

**HOW MENTAL FATIGUE INFLUENCES NEUROVASCULAR COUPLING IN  
POST-CONCUSSION SYNDROME:  
A PRELIMINARY PILOT STUDY**

by

Liam Connor Tapsell

B.Sc., The University of Western Australia, 2017

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF  
THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

The College Of Graduate Studies

(Health and Exercise Sciences)

THE UNIVERSITY OF BRITISH COLUMBIA

(Okanagan)

January 2021

© Liam Connor Tapsell, 2021

The following individuals certify that they have read, and recommend to the College of Graduate Studies for acceptance, a thesis/dissertation entitled:

HOW MENTAL FATIGUE INFLUENCES NEUROVASCULAR COUPLING IN POST-CONCUSSION SYNDROME: A PRELIMINARY PILOT STUDY

submitted by Liam Connor Tapsell in partial fulfillment of the requirements of the degree of Master of Science.

Dr. Paul van Donkelaar, Faculty of Health and Social Development/ School of Health and Exercise Sciences

---

Supervisor

Dr. Brian Dalton, Faculty of Health and Social Development/ School of Health and Exercise Sciences

---

Supervisory Committee Member

Dr. Chris McNeil, Faculty of Health and Social Development/ School of Health and Exercise Sciences

---

Supervisory Committee Member

Dr. Kathryn Schnieder, University of Calgary

---

External Examiner

## Abstract

*Introduction:* Although most concussions have symptoms only lasting a few days, some leave impact for months or more, becoming post-concussion syndrome (PCS). With PCS, there can be reduced capacity of mental processes, this is called mental fatigue. It is unknown how mental fatigue manifests in the brain, which limits treatment to those affected. It is possible that the relationship between neural activation and blood flow could provide insight. *Methods:* 4 participants completed a questionnaire on their concussion history and symptoms. They then completed a self-report survey on how mentally fatigued they felt, as well completing a transcranial Doppler (ultrasound) measure of the middle cerebral artery (MCA) and posterior cerebral artery (PCA) response to stimuli in and simple reaction time (SRT) before and after a 45-60-minute task designed to induce mental fatigue. *Results:* It was found that changes in mental fatigue questionnaire responses had a strong, positive correlation with both number of PCS symptoms ( $R=0.99$ ) and symptom severity ( $R=0.94$ ). Higher levels of mental fatigue were strongly associated with lower time to cerebral blood flow (CBF) peak (PCA=-0.75, MCA=-0.72) and lower increases in CBF from rest to peak stimulation (PCA=-0.67, MCA=-0.56). Higher changes in mental fatigue were strongly associated with worse SRT in both a visual task ( $R=0.52$ ) and an auditory task (0.98). *Discussion:* These preliminary data are the first to indicate a physiological manifestation of mental fatigue as a PCS symptom, improving our understanding of the symptom. Interventions for physiological symptoms could be adapted to improve PCS-based mental fatigue.

## **Lay Summary**

This study investigated the effect mental fatigue has on cerebral blood flow in people with post-concussion syndrome. It was found that as mental fatigue increased, cerebral blood flow would respond faster to stimuli than when unfatigued but not as strongly. It was also found that simple reaction time was worsened by mental fatigue. These results are the first indicators of physiological impact of mental fatigue as a post-concussion syndrome symptom. This improvement in our understanding of mental fatigue can lead us to better management and treatment for those who have had their work, school and personal lives impacted by it.

## **Preface**

Chapter 1. I wrote Chapter 1 with instrumental feedback from Prof. Paul van Donkelaar, Dr Brian Dalton and Dr Chris McNeil.

Chapter 2-5. Prof. van Donkelaar, Dr Jon Smirl and I designed the experiment, with invaluable advice given by Dr Dalton and Dr McNeil. Data collection was completed by myself, with the assistance of Kira Fearn and Kailey Newell. This study was completed at the University of British Columbia – Okanagan campus. I completed all data analyses and wrote the manuscript, which was critically-reviewed by Prof. van Donkelaar, Dr Dalton and Dr McNeil.

## Table of Contents

Abstract.....	iii
Lay Summary.....	iv
Preface.....	v
Table of Contents.....	vi
List of Tables.....	ix
List of Figures.....	x
Acknowledgements .....	xi
Dedication .....	xii
<b>Chapter 1: Introduction .....</b>	<b>1</b>
1.1 Concussion.....	1
1.1.1 Post-Concussion Syndrome.....	2
1.1.2 Management and Treatment of Post-Concussion Syndrome .....	4
1.2 Mental Fatigue.....	5
1.2.1 Mental Fatigue in Post-concussion syndrome.....	7
1.3 Neurovascular Coupling.....	8
1.3.1Neurovascular Coupling in Post-Concussion Syndrome.....	10
1.4 Purposes and Hypotheses.....	12
<b>Chapter 2: Methods.....</b>	<b>13</b>
2.1 Ethical approval .....	13
2.2 Participants.....	13

2.3 Experimental protocol.....	13
2.4 Experimental measures.....	14
2.4.1 Visual Analogue Scale – fatigue.....	14
2.4.2 Simple reaction time tasks.....	14
2.4.3 Cerebrovascular measures.....	15
2.4.4 Neurovascular coupling.....	15
2.4.5 Fatigue-inducing task.....	16
2.4.6 Rivermead Post-Concussion Symptoms Questionnaire.....	16
2.5 Data analyses .....	16
2.6 Statistical Analyses.....	17
<b>Chapter 3: Results.....</b>	<b>19</b>
3.1 Important note.....	19
3.2 General characteristics.....	19
3.3 Simple reaction time.....	19
3.4 PCA velocity.....	20
3.5 MCA velocity.....	20
3.6 Blood pressure.....	21
3.7 Individual Descriptive Results.....	21
<b>Chapter 4: Discussion.....</b>	<b>25</b>
4.1 The impact of mental fatigue on simple reaction time.....	25
4.2 The impact of mental fatigue on CBF response.....	25

4.3 Comment on individual results.....	26
4.3 Clinical implications.....	27
<b>Chapter 5: Conclusion.....</b>	<b>28</b>
5.1 Cerebral blood flow in PCS under mental fatigue.....	28
5.2 Limitations.....	28
5.2.1 Experimental limitations.....	28
5.2.2 Technical considerations.....	29
5.3 Future studies.....	29
References.....	30
Appendix.....	43

## List of Tables

<b>Table 1.</b> Individual and mean scores for measured variables.....	54
--	----

## List of Figures

<b>Figure 1:</b> Representative trace of $\Delta PCAv$ .....	18
<b>Figure 2:</b> Change in mental fatigue relative to other variables.....	23
<b>Figure 3:</b> Response of cerebral blood velocity to a pattern-repetition task.....	24

## Acknowledgements

I would like to thank my supervisor, Prof. Paul van Donkelaar, firstly for accepting me into this MSc program and then for his continued interest in my project and my learning. It has been a great experience both academically and personally, none of which would have been possible without the environment of reflection and innovative questioning that Prof. van Donkelaar created.

I would like to give my appreciation to Dr Brian Dalton, who always allowed me space in his lab when my own was lonely. With me starting this program with little experience in neurophysiology, Dr Dalton's teaching in both formal and informal settings have not only contributed to this project but also to my interest in each subject.

A great gratitude is also owed to Dr Chris McNeil, who was not only available for questions great and small but answered them with extensive discussions to ensure my understanding. Formal teaching from Dr McNeil has also fostered my fascination, and led me towards future projects I will soon be undertaking.

To my lab mates, and those in Dr Dalton's lab, thank you for your support academically and emotionally. In the highs and lows of this project you were there, the importance of cannot be overstated.

Thank you to my parents and sisters. I know you didn't always understand what I was doing, but you never failed to support it. This would not have been possible without you all.

To Hannah, in the duration of this project we have engaged and wed. Perhaps it is the fun you constantly bring to my life that made the time go so fast. Your encouragement, your kindness and your love has been so important to my perseverance. Thank you.

## **Dedication**

To the knowledge that all we can measure, we can manage.

## Chapter 1: Introduction

This thesis investigated the effect of mental fatigue on neurovascular coupling in people with post-concussion syndrome. The following sections outline the literature relevant to the design of the thesis.

### 1.1 Concussion

Researchers often study concussions using differing operational definitions to one another, making comparisons between published studies difficult (McCrary, et al., 2017); however, a consistent feature of these definitions is a focus on the functional impact of the injury as opposed to structural deficits (Giza, et al., 2013). Diagnostic criteria also include a force imparted to the head, or another part of the body that transmits to the head, with symptoms either appearing instantly or developing over minutes to hours (McCrary et al., 2017). A concussion causes alterations in the brain that can present as symptoms in many ways, categorized under; somatic, emotional, cognitive, physical, sleep and balance impairment (McCrary et al., 2017), as well as affecting heart rate and heart rate variability (Gall et al., 2004; Hanna-Pladdy et al., 2001; M. L. King et al., 1997).

Traumatic brain injury, of which concussion is a subset, is a large contributor to death and disability (Rubiano et al., 2015) with 64-74 million incidents per year globally (Dewan et al., 2018). The majority of people who sustain these injuries recover within a short timeframe of 3-10 days (Bleiberg et al., 2004; Macciocchi et al., 1996; McCrea et al., 2002; Pellman, Lovell, et al., 2004). A large cohort study assessed the baseline measures of 1631 college athletes' self-reported symptoms, cognitive functions and balance control, then re-assessed when participants sustained a concussion and compared changes to healthy controls (McCrea et al., 2003). Results showed that balance deficits due to sport-related concussions returned to baseline measures within 3-5 days, with self-reported symptoms and cognitive functions recovering within 7 days. The effects of concussion can be short-lived for return to play, with an average of a 16-day wait following sport-related concussion to reduce the risk of further head injury (McCrea et al., 2020), as well as for return to work, with 74% of people able to do so after one month (Chu et al., 2017). As such, the effects concussions have on a person's life are often short-lived. However, for a significant minority, the symptoms from their concussion can be ongoing for months, or even years.

Animal models of brain injury demonstrate a neurometabolic cascade that involves the release of excitatory neurotransmitters leading to neuronal depolarization

and dysregulation of some ions, such as  $K^+$  (Giza, Christopher & Hovda, 2001). This ultimately leads to the metabolism of cellular glucose increasing beyond appropriate levels and the resulting mitochondrial dysfunction causing a subsequent period of decreased glucose metabolism in the injured brain (Shrey et al., 2011). There are known effects of concussion to the autonomic nervous system (La Fountaine et al., 2009, 2011) and to the control of cerebral blood flow (Clausen et al., 2016; Leddy et al., 2013; Meier et al., 2015) for up to a month during average recovery.

