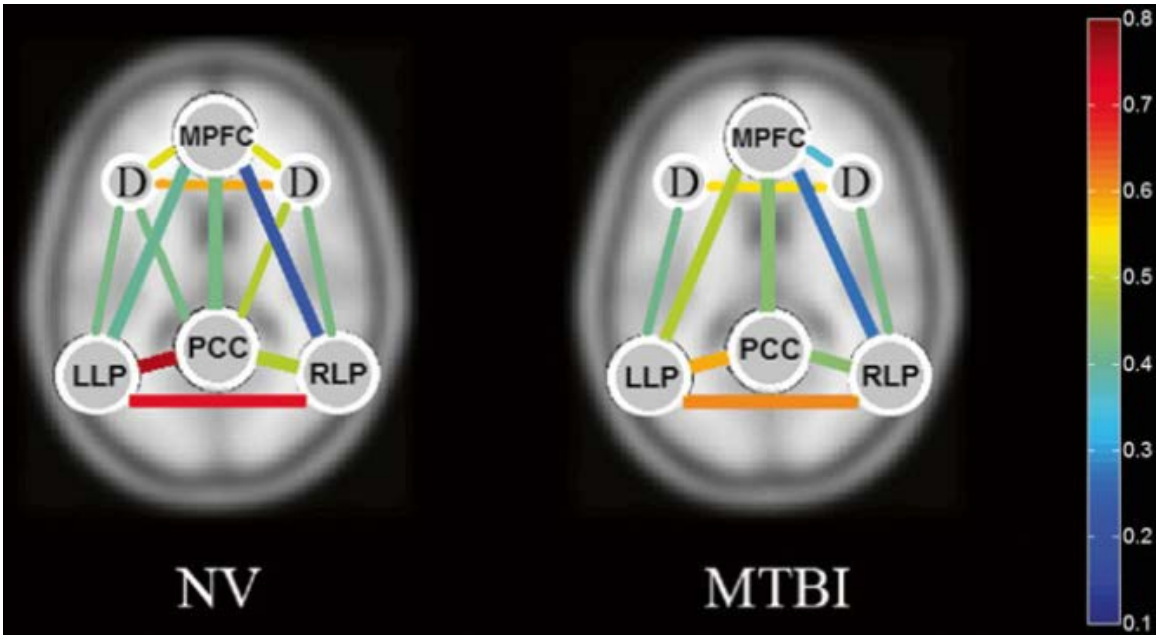

Figure 3 - Normal volunteer (NV) and concussion participant's resting state brain region correlations. The regions of interest were the medial prefrontal cortex (MPFC), the dorsolateral prefrontal cortex (D), the posterior cingulate cortex (PCC), the left lateral parietal area (LLP), and the right lateral parietal area (RLP). Usually, a connection is considered valid if $r > 0.3$. Adapted from Sloubonov et al. (2012). Copyright permission has been granted to use this figure.

A similar study reconfirmed these findings in a post-exercise setting in which all scans occurred after being medically cleared and without neuropsychological deficits. However, this research group did not report any differences in a resting state, which may be explained by the previous cohort's increased number of previous concussions versus the post-exercise group's null history (Slobounov et al., 2012; Zhang et al., 2012).

In moving forward with the Ommaya and Gennarelli model's (1974) explanation of concussion symptoms, it is reminded that this model also sought to explain loss of consciousness. When the model was first proposed, the EEG research of the time showed that the reticular activating system was the driver of consciousness. Thus, lesions to this area, based on EEG data, suggested two possible outcomes: either consciousness or incapacitation (Shaw, 2002).

Since that time researchers have shown that the reticular activating system (RAS) houses nuclei that synthesize and project prominent neurotransmitters, and that it is still part of a diffuse network of nuclei within the brainstem which moderate efferent and afferent stimuli. Furthermore, the RAS has thalamic and cortical relays, both of which can directly and indirectly contribute to consciousness and/or arousal by increasing or withdrawing neural inputs (Gaetz, 2004). Since the RAS mediates efferent and afferent information flow, it is implied that the RAS can project up to the cortex, and that the frontal lobe can project down to the medulla. Thus, the frontal lobe can directly influence medullary nuclei (such as the locus coeruleus), and can also indirectly influence the hindbrain through amygdalar and hippocampal influence on the thalamus (Bishop & Neary, 2015; Lovallo, 2005; Moody, Panerai, Eames, & Potter, 2005; Taylor et al., 2010). It is important to note that the locus coeruleus is responsible for the

synthesis and projection of norepinephrine, and thus the direct and indirect influences of higher brain centers will influence both consciousness and arousal state. Losing the frontal lobes' contribution can directly affect the medulla, and can also cause further damage by dampening the inputs that are associated with the frontal lobes' stimulation of the hippocampus and amygdala (Bishop & Neary, 2015; Bowers, Cullinan, & Herman, 1998; Herman, Ostrander, Mueller, & Figueiredo, 2005; Myers, Mark Dolgas, Kasckow, Cullinan, & Herman, 2013).

To corroborate this notion, studies of TBI and cerebral autoregulation have repeatedly shown that injuries to the frontal lobe affect how the medullary regions responsible for flow-pressure regulation are impaired, with the amount of impairment directly related to injury severity (Brady et al., 2009; Czosnyka et al., 2001; Zweifel et al., 2008). This relationship has been demonstrated using standardized transcranial Doppler (TCD) approaches, and from simpler inferences such as heart rate variability (Blake et al., 2015; Gall, Parkhouse, & Goodman, 2004; Ryan et al., 2011). Recently, the TCD and heart rate variability approaches used with TBI have been applied to concussion research and have shown that autonomically controlled systems are impaired following a concussion (Gall et al., 2004; Len et al., 2011).

2.3.2c – Concussion pathophysiology. Concussion and TBI pathophysiology share some overlapping pathomechanic and pathophysiology mechanisms. In terms of acquiring an injury, the major difference between concussion and TBI is that TBI injury mechanisms can also generate forces that are absorbed by the skull, and do not transfer into the brain being in a state of inertia (Nortje & Menon, 2004; Werner & Engelhard, 2007). If a TBI is sustained with kinetically transferred energy, the force being

transferred is more severe than that of a concussion and may also cause internal haemorrhaging.

Within these closed-head injuries, the initial trauma creates an ischemia-like metabolic cascade of events. Membrane permeability, which includes a myriad of voltage-gated channels and ion pumps are all disrupted. Consequently, calcium and sodium flux into the cell, and potassium fluxes out into the extracellular matrix (Floyd, Gorin, & Lyeth, 2005; Golding, 2002; Palmer et al., 1993; Yi & Hazell, 2006). This presents an extreme challenge to the processes which maintain cellular homeostasis, as described in previous sections.

The initial neuron damage also includes physically altering mitochondrial membranes, and increasing calcium sequestering within these same mitochondria (Verweij et al., 2000). Correcting for these electrochemical changes requires a large amount of energy, which can no longer be obtained through aerobic means because of the mitochondrial damage. Hence, the ischemia-like cascade is set in motion as ATP stores are depleted, and anaerobic glycolysis accumulates lactic acid (Golding, 2002; Werner & Engelhard, 2007). This physiological scenario (where oxygen can no longer assist with ATP generation to reverse chemical gradients), is likely a juncture between TBI and mild brain injuries (internal haemorrhaging aside). There are multiple detailed concussion pathophysiology reviews available in the published literature which show that once intracellular ions cannot be reversed with homeostasis mechanisms – ischemia, edema, and excitotoxicity differentiate these injuries (Barkhoudarian et al., 2011; Bigler & Maxwell, 2012; Collins et al., 2012; Gaetz, 2004; Len & Neary, 2011; Nortje &

Menon, 2004; Palmer et al., 1993; Signoretti, Lazzarino, Tavazzi, & Vagnozzi, 2011; Signoretti, Vagnozzi, Tavazzi, & Lazzarino, 2010; Werner & Engelhard, 2007).

In discussing concussion pathophysiology specifically, the milder perturbations in neuronal membranes have been documented with horseradish peroxidase, which is up-taken by all parts of a neuron except an intact axon. This technique indicated that the nerve axon and soma could not initially be differentiated, and infers that neuronal membranes are indeed perturbed. By days 9-14 post-injury, some degenerative and some regenerative processes were well underway (Gaetz, 2004).

As seen in **Figure 4** (and as previously implied), when a concussion disturbs a neuronal membrane, metabolic and electrochemical consequences are observed which are unique to this level of severity. One outcome is that voltage-gated proteins (amongst other ion channels) can be disfigured, which allows for an indiscriminate flux of ions (which eventually reverses). In the interim, increased extracellular potassium, and increased intracellular calcium and sodium are observed. This ion flux is further compounded by the wide spread and excessive release of excitatory amino acids (EAA – glutamate), which stimulate NMDA receptors to influx calcium. This widespread stimulation of NMDA receptors occurs at the site of injury and at downstream neurons (Barkhoudarian et al., 2011). Seeing as the mass EAA release is reversible (unlike TBIs), it is likely that this process only further contributes to the suppression of neurons (Barkhoudarian et al., 2011). Moreover, an electrochemical suppression of neuronal activity directly plays into the previously mentioned psycho-motor deficits that are mediated by the DLPFC (Barkhoudarian et al., 2011; Goodale & Milner, 1992; Howell et al., 2013; Sakagami et al., 2006).

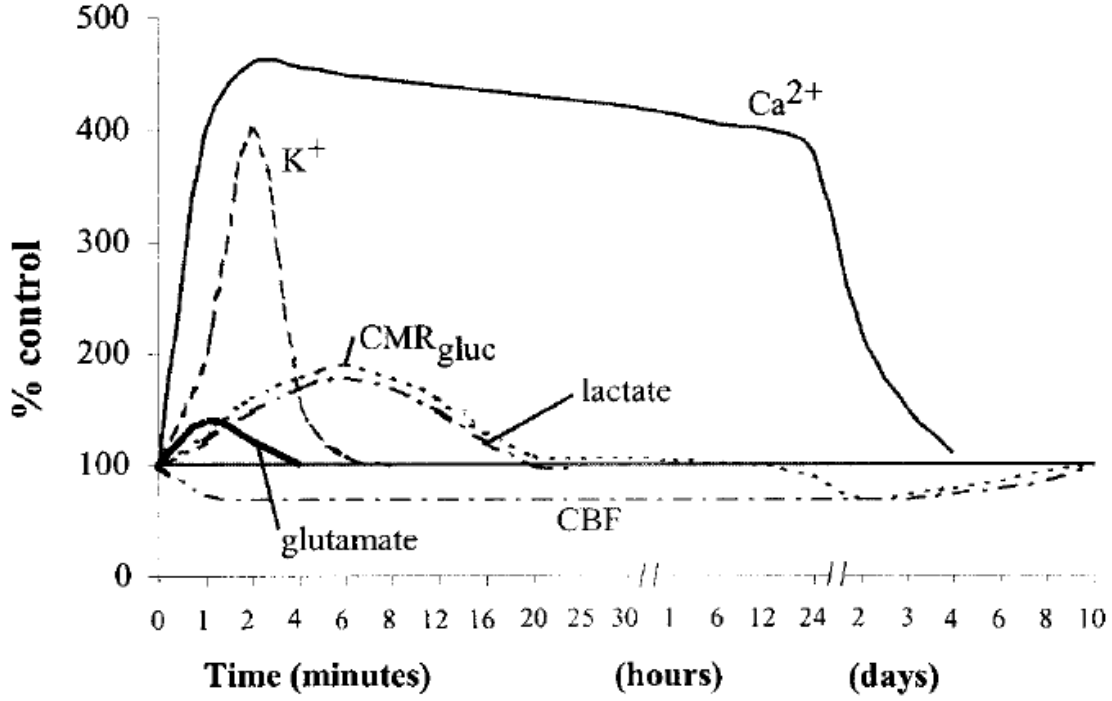

Figure 4 - Time line and characteristics for some of the metabolic and electrochemical changes associated with concussion. CMR_{gluc} = cerebral metabolic rate of glucose oxidation; CBF = cerebral blood flow. Adapted from Giza & Hovda (2001). Copyright permission has been granted to use this figure.