### **1.1.1 Post-concussion syndrome**

Post-Concussion Syndrome (PCS) is the abnormal persistence of symptoms due to a concussion, although specifics of a diagnosis are highly debated among both researchers and physicians. The 10<sup>th</sup> edition of the International Classification of Diseases (*ICD-10*, 2011), issued by the World Health Organisation, requires a diagnosis of PCS to find a minimum of three of the following symptoms; headache, dizziness, fatigue, irritability, difficulty in concentrating and performing mental tasks, impairment of memory, insomnia, and reduced tolerance to stress, excitement or alcohol, for an undefined duration. Despite this being the predominant guideline on diagnosis, when physicians were surveyed on the matter, fewer than 20% claimed to require three or more symptoms, with over 50% only requiring one symptom (Rose et al., 2015). With the ICD-10 not offering guidance in terms of the duration symptoms must be present, and with PCS not being featured at all in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychology Association, 2013), physicians and researchers must devise their own suitable criteria. It is perhaps for this reason that there is a large spread in what surveyed physicians had decided to use for their own diagnoses (Rose et al., 2015), with 26% requiring less than two weeks duration of symptoms, 20% requiring two weeks to a month, 33% requiring one to three months and 11% requiring more than three months. The importance of growing consensus on these definitions cannot be overstated as they inevitably impact all other research on PCS, particularly because the number of symptoms present can influence expected recovery time (Hiploylee et al., 2017) and that various symptoms change prevalence over time (Barker-Collo et al., 2016), with depression and tearfulness increasing from 1-month to 12-months post-injury.

Given the conflicting definitions, incidence rates are often difficult to interpret in the literature. This is also due to the fact that the most commonly studied concussions are those presented to the emergency department and sport-related concussions, with the former over-representing more severe cases (Iverson, 2005). Approximately 35%

of sport-related concussions are presented to the emergency room (Sosin, 1996), 30% are likely to persist beyond expected recovery time of 7-10 days (de Bousard et al., 2005; McCrory et al., 2017). It has been shown that 8.1% of sport-related concussions will have symptoms which persist beyond this typical timeframe (Pellman, Viano, et al., 2004), although smaller studies have found that figure to be beyond 30% (McCrory et al., 2000). Ranges and contrasting results such as this are anticipated in the world of concussion research due to the individuality of each injury and the many factors influencing whether symptoms are likely to persist. The number of symptoms exhibited in the acute concussion phase is positively correlated with a prolonged recovery (Hiploylee et al., 2017) with prolonged headache, amnesia and fatigue being the symptoms most frequently associated with PCS developing (Asplund et al., 2004).

In individuals with PCS with symptom durations of 3 months to 17 years, headaches, difficulty concentrating and fatigue were the only symptoms reported in more than half of participants. (Hiploylee et al., 2017). It was found that the effects those with PCS were reporting at greatest severity compared to healthy controls, just 30 days after injury, were fatigue, doing things slowly, poor balance, difficulty thinking clearly and dizziness (Paniak et al., 2002). In a study investigating effects 10 years after injury, participants reported the most significant changes since before their concussions in irritability, anxiety and trouble hearing conversations (O'Connor et al., 2005). It was also asserted that those with PCS, compared to those with standard recovery of a concussion, were more likely to experience somatic (physical) and cognitive symptoms than they were affective symptoms (Hiploylee et al., 2017).

Beyond the acute phase of concussion, during normal or prolonged recovery, the damage from a concussion can be metabolic (Giza, Christopher & Hovda, 2001), physiological (McKeag & Kutcher, 2009) and microstructural (Bazarian, 2010). Autonomic dysfunction after traumatic brain injury (TBI) is believed to represent a degree of uncoupling between the brain's autonomic centres and the cardiovascular system (Goldstein et al., 1998) that should improve with TBI recovery (Meglič et al., 2001). It has been found that those symptomatic of a concussion have shown unsuitable heart rates (Hinds et al., 2016) and blood pressure (Hilz et al., 2011), suggesting reduced sympathetic and parasympathetic nervous system function which could manifest as light-headedness and dizziness (Leddy et al., 2017). As further evidence of autonomic nervous system impact, it was found that 70% of adolescents with PCS were found to have abnormal cardiac tilt-table results (Heyer et al., 2016) and that athletes with PCS have exercise intolerance (Kozlowski et al., 2013) which is

possibly rooted in altered control of CBF during exercise (Leddy et al., 2017), including disproportionate increases during exercise.

### **1.1.2 Management and treatment of post-concussion syndrome**

Historically, it has been suggested that concussions can best be managed with physical and cognitive rest for an indefinite amount of time post-injury. This advice was based not on evidence of reliable recovery but on the theory of balancing the high energy metabolism anticipated (Giza, Christopher & Hovda, 2001). Unfortunately, this approach is still in use in some clinics. Based on more recent research, it is now thought that those rest prescriptions are not effective in many cases and is even detrimental to the recovery of autoregulatory systems impacted by concussion (Leddy et al., 2007; McCrory et al., 2017). When devising a way of better managing PCS, Ellis, Leddy and Willer (2015) took the approach of categorizing different types of the disorder, classifying the previously-outlined issues with heart rate, blood pressure and CBF as physiologic post-concussion disorder (PCD), along with vestibulo-ocular PCD and cervicogenic PCD. Evidence now suggests the recommendation for improved recovery for physiologic PCD is individualized subthreshold aerobic exercise, as determined from the Buffalo Concussion Treadmill Test (Leddy et al., 2010), which has shown to improve symptoms, fitness and autonomic function (Baker et al., 2012). Vestibular therapy and repositioning techniques are effective in treating vestibular-based symptoms of concussion (Alsalaheen et al., 2010; Clarke, 2016; Gottshall & Hoffer, 2010), as they re-integrate vestibular, visual and somatosensory systems. 90% of those with visual impairment from a concussion displayed improvements from individualized vision therapy or reading exercises (Ciuffreda et al., 2008; Han et al., 2004). When managing PCS with cervicogenic-related symptoms, a combination of cervical and vestibular physiotherapy can reduce symptoms duration (Schneider et al., 2014). Regardless of the symptoms experienced, a degree of appropriate exercise is recommended to minimize physical deconditioning and when this is combined with cervical and vestibular therapy, 64% of patients with symptoms describing multiple PCDs returned to full function within 1 year (Baker et al., 2012). In terms of general recommendations in cases of prolonged recovery, education around expected recovery time and compensatory strategies (Mittenberg et al., 1996; Ponsford et al., 2002), as well as psychological intervention (Mittenberg et al., 2001), have been shown to reduce symptoms reported at 3 and 6 months after injury. Symptom-targeting medications, such as anti-depressants, have shown little evidence as an effective treatment (Leddy et al., 2012).

## 1.2 Mental Fatigue

The study of mental fatigue dates back to 1891 when Angelo Mosso found that his co-workers' muscular endurance decreased following a day of lectures and examinations (Giulio et al., 2006). In researching neuromuscular fatigue, a dominant definition has been "a reduced capacity for maximal performance" (Carroll et al., 2016), however mental fatigue is more often defined as a psychobiological state caused by prolonged periods of demanding cognitive activity (Hancock et al., 2000; Job & Dalziel, 2001). This definition appears to refer specifically to acute mental fatigue rather than the chronic state, and the matter is further complicated by the many different manifestations depending on the affected domain (Russell et al., 2019). Acute mental fatigue appears even in healthy people after prolonged work, whereas mental fatigue as a symptom of disease or disorder has large and negative impacts on social and occupational life (Boksem & Tops, 2008) and may even have different biological substrates than the acute manifestation (Boksem & Tops, 2008). For these reasons, it is believed an appropriate definition is closer to that of neuromuscular fatigue, where mental fatigue is any acute reduction in the capacity of mental processes due to activity. It has been shown that any mental fatigue experienced is more dependent on the relationship between energy expended and reward gained (Hulst & Geurts, 2001; Siegrist, 1996) than it is on energy expended alone (Park et al., 2001; Sparks et al., 1997). This was shown through poor psychobiological outcomes being associated with longer over-time hours only in low-reward jobs and these outcomes lead to burn-out symptoms and worsened home-work interference (Hulst & Geurts, 2001). From this, a proposal was put forward that the feeling of mental fatigue corresponds to a drive to abandon behaviour based on an alteration in perceived worthiness of expending the required energy to achieve the anticipated reward (Boksem & Tops, 2008).

Mental fatigue is mostly identified through subjective measures such as tiredness, lack of energy and decreased motivation/alertness, or through a decline in accuracy and reaction time in a cognitive-motor task (Marcora et al., 2009; Van Cutsem et al., 2017). Many features of mental fatigue could stem from the reduced probability that actions will be regulated by high-level control processes (Lorist et al., 2000; Meijman, 2000). Focus, planning and adaptability following negative outcomes are all skills that are found to decrease with mental fatigue (van der Linden, Frese, & Meijman, 2003; van der Linden, Frese, & Sonnentag, 2003; van der Linden & Eling, 2006). Mental fatigue leads to increased difficulty in sustaining attention (Boksem et al., 2006) as well as decreased technical skill and decision-making (Smith et al., 2018;

Van Cutsem et al., 2017). People in a state of mental fatigue have been shown to have impaired ability to regulate emotions (Grillon et al., 2015), reduced analytic processing (van der Linden, Frese, & Meijman, 2003) and a perception that tasks feel harder to perform (Russell et al., 2019; Van Cutsem et al., 2017), indicative of a reduced capacity in mental processes. Increased mental fatigue has been identified to increase resistance to further mental effort (van der Linden, Frese, & Meijman, 2003), but not resistance to physical effort (Marcora et al., 2009). Regardless, mental fatigue does reduce performance in endurance-based activities (Smith et al., 2018), including a decrease in time to exhaustion and increase in rate of perceived exertion in high-intensity endurance cycling (Marcora et al., 2009). There has been evidence of reduced exercise tolerance (Marcora et al., 2009) which, according to the psychobiological model of exercise performance (Marcora, 2008a; Marcora et al., 2008b), may be influenced by increased mental fatigue without any other physiological changes. This may be further impacted by changes in autonomic control caused by mental fatigue (Critchley et al., 2003; Williamson et al., 2006) due to changes in anterior-cingulate cortex activity (Cook et al., 2007; Lorist et al., 2005), thus increasing cardiovascular strain.

EEG data have revealed an error-related negativity, a feature of event-related potentials that is associated with the subject making a mistake (Falkenstein et al., 1990; Gehring et al., 2018), the size of which has been reported to have a smaller amplitude when the anticipated rewards of a task are lower (Gehring et al., 1993). This smaller-sized error-related negativity was also seen in fatigued subjects, with motivation resulting in an increased size (Boksem et al., 2006; Lorist et al., 2005). Given the role dopamine plays in creating a robust error-related negativity (Holroyd & Coles, 2002) and also in the regulation of energy expenditure (Szechtman et al., 1994), it was proposed that this neurotransmitter is involved in the development of mental fatigue (Boksem & Tops, 2008). Further to this point, disrupted dopaminergic function in the basal ganglia and cortical fibres has been causally linked to mental fatigue (Chaudhuri & Behan, 2000; Lorist & Tops, 2003). An injury to the basal ganglia can disrupt the perception of rewards when beginning an activity (Nauta, 1986), which is possibly why many diseases that show basal ganglia dysfunction involve mental fatigue as a symptom (Chaudhuri & Behan, 2000), such as in Parkinson's Disease (Lou et al., 2001). In its more chronic form, mental fatigue could originate through the hypothalamic-pituitary-adrenal axis (Boksem & Tops, 2008). The hormone cortisol is involved in initiation of energy use (Sapolsky et al., 2000), increases dopaminergic

activity (Dallman et al., 2006) and energy perception (Tops et al., 2006, 2007). However, when an uncontrollable situation (one low in personal choice) with an unfavourable cost-reward balance causes persistent stress there is a decrease in cortisol, leading to a possibly permanent decrease in motivation to expend energy (McEwen & Wingfield, 2003; Porges, 2001; Tops et al., 2008). To further this point, low levels of cortisol have been found alongside chronic fatigue as a symptom in certain syndromes, such as fibromyalgia (Fries et al., 2005). Lower levels of cortisol are also connected to clinical depression (Gold & Chrousos, 2002), a common symptom of PCS (Hart et al., 2011).

### **1.2.1 Mental Fatigue in post-concussion syndrome**

There is evidence to suggest that mental fatigue is the most severe kind of fatigue reported in those with PCS (Schoenberger et al., 2001), as measured by the multidimensional fatigue inventory. The multidimensional fatigue inventory is 20-item self-report measure that measures total fatigue as well as its dimensions; general, physical, mental, reduced motivation and reduced activity (Smets et al., 1995). Schoenberger and co-workers (2001) distributed the Multidimensional Fatigue Inventory questionnaire to those who were still experiencing symptoms at least 12 months after a concussion and found they reported an average of 16.42 out of a maximum 20 in mental fatigue severity, with physical fatigue being reported at 13.42 out of maximum 20. For all who sustain a concussion, research has shown general fatigue to be a common and persistent problem following the injury (Belmont et al., 2006; Ponsford et al., 2011) and over half reported fatigue to have negative consequences on participation in everyday activity following the injury (Cantor et al., 2008). Mental fatigue was more prevalent in participants 3 months after a concussion than any other symptom, compared to prevalence in healthy controls (Ponsford et al., 2011). In this study, fatigue was found in 37.1% of participants who sustained a concussion, which was also more than any other symptom. At 1 year following a hospital-diagnosed concussion, mental fatigue attributed to head trauma was reported in 21% of questionnaire responders (Middelboe et al., 1992). In specifically those with PCS, fatigue was reported by 61% of individuals 3 months after injury and ranked in the top 6 most reported symptoms at every tested interval ranging from 1 to 12 months (Naalt et al., 1999).

Anxiety and depression both predict experiencing fatigue post injury (Kempf et al., 2010; Ponsford et al., 2012). Those reporting fatigue at 3 months were found to be more likely to report depression and anxiety at 6 months compared to those without

fatigue (Norrie et al., 2010). High concussion-based fatigue scores were associated with a greater likelihood to take analgesic medication, although there was not any correlation with other medication types (Ponsford et al., 2012). In terms of management, investigations into pharmacological treatments to fatigue have shown no clear evidence of their efficacy (DeMarchi et al., 2005). Higher fatigue scores following concussion are related with lower sleep quality (Bushnik et al., 2008; Ponsford et al., 2012) and significant overlap has been found between fatigue and insomnia, as well as with irritability at 3 months post-injury (Meares et al., 2011). Fatigue severity at 1-week post injury predicts PCS at 3 months, and that at 3 months predicts symptoms at 6 months (Norrie et al., 2010). For individuals with a concussion, there is an association between symptoms of fatigue and cognitive dysfunction and poorer motor ability than those with fewer/weaker symptoms of fatigue (Bushnik et al., 2008; Johansson, 2009; Zaben et al., 2013).

There are many hypothesized ways fatigue manifests after a concussion, including neuroanatomical, functional, psychological, biochemical, endocrine and sleep-related, as well as combinations of these factors (Prins et al., 2006). The coping hypothesis suggests that mental fatigue manifests as a consequence of the extra effort necessary to overcome other cognitive issues developed from the concussion (Van Zomeran, 1984). During a cognitive task, it was found that those with concussion symptoms would experience a rise in blood pressure while healthy controls saw a decline despite similar task success (Riese, 1999). Other than limited blood pressure research (Riese, 1999), investigations into markers of physiological processes in fatigue of individuals with a concussion are importantly lacking (Mollayeva et al., 2014).

### **1.3 Neurovascular coupling**

The brain does not have its own energy stores but is supplied with energy through glucose and oxygen delivered via cerebral blood flow (Iadecola, 2017). Not receiving these energy substrates can lead to cognitive impairment (Iadecola, 2013) or, if restricted for an extended period, brain damage and death (Iadecola, 2017). Blood flow (and therefore the flow of nutrients) is higher in areas of the brain with greater activity, like white matter (Sokoloff, 1996). Any region that increases its neural activity will, in turn, result in an acute increase in cerebral blood flow (Chaigneau et al., 2003; Freygang & Sokoloff, 1958). This response is temporally, and spatially, exact enough to allow for functional brain imaging (Raichle & Mintun, 2006). There is a recent exploration of the link between neurovascular uncoupling and neurodegeneration (de

la Torre, 2017), with neurovascular dysfunction being seen in PCS (McKee & Robinson, 2014) as well as Alzheimer's (Kisler et al., 2017), Idiopathic Parkinson's disease (Janelidze et al., 2015), and Frontotemporal dementia (Martin et al., 2001).

The increase in blood flow with neural activity is also thought to clear out unwanted and toxic by-products of the activity, such as CO<sub>2</sub> and tau (Tarasoff-Conway et al., 2015; Zhu et al., 2006). Due to this, a feedback model of neurovascular coupling was developed, hypothesising that these toxins, many of which are vasodilators, initiate the increased blood flow to the area (Freeman & Li, 2016; Ko et al., 1990). However, there is evidence against this feedback model being the main driver of changes in cerebral blood flow such as, increased blood flow in environments with excess oxygen and glucose, along with the occurrence of surplus deliveries of O<sub>2</sub>. An opposing hypothesis suggests a feedforward model where neurovascular signalling pathways release vasoactive by-products, including potassium ions, nitric oxide and prostanoids (Attwell et al., 2010; Attwell & Iadecola, 2002; Drake & Iadecola, 2007). Newer lines of evidence around cerebral blood flow suggest it is not a matter of which one of these two models underlie neurovascular coupling, but rather each model's contribution. Regional hypoxia, promoting vasodilation, varies considerably depending on structure and stimulus (Lyons et al., 2016) and, at the start of activity, red blood cells experience increased deformability, which increases capillary flow (Wei et al., 2016). Collectively, this research suggests an initial flow response may be triggered by the feedforward mechanism described, with the feedback mechanism responding to adjust cerebral blood flow to appropriately meet metabolic demands (Iadecola, 2017). This cooperation between the feedforward and feedback model would explain the vascular response peaking after stimulus onset before settling at a lower level (Drew et al., 2011; Freeman & Li, 2016; Ngai et al., 1988). A study of brain slices has shown that an increase in transmural flow was able to enhance cell activity (Kim et al., 2016; Moore & Cao, 2008), suggesting a possibility of a reversal in the cause-effect relationship of neurovascular coupling: the hemo-neural hypothesis.

It has been estimated that capillary dilation is responsible for 84% of the flow increase from neural activation (Hall et al., 2014), as with their large surface area even small dilations can lead to large changes in flow (Attwell et al., 2010). Other studies show evidence of arteriole relaxation upstream of activated areas is responsible for neurovascular coupling, finding that capillary diameter was unchanged with activation of somatosensory areas (Drew et al., 2011; Hill et al., 2015; Wei et al., 2016). The disagreements in vasoactivity of capillaries could be due to different cells on which the

studies focused (Iadecola, 2017) or due to the resolution of imaging (Drew et al., 2011).

One valid method of assessing blood flow in some arteries of the brain (anterior cerebral artery, middle cerebral artery and posterior cerebral artery) is a Doppler ultrasound of blood velocity, a proxy measure of flow, used since 1965 (Miyazaki & Kato, 1965). Doppler ultrasound has since been used in surgery (Friedrich et al., 1980; Nornes et al., 1979) and neurological practice (Brisman et al., 1970), although adult bones can attenuate the signal at high frequencies, with 1 to 2 MHz signals performing best (Aaslid et al., 1982). The area above the zygomatic arch has been identified as an ultrasonic window and, as such, where to find the strongest signal. If the angle between the ultrasonic beam and the artery of focus is between 0° and 30°, the maximum error in measured flow will be less than 15% (Aaslid et al., 1982).