Reversing the intracellular ion concentration requires the activation of mitochondria to produce energy. The needed energy is ultimately a longer-term consequence of concussion, as the rate of glucose oxidation and cerebral blood flow are decreased for a prolonged period. While not fully understood why blood flow is decreased, it has been speculated that calcium, potassium, and nitric oxide all play a role in this observed decrease (Bishop & Neary, 2015; Gardner et al., 2014). After 7-10 days, oxidation and cerebral blood flow generally return to baseline, which is consistent with the human timeline for return-to-play. During this time, alternative energy sources are recruited, as evidenced by lowered N-Acetylaspartate (NAA), and NAA:creatine ratios post-injury (Signoretti, Vagnozzi, et al., 2010).

The mismatch in energy requirements versus energy production has also been an area of research, as there are a multitude of factors which likely lead to this outcome. One postulation is that rates of glucose oxidation are related to mitochondrial sequestering of calcium which inhibits the ability to utilize oxygen as the final acceptor for ATP synthesis. This premise is supported by the lowered NAA:creatine ratios (Signoretti, Di Pietro, et al., 2010). Another area of research that has implications for altered glucose oxidation sought to better understand the microvessel damage associated with hypoperfusion, and ischemia, by exposing rats to fluid percussion injuries of 2 and 3 atmospheric pressures. These pressures were used to represent a severe / high risk concussion and a severe TBI, respectively. Results showed that the vascular density and diameters of larger cerebral vessels (arterioles and venules), and microvasculature were further reduced with increasing injury severity (Park, Bell, Siddiq, & Baker, 2009).

2.3.4 – NIRS applications to brain injury. At this point in the review, healthy electrochemical homeostasis, healthy cytoarchitectural homeostasis, and neural metabolite delivery regulation (i.e., chemodetection physiology) have been discussed. The physiology of brain injury from a cellular level has also been explored, and has briefly been related back to healthy regulatory processes. The key points at this juncture of the thesis are: 1) electrochemical homeostasis is a crucial process for healthy neuronal and cerebrovascular function (Barkhoudarian et al., 2011; Filosa & Blanco, 2007; Forstermann & Sessa, 2012; Huckstepp & Dale, 2011; Len et al., 2013; Mutch et al., 2014; O'Leary & Wyllie, 2011); 2) intracellular calcium and potassium regulation are crucial for healthy functions; and 3) taken together, neuronal and cerebrovascular processes after injury are dysregulated because of altered metabolic, calcium, and potassium fluxes. This has been confirmed in humans using various devices (Kontos et al., 2014; Len et al., 2013; Meier et al., 2015; Mutch et al., 2014; Urban et al., 2015).

One such measure to assess human cerebrovascular dysregulation is near infrared spectroscopy (NIRS). NIRS uses specific wavelengths of infrared light which can be absorbed by oxy- and deoxy-hemoglobin (HbO_2 and HHb) (Delpy & Cope, 1997; Duncan et al., 1994; Ferrari, Mottola, & Quaresima, 2004; Ferrari & Quaresima, 2012; Quaresima, Bisconti, & Ferrari, 2012). These wavelengths can pass through the skull and reflect the relative changes in HbO_2 and HHb to assess the outer cortex's metabolic delivery in healthy and in injured participants (Fabiani et al., 2014; Kontos et al., 2014; Molinari et al., 2006; Steiner et al., 2009; Urban et al., 2015). For a detailed description of the theory and principles of NIRS, the reader is suggested to review papers by Elwell & Cooper, 2011; Ferrari et al., 2004; and Pellicer & Bravo, 2011.

2.3.4a - Traumatic brain injury. Guidelines for traumatic brain injuries have stated that oxygen measures are imperative for monitoring outcomes, and ensuring no further ischemic damage occurs (Povlishock & Bullock, 2007). Because lives truly hang in the balance and the need for bed-side monitoring is imperative during TBI, the wide-spread use of NIRS has been limited because there is still some uncertainty regarding skin blood flow, and sensitivity to ischemic challenges. Furthermore, traumatic brain injuries also present other unique NIRS-interpretation challenges, such as the increased light absorption that occurs when blood is sequestered in a fractured skull. Ironically, this high hemoglobin absorption rate may serve as a valuable application when imaging equipment is not readily available (Haitsma & Maas, 2007).

Because of these ethical implications, human research initially recruited TBI patients whom had already graduated from a rehabilitation program. The research group tracking long-term TBI recovery with NIRS had two questions: 1) how reliable is relative hemoglobin changes for tracking long-term outcomes after TBI; and 2) what kind of hemoglobin differences occur between TBI and healthy participants during rhythmic maximal hand grip challenges (Bhambhani, Maikala, Farag, & Rowland, 2006). In terms of reliability measures post-TBI, it was revealed that similar hemodynamic responses were generated in both groups during the hand grip protocol, with TBI participants generating more variance in the hemoglobin signals compared to controls. Moreover, there were no significant differences within either group's hand grip trials, but a main effect for group was found with TBI participants having lower pre-frontal cortex hemoglobin concentration during the hand grip task than healthy controls (Bhambhani et al., 2006).

The aforementioned main effect between controls and the rehabilitated TBI participants was recently built upon through controlled fluid percussion injuries of 1.6, 2.0, and 2.4 atmospheric pressures in rats (Kuo et al., 2013). It noted that a value of 1.6 atm is likely a good representation of a moderate-risk concussion. As expected, the severity of injury was linearly associated with the volume of damaged tissue. Moreover, the changes in hemoglobin revealed a negative relationship with injury severity – the lowest injury severity had the highest levels of oxyhemoglobin (which were higher than pre-injury values), and the highest injury severity had the lowest HbO_2 levels (Kuo et al., 2013).

Another research group (Zweifel et al., 2010) has utilized NIRS in human subjects who were in the acute TBI phase, but used NIRS only as an exploratory device. The purpose of this study was to examine the relationships (via correlations) between different brain injury metrics. The brain injury metrics themselves were generated using correlations between TCD, ICP, and NIRS measures. These brain injury metrics included the moving correlation between TCD-recorded middle cerebral artery flow velocity and CPP (Mx); the moving correlation between CCP and total oxygenation saturation index (TOx); and the moving correlation between the total oxygen saturation index and mean arterial pressure (TOxA) (Zweifel et al., 2010). The relationship between the Mx and TOx, and the relationship between the Mx and TOxA, were not significant. However, when these relationships were dichotomized into values above and below a previously published Mx-generated mortality threshold of 0.15 - 0.25, with the area under the curve for TOx was 0.804, and 0.706 for TOxA. This indicates that while the TOx and Mx relationship is somewhat unrelated, there is still promise for TOx

and TOxA to assess CPP and potentially stratify TBI patients based on mortality. Further still, measuring CPP is highly invasive, and would likely not be used for patients who have subarachnoid haemorrhaging that is not considered life threatening. Hence, the standard measures of blood pressure can be combined with the non-invasive and easy-to-use NIRS measures (Zweifel et al., 2010).

2.3.4b - Concussion. To this author's knowledge, only two articles have specifically investigated concussion with NIRS measures. The first research group recruited 14 individuals who sustained a sport concussion within the previous 15 - 45 days, and were still symptomatic at the time of testing (Kontos et al., 2014). A 6 detector by 8 source (32 channel) fNIRS was positioned over the frontal lobe using the EEG 10-20 system. This placement was designed to cover the bilateral areas of the inferior dorsolateral, and prefrontal cortices. The fNIRS application was concomitantly utilized during a common neuropsychological test (ImPACT) in which each component of the test was treated as a new block, with 30s of rest in between new trials. Collectively, the ImPACT test consists of a word memory task, a shapes memory task, a symbol match task, a colour match task, a three-letters memory task, and a X's and O's spatial memory task.

In the word memory task, concussed participants had poorer behavioural performance on the percent of correct word memory module, and the delayed word memory recall. The fNIRS measures during the recall showed a suppression of HbO_2 in concussed individuals in the left dorsolateral region, with the delayed recall showing increased oxyhemoglobin in a concussed left dorsolateral region (Kontos et al., 2014).

For the design memory task, the injured party performed worse during the immediate recall phase at correctly identifying shapes that were not part of the task. During this time, concussed participants also had significantly less hemoglobin change in the frontal area than controls. The delayed recall for designs did not show any significant hemoglobin differences either, though there was a trend of increased activation in the concussed group. Once again, the delayed recall did have significant behavioural differences with fewer correct inhibition responses for injured participants (Kontos et al., 2014).

The symbol-match task had significantly higher oxyhemoglobin levels in the control group than the injured group. Behaviourally, the concussed group had fewer total correct responses.

Overall, these results show less HbO_2 delivery to tissues during cognitive tasks than what is observed in healthy controls. This is typically not seen in similar fMRI studies, as increased activation has often been cited. However, these citations are based on simple cognitive loads such as an *n*-back test of 1. More difficult tasks (i.e., *n*-back tests of 2 or 3) have shown similar suppressions to the current study in activated areas compared to healthy people (Kontos et al., 2014).

The second research group (Urban et al., 2015) to use NIRS technology for concussion purposes created a fNIRS measure of connectivity within (and between) the two sects of the motor cortex (M1). This was done by calculating the coherence values for both halves of the motor cortex in both concussed and control participants. Once calculated, each hemisphere of the concussed participant's motor cortex was compared to the other half (i.e., concussed left M1 coherence versus concussed right M1

coherence); and was also compared to the healthy subject's same half (i.e., concussed right M1 coherence versus healthy right M1 coherence) (Urban et al., 2015). These coherence comparisons were made during rest, and during a unilateral finger tapping task. In a resting state, only the concussed group's left versus right M1 coherence values were significantly different, but neither hemisphere's coherence was different when compared to healthy controls. During the unilateral M1 activation, the healthy controls (once again) showed no differences in coherence between their hemispheres. Concussions again showed left versus right M1 coherence differences between their hemispheres during M1 activation. During M1 activation it was also shown that the right hemisphere's coherence was different when concussed participants were compared to controls (Urban et al., 2015).

These findings are similar to fMRI measures that show a disconnect between functional networks (Johnson et al., 2012; Slobounov et al., 2012; Slobounov et al., 2010; Urban et al., 2015; Zhang et al., 2012). However, it is noted that this group's concussion participants (Urban et al., 2015) were recruited 158 ± 131 days post injury, which does not allow for an accurate timeline of concussion pathophysiology recovery.

To further emphasize the previous sentence, it is clear that the NIRS research groups (Kontos et al., 2014; Urban et al., 2015), and the previously mentioned fMRI research teams (Johnson et al., 2012; Slobounov et al., 2012; Zhang et al., 2012) are using two different subject pools. Both NIRS reports have participants who are clearly not in the acute stages of injury (but are symptomatic), and the fMRI team involves subjects who are just on the verge of being cleared to return-to-play.

One fMRI study that has a somewhat-relatable participant demographic to the fNIRS-ImPACT study (Kontos et al., 2014), used serial measurements of blood oxygen level dependant signals in an acute injury period (Meier et al., 2015). The fMRI project reported lower oxygen values within the insular cortex, and regions of the temporal lobe; but these lowered fMRI values were only lower when days 0-3 were compared to days 6-13, and days 25-44 (Meier et al., 2015). Again, this timeline is similar to the participants in the fNIRS-ImPACT study, where measurements were recorded within a 15-45 day post-injury time period (Kontos et al., 2014). Another fMRI study focused on blood oxygen-level dependent (BOLD) signal changes that are occurring within a standardized CO_2-response atlas, and found significant reductions in CO_2 responses in the visual cortex (Mutch et al., 2014). This research however, was focused on participants who were diagnosed as having post-concussion syndrome (Mutch et al., 2014).

In terms of potential applications, there are other NIRS-concussion avenues that can be explored. One avenue would be to replicate acute bouts of hypercapnia, as the changes reported during macro-vascular measures with TCD will likely also be present in a microvascular setting (Len et al., 2011, 2013). Additionally, NIRS can also be applied when returning athletes to full contact. It is known that cerebral oxygenation increases until the respiratory compensation threshold, after which, increased oxygen extraction occurs. This is characterized by decreases in oxyhemoglobin and increases in deoxyhemoglobin, with fitness causing oxygen extraction to be more pronounced (Rooks, Thom, McCully, & Dishman, 2010). Hence, it is plausible that NIRS could be used during the initial return-to-play cycle ergometer test, and potentially serve as an early warning system per se. When compared to their baseline, it may be discovered that

the athlete is extracting far too much oxygen for the given workload (Bishop & Neary, 2015). The two applications stated would greatly aide clinicians in assessing both the recovery and the return to activity process.

2.4 - Literature Review Summary

This literature review has sought to discuss healthy neural and cerebrovascular physiology, and how it relates to brain injury. Regarding the neurophysiology section, the overarching goal was to describe nervous system functions at a cellular scale, and how these cellular processes link cerebrovascular regulation to neural activity.

Neural function was introduced through some of the proposed theories and mechanisms that govern cellular homeostasis in which control theory was heavily cited. Specifically, scaled error detection feedback, and bang-bang feed-forward mechanisms were highlighted for the possibility of regulating intracellular calcium (O'Leary & Wyllie, 2011). It was also mentioned that, irrespective of how cellular homeostasis is modelled, the neuron's inputs and outputs are continuously modifying each other, which leads a neuron to be inherently neuroplastic (Coveney, 2003; O'Leary & Wyllie, 2011).

Having highlighted the many ways ion balances can be maintained and indirectly monitored, the inverse linkage between electrophysiology and cytoarchitecture was discussed. Cyclic Adenosine monophosphate (cAMP) was cited as having feed-forward and feedback (intrinsic) properties. These included activation of PKA/C to modulate the NMDA receptor (feed-forward ion regulation), increase genetic expression of NMDA receptors (ion regulation feedback), enhanced golgi body NMDA receptor recycling (feedback), and down-regulating microtubule associated protein activity - which inhibits dendrite growth. The enhancements to the NMDA receptors will ultimately inhibit

microtubule degradation, and ultimately lead to stabilized cytoarchitecture (Rebola et al., 2010; Tripodi et al., 2008; Turrigiano et al., 1994).

Because neurons exhibit the aforementioned properties, it is no surprise that autonomic neurocircuits, and the entire nervous system, all exhibit these properties. The brain injury section of this thesis discussed damage to the cellular structures of the frontal lobe and how they can affect the ability to regulate the aforementioned processes. This has implications for the global detection-response system for environmental and visceral stimuli. This includes executive function/motor learning, monitoring arousal, and other autonomic functions such as cerebral blood flow regulation (Bishop & Neary, 2015; Chang et al., 2013; Goodale & Milner, 1992; Guskiewicz, 2011; Sakagami et al., 2006; Thayer et al., 2012).

This review also discussed how the physiology of chemodetection (global or regional) can be perturbed following a concussion. It was stated that global chemodetection relies on both peripheral and central integration. Peripheral chemo- and pressure signals are sent via the glossopharyngeal nerve (into the nucleus of the solitary tract), and vagus nerve (into the dorsovagal motonucleus), respectively. These chemo- and pressure signals are integrated within the medulla which relies on a diffuse network of nuclei that are responsible for regulating cardiorespiratory function (Ainslie & Duffin, 2009; Erlichman et al., 2009; Spyer & Gourine, 2009; Wilson-Pauwels et al., 1988).

Again, it was highlighted that the vasodilator mechanisms that guide global or regional chemodetection physiology may also be perturbed following injury (Bishop & Neary, 2015; Gardner et al., 2014). Physiologically, the metabolically active (healthy) neurons will increase the amount of nitric oxide through cAMP-PKA/C pathways, which

will have a vasodilator effect on nearby microvessels (Forstermann & Sessa, 2012). Similarly, the CO_2 diffusing out of neurons and microglia from the heightened demand for energy can lower pH, which can inhibit the ability of calcium to facilitate smooth muscle cross bridge formation, and thus, inhibit vasoconstriction. This is thought to occur by activating voltage gated potassium channels, which can limit the amount of cytoplasmic calcium because potassium is also positively charged (Faraci & Sobey, 1996; Golding, 2002; Jackson, 2005). More specifically, the aforementioned vasodilation mechanisms work to limit the effect that calmodulin has on myosin light chain kinase (which promotes vasoconstriction), in favour of myosin light chain phosphatase (which promotes vasodilation) (Forstermann & Sessa, 2012; Kaneko-Kawano et al., 2012).

The brain injury component of these chemodetection processes hinge on the regulation of ions and metabolite flow and exchange. In short, the increased cellular membrane permeability from a concussion will cause an influx of sodium and calcium that is paired with the efflux of potassium. This causes downstream mass release of excitatory amino acids which further compounds the amount of ion influx, and suppresses healthy neuronal function. The inability to reverse these ion influxes hinders aerobic ATP production, which only further confounds the ability to restore and regulate intracellular calcium and regulate blood flow (Barkhoudarian et al., 2011; Bishop & Neary, 2015; Gaetz, 2004; Gardner et al., 2014). Thus, the hindered regulation of calcium and potassium after concussion likely alters the ability of carbon dioxide and nitric oxide to influence blood flow (Gardner et al., 2014).

Furthermore, it is noted that injured neurons are found in the frontal lobe and/or outer layers of the cortex, and yet, cortical chemodetection, or medullary chemodetection can be altered after cortical injury. This has been observed in injury-versus-control studies, where heart rate variability, transcranial Doppler, fMRI, and NIRS have all measured autonomic and/or motor learning physiology differences (Blake et al., 2015; Brady et al., 2009; Johnson et al., 2012; Lang et al., 2003; Len et al., 2013; Meier et al., 2015; Mutch et al., 2014; Ryan et al., 2011; Slobounov et al., 2012; Zhang et al., 2012; Zweifel et al., 2008, 2010).

In terms of connecting these pathophysiology studies, credence must be paid to the brain injury model set forth by Ommaya and Gennarelli (1974). This model not only lays the foundations for pathomechanically separating concussion from TBI, but it also shows that an injury to the frontal lobe can affect both motor learning physiology, and medullary processes. To highlight this model, it was stated that the kinetic transfer of oblique forces can create shearing vectors within the cortex and sub-cortex; this can result in further damage and perturbations to the brain stem, and can also facilitate the loss of consciousness (M. Gaetz, 2004; Ommaya & Gennarelli, 1974; Shaw, 2002).

Even though this model loosely identifies how a concussion can be sustained, there are still issues regarding the management of concussion. As stated in the introduction and literature review, prominent cognitive tests such the ImPACT test, and the SCAT's balance assessment, need to be more reliable, valid, and objective (Bigler, 2015; Buckley et al., 2016; Erdal, 2012; Finnoff et al., 2009; Guskiewicz, 2011; Hunt et al., 2009; Iverson et al., 2006, 2003; Moser, Schatz, Neidzwski, & Ott, 2011; Onate et

al., 2007; Resch, Macciocchi, et al., 2013; Resch, Driscoll, et al., 2013; Schatz & Ferris, 2013; Schatz et al., 2006; Susco et al., 2004; Wilkins et al., 2004).

While cognitive and balance measures need to be more objective (and must be sensitive enough to discern a concussed from a healthy individual), the lack of objective physiological protocols and research findings hinders concussion management and rehabilitation (Blake et al., 2015; Eierud et al., 2014; Gardner et al., 2014).

This review ended by highlighting the recent research associated with NIRS' ability to measure relative cerebral hemoglobin changes after sport concussions. The first project used fNIRS measures during cognitive tasks, and reported HbO_2 values that were generally lower than healthy controls. These oxy-hemoglobin measures were opposite of what is typically cited with reference to fMRI measures, but this was explained in part because the previous research cited the increased oxygen levels were reported during low-level cognitive tasks that may not require the same amount of metabolic resources needed to perform high level cognition (Kontos et al., 2014). The other fNIRS study also reported similar changes to that of reduced connectivity measured using fMRI, as inter- and intra-hemispheric coherence values in the motor cortex were reduced during finger tapping tasks (Urban et al., 2015).

3.0 Research Outcomes and Hypotheses

The focus of this research was to determine if the relative cerebral hemoglobin changes can serve as an objective physiological measure to assess concussion. Using a hypercapnic paradigm to measure post-injury changes, this project addressed the following outcomes and hypotheses:

Outcome 1) To investigate potential relative changes in pre-frontal cortex oxyhemoglobin (HbO_2) and deoxyhemoglobin (HHb) concentrations following a sport concussion during rest. It was hypothesized that resting post-concussion HHb would be higher, and resting post-concussion HbO_2 lower, when compared to resting healthy control values.

Outcome 2) No projects could be found that pair relative pre-frontal cortex hemoglobin concentration changes during breath-hold-induced hypercapnia with the intent to assess concussion recovery. In using the previously mentioned paradigm to assess injury, the difference in relative hemoglobin concentration changes between rest and peak hypercapnia will be assessed using a within- and between-subject design. The within-subject design compares rest and peak hypercapnia values in all participants. It is hypothesized that the within-subject design does not show significant results for rest versus peak hypercapnia after a concussion is sustained, but does reveal significant differences in healthy controls. When comparing between subjects, it is hypothesized that HHb changes from rest to peak hypercapnia will be higher, and HbO_2 differences from rest to peak will be lower following concussion.

Outcome 3) Researchers have postulated that disease and/or injury suppresses the amount of healthy variance and randomness that is associated with physiological processes (Pincus, 1991; Thayer et al., 2012). Thus, HHb and HbO_2 concentration change standard deviation (HHb SD and HbO_2 SD), were compared using a within- and between-subject design. Resting versus hypercapnia values were compared within-subject, and standard deviation changes from rest to peak was compared between subjects. It was hypothesized that the hemoglobin SD changes between rest and peak

hypercapnia (i.e., the between-subject condition), would be lower following injury, and would return to normal throughout recovery. It was also hypothesized that the within-subject comparisons would reveal no significant differences between rest and hypercapnia for concussed groups, but would reveal differences in healthy participants.

3.1 – Experimental Design

3.1.1 – Demographics. Participants (N = 148 total; healthy n = 115; days 1-3 n = 14; days 4-6 n = 8; days 7-14 n = 11) were recruited from the University of Regina (U of R) Men's Hockey and Football teams, with additional subjects being recruited from Junior and Western Hockey League (WHL) teams. The Junior team players can be drafted into the elite category, and the WHL team players can then be drafted into the National Hockey League, and/or the American Hockey League. These participants were purposively selected as it has been documented that athletes who play these sports are more susceptible to sustain a concussion when compared to non-contact sports, across all game-hours and practice-hours (Goodman, Gaetz, & Meichenbaum, 2001; Guerriero et al., 2012). All participants were contacted through each team's medical staff. Additional injured participants were recruited from within the community and were athletes who are of similar fitness (as indicated by the league in which they play), with similar age, height, and weight. Athletes with previous concussions, but fully recovered and cleared to play at the time of baseline testing were included in this study.

3.1.2 – Participant familiarization. This project received ethics approval from the University of Regina Ethics Board (#55R1213, **Appendix A**). Upon entering the laboratory, each participant completed the informed consent, as well as medical history,

concussion history, pre-testing activity questions, and the 3rd Sport Concussion Assessment Tool (SCAT3) symptom scale (see Appendix A). The informed consent stated the purpose of the testing and the procedures. If the participant was a minor, the informed consent was signed by the athlete and a parent or acting guardian, such as the team's Athletic Trainers and/or Physiotherapist. Using a medical professional is deemed appropriate in situations when elite athletes compete in provinces that are outside of their home province, or when the medical professionals typically see the athletes for which they are responsible multiple times a week (Harrison et al., 2004).

Following informed consent, participants filled out a medical history form and a concussion history form. The medical history form screened for the following: age, height and mass, highest level of education, major family illnesses, early family mortality (< 50 years), prescription and non-prescription medications, and conditions currently being monitored by a physician, learning disabilities, and previous drug abuse. Medical exclusion criteria may eliminate: those who ingest mediations that alter cardiovascular physiology, those who smoke, and/or those who have neurological (e.g., epilepsy, brain tumour), respiratory (e.g., asthma, chronic bronchitis), or cardiovascular (e.g., hyper/hypotension) medical conditions.