### **1.3.1 Neurovascular coupling in post-concussion syndrome**

Using blood oxygen-level dependent signalling, fMRI shows site-specific changes in CBF in those with PCS (Dean et al., 2015; Eierud et al., 2014): in particular, attention-related areas showed increased CBF (e.g. anterior cingulate) whereas temporal and working memory-related areas showed decreased CBF (e.g. left prefrontal). These abnormalities indicate issues with the blood flow response to neuronal activation or the neuronal activation itself (or both) but cannot distinguish between the two. Given that concussions are observed with, if not defined by, a lack of observable structural damage, the source of the abnormalities is likely due to a neurovascular uncoupling (Epps & Allen, 2017). There is further evidence that this uncoupling is significant in the manifestation of PCS (Bartnik-Olson et al., 2014; da Costa et al., 2016; Ellis et al., 2016; Len et al., 2011; Mutch et al., 2016) and the expression of its symptoms (Ellis, Leiter, et al., 2015; Giza, Christopher & Hovda, 2014). The dysfunction of CBF and its reactivity to stimuli in PCS is thought to be due to damage that is both functional and microstructural (Epps & Allen, 2017). Functional damage refers to the metabolic disturbances, protein degradation and other processes contributing to chronic cell death (Giza, Christopher & Hovda, 2014). Microstructural damage following a concussion can include neurofilament phosphorylation and mechanical damage to microtubules (Giza, Christopher & Hovda, 2014), which can result in dysregulation of CBF when occurring to the neurons responsible (Conder & Conder, 2014). This may be observed as decreased anterior and posterior cerebral circulation, as well as decreased global CBF (Heyer et al., 2016; La Fontaine et al., 2016; Wang, Nelson, et al., 2015; Wang, West, et al., 2015). Dysregulation of CBF in PCS can contribute to

intracerebral steal (Banik et al., 2017), where neuronal activation in one area may contribute to increased blood flow to another area, rather than its own, further complicating neuronal recovery (Kim et al., 2012). It has been proposed that neurovascular recoupling is possible through neurocognitive challenging (Epps & Allen, 2017), however this is complicated by the high mental fatigue those with poor neurovascular coupling experience (Leddy et al., 2013). It is for this reason that recovery treatments are recommended to make use of the post exercise recovery boost (Epps & Allen, 2017), an acute increase in cognitive ability following exercise. Research has shown taking advantage of this phenomenon prior to a long duration of cognitive work, along with aerobic and strength-based exercise, could be instrumental in restoring dysfunctional neurovascular coupling for individuals with PCS (Epps & Allen, 2017).

With the specificity of PCS treatment towards specific sub-disorders, knowledge of the mechanism(s) underlying mental fatigue is critical. If mental fatigue is of a physiological origin, then it is likely that the known biological signs of mental fatigue would be present as the symptom worsens. One of these biological signs could be neurovascular uncoupling, or cerebral blood flow at an inappropriate level (i.e. above or below that of a healthy person with the same environment and stimuli).

## **1.4 Purposes and Hypotheses**

The purpose of this study was to use neurovascular coupling to investigate whether mental fatigue manifests physiologically in individuals with post-concussion syndrome.

The following hypotheses were proposed:

- 1) Following a mentally fatiguing task, subjects with post-concussion syndrome would have a larger increase in cerebral blood flow compared to healthy controls during a pattern-repetition task.
- 2) The difference between pre-task and post-task cerebral blood flow changes would be greater for individuals with post-concussion syndrome compared to healthy controls.
- 3) In all individuals, the changes in cerebral blood flow response to a stimulus would negatively correlate with scores from a self-reported mental fatigue questionnaire.

## **Chapter 2: Methods**

### **2.1 Ethical approval**

Following verbal and written explanation of the study, written informed consent was acquired. This study was approved by the University of British Columbia Clinical Research Ethics Board (H19-00405) and all procedures were conducted in accordance with the Declaration of Helsinki.

### **2.2 Participants**

A total of 60 participants (aged 19-35) were to be recruited for the present study, through the university as well as local physiotherapists, athletic therapists, and coaches. Male (n=30) and female (n=30) participants were eligible to participate after classification into 1 of 3 groups: 1) Multiple Concussions (MC) – individuals who are no longer symptomatic of a TBI but have suffered >1 concussion between 30 days and 2 years prior to testing (n=20); 2) PCS – individuals who, at the time of testing, had continuing symptoms as a result of one or more previous concussions (n=20); and 3) Controls – individuals who, at the time of testing, had not experienced a concussion and were matched by age, sex and education level (n=20). Due to the COVID-19 pandemic preventing data collection, only a small number of participants with PCS (n=4, females=3) completed the study. Although pilot testing was completed with healthy controls, no data collected from those sessions was practical for analysis. Given matching criteria for healthy controls, they were to be recruited and collected after participants with PCS and MC, however this was never able to transpire. Exclusion criteria included any history of cerebrovascular, cardiovascular, or respiratory disease and were not taking any prescription medication at their time of participation.

### **2.3 Experimental protocol**

For the day of testing, participants were instructed to maintain their regular daily habits until the protocol began. First, participants completed the Rivermead Post-Concussion Questionnaire and stated the number of previous concussions they had experienced and when their most recent concussion took place. After this, participants were set up at the KINARM End-Point Lab (BKIN Technologies Ltd., Kingston, ON, Canada) for the remainder of the protocol and instructed to complete a modified Visual Analogue Scale (VAS-Fatigue)(Lee et al., 1991) designed to assess acute mental fatigue. Participants then completed both an auditory-based and visual-based simple reaction time task (with the order randomized for each participant). Participants then underwent

the neurovascular coupling protocol immediately followed by a fatigue-inducing task that lasted 45 to 60 min. At completion of the fatigue-inducing task, participants completed the pre-fatigue protocol again, in the following order; neurovascular coupling, VAS-Fatigue, simple reaction time tasks (auditory/visual tasks in the same order as they were completed prior to fatiguing task).

## **2.4 Experimental measures**

### **2.4.1 Visual Analogue Scale - Fatigue**

The present study used a modified version of the VAS-Fatigue created and validated by Lee, Hicks and Nino-Murcia (1991), provided in the appendix. The questionnaire consists of 16 scales, each of 10 cm length, on which participants would mark a “X” as to how they were feeling at the time of the task. The questionnaire begins with an unrelated scale so researchers can ensure participant understanding. The modifications made were to remove all questions related specifically to neuromuscular fatigue, including: how active the participant feels, how much the participant desires to lie down, and how much effort the participant feels it is to move their body. In addition to these changes, the scale used in the present study added a final scale asking participants for their motivation to do well in the assigned tasks. For questions 1-5 and 10-15, an “X” further to the right indicates greater fatigue, for questions 6-9 and 16, an “X” further to the left indicates greater fatigue.

### **2.4.2 Simple reaction time tasks**

Participants received instructions and completed 10 trials of each of the following tasks (Cognitive Fun, 2008) before and after the fatiguing protocol. Both tasks took place on a laptop computer, placed 50 cm from the participant’s face, without the use of headphones. Participants were allowed to use whatever sensory aids (prescription glasses, hearing aids) that they use in normal day to day life. Participants were aware of their score after each trial.

Visual: a small red dot was at the center of a computer screen, participants were asked to press the space bar when this was replaced with a large green dot that would appear after a random interval (0 to 5 seconds) into the trial and remained on the screen until the participant’s response.

Auditory: participants would pay attention to the computer and were asked to press the space bar when a 50 decibel, 400 Hz noise sounded 0 to 5 seconds after trial onset, which silenced after 0.2 seconds.

### **2.4.3 Cerebrovascular measures**

Transcranial Doppler (TCD) ultrasound (2-MHz, Spencer Technologies, Seattle, WA, USA) was used to assess cerebral blood velocity, as an index of CBF, in the left MCA and right PCA. Using the location and standardization techniques of Smirl et al. (2015), both vessels were insonated by the TCD probes through the trans-temporal window and held in place with a specialized headband (model M600 bilateral head frame, Spencer Technologies). To account for dynamic changes in blood pressure, it was measured using finger photoplethysmography, with the height difference between the finger and the brachial artery accounted for via a brachial cuff (Finometer; Finapres Medical Systems, Amsterdam, The Netherlands), a reliable measurement of dynamic blood pressure that has shown validity through correlation with intra-arterial measures (Omboni et al., 1993; Sammons et al., 2007). End-tidal partial pressure of carbon dioxide (PETCO<sub>2</sub>) and oxygen (PETO<sub>2</sub>) was sampled with a mouthpiece and monitored with an online gas analyser (ML206; AD Instruments, Colorado Springs, CO, USA), calibrated with a known gas concentration prior to each collection. All data were time-aligned and collected at a sampling frequency of 1000 Hz using an 8-channel PowerLab (AD Instruments, Colorado Springs, CO, USA) and stored using commercially available software (LabChart version 7.1; AD Instruments, Colorado Springs, CO, USA).

### **2.4.4 Neurovascular Coupling**

This component of testing involved 8 trials of a 20-second eyes-closed period followed by an approximately 45-second eyes-open period. The eyes-open period involves the participant using the KINARM, with the program Dexterit-E 3.7 running a version of the Spatial Span task with modified length. The following is an excerpt from the designers outlining the task:

*During each trial of the task, the subject must reach to a starting location, after which 12 squares are displayed in a 3x4 grid. A sequence of squares will light up in random order. The subject is instructed to replay the sequence by reaching and pausing at the appropriate squares. If the subject can correctly replay the sequence, then on the next trial the length of the sequence will increase by 1, up to a maximum of 12. If the subject makes an error or takes too long then on the next trial the length of the sequence will be shorter by 1, down to a minimum of 1. A trial will time out if the subject takes longer than  $(\text{sequence length} + 1) * 3$  seconds to complete a sequence. For instance, if the sequence length is 4 then the maximum time for the trial is 15 seconds  $((4 + 1) * 3)$ .*

All participants in the present study used the Adult version of the task, which involved the 3 × 4 grid composed of 3 × 3 cm squares, with 6 cm centre-to-centre spacing. The sequence length was not reset at any point throughout testing, so it would always be at the participants current cognitive limit. Rather than a set time for the eyes-open component of the neurovascular coupling measurement, participants would complete 3 sets of pattern repetition, one immediately after the other, before being instructed to close their eyes and the program would be paused.

#### **2.4.5 Fatigue-inducing task**

Participants would continue with the Spatial Span task described above, without any eyes-closed component, for 180 sets of pattern repetition. Due to the modified length of the program, participants would not have any rest time for the duration of the trials or post-fatigue testing. Participants were not informed of how many trials they would be completing, but prior to their participation were informed this component would take 45 to 60 minutes. This range was due to the fact that some participants took longer to complete the task than others.