The concussion history form screened for the following aspects of each injury: the date of each previous concussion, the sport in which the injury was acquired, the age of the participant at the time of injury, if a hospital visit occurred, if consciousness was lost, how long a variety of symptoms (memory issues, headaches, dizziness, irritability) persisted following each concussion, and the time it took to fully return-to-play.

Following these history forms, a questionnaire was completed regarding the previous 24 hours of activity that lead up to the testing period. These questions include alcohol intake, caffeine ingestion, tobacco usage, exercise participation, and any other activities that could potentially compromise the outcomes of the procedure. All participants were informed to refrain from alcohol and tobacco products at minimum 12 hours before visiting the Concussion Testing Laboratory, though 24 hours was preferred. Participants were also asked to avoid strenuous physical activity 8 hours prior to visiting, and to avoid caffeinated beverages 6 hours prior to visiting (Kennedy & Haskell, 2011; Wishart et al., 2006). A last request was that those athletes who ingest Tylenol or Advil, refrain from doing so for six hours prior to testing (Wishart et al., 2006). Participants who did not abide by these pre-screening conditions were excluded from analysis.

Finally, the 3rd Sport Concussion Assessment Tool (SCAT3) symptom scale was used to assess how the participant was feeling at time of testing (see Appendix A for the full list of symptoms), and is a valid measure of concussion symptomology (Eckner & Kutcher, 2010) . This metric uses a Likert scale for various concussion-related symptoms, and is still used on updated editions of the SCAT (Aubry et al., 2002; McCrory et al., 2009).

3.1.3 – Equipment. The NIRS device (PortaLite, Artinis Medical Systems, The Netherlands) consisted of six light emitting diodes (three pair of LEDs) and one receiver. The LEDs use continuous wave outputs and was sampled at 10Hz. The LED setup is as follows: pair 1(760nm and 843nm) is located 30mm from the receiver, pair 2 (761nm and 845nm) is 35mm from the receiver, and pair 3 (762nm and 848nm) is 40mm from the receiver. The LEDs and receiver were covered by a black cloth so as not to

contaminate the recording with external infrared light. Both the device and cloth were held in place by an adjustable headpiece. External infrared light was indirectly monitored by the quality control factor (QCF). The differential path length factor was calculated from an age-based equation described elsewhere (Duncan et al., 1994). The receiver-end of the device was placed above the medial aspect of the right supraorbital process, approximately 1 cm above the eyebrow, with the LED transmitters being on the lateral side of this ridge. This location was chosen as it avoids the sinus, can be easily reproduced, and is in a location of poor skin blood flow (Molinari et al., 2006). Neuroanatomically this region represents approximately the border between the ventromedial and ventrolateral prefrontal cortex.

3.1.4 – Procedure. ***3.1.4a – Baseline protocol.*** Once the equipment was calibrated and placed on the participant, verbal instructions regarding the order of the experiment were given. As seen in **Figure 5**, the experiment began with 5 minutes of spontaneous resting data (eyes open), with minutes 6 to 10 consisting of 5 hypercapnic challenges (breath-holds – BH). The beginning of each minute starts with a 20 second breath-hold, followed by 40 seconds of normal breathing, and is repeated 5 consecutive times (Len et al., 2013). Participants were instructed to not use a Valsalva maneuver. Once the 5th hypercapnic challenge was completed, the experiment session was over.

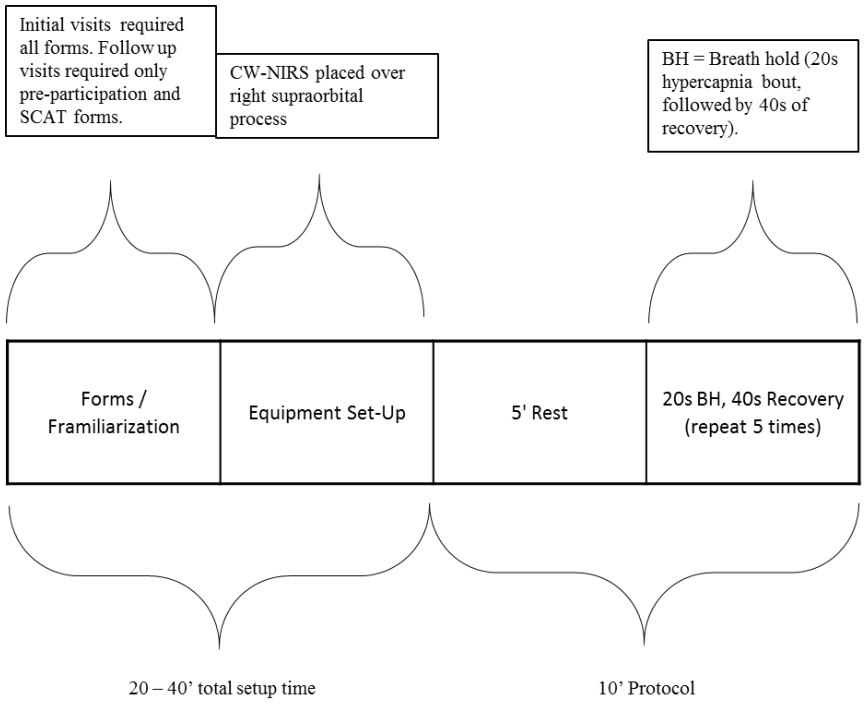

Figure 5 – Schematic representation of the experimental procedure

3.1.4b – Sports concussion protocol. Athletes who sustained a concussion were diagnosed by personnel who are either student athletic trainers, Canadian Certified Athletic Trainers, Physical Therapists, or Medical Doctors. Following injury, participants visited the laboratory at a time of their convenience, to have their cerebrovascular physiology and SCAT3 symptoms measured (via baseline protocol). Although it is not scientifically ideal to have participants enter a study at uncontrolled timelines, the data collection method reflects the current state of concussion management, and the visit is categorized in terms of days post injury.

Return-to-play decisions for the athletes were outside of the scope for this study, but as symptoms abated, return-to-play decisions were made by the participant's acting physician. Ideally, a modified version of the British Columbia – Concussion Recovery Protocol (BC-CRP) was used for return-to-play, and is described elsewhere (Gaetz & Iverson, 2009). Following completion of the completion of the BC-CRP, athletes followed the return-to-play guidelines set forth at the Zurich Consensus Statement (McCrory et al., 2009). This includes engaging in sport specific exercise, which can include warm-ups, non-contact drills, and conditioning. With no complications, the next practice included all previous drills, with further integration of contact drills. Lastly, if no symptoms presented, the athlete was allowed to engage in full-contact sport.

3.1.5a – Data processing. Within the NIRS software package there are tools used for marking events, and biasing (otherwise known as zeroing), the chromophore concentration, so that any data point can be used as the reference value for the relative micromolar (μM) concentration changes. For each participant, the chromophore bias

was placed at the event marker which indicated the onset of the five minutes of rest. All data were then exported (Microsoft Excel, Microsoft Office Home, Redmond, Washington, USA, 2012) from the acquisition software at 10 Hz, as relative changes in oxy- and deoxy-hemoglobin concentrations. The NIRS Quality Control Factor (QCF) was then inspected to ensure the value did not fall below 0.98, as this indicates that extraneous light had contaminated the recording. If the QCF was below 0.98, the data associated with these time series were eliminated. All other background noise not associated with the QCF was manually removed.

Because there were 5 consecutive breath-hold cycles that were a minute in length, each of the 5 x 1-minute cycles (after removing the background noise) was averaged together on a second-by-second basis. In essence, the 1st ten data points, representing the 1st second (1s) of each of the 5 cycles (50 data points total), was averaged. Then, the 2nd set of 50 data points (representing 10 data points for each of the 5 x 2s) was averaged. This continued until the 50 data points representing 60s, from each of the 5 cycles, was averaged. The same data analysis process was used on the resting data to generate an averaged 1 minute resting cycle.

The averaging of 5 x1 minute cycles also accounts for the manual removal of background noise. For example, if 1s (10 data points) are removed, the gap of data will be accounted for by the average of the remaining 40 data points that are associated with the other 4 cycles. Furthermore, if the removal of background noise resulted in time points which could not be accounted for by the average of the remaining cycles of data then a 0.5 Hz low frequency filter was applied to the original data (Kainerstorfer, Sassaroli, Tgavalekos, & Fantini, 2015; Steiner et al., 2009). This filtered data were then

re-exported and re-processed. Of all healthy participants (n = 115), 23 participants (20.0%) had their data filtered and reanalyzed. In days 1-3 post injury (n = 14), 3 people (21.4%) had their data filtered, with days 4-6 (n = 8), and days 7-14 (n = 11), only one participant data were filtered (12.5 % and 9.1%, respectively).

Once the averaged one minute cycles for HHb and HbO_2 were created for resting and hypercapnia challenges, a similar process was used for creating a 1 minute standard deviation (SD) cycle for rest and hypercapnia. To clarify, using data that were free of background noise, a second-by-second 1 minute SD cycle was created by taking the SD of 50 data points representing 1s for minutes 1-5, then the SD of the next 50 data points represent 2s for minutes 1-5, all the way through to the SD of the 60th second of minutes 1-5.

Once the average 1 minute hypercapnia cycle for each participant was constructed, all of the eligible participant's 1 minute averaged hypercapnic cycles were averaged together into one grand 1 minute cycle. This grand cycle was graphed so that the peak hypercapnia change could be identified. The peak change time segment identified was from seconds 26 – 31. This 26-31s time segment was then used for each participant where the average relative hemoglobin concentration changes (and standard deviations) were averaged. For rest, the 1 minute averaged cycle for each participant was condensed into a single average for concentration changes and standard deviations. The resting and hypercapnia metrics were then used to assess changes in hemoglobin concentrations and standard deviations where peak hypercapnia was subtracted from resting averages.

Lastly, the SCAT3 symptom inventory was used to create total symptoms, and symptom severity, for each participant. All concussion-NIRS data were aggregated into days 1-3 (D1-D3), 4-6 (D4-D6), and 7-14 (D7-D14), and used the same methods for data analysis as previously stated.

3.1.5b – Statistical analysis. One of the outcomes of this project was to investigate the resting changes in oxyhemoglobin, deoxyhemoglobin, and their associated standard deviations following a sport concussion. Thus, 4 different between-subject, 1x4 unweighted quadratic ANOVAs were used to assess the 1 minute averaged cycle, and 1 minute SD cycle, for resting HbO_2 and HHb (PASW V.21, Chicago, USA, 2015). Unweighted quadratic ANOVAs were used because recovery from injury does not always follow a linear path, and was unweighted because the typical dose-response nature that can be applied to quadratic ANOVAs was not known (Field, 2009; Meier et al., 2015). These ANOVAs used the Welch test for unequal variance, and if positive, was paired with the Games-Howell post-hoc test. To combat unequal sample sizes (with negative Welch tests), the Hochberg post-hoc test was used (Field, 2009).

Two other outcomes from this project were aimed at evaluating the differences in relative concentration changes (and standard deviations) between rest and peak hypercapnia. These changes were assessed using a between- and within-subject design. In comparing between-subjects, 4 separate 1 x 4 quadratic, unweighted ANOVAs were used to analyze hypercapnia changes for both HbO_2 and HHb concentrations, as well as their respective SD values (Field, 2009). These ANOVAs were paired with the Welch test for unequal variance, and either the Games-Howell post-hoc test for Welch-positive ANOVAs, or the Hochberg post-hoc test for Welch-negative unequal sample size

ANOVAs (Field, 2009). For the within-subject design, all participants had peak hypercapnia concentrations and SDs compared to rest, using student's t-test (PASW V.21, Chicago, USA, 2015).

The demographic information (age, height, weight,), and both the total symptoms and symptom severity, were also assessed using a 1 x 4 ANOVA with the previously stated statistical criteria. Lastly, the alpha level for significant differences was set at $p < 0.05$.

3.1.6 – Results. ***3.1.6a – Demographics.*** Of the 14 participants who arrived in the laboratory within D1-D3, 3 of these participants were assessed within 24 hours, 6 individuals were assessed within 48 hours, and 5 were assessed within 72 hours. Within D4-D6, 3 participants were assessed on day 4, 4 participants were assessed on day 5, and one participant was asseessed on day 6. Within days 7-14, 3 participants were assessed on day 7, 2 were assessed on day 8, one individual was assessed on day 9, two were assessed on day 10, one was assessed on day 12, one was assessed on day 13, and one assessed on day 14. As seen in **Table 2**, there were no statistically significant differences between groups for age, height, or body mass between control and concussion participants. There was a significant ANOVA ($F[1, 144] = 50.80$, $p < 0.001$) for symptom severity, with a significant increase in symptom severity when comparing healthy controls ($n = 115$, 2.56 ± 4.13) to D1-D3 ($n = 14$, 28.07 ± 22.56, $p < 0.01$). Moreover, a general trend of declining symptom severity exists throughout recovery, but this was not statistically significant. For number of symptoms, a significant ANOVA was also found ($F[1,144] = 58.99$, $p < 0.001$), with group differences also found when comparing healthy controls ($n = 115$, 1.68 ± 2.15) , to D1-D3 ($n = 14$, 11.5 ± 5.56, $p <$

0.001), D4-D6 (n = 8, 11.75 ± 7.44, $p < 0.05$), and D7-D14 (n = 11, 7.82 ± 4.96, $p <$ 0.01) .

Table 2

Demographic and SCAT3 information of participants.

Participant Information	Quadratic ANOVA (unweighted) p-value	Welch Unequal Variance p-value	Participant Category	Mean ± SD
Age (years)	0.056	0.23	a) Control (n = 115) b) D1-D3 (n = 14) c) D4-D6 (n = 8) d) D7-D14 (n = 11)	18.37 ± 1.87 19.71 ± 2.92 20.13 ± 3.6 19.18 ± 2.93
Height (cm)	0.55	0.95	a) Control (n = 115) b) D1-D3 (n = 14) c) D4-D6 (n = 8) d) D7-D14 (n = 11)	183.12 ± 5.95 182.71 ± 4.43 181.75 ± 7.36 183.36 ± 8.46
Body Mass (kg)	0.71	0.88	a) Control (n = 115) b) D1-D3 (n = 14) c) D4-D6 (n = 8) d) D7-D14 (n = 11)	85.00 ± 10.47 82.89 ± 13.33 87.19 ± 16.95 87.45 ± 16.18
Symptom Severity	< 0.001*	< 0.001 *	a) Control (n = 115) b) D1-D3 (n = 14) c) D4-D6 (n = 8) d) D7-D14 (n = 11)	2.56 ± 4.13 * a-b 28.07 ± 22.56 25.69 ± 23.50 13.27 ± 11.62
Number of Symptoms	< 0.001*	< 0.001 *	a) Control (n = 115) b) D1-D3 (n = 14) c) D4-D6 (n = 8) d) D7-D14 (n = 11)	1.68 ± 2.15 *a-b,*a-c,*a-d 11.5 ± 5.56 11.75 ± 7.44 7.82 ± 4.96

Significant differences are identified by '*' and the corresponding letters (e.g., *a-b = significant difference between 'a' and 'b' participant categories at $p < 0.05$). D1-D3= 'day 1 – day 3 post injury', D4-D6 = 'day 4 – day 6 post injury', D7-D14 = 'day 7 –day 14 post injury'.

3.1.6b – Resting NIRS concentrations and standard deviations. There was a significant ANOVA for resting HbO_2 concentrations (F[1, 144] = 19.29, $p < 0.01$), with D7-D14 (n = 11, -0.44 ± 1.64 µmol) being significantly lower than D1-D3 (n = 14, 1.22 ± 1.40 µmol, $p < 0.05$). Moreover, D7-D14 was also significantly lower than D4-D6 (n = 8, 1.56 ± 1.91 µmol, $p < 0.05$). There were no significant differences for any other concentration, or concentration SD. See **Table 3** for all resting variables, and respective significant findings, and **Figure 6** for a representation of the resting oxyhemoglobin differences.

Table 3

Resting NIRS concentrations, and standard deviations (SD) of participants.

Hemoglobin Measurement	Quadratic ANOVA (unweighted) p-value	Welch p-value	Participant Category	Mean ± SD
Relative HbO_2 (µmol) 1 Min Resting Avg	0.005*	0.073	a) Control (*n* = 115) b) D1-D3 (*n* = 14) c) D4-D6 (*n* = 8) d) D7-D14 (*n* = 11)	0.83 ± 1.51 1.22 ± 1.40 *b-d 1.56 ± 1.91 *c-d -0.44 ± 1.64
Relative HbO_2 SD (± µmol)1 Min Resting Avg	0.63	0.13	a) Control (*n* = 115) b) D1-D3 (*n* = 14) c) D4-D6 (*n* = 8) d) D7-D14 (*n* = 11)	0.94 ± 0.39 0.87 ± 0.21 1.29 ± 0.51 1.12 ± 0.51
Relative HHb (µmol) 1 Min Resting Avg	0.98	0.83	a) Control (*n* = 115) b) D1-D3 (*n* = 14) c) D4-D6 (*n* = 8) d) D7-D14 (*n* = 11)	-0.45 ± 0.65 -0.42 ± 0.45 -0.33 ± 0.55 -0.29 ± 0.61
Realtive HHb SD (± µmol) 1 Min Resting Avg	0.55	0.13	a) Control (*n* = 115) b) D1-D3 (*n* = 14) c) D4-D6 (*n* = 8) d) D7-D14 (*n* = 11)	0.37 ± 0.27 0.32 ± 0.13 0.54 ± 0.31 0.58 ± 0.40

Significant differences are identified by '*' and the corresponding letters (e.g., *a-b = significant difference between 'a' and 'b' participant categories at $p < 0.05$). D1-D3= 'day 1 – day 3 post injury', D4-D6 = 'day 4 – day 6 post injury', D7-D14 = 'day 7 –day 14 post injury'.

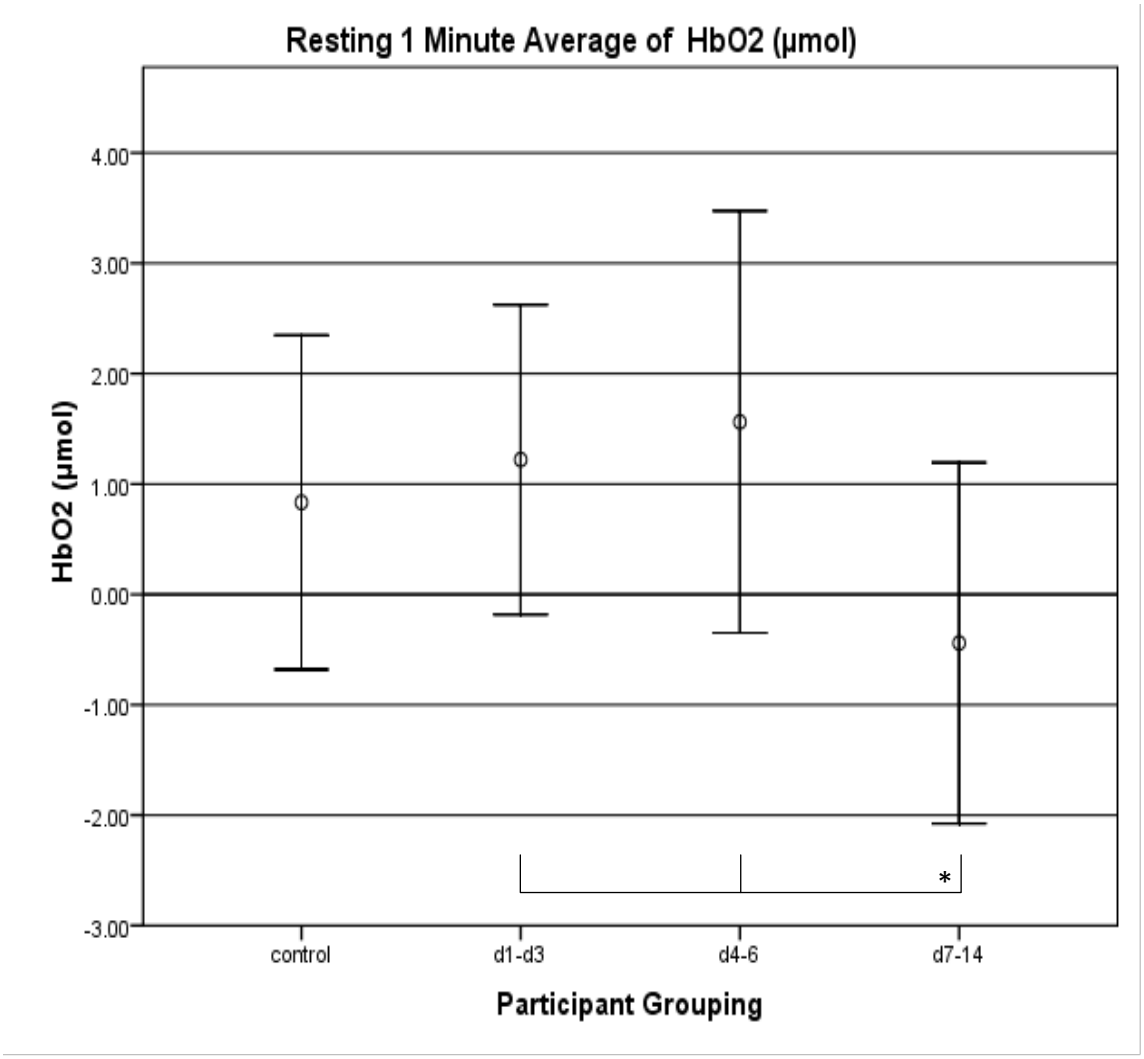

Figure 6 - Averaged relative change in oxyhemoglobin concentrations. Significant differences (*) were found between d7-14 versus d1-3, and d4-6 ($p < 0.05$). No differences were found compared to rest across all groups.

3.1.6c – Rest to peak hypercapnia concentration and standard deviation change – between subject analysis. There were no significant differences when comparing the changes in oxy- or deoxy-hemoglobin concentration from rest to peak breath-hold (See **Table 4**, and **Figure 7**). However, as reported in **Table 4** and illustrated in **Figure 8**, the ANOVA for change in oxyhemoglobin SD from rest to peak hypercapnia was significant ($F[1, 144] = 10.54$, $p < 0.001$). The HbO_2 SD was significantly different when comparing the control's HbO_2 SD change ($n = 115$, 0.13 ± 0.54 µmol) to that of D1-D3 ($n = 14$, -0.15 ± 0.28 µmol, $p < 0.05$), and D4-D6 ($n = 8$, -0.42 ± 0.43 µmol, $p < 0.05$). It is also documented that the HbO_2 SD during peak hypercapnia (seconds 26 – 31) decreases for D1-D3, and D4-D6, but is increased for controls and D7-D14. This indicates that the HbO_2 SD for D1-D3 and D4-D6 are lower than their resting levels, and vice versa for controls and D7-D14.

Table 4

Relative hemoglobin concentration and standard deviation (SD) changes, from rest to peak hypercapnia.

Hemoglobin Measurement	Quadratic ANOVA (unweighted) p-value	Welch p-value	Participant Category	Mean ± SD
Averaged Relative HbO2 (µmol) 'rest-to-peak hypercapnia change'	0.59	0.92	a) Control (n = 115) b) D1-D3 (n = 14) c) D4-D6 (n = 8) d) D7-D14 (n = 11)	1.33 ± 1.53 1.27 ± 0.84 1.29 ± 1.39 1.67 ± 1.73
Averaged Relative HbO2 SD (± µmol) 'rest-to-peak hypercapnia change'	0.001*	0.005 *	a) Control (n = 115) b) D1-D3 (n = 14) c) D4-D6 (n = 8) d) D7-D14 (n = 11)	0.13 ± 0.54 * a-b, a-c -0.15 ± 0.28 -0.42 ± 0.43 0.25 ± 0.80
Averaged Relative HHb (µmol) 'rest-to-peak hypercapnia change'	0.6	0.8	a) Control (n = 115) b) D1-D3 (n = 14) c) D4-D6 (n = 8) d) D7-D14 (n = 11)	-0.0089 ± 0.54 -0.078 ± 0.41 -0.017 ± 0.19 0.0074 ± 0.15
Averaged Relative HHb SD (± µmol 'rest-to-peak hypercapnia change')	0.17	0.043 *	a) Control (n = 115) b) D1-D3 (n = 14) c) D4-D6 (n = 8) d) D7-D14 (n = 11)	0.059 ± 0.18 -0.048 ± 0.11 -0.017 ± 0.19 0.0074 ± 0.15

Significant differences are identified by '*' and the corresponding letters (e.g., *a-b = significant difference between 'a' and 'b' participant categories at $p < 0.05$). D1-D3= 'day 1 – day 3 post injury', D4-D6 = 'day 4 – day 6 post injury', D7-D14 = 'day 7 –day 14 post injury'.