#### **2.4.6 Rivermead Post-Concussion Symptoms Questionnaire**

The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) was developed in 1995 for the quantification of severity in both acute and persisting concussion symptoms (King et al., 1995). Widely used and freely available, the RPQ involves a severity rating between 0 (not experienced) and 4 (severe) on the 16 most common symptoms of concussion. The RPQ also includes a section to write-in symptoms experienced that are not covered by previous questions and designate them a rating. The RPQ has been found to have good test-retest and inter-rater reliability (King et al., 1995) and excellent construct validity (de Guise et al., 2016).

#### **2.5 Data analyses**

Each participant's VAS-Fatigue scale was scored by the number of centimeters their "X" is from the left end (questions 1-5 and 10-15) or the right end (questions 6-9 and 16) of the scale. These measures were summed to give a total VAS-Fatigue score each time the questionnaire was completed (pre- and post-fatigue). Means from the 10 trials of both visual and auditory simple reaction time measures were recorded both pre- and post-fatigue. All cerebrovascular measures were extracted at 5 Hz by LabChart, where the mean trace was used for analyses. For both MCA and PCA, the mean velocity for the final 5 seconds of the eyes-closed period was used as the baseline, with CBF in the eyes-open period presented as a percentage increase from

the baseline immediately before it, allowing for the calculation of peak increase, time to peak increase and area under the curve (from stimulus onset until peak).

An average of SRT-V, SRT-A, peak, time to peak and area under the curve was calculated for each participant before and after the fatiguing task. Area under the curve was calculated with baseline=0 (Figure 1). A delta ( $\Delta$ ) of each of these neurovascular coupling calculations, along with simple reaction time and VAS-Fatigue was calculated by subtracting the pre-fatigue score from the post-fatigue score and was expressed as a raw value or as a percentage of the pre-fatigue level.

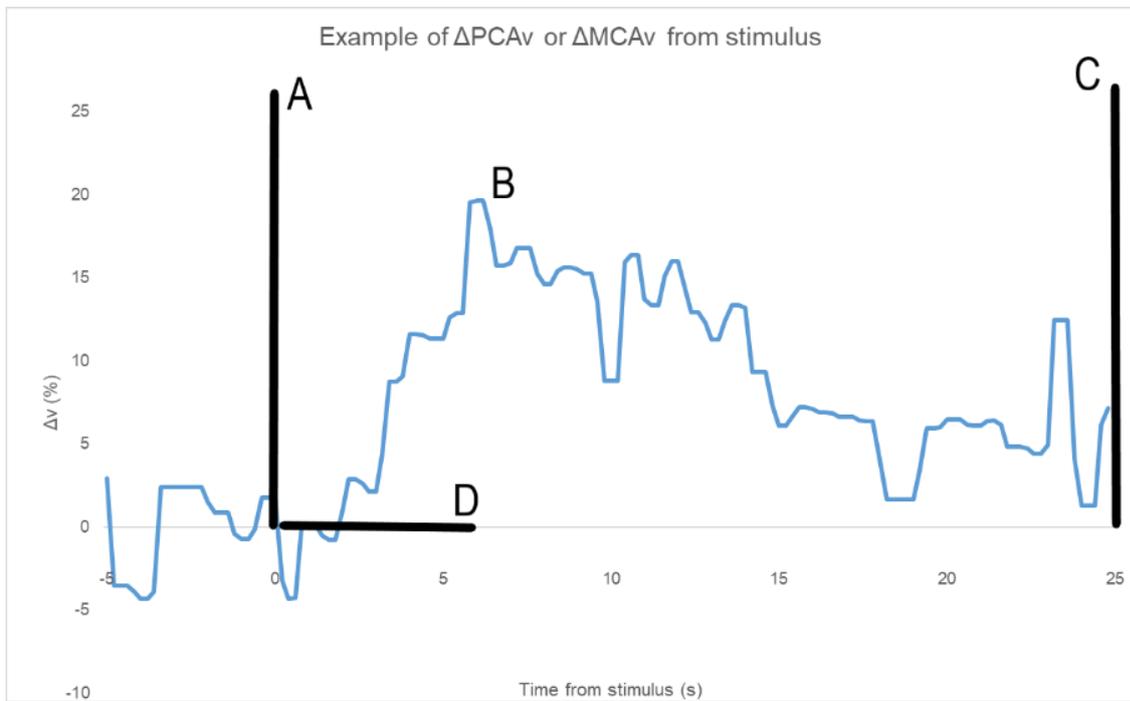
## **2.6 Statistical analyses**

Results are presented as median (range) between all participants. Wilcoxon signed-rank test was then applied to find if there were differences between pre-fatigue and post-fatigue scores. Spearman rank correlation was calculated between change in fatigue and change in: SRT-V, SRT-A and CBF results.

Additionally, descriptive results were calculated for each participant.

*Disclaimer: The description of statistical analyses that follows is what was originally proposed for this study, however the limited participants made it such that descriptive analyses would be more appropriate.*

Statistical software SPSS (version 22, IBM, New York, USA) would be used to calculate an analysis of variance (ANOVA) for  $\Delta$ peak,  $\Delta$ time to peak and  $\Delta$ area under the curve for both PCAv and MCAv among controls, MC and PCS groups. Furthermore, a Pearson correlation would be calculated for each group between  $\Delta$ VAS-Fatigue scores and  $\Delta$ PCAv.



**Figure 1:** Representative trace of  $\Delta$ PCAv (also applicable to MCAv). “A” is the point at which participants were instructed to open their eyes, “B” is PCAv peak. Between “A” and “C” is the space from which area under the curve is calculated and “D” is time to peak.

## Chapter 3: Results

### 3.1 Important Note

Data were collected from only 4 participants (all in the PCS group) prior to research being curtailed. As a result, there are not enough data collected to calculate ANOVAs, nor reliable correlation coefficients, all those shown below should not be considered indicative of the population but have been analyzed with all available data. Due to the low number of participants, power is very low so there may be significance between variables where none was found with the current data.

### 3.2 General Characteristics

Participants completed the testing session a median of 380 (range: 30-750) days after their most recent concussion and reported experiencing 4 (range: 1-6) concussions. Participants scored 29.5 (range: 10-33) on the Rivermead post-concussion questionnaire which included 11 (range: 8-13) symptoms at the time of testing. Participants reported a modified VAS-F score of 47 (range: 41-62) at test onset and 79 (range: 25-105) at test completion, with an increase from pre-task of 50.5% (range: -39.0-114.3). There was a strong positive correlation between the change in VAS-F score and the Rivermead post-concussion questionnaire score ( $R=0.95$ ,  $p=0.05$ ), as well as with number of symptoms currently experienced ( $R=1.00$ ,  $p=0.08$ ).

### 3.3 Simple Reaction Time

Prior to the fatiguing task, participants had a simple reaction time of 272.7 ms (range: 247.5-337.4) in the visual test and 204.1 ms (range: 182.3-245.5) in the auditory test. After completing the fatiguing task, simple reaction time was 292.8 ms (range: 262.2-335.5) in the visual task and 228.9 ms (range: 191.0-262.0) in the auditory task. These results indicated a small to medium effect of simple reaction time slowing by  $5.0 \pm 5.6\%$  ( $d=0.36$ ) and  $9.5 \pm 13.6\%$  ( $d=0.66$ ) for the visual and auditory tasks, respectively. Wilcoxon test shows there was no significant difference for SRT-V ( $p=0.89$ ) or SRT-A (0.49). The data available suggest that the magnitude of the VAS-F increase is, insignificantly, strongly correlated to the increase (slowing) of simple reaction time in the visual ( $R=0.6$ , 0.42) and auditory task ( $R=1.0$ , 0.08), as shown in Figure 2A.

### 3.4 PCA velocity

Prior to the fatiguing task, blood velocity through the PCA increased 21.8% (range: 18.3-28.1) from the baseline value ( $41.4 \pm 6.1$  cm/s) during activity and, after the fatiguing task, this increase from baseline ( $40.7 \pm 3.7$  cm/s) was 20.1% (range: 17.9-22.5) during activity (Figure 3A). Time to PCAv peak was 14.8 s (range: 9.5-15.4) prior to the fatiguing task and 20.4 s (range: 16.2-28.0) after the fatiguing task. There was a medium effect of the fatiguing task on PCA response ( $d=0.71$ ) and a strong effect on time to PCAv peak ( $d=1.02$ ) from the fatiguing task. Wilcoxon test shows neither peak (0.49) nor time to peak (0.20) significantly changed due to the fatiguing task. Higher changes in VAS-F score showed a strong negative, though insignificant, correlation with change in PCAv response ( $R=-0.6$ ,  $p=0.42$ ) and a weak negative, insignificant correlation with time to PCAv peak ( $R=-0.2$ ), as shown in Figure 2B/C. Area under the curve of  $\Delta$ PCAv was 125.7% $\cdot$ s (range: 66.5-144.2) prior to the fatiguing task and 131.5% $\cdot$ s (range: 67.52-136.39) after the task. Change in fatigue had no effect on area under the curve of  $\Delta$ PCAv over time ( $d=-0.03$ ), with Wilcoxon test supporting that ( $p=0.20$ ). Fatigue changes showed an insignificant, moderate negative correlation with area under the curve ( $R=-0.4$ ,  $p=0.75$ ) (Figure 2D).

### 3.5 MCA velocity

Prior to the fatiguing task, MCAv increased 17.7% (range: 14.7-17.9) from the baseline value ( $58.2 \pm 3.2$  cm/s) during activity and after the fatiguing task this increase from baseline ( $55.7 \pm 2.5$  cm/s) was 15.7% (range: 15.1-16.0) during activity (Figure 3). Time to peak for MCAv was 23.7 s (range: 19.0-26.1) pre-fatigue and 24.6 s (range: 16.4-26.0) post-fatigue. This indicates the fatiguing task had a medium effect on MCAv response ( $d=0.59$ ) and a small effect on MCAv time to peak ( $d=0.27$ ). Wilcoxon test showed no significant difference in peak ( $p=0.343$ ) or time to peak ( $p=1$ ) from the fatiguing task. Higher changes in VAS-F score had an insignificant moderate negative correlation to change in MCAv response ( $R=-0.4$ ,  $p=0.75$ ) and time to MCAv peak ( $R=-0.4$ ,  $p=0.75$ ), (Figure 2B/C). Area under the curve of  $\Delta$ MCAv was 95.8% $\cdot$ s (range: 85.2-136.3) prior to the fatiguing task and 73.8 % $\cdot$ s (range: 64.6-106.1) after the task. Change in fatigue had a large impact on area under the curve of  $\Delta$ MCAv over time ( $d=0.91$ ), although Wilcoxon showed no significant change ( $p=0.2$ ). Fatigue changes showed an insignificant moderate negative correlation with area under the curve ( $R=-0.4$ ,  $p=0.75$ ) (Figure 2D).