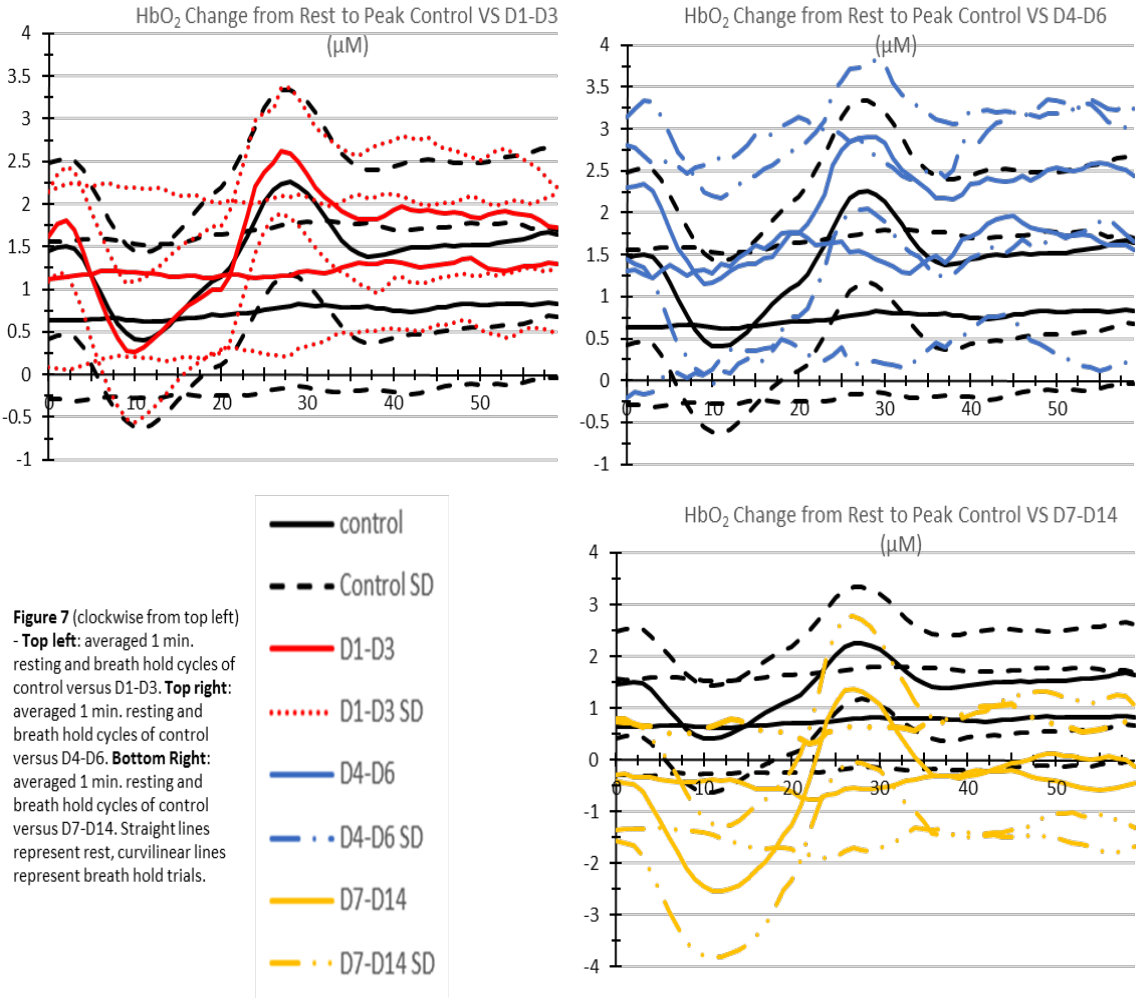

Figure 7 (clockwise from top left) - **Top left**: averaged 1 min. resting and breath hold cycles of control versus D1-D3. **Top right**: averaged 1 min. resting and breath hold cycles of control versus D4-D6. **Bottom Right**: averaged 1 min. resting and breath hold cycles of control versus D7-D14. Straight lines represent rest, curvilinear lines represent breath hold trials.

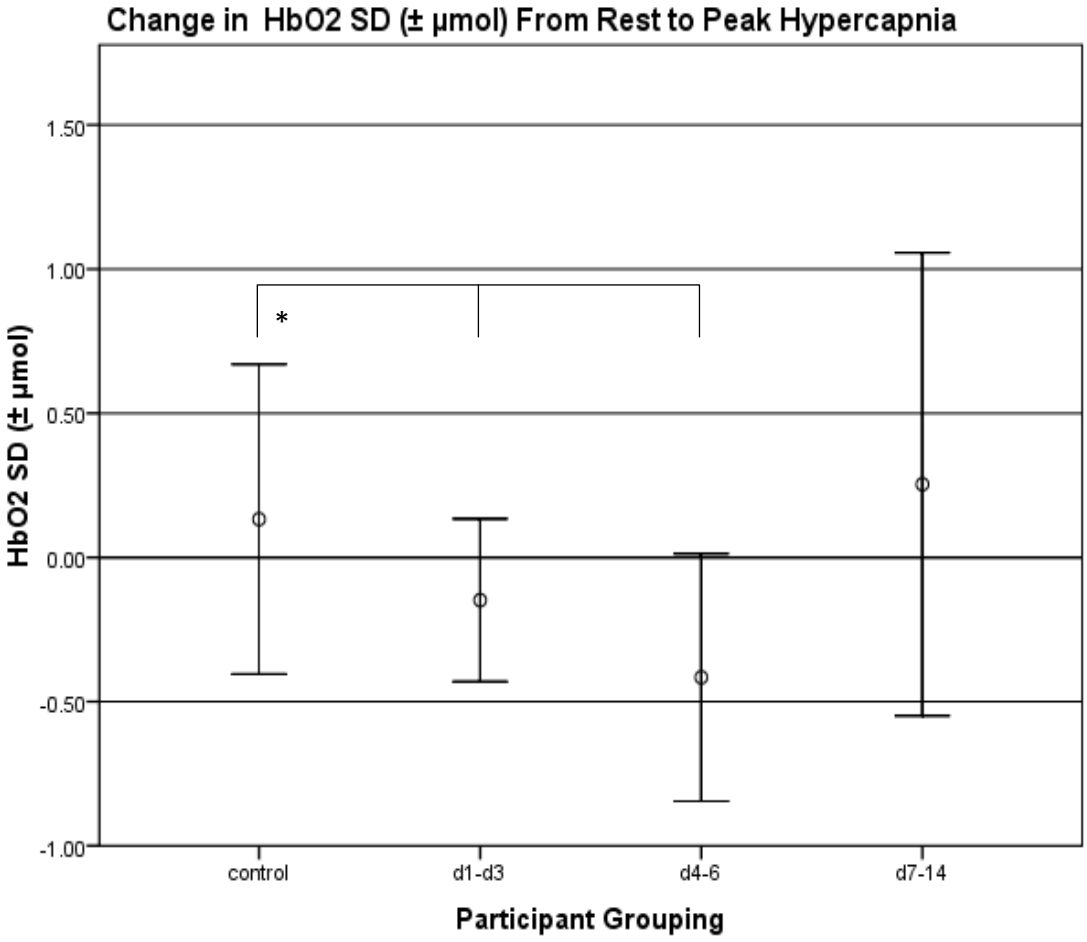

Figure 8 - HBO_2 SD (± µmol) change averaged from 1-minute rest to averaged peak hypercapnia (hypercapnia averaged from 26-31s). Significant differences (*) were found between controls versus d1-3, and controls versus d4-d6 ($p < 0.05$)

3.1.6d – Rest to peak hypercapnia concentration and standard deviation change – within subject analysis. As a reminder, this section had each group's peak hypercapnia hemoglobin concentrations (and standard deviations) compared to their own resting values. The results from these resting versus hypercapnic comparisons can be seen in **Table 5**.

Beginning with healthy controls, the small HHb concentration decrease during peak breath-holds (compared to rest) was not significantly different. However, the HHb SD changes were significantly different, with peak hypercapnia showing an increase in HHb SD compared to rest. The t-test for control participant's HbO_2 concentration change was significantly different ($p < 5.0$ x10-15) indicating peak hypercapnia is statistically higher than rest. Moreover, HbO_2 SD also had a significant t-test ($p < 0.01$), indicating that healthy HbO_2 SD during peak hypercapnia is statistically higher than resting SD values, which is similar to the HHb SD comparison.

Table 5

Relative hemoglobin concentration and standard deviations (SD) for rest and peak hypercapnia, for each participant grouping.

Hemoglobin Measurement	Participant Category	Resting Values (Mean ± SD)	Peak Hypercapnia Values (Mean ± SD)	t-statistic	t-statistic p-value
HbO_2 (µmol)	a) Control (n = 115)	0.83 ± 1.51	2.16 ± 2.30	-9.29	*< 5.0E-15
	b) D1-D3 (n = 14)	1.22 ± 1.40	2.49 ± 1.73	-5.66	*<1.0E-4
	c) D4-D6 (n = 8)	1.56 ± 1.91	2.85 ± 2.04	-2.63	*0.05
	d) D7-D14 (n = 11)	-0.44 ± 1.64	1.23 ± 2.40	-3.2	*<0.01
HbO_2 SD (± µmol)	a) Control (n = 115)	0.94 ± 0.39	1.09 ± 0.60	-3.12	*<0.01
	b) D1-D3 (n = 14)	0.87 ± 0.21	0.72 ± 0.22	1.96	0.07
	c) D4-D6 (n = 8)	1.29 ± 0.51	0.88 ± 0.39	2.74	*<0.05
	d) D7-D14 (n = 11)	1.12 ± 0.51	1.37 ± 0.71	-1.05	0.32
HHb (µmol)	a) Control (n = 115)	-0.45 ± 0.65	-0.46 ± 0.90	0.18	0.861
	b) D1-D3 (n = 14)	-0.42 ± 0.45	-0.49 ± 0.73	0.71	0.49
	c) D4-D6 (n = 8)	-0.33 ± 0.55	-0.33 ± 0.55	1.11	0.31
	d) D7-D14 (n = 11)	-0.29 ± 0.61	-0.34 ± 1.02	0.32	0.75
HHb SD (± µmol)	a) Control (n = 115)	0.37 ± 0.27	0.43 ± 0.35	-3.51	*<0.01
	b) D1-D3 (n = 14)	0.32 ± 0.13	0.28 ± 0.12	1.61	0.13
	c) D4-D6 (n = 8)	0.54 ± 0.31	0.52 ± 0.38	0.26	0.8
	d) D7-D14 (n = 11)	0.58 ± 0.40	0.59 ± 0.30	-0.16	0.88

Significant differences are identified by '*' at $p < 0.05$. D1-D3= 'day 1 – day 3 post injury', D4-D6 = 'day 4 – day 6 post injury', D7-D14 = 'day 7 –day 14 post injury'.

For D1-D3, the HHb concentration was not significantly different when comparing peak hypercapnia to rest. Moreover, the D1-D3 HHb SD during hypercapnia was lower than rest, but was not significantly different. Regarding D1-D3's HbO_2 concentrations, peak hypercapnia was significantly higher than rest ($p < 1.0x\ 10\text{-}4$). The HbO_2 SD comparison of hypercapnia to rest for D1-D3 revealed lower variance during peak hypercapnia than rest, but was not significantly different. This was opposite of healthy controls, who had statistically increased variance during hypercapnia.