### 3.6 Blood Pressure

Prior to the fatiguing task, blood pressure increased 29.9% (range: 19.1-41.3) from the baseline value during activity and after the fatiguing task blood pressure increased 22.5% (range: 18.2-35.2) during activity. This indicates the fatiguing task had a medium effect on blood pressure ( $d=0.62$ ), with Wilcoxon test showing no significant change (0.343).

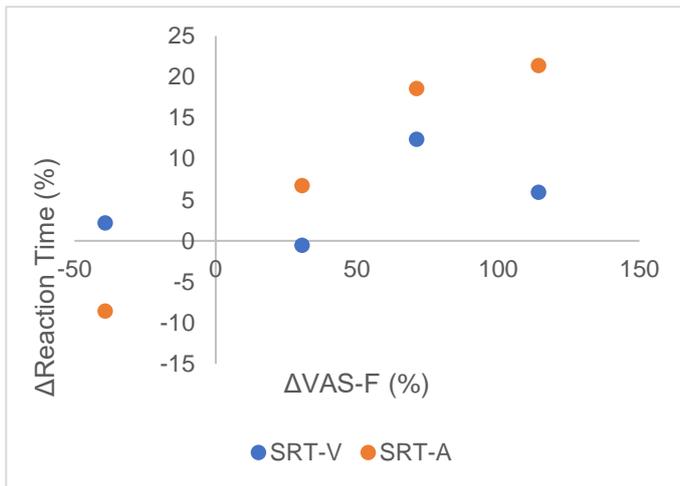
### 3.7 Individual Descriptive Results

*Participant 1:* This participant (RPQ=10) was the only one to see a decrease in fatigue after completing the fatigue-inducing task, moving from a VAS-F score of 41 to 25. Their SRT-A value also decreased, from 208.9 ms to 191.0 ms. Their CBF results were also incongruent with others as there was increase in MCAv time to peak (pre=21.2 s, post=26.0 s), MCAv area under the curve (pre=88.4 %s, post=106.05 %s) and PCAv area under the curve (pre=66.49 %s, post=129.35 %s) for participant 1 but a decrease in these variables for participants 2, 3 and 4. Their PCAv results for peak (pre=8.4 cm/s, post=7.9 cm/s) and time to peak (pre=9.5 s, post=26.0 s) moved in the same direction as the majority of others, however they had the largest difference in the latter by a considerable margin.

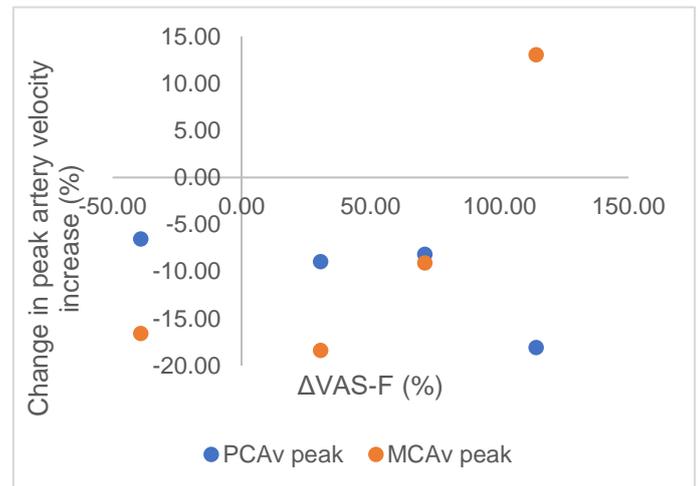
*Participant 2:* This participant (RPQ=26) also saw a minor improvement in a reaction time task after the fatigue-inducing task, with SRT-V decreasing from 337.4 ms to 335.5 ms. Participant 2 decreased in PCAv time to peak (pre=23.6 s, post=21.1 s), a variable which saw participants 1,3 and 4 increase. Participant 2 saw the most severe decreases in area under the curve for PCAv (pre=110.4 %s, post=67.5 %s) and MCAv (pre=136.3 %s, post=68.1 %s).

*Participant 3:* This participant (RPQ=33) saw a detrimental effect of the fatigue-inducing task on reaction time, with both SRT-V (pre=277.8 ms, post= 312.3 ms) and SRT-A (pre=199.36 ms, post= 236.45 ms) increasing. Their CBF peak decreased after the fatigue-inducing task for both PCAv (pre= 9.33 cm/s, post=8.57 cm/s) and MCAv (pre=9.69 cm/s, post=8.81 cm/s). Participant 3 saw an increase in PCAv time to peak (pre=14.2 s, post=16.1 s) and a decrease in area under the curve for the PCAv (pre=144.2 %s, post=136.4 %s) from the fatigue-inducing task. Their MCAv decreased in both time to peak (pre=23.7 s, post=22.17 s) and area under the curve (pre=103.3 %s, post=79.6 %s).

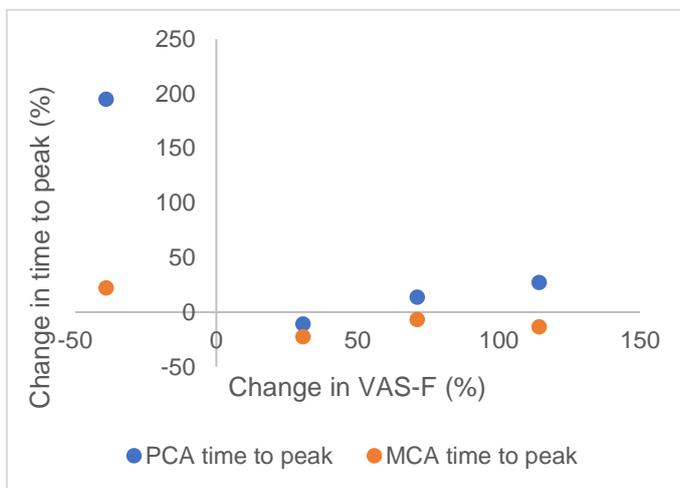
*Participant 4:* This participant (RPQ=33) had the largest increase in VAS-F score from the fatigue-inducing task (pre=49, post=105). From the fatigue-inducing task they had an increase (slowing) in SRT-V (pre=247.5 ms, post=262.2 ms) and SRT-A (pre=182.3 ms, post=221.3 ms). They were the only participant to increase in MCAv peak (pre=8.1 cm/s, post=9.1 cm/s). MCAv time to peak (pre=19.0 s, post=16.4 s) and MCAv area under the curve (pre=85.2 %s, post=64.6 %s) both saw decreases. PCAv time to peak increased (pre=15.4 s, post=19.7 s) while PCAv area under the curve decreased (pre=140.9 %s, post=133.7 %s).