For D4-D6, HHb concentrations were not significantly different when comparing peak hypercapnia to rest. Unlike healthy controls, the HHb SD during hypercapnia was not significantly different from rest, but was slightly less than resting. The D4-D6 HbO_2 concentrations for peak hypercapnia versus rest revealed peak hypercapnia to be significantly different from rest ($p < 0.05$). Similar to D1-D3, the HbO_2 SD for D4-D6 was again lower than rest, and reached statistical significance ($p < 0.05$). Again, this SD trend was opposite of healthy controls who had statistically increased variance during hypercapnia. The D7-D14 period revealed that HbO_2 SD during hypercapnia was once again greater than resting values (which is similar to healthy participants), although the value was not significant. Moreover, the HbO_2 concentrations during hypercapnia were still greater than rest ($p < 0.01$). Lastly, the hypercapnia HHb SD was higher than rest but was not significantly different, nor were the HHb concentration differences for hypercapnia versus rest.

4.0 - Discussion

This cross-sectional study examined the relative changes in pre-frontal cortex hemoglobin concentration post-concussion (and the relative hemoglobin concentration

SDs) during rest, and during breath-hold induced hypercapnia. When the above results are integrated, the most consistent finding was that healthy physiological variances were reduced after a mild brain injury (**Table 4** and **Table 5**). A second integrated finding was that the breath-hold induced hypercapnia protocol likely represents hyperemia (i.e., a global chemodetection response generated in the medulla), and not a regional matching of blood flow to metabolic demands. This is evidenced by the lack of within-subject HHb findings, which were complimented by significant within-subject HbO_2 increases during hypercapnia versus rest (**Table 5**). Another major finding was that resting HbO_2 in D1-D3 and D4-D6 were significantly greater than D7-D14; but none of these values were different compared to controls (**Table 3** and **Figure 6**). Lastly, it was noted that the changes in hemoglobin concentration from rest to peak hypercapnia were not significantly different when comparing between groups. Hence, the null hypothesis for hypercapnic changes in hemoglobin for within- and between-subject analysis is accepted. Alternately, the null hypothesis regarding the reduction in variance post brain injury is rejected.

To compare these findings to previous research, it is first noted that no other NIRS project has aggregated hemoglobin concentrations (HbO_2 and HHb) into discrete days post-injury and then compared these values to healthy controls (Kontos et al., 2014; Urban et al., 2015). Furthermore, previous NIRS-concussion projects have relied on comparing regional changes in hemoglobin that were induced by motor learning physiology (Kontos et al., 2014; Urban et al., 2015). In comparison, this project does not use a neurocognitive test to evoke cortical blood flow and oxygenation changes. Instead, this project relied on a build up of global CO_2. Based on the within-subject HHb and

HbO_2 results, this CO_2 build up likely results in an increase in flow that was not generated by a cortical increase in metabolic demand.

The closest study to compare the resting post-injury changes in hemoglobin concentration is a BOLD-fMRI study which measured healthy participants and concussed participants at 0-3, 6-13, and 25-44 days post-injury (Meier et al., 2015). The linkage between this fMRI study and the current results are that both projects showed no differences in resting cerebral hemodynamics when comparing concussed participants compared to controls. Rather, significant differences in the fMRI study and the current study were only found when comparing acute injury timelines to a prolonged recovery timeline of approximately a month (Meier et al., 2015). A similar statistical significance pattern of acute versus prolonged recovery was also observed using a transcranial Doppler study that monitored concussion recovery, though this pattern was observed during breath-hold induced hypercapnia (Len et al., 2013).

To further complicate matters, the Meier et al. (2015) fMRI study reported lower oxygen values in the acute phase of recovery, which increased over time. However, the current project reported increased HbO_2 in the acute phase of injury, which then lowered over time. While these two different measures of cerebral oxygenation typically correlate quite well under healthy flow-metabolite coupling circumstances (Fabiani et al., 2014; Huppert, Hoge, Diamond, Franceschini, & Boas, 2006), it is clear that these results will require additional prospective studies. It is also noted that the increases in BOLD-fMRI versus the decreases in hemoglobin concentration may be due to the fact that BOLD-fMRI measures oxygen volume in a determined space (in microliters), whereas NIRS measures the absorbance of infrared light, and calculates the concentration in

relative change. Moreover, the BOLD-fMRI findings were measured in slightly more subcortical areas (the dorsal midinsular cortex and the superior temporal sulcus) (Meier et al., 2015), whereas the current study only measured the right prefrontal cortex.

The current hypercapnia change and standard deviation results are difficult to compare to the previously mentioned NIRS and transcranial Doppler studies. These previous projects either focused on neurocognitive testing, or a 20s breath-hold paradigm with a different cerebrovascular measurement, i.e., transcranial Doppler (Kontos et al., 2014; Len et al., 2013; Meier et al., 2015). Because the current project found no statistically significant changes in HbO_2 and HHb for rest to peak hypercapnia between group comparisons, only speculations can be made. The first speculation is that, global chemodetection to track concussion recovery may be better suited to scientific tools that can measure large regions of hemodynamic function (such as transcranial Doppler and fMRI) (Len et al., 2013; Mutch et al., 2014). Naturally, this is a limiting factor of the present study, as a single receiver-by-3 pair LED was chosen as the NIR-device. Thus, it is possible that measuring a larger cortical region of the brain with fNIRS may have generated significant hypercapnia results following injury. Alternatively, the lack of significant findings could also be due to the low concussion sample size, which was another limitation in the present study. Moreover, another speculation which builds off the premise of measuring a larger brain region is that NIRS measurements may better capture impairment when a cognitive task is employed.

The last result of interest was the loss of hemoglobin concentration SD, which occurred when acutely concussed participants initiated a breath-hold. The HHb within-subject results displayed a loss of statistically higher HHb SD after concussion, whereas

D1-D3 and D4-D6 HbO_2 SD during hypercapnia was lower than resting values, and statistically was different when compared to healthy controls. These hemoglobin SD results reinforce previous healthy variance research (that has utilized various measurement tools under various physiological impairments), to show that variance in a given system is lost when one part of the system (or subsystem) no longer functions within a healthy range (Bishop & Neary, 2015; Cerutti, Hoyer, & Voss, 2009; Costa et al., 2005; Coveney, 2003; La Fountaine, Heffernan, Gossett, Bauman, & De Meersman, 2009; Papaioannou, Giannakou, Maglaveras, Sofianos, & Giala, 2008; Pincus, 1991; Thayer et al., 2012).

Although it is well documented that both CO_2 – potassium relations, and nitric oxide presence can effect calcium's ability to induce vasoconstriction, the mechanisms by which healthy or dysregulated variance interact with cerebrovascular subsystems is not well understood (Moody et al., 2005; Panerai, 2009). Moreover, the pathophysiology of brain injury is also still being researched, as high (prolonged) intracellular calcium does effect metabolism and blood flow, but the dose-response relationships between severity and pathology and are still questioned (Barkhoudarian et al., 2011; Bigler & Maxwell, 2012; Park et al., 2009). Based on the previous findings which indicate a loss of variance (in spite of not fully knowing the physiological mechanisms), the measures of cerebrovascular variance warrants further research.

4.1 – Conclusion

This project demonstrated that non-invasive pre-frontal cortex hemoglobin concentrations hold potential for monitoring sport concussion recovery, particularly based on resting hemoglobin changes and its variance (SD). Thus, it is recommended

that future NIRS-concussion projects better attempt to serially monitor injury, measure a larger area of cortical activity, and continue to measure hemoglobin standard deviations.

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6.0 APPENDICES

6.1 - APPENDIX A – Informed Consent Documentation

See full informed consent document on the following page.

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6.1.1 - Concussion study information sheet

Title of Project:

Integration of multimodal imaging techniques for assessment and diagnosis of concussion or mild traumatic brain injury (mTBI) ***REB 55R1213***

Principle Investigator(s):

Dr. J. Patrick Neary, PhD
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The university and those conducting this project subscribe to the ethical conduct of research and to the protection at all time of the interests, comfort, and safety of participants, and this project has been approved the University of Regina Ethics Board (#55R1213). This form and the information it contains are given to you for your own protection and full understanding of the procedures in this research. Your signature on this form will signify that you have received a document that describes the procedures, objectives, possible risks, and benefits of this research project, and that you have received an adequate opportunity to consider the information in the document, and that you voluntarily agree to participate in the project.

Purpose: This project is aimed at understanding the physiological responses during rest, during changes in respiration (breathing) rate, and during exercise following a concussion. It is hoped that this research will provide future treatment and return-to-play guidelines for concussed athletes.

Procedures: This testing will be performed in a laboratory setting that will ensure your privacy. This testing will last approximately one-hour in duration. You will be asked to complete some medical information forms, and then to perform a series of repeated breath-holds for 5 minutes (20 sec hold:40sec normal breathing x 5 repeats) and/or a repeated hyperventilation test (or normal breathing to a gas mixture of increased carbon dioxide, 3%) will be done after a 5 minute baseline data collection. You will also be asked to perform a simple test with your eyes closed and then open, and reading a passage in a book or doing a computerized test. This will be repeated 2-4 times and will take about 5-6 minutes. You will be asked to perform a Squat-Stand maneuver where you squat for 5 or 10seconds and stand for 5 or 10seconds, repeated for 5 minutes. An exercise session on a cycle ergometer will also be performed when you are asymptomatic. The workload will be increased every 5 minutes (80W, 120W, 160W) to elicit mild, moderate and intense heart rates.

During testing, you will be connected to medical equipment. One device is a probe that will measure your brain blood flow (called a transcranial Doppler ultrasound probe), another device will measure your brain oxygenation levels (called near infrared spectroscope), ECG electrodes to measure heart rate, a finger blood pressure monitor, and a mouthpiece to record expired gases when you breathe. All equipment is non-invasive and is completely safe, and has been used in hundreds of research projects. If you sustain [or have sustained] a concussion, you will be asked to return to the laboratory to be re-tested on Day 1-3, Day 3-5, Day 7-10, Day 21, and D30 post-concussion as stated above.

Potential Risks and Discomforts: There is a possibility that if you are still suffering from a concussion you may experience headaches during the testing. If this occurs, you may stop the testing immediately and the appropriate measures will be taken to ensure your comfort. The exercise protocol will only be performed when you are symptom free, and is designed to elevate your heart rate and is not designed to cause you discomfort. You may feel fatigued during the exercise protocol and this is a normal response. If you feel, at any time, that you need to stop cycling, you may do so without penalty. The research equipment and techniques that we will use in this testing have been used in our previous research conducted by Dr. Patrick Neary at the University of Regina.

Possible Benefits to Subject and/or Society: This research study may provide you with an opportunity to gain some knowledge and education about concussions in sport. Your participation in this study may also assist us, the researchers, to determine when it is safe to return-to-play.

Confidentiality: Any information that is obtained during this study will be kept confidential to the full extent permitted by law. Participants will be given a unique identification number and any information provided will be marked with this ID number. All confidential materials will be locked in a filing cabinet in Dr. Patrick Neary's laboratory or office. Graduate students Scott Bishop and Tanis Burnett will also have access to the coded data for their research. If we publish our data, only average results will be reported and thus you will not be identified. In the event that the researchers find evidence that the athlete may still be concussed, this information will be passed on to you, your parents/guardian/family doctor, or team's athletic therapist(s) and team physician for your safety. However, our data cannot be used to confirm the diagnosis of a concussion.

Participants and Withdrawal: If you feel, at any time, that you would like to withdraw from the research study, you may do so freely and without consequence. Your right to withdraw data from the study will apply for 3 months from the date of your involvement in the study. After this time it is possible that some form of research dissemination will have already occurred and it may not be possible to withdraw your data.

Feedback: You will have full access to your individual test results, upon request, once the data has been analyzed.

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Questions: This project was approved by the Research Ethics Board, University of Regina. If research participants have any questions or concerns about their rights or treatment as participants, they may contact the Chair of the Research Ethics Board at (306) 585-4775 or by e-mail at research.ethics@uregina.ca. If, at any time, you have questions about this study, feel free to ask any of the investigators.

Participation is voluntary and you may withdraw at any time without penalty. Refusal to participate in this study will not influence or affect the management of your injury and your return to activity. Please complete the section on the following page. Thank you for your participation.