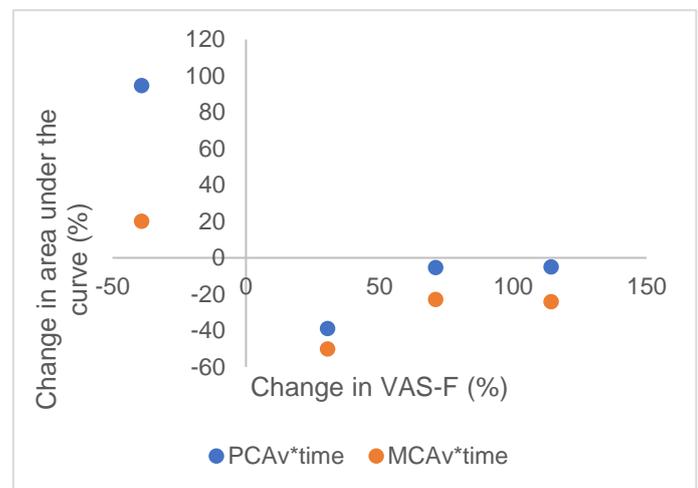
**A**



**B**

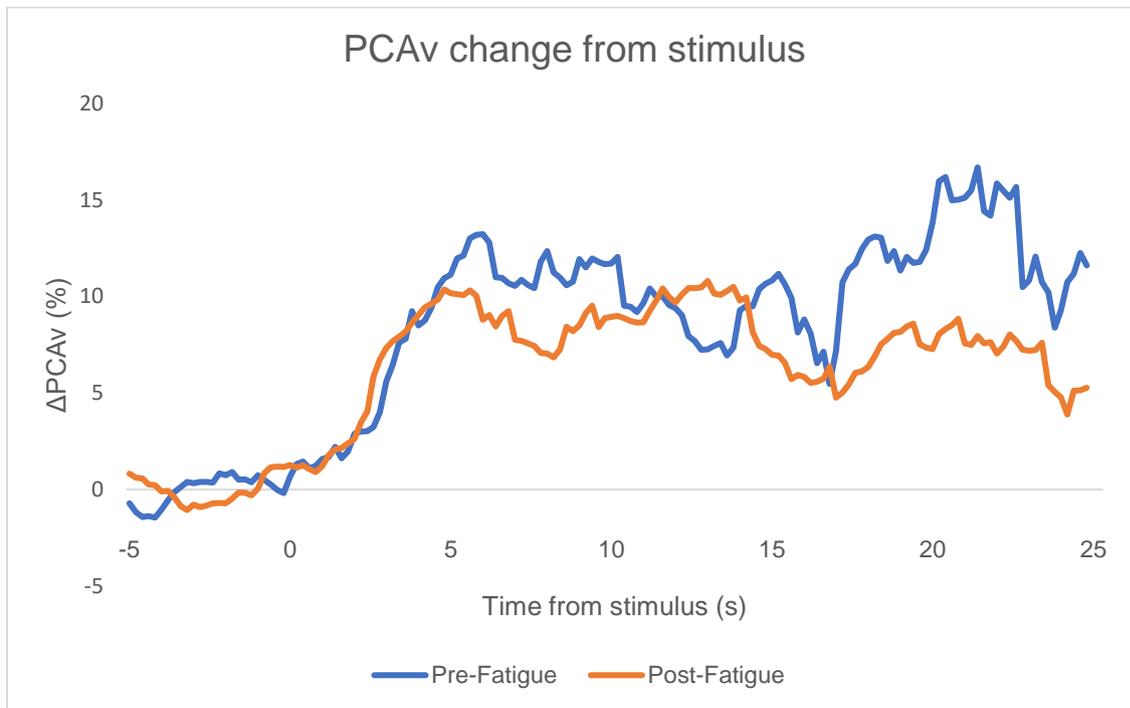


**C**

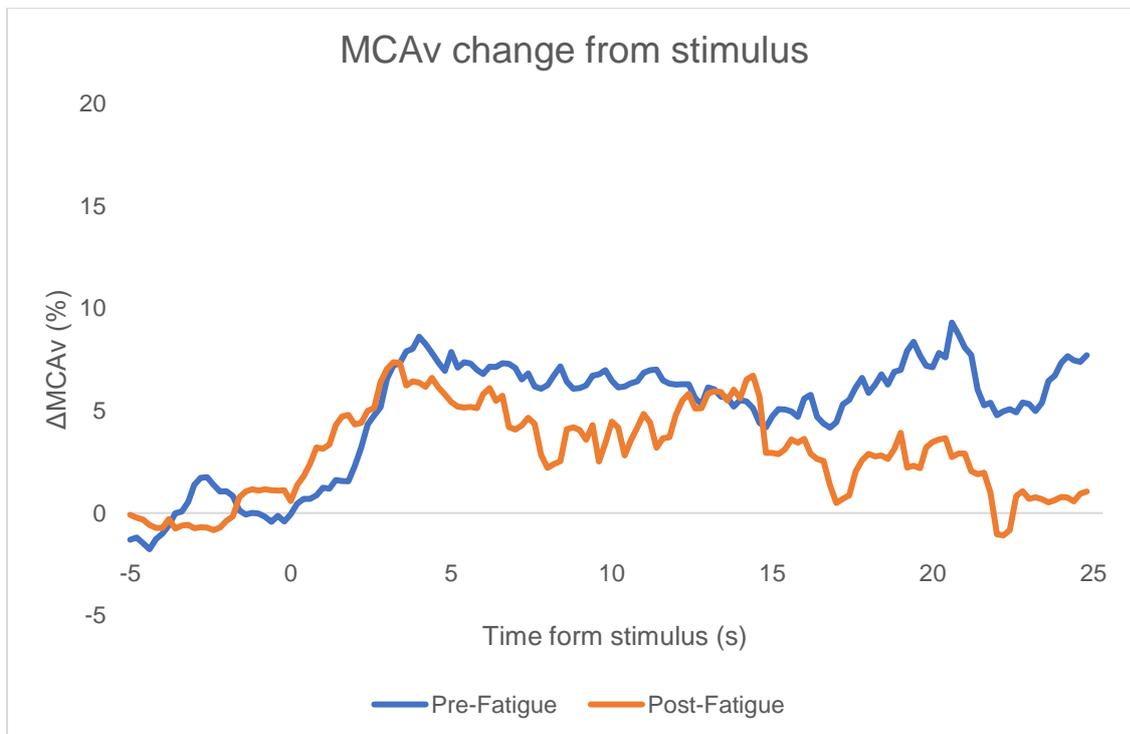


**D**

**Figure 2:** Each participant's change in mental fatigue (as reported on the visual analogue scale – fatigue) before and after the fatiguing task compared with “A” change in simple reaction time to visual stimulus (SRT-V) and auditory stimulus (SRT-A); “B” artery response to cognitive stimulus; “C” cerebral blood flow time to peak and; “D” area under the curve of cerebral blood flow response to stimulus.



**A**



**B**

**Figure 3:** Average response of cerebral blood velocity in all 4 participants to a pattern-repetition task from 5 seconds before task commencement to 25 seconds after task commencement. A) Posterior cerebral artery B) Middle cerebral artery.

## **Chapter 4: Discussion**

Due to the small sample size of this study, the reported findings are not generalizable, however, these data can be used to indicate areas worthy of further research. Hypotheses 1 and 2 involved the comparison between those with PCS and healthy controls, any level of confirmation for these hypotheses is not possible given no healthy controls completed the testing protocol. The results showed evidence in support of hypothesis 3, that increased mental fatigue is correlated with smaller increases in CBF from rest to stimulation in people with PCS.

### **4.1 The impact of mental fatigue on simple reaction time**

The slower simple reaction time for the auditory stimulus compared to the visual stimulus was expected and is consistent with previous research (Shelton & Kumar, 2010). Both auditory and visual simple reaction time worsened after completing the fatiguing task. This is more likely to be because of the mental fatigue examined than any neuromuscular fatigue having significant impact, given the deteriorations mental fatigue is known to cause (Boksem et al., 2005; Smit et al., 2004). The increase in simple reaction times could also have been caused by a decrease in drive or motivation given the repetitive nature of the fatiguing task (Dirnberger et al., 2004). According to the hypothesis of mental fatigue by Boksem & Tops (2008), however, an increase in mental fatigue and a decrease in drive may be essentially the same.

Higher levels of mental fatigue correlated better with simple reaction time to auditory cues than it did to that of visual cues. One possible explanation for this is related to the similarity between the fatiguing task (visual spatial span task) and the visually-cued reaction time task (Matthews & Desmond, 2002; Smit et al., 2004). This similarity has the potential to limit the deterioration in the task from mental fatigue compared to a more novel task that would require voluntary allocation of attention (Boksem et al., 2006; Lorist et al., 2000). If the auditory simple reaction time task involved voluntary allocation of attention, or top-down control, then there is a necessary level of control stabilisation that is considered vulnerable to fatigue (Lorist et al., 2005; Smit et al., 2004).

### **4.2 The impact of mental fatigue on CBF response**

The strong negative correlations between both PCAv and MCAv peak with changes in fatigue score suggest that, in someone with PCS, CBF cannot match the efforts necessary. These smaller increases of CBF response to a stimulus is likely to be

associated with a decrease in neural activity (Chaigneau et al., 2003; Freygang & Sokoloff, 1958) and poorer cognitive performance (Iadecola, 2013). What is still not known is whether this reduced CBF response is directly responsible for the decrease in neural activity or if that is a consequence of mental fatigue through other means and CBF is matching this new level of maximum activity. The former would be true if the hemo-neural hypothesis is to be believed (Kim et al., 2016; Moore & Cao, 2008), however, the traditional understanding of neurovascular coupling would suggest the latter explanation (Iadecola, 2017).

The link between mental fatigue and time to CBF peak is important, as it was found that greater increases in fatigue were highly correlated with a lower MCAv and PCAv time to peak. Decreased time to peak has previously been reported as a symptom of acute concussion (Mayer et al., 2013) and has been described as likely being an intentional compensation for the injury. This abnormality, highly correlated with fatigue, is the best indication from the present study that the mental fatigue experienced in PCS has a physiological expression. This expression is best explained as known neurovascular symptoms of a concussion changing in proportion to mental fatigue.

#### **4.3 Comment on Individual Results**

With the low power in this study from the small sample size, looking at patterns emerge between participants helps identify target areas for future research in a fully powered sample. Of particular interest is participant 1, being the only one to report a decrease in fatigue, it is interesting to investigate other variables that changed differently to other participants. These variables were SRT-A, MCAv time to peak and area under the curve for MCAv and PCAv. These variables are key to interpreting the results of this study, as area under the curve incorporates multiple CBF concepts and a consistent impact on this from fatigue could be a strong indication of physiological effects of PCS-based mental fatigue. Additionally, SRT-A being more susceptible to mental fatigue after the vision-based fatiguing task than SRT-V is important to understanding how those with PCS may respond to different kinds of mental rehabilitation activities.

With participants that share similar VAS-F effects and similar RPQ scores often seeing CBF respond comparably, further investigation in a fully powered sample is warranted. These variables are SRT-V, MCA time to peak, as well area under the curve for both PCAv and MCAv.

#### **4.4 Clinical Implications**

The worsening of a physiological symptom relating to neural activity under mental fatigue is similar to the way neuromuscular fatigue (during exercise) is expected to worsen other physiological symptoms of a concussion (Leddy et al., 2010). Together, these points could be used to support the hypothesis of mental fatigue as (at least partly) a physiological symptom of PCS, and those who experience it greater than other symptoms as exhibiting physiologic PCD (Ellis, Leddy, et al., 2015). If correct, this advancement of understanding in how mental fatigue manifests in those with PCS will improve the ability to manage and treat the symptom, and perhaps the disorder. The current recommended recovery for those with physiologic PCD is individualised sub-threshold aerobic exercise (Baker et al., 2012) and while this alone may improve long-term mental fatigue it could also be necessary to apply the treatment to a cognitive context. The threshold for physical work is determined by not exacerbating PCS symptoms (Leddy et al., 2010) and while it may not be practical to measure changes in CBF time to peak during cognitive rehabilitation, the VAS-F (or modified version) or simple reaction time tests may offer a simple tool to monitor worsening symptoms of mental fatigue. A detriment in performance can also work as a valuable indicator of fatigue in both physical and cognitive tasks. Automated tasks that do not require high levels of top-down control would be useful for a kind of cognitive rehabilitation, due to the robustness of mental fatigue during such activities (Boksem et al., 2006; Lorist et al., 2005).

## **Chapter 5: Conclusion**

This thesis investigated the effects of mental fatigue through a pattern-repetition task on cerebral blood flow through the PCA and MCA in people reporting PCS symptoms. The following section outlines the key conclusions, limitations, and areas worthy of further investigation.

### **5.1 Cerebral blood flow in PCS under mental fatigue**

Overall findings of this study indicate: 1) Both greater number of PCS symptoms and greater symptom severity are associated with higher self-reported levels of fatigue from a given task; 2) Similarity between tasks and areas the tasks activate can possibly minimise the effect mental fatigue has on performance, as shown by the higher level of correlation VAS-F score had with simple reaction time on an auditory task than a visual task; 3) On an individual level, increases in fatigue were associated with changes in area under the curve for PCA and MCA in those with PCS; 4) the largest associations with increasing fatigue in those with PCS were worsening reaction time and PCA response and; 5) From this change in CBF response, it is understood that the mental fatigue experienced as a PCS symptom is a physiological phenomenon and should be managed or treated as such.

These conclusions, if further data are consistent, would support Hypothesis 3 of the present study but conclusions on the other two hypotheses are still uncertain.