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6.1.2 - Consent for subjects to participate in this research project

Title of Project: *Integration of multimodal imaging techniques for assessment and diagnosis of concussion or mild traumatic brain injury (mTBI)* ***(REB 55R1213).***

- I understand that my participation in this study is voluntary and that I may withdraw my participation in this experiment at any time, without any consequences.

- I am aware that I will be expected to disclose any previous concussion injuries I have sustained.

- I have been informed that all information collected from me will be treated confidentially, and will be locked in the filing cabinet of the principle investigator(s), Dr J. Patrick Neary, and graduate students Scott Bishop and Tanis Burnett will also have access to your data for their research. Research undergraduate students Ryan Deck and Mackenzie Wekerle, and Medical Student Danny Diep, will have access to your results to assist with data analysis.

- I understand that if I sustain [have previously sustained] a concussion, I will be asked to participate in further testing procedures as outlined in the study information sheet.

- I have been assured that I may contact Dr. Patrick Neary at patrick.neary@uregina.ca (306-585-4844) at any time if I have questions or would like more information directly related to this study. I may obtain a copy of my results, upon completion of the study, by contacting the above person.

- This project was approved by the Research Ethics Board, University of Regina. If I have any questions or concerns about my rights or treatment as a participant, I may contact the Chair of the Research Ethics Board at (306) 585-4775 or by e-mail at research.ethics@uregina.ca.

- I understand the contents of this form, and I agree to participate in this research study.

- I have received a copy of the information sheet and informed consent form for my records.

NAME (Please print legibly):

_____

ADDRESS:

_____

_____Phone:_____

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SIGNATURE: _____ DATE: _____

PARENTAL/GUARDIAN SIGNATURE_____

WITNESS: _____

Please Note: ***A future objective of Dr. Neary is to consult to professional sport, and therefore information learned in this research could be used to develop novel software for the diagnosis of concussion and possible commercialization for financial gain. However, your data will remain completely anonymous. You are entitled to ask any questions regarding this research for financial gain.***

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6.1.3 – Research ethics board certificate of renewal approval

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Research Ethics Board
Certificate of Renewal Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	REB#
Dr. Patrick Neary	**Kinesiology and Health Studies**	**U of R 55R1213; U of S BEH 12-236**

TITLE
Integration of Multimodal Imaging Techniques for Assessment and Diagnosis of Concussion or Mild Traumatic Brain Injury (mTBI)

ORIGINAL DATE of APPROVAL	NEW EXPIRY DATE WITH THIS RENEWAL	TODAY'S DATE
December 12, 2012	**December 12, 2016**	**November 13, 2015**

Full Board Meeting ☒

Delegated Review ☐

RENEWAL CERTIFICATION
The University of Regina Research Ethics Board has renewed the above-named research project for an additional 12 months beginning December 12, 2013.

Any significant changes to your proposed method, or your consent and recruitment procedures should be reported to the Chair of the Research Ethics Board for consideration in advance of implementation.

ONGOING REVIEW REQUIREMENTS
In order to receive annual renewal, a status report must be submitted to the REB Chair for Board consideration within one month of the current expiry date each year the study remains open, and upon study completion. Please refer to the following website for further instructions:
http://www.uregina.ca/research/REB/main.shtml

Ara Steininger
Research Ethics Board

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5.1.4 - Demographic information

DISCLAIMER:

The following questions are for the sole purpose of better understanding current brain injuries, and post-brain injury brain physiology. All questions answered herein will not be used for any other purpose, and will be kept confidential to the full extent permitted by law. All information will be stored in a locked filing cabinet. Only your ID# will used in the analysis database, and will only be cross-referenced with your actual name if you want or require additional testing. Dr. Neary, and graduate students Scott Bishop and Tanis Burnett will also have access to these files for their research. Please answer all questions as honestly as possible.

GENERAL INFORMATION / INSTRUCTIONS:

Please use the grey boxes to answer all questions as best, and as honest as possible. Most questions only require you place a number in each grey box, so read carefully, and feel free to ask the researchers questions at anytime.

Name
Date (dd/mm/yyyy)
ID# (will be given to you)
Which number describes you best: 1=non-varsity athlete with no history of concussion; 2=Varsity Athlete, with no history of concussion; 3=Varsity athlete with concussion history but no Post Concussion Syndrome; 4=Varsity Athlete with Post Concussion Syndrome; 5=non-varsity athlete with history of concussion but no Post Concussion Syndrome; 6=non-varsity athlete with Post Concussion Syndrome
2
Type in '0' if this is a baseline test, or '1' if this is for clinical purposes
0
If this is for clinical purposes, what visit number is this?

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If this is for clinical purposes, what day post injury is this?

What Gender are you? '0'=Male; '1'=Female; '2'=I Identify outside of the first two categories

0

How old are you? (please respond in years, with no decimals)

What is your height in centimeters? (this will be measured for you)

What is your weight in Kilograms? (this will be measured for you)

What is your dominant hand? ('0'=right handed; '1'=left handed)

0

GENERAL MEDICAL HISTORY:

The following section asks questions regarding your family's medical history. Please answer the questions to the best of your ability.

Date of Birth (dd/mm/yyyy)

Please indicate the highest degree you earned in school ('0'=not completed high school; '1'=completed highschool; '2'=completed undergraduate college/university; '3'=completed graduate studies; '4'=medical or law degree)

Do any major illness run in your family? ('0'=no; '1'=yes)

If you answered yes to the above question, please elaborate below

Other than accidents or injury, has any family member died suddenly at <50 years of age? ('0'=no; '1'=yes)

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If you answered yes to the above question, please elaborate below
Are you currently under a doctor's care for any medical conditions? ('0'=no; '1'=yes)
If you answered 'yes' to the above question, please indicate below what condition you have.
Have you recently gained more than 15 lbs? ('0'=no; '1'=yes)
0
Have you recently lost more than 15 lbs? ('0'=no; '1'=yes)
0
Does anybody in your immediately family suffer from Alzheimer's disease? ('0'=no; '1'=yes)
0
Have you ever had encephalitis or meningitis? ('0'=no; '1'=yes)
0
Have you ever been diagnosed with a brain tumor? ('0'=no; '1'=yes)
0
Have you ever been treated for alcohol or drug abuse? ('0'=no; '1'=yes)
0
Have you ever been diagnosed as learning disabled? ('0'=no; '1'=yes)
0
Were you placed in special classes in school due to learning or behavioural problems? ('0'=no; '1'=yes)
0
Have you ever been hospitalized with mental or emotional problems? ('0'=no; '1'=yes)
0

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CONCUSSION HISTORY:

The following section asks questions about the events and nature of your previous concussions. Please answer the questions to the best of your knowledge. If you have no conussion history, please answer the question below with a '0' and proceed to the next section (pre-participation).

How many Concussions have you previously had? (1,2,3... Etc.)

0

Concussion 1 (most recent)

Date of Injury (to the best of your memory)

How did it happen? (Please describe below)

What age were you? (in years)

Did you see a doctor?(No='0'; Yes='1')

Did you go to a hospital (No='0'; Yes='1')

To the best of your knowledge, how long were you knocked out for? (never lost consciousness='0'; less than 30s='1'; less than 1min.='2'; less than 2min.='3'; over 2min.='4')

How long did your confusion or memory problems last after the injury? Please specify the time line (e.g. 5 minutes, 2 weeks)

Did you suffer from permanent thinking or memory problems after injury? (No='0'; Yes='1')

Did you have memory loss for events before the injury? (No='0'; Yes='1')

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Did you suffer from headaches, fatigue, visual problems, dizziness, or other symptoms after the injury? (No='0'; Yes='1')

How long did your headaches, fatigue, visual problems, dizziness, or other symptoms last after the injury? (e.g. 2 weeks, 1 month)

Did you suffer from increased irritability, depression, anxiety, or other emotional symptoms after injury? (No='0'; Yes='1')

How long did your increased irritability, depression, anxiety, or other emotional symptoms last after injury? (e.g. 2 weeks, 1 month)

Were you wearing a mouthpiece at the time of your concussion? (No='0'; Yes='1')

At what level of hockey were you playing when the concussion occurred?

Did you see a doctor?(No='0'; Yes='1')

Did you go to a hospital (No='0'; Yes='1')

To the best of your knowledge, how long were you knocked out for? (never lost consciousness='0'; less than 30s='1'; less than 1min.='2'; less than 2min.='3'; over 2min.='4')

How long did your confusion or memory problems last after the injury? Please specify the time line (e.g. 5 minutes, 2 weeks)

Did you suffer from permanent thinking or memory problems after injury? (No='0'; Yes='1')

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Did you have memory loss for events before the injury? (No='0'; Yes='1')

Did you suffer from headaches, fatigue, visual problems, dizziness, or other symptoms after the injury? (No='0'; Yes='1')

How long did your headaches, fatigue, visual problems, dizziness, or other symptoms last after the injury? (e.g. 2 weeks, 1 month)

Did you suffer from increased irritability, depression, anxiety, or other emotional symptoms after injury? (No='0'; Yes='1')

How long did your increased irritability, depression, anxiety, or other emotional symptoms last after injury? (e.g. 2 weeks, 1 month)

Were you wearing a mouthpiece at the time of your concussion? (No='0'; Yes='1')

At what level of hockey were you playing when the concussion occurred?

NOTE: the questions from concussion history (above) are repeated for up to six concussions, but have been removed due to space limits.

PRE-PARTICIPATION ACTIVITY:

Please fill this section out immediately before the test.

How long ago did you consume your last meal? (within the hour='0'; within two hours='1'; within four hours='2'; over four hours ago='3')

Have you consumed any alcoholic beverages in the last 24 hours? (No='0'; Yes='1')

0

If you have consumed alcohol, how many drinks drinks? Please type in the number below

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(e.g. 2 beers and a glass of wine = '3')
If you have consumed alcohol, how many hours ago was your last drink? (within the last 3 hours='0'; three to six hours ago='1'; six to nine hours ago='2';nine to twelve hours ago='3'; over twelve hours ago='4')
Have you consumed any caffeinated beverages in the last 24 hours? (No='0'; Yes='1')
0
If you have consumed caffeine, how many drinks drinks? Please type in the number below (e.g. 2 cans of coke and a cup coffee = '3')
If you have consumed caffeine, how many hours ago was your last drink? (within the last hour='0'; one to three ago='1'; three to six hours ago='2'; six to nine hours ago='3'; over nine hours ago='4')
Have you take any medication (including contraceptives) in the last 24 hours? (No='0'; Yes='1')
0
If you have taken any medication, please list the names below (e.g….medication 1,medication 2, medication 3, etc.)
In the same order you have listed your above medications, please state how many hours ago each medciations was consumed
Medication1
Medication 2
Medication 3
Medication 4
How many hours of sleep did you get last night?

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For females only: please indicate the day of your menstrual cycle (e.g. if you are just beginning your period please place a '1' [for day 1] below… if you use contraceptives please put the current day's pill number below)

Have you participated in any exercise in the last 24 hours? (No='0'; Yes='1')

If you have participated in exercise, how long ago was it performed? please answer in hours

Is there anything else that you feel would affect the results of this test? (e.g. stressful situations, motor vehicle accidents etc).

CONCUSSION SYMPTOM SCALE:

Please fill this out immediately before testing. Below are a list of symptoms commonly felt with concussion, please rank how you are currently feeling with regard to each symtpom on a scale of 0-6. (e.g. ranking your current headache with a score of '6' would tell the researchers that you currently have the worst headache of your life; where a score of '0' would indicate you have no headache)

Headache
0
"Pressure in head"
0
Neck pain
0
Balance problems or dizzy
0
Nausea or vomiting
0
vision problems
0
hearing problems/ringing
0
"Don't feel right"
0

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Feeling "dinged" or "dazed"
0
Confusion
0
Feeling slowed down
0
Feeling like "in a fog"
0
Drowsiness
0
Fatigue or low energy
0
More emotional than usual
0
Irritability
0
Difficulty concentrating
0
Difficulty remembering
0
Sadness
0
Nervous or anxious
0
Trouble falling asleep
0
Sleeping more than usual
0
Sensitivity to light
0
Sensitivity to noise
0
Other
0