### **5.2 Limitations**

#### **5.2.1 Experimental Limitations**

Time to peak in PCA<sub>v</sub> and MCA<sub>v</sub> were both important variables from which conclusions were drawn, however, with lower MCA<sub>v</sub> and PCA<sub>v</sub> peaks expected under mental fatigue, time to peak would also be expected to decrease. As such, rate-to-peak could be a more robust measure, where the increase (in cm/s or as a percentage) is divided by the time to peak. This removes the increase of CBF from rest to peak as an influence on time to peak.

The use of pattern repetition as the CBF-activating task had its benefits but the time to peak often involved both a watching component and a repeating component. This ultimately meant that if different areas of the brain were active in watching a pattern compared to completing the pattern then it should not be expected to see a linear increase in blood flow to that area, but rather increases and decreases as needed. A task that achieved the same levels of difficulty and arousal that could

activate one area continuously could be more practical when investigating peak and time to peak of blood flow in cerebral arteries.

It is likely that Participant 1, who reported lower levels of fatigue after the fatiguing protocol, will be found to be an outlier as more data are collected. However, it is important to note currently collected data suggest 1 in 4 participants may not respond to the fatiguing task. Whether this is due to the nature of the task, individual skillsets or another factor is unknown but it is for this reason that the possibility of completing the task to a set fatigue level rather than a set number of trials should be explored in future research.

### **5.2.2 Technical Considerations**

The use of a non-invasive measure for cerebral blood flow velocity via transcranial Doppler ultrasound is a limitation on the accuracy of the data presented. PCA and MCA velocity are only reflective of flow through the arteries when there is no change in their diameter. It is unclear whether repetitive cognitive work can cause changes in artery diameter but, if this were to occur, there would be an incorrect estimation of flow and any correlations found would not necessarily be valid.

Related parametric analyses often have more power than the non-parametric analyses conducted. However, with the nature of data available at this stage the analyses conducted were most suitable. This may change as more data are collected and the most suitable statistical analyses will be presented, either in addition to or in place of those presented here.

### **5.2.3 Future Studies**

The aim of this study was to find physiological manifestations of mental fatigue in PCS via investigation into changes in CBF, such manifestations were found but a causal relationship could not be established. Future investigations that aim to find if mental fatigue occurs due to reduced CBF or if the reduced peaks were due to lower neural activation would be valuable in properly understanding the symptom and how to manage it.

If further data are consistent with those presented, then mental fatigue could be treated as a symptom of physiologic PCD. Future investigations should be devised to establish the efficacy of existing treatments for physiologic PCD as well as treatments adapted to fit a cognitive symptom.

## References

- Aaslid, R., Markwalder, T.-M., & Nornes, H. (1982). Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *Journal of Neurosurgery*, *57*(6), 769–774. <https://doi.org/10.3171/jns.1982.57.6.0769>
- Alsalaheen, B. A., Mucha, A., Morris, L. O., Whitney, S. L., Furman, J. M., Camiolo-Reddy, C. E., Collins, M. W., Lovell, M. R., & Sparto, P. J. (2010). Vestibular Rehabilitation for Dizziness and Balance Disorders After Concussion. *Journal of Neurologic Physical Therapy*, *34*(2), 87–93. <https://doi.org/10.1097/NPT.0b013e3181dde568>
- Asplund, C. A., McKeag, D. B., & Olsen, C. H. (2004). Sport-Related Concussion: Factors Associated With Prolonged Return to Play. *Clinical Journal of Sport Medicine*, *14*(6), 339–343.
- American Psychology Association (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. American Psychiatric Pub.
- Attwell, D., Buchan, A. M., Charpak, S., Lauritzen, M., MacVicar, B. A., & Newman, E. A. (2010). Glial and neuronal control of brain blood flow. *Nature*, *468*(7321), 232–243. <https://doi.org/10.1038/nature09613>
- Attwell, D., & Iadecola, C. (2002). The neural basis of functional brain imaging signals. *Trends in Neurosciences*, *25*(12), 621–625. [https://doi.org/10.1016/S0166-2236\(02\)02264-6](https://doi.org/10.1016/S0166-2236(02)02264-6)
- Baker, J. G., Freitas, M. S., Leddy, J. J., Kozlowski, K. F., & Willer, B. S. (2012). Return to Full Functioning after Graded Exercise Assessment and Progressive Exercise Treatment of Postconcussion Syndrome. *Rehabilitation Research and Practice*, *2012*. <https://doi.org/10.1155/2012/705309>
- Banik, S., Fisher, J. A., McKetton, L., & Venkatraghavan, L. (2017). Mapping intracerebral steal during a hypercapnic challenge. *Canadian Journal of Anaesthesia = Journal Canadien D'anesthésie*, *64*(12), 1265–1266. <https://doi.org/10.1007/s12630-017-0940-y>
- Barker-Collo, S., Theadom, A., Jones, K., Ameratunga, S., Feigin, V., Starkey, N., Dudley, M., & Kahan, M. (2016). Reliable Individual Change in Post Concussive Symptoms in the Year Following Mild Traumatic Brain Injury: Data From the Longitudinal, Population-based Brain Injury Incidence and Outcomes New Zealand in the Community (Bionic) Study. *JSM Burns and Trauma*, *1*(1), 1006.
- Bartnik-Olson, B. L., Holshouser, B., Wang, H., Grube, M., Tong, K., Wong, V., & Ashwal, S. (2014). Impaired Neurovascular Unit Function Contributes to Persistent Symptoms after Concussion: A Pilot Study. *Journal of Neurotrauma*, *31*(17), 1497–1506. <https://doi.org/10.1089/neu.2013.3213>
- Bazarian, J. J. (2010). Preface. *The Journal of Head Trauma Rehabilitation*, *25*(4), 225–227. <https://doi.org/10.1097/HTR.0b013e3181e7f784>
- Belmont, A., Agar, N., Hugeron, C., Gallais, B., & Azouvi, P. (2006). Fatigue et traumatisme crânien. *Annales de Réadaptation et de Médecine Physique*, *49*(6), 283–288. <https://doi.org/10.1016/j.annrmp.2006.04.017>
- Bleiberg, J., Cernich, A. N., Cameron, K., Sun, W., Peck, K., Ecklund, J., Reeves, D., Uhorchak, J., Sparling, M. B., & Warden, D. L. (2004). Duration of Cognitive Impairment After Sports Concussion. *Neurosurgery*, *54*(5), 1073–1080. <https://doi.org/10.1227/01.NEU.0000118820.33396.6A>
- Boksem, M. A. S., Meijman, T. F., & Lorist, M. M. (2005). Effects of mental fatigue on attention: An ERP study. *Cognitive Brain Research*, *25*(1), 107–116. <https://doi.org/10.1016/j.cogbrainres.2005.04.011>
- Boksem, M. A. S., Meijman, T. F., & Lorist, M. M. (2006). Mental fatigue, motivation and action monitoring. *Biological Psychology*, *72*(2), 123–132. <https://doi.org/10.1016/j.biopsycho.2005.08.007>

- Boksem, M. A. S., & Tops, M. (2008). Mental fatigue: Costs and benefits. *Brain Research Reviews*, 59(1), 125–139.  
<https://doi.org/10.1016/j.brainresrev.2008.07.001>
- Brisman, R., Grossman, B. L., & Correll, J. W. (1970). Accuracy of transcutaneous Doppler ultrasonics in evaluating extracranial vascular disease. *Journal of Neurosurgery*, 32(5), 529–533. <https://doi.org/10.3171/jns.1970.32.5.0529>
- Bushnik, T., Englander, J., & Wright, J. (2008). Patterns of Fatigue and Its Correlates Over the First 2 Years After Traumatic Brain Injury. *The Journal of Head Trauma Rehabilitation*, 23(1), 25–32.  
<https://doi.org/10.1097/01.HTR.0000308718.88214.bb>
- O'Connor, C., Colantonio, A., Polatajko, H. (2005). *Long Term Symptoms and Limitations of Activity of People With Traumatic Brain Injury: A Ten-Year Follow-Up*. Psychological Reports; Psychol Rep.  
<https://doi.org/10.2466/pr0.97.1.169-179>
- Cantor, J. B., Ashman, T., Gordon, W., Ginsberg, A., Engmann, C., Egan, M., Spielman, L., Dijkers, M., & Flanagan, S. (2008). Fatigue After Traumatic Brain Injury and Its Impact on Participation and Quality of Life. *The Journal of Head Trauma Rehabilitation*, 23(1), 41–51.  
<https://doi.org/10.1097/01.HTR.0000308720.70288.af>
- Carroll, T. J., Taylor, J. L., & Gandevia, S. C. (2016). Recovery of central and peripheral neuromuscular fatigue after exercise. *Journal of Applied Physiology*, 122(5), 1068–1076.  
<https://doi.org/10.1152/jappphysiol.00775.2016>
- Chaigneau, E., Oheim, M., Audinat, E., & Charpak, S. (n.d.). *Two-photon imaging of capillary blood flow in olfactory bulb glomeruli*. 6.
- Chaudhuri, A., & Behan, P. O. (2000). Fatigue and basal ganglia. *Journal of the Neurological Sciences*, 179(1), 34–42. [https://doi.org/10.1016/S0022-510X\(00\)00411-1](https://doi.org/10.1016/S0022-510X(00)00411-1)
- Chu, S. Y., Tsai, Y. H., Xiao, S. H., Huang, S. J., & Yang, C. C. (2017). Quality of return to work in patients with mild traumatic brain injury: A prospective investigation of associations among post-concussion symptoms, neuropsychological functions, working status and stability. *Brain Injury*, 31(12), 1674–1682. <https://doi.org/10.1080/02699052.2017.1332783>
- Ciuffreda, K. J., Rutner, D., Kapoor, N., Suchoff, I. B., Craig, S., & Han, M. E. (2008). Vision therapy for oculomotor dysfunctions in acquired brain injury: A retrospective analysis. *Optometry - Journal of the American Optometric Association*, 79(1), 18–22. <https://doi.org/10.1016/j.optm.2007.10.004>
- Ernst, A., Basta, D., Seidl, R.O., Todt, I., Scherer, H., Clarke, A. (2016). Management of Posttraumatic Vertigo. *Otolaryngology—Head and Neck Surgery*. <http://journals.sagepub.com/doi/10.1016/j.otohns.2004.09.034>
- Clausen, M., Pendergast, D. R., Willer, B., & Leddy, J. (2016). Cerebral Blood Flow During Treadmill Exercise Is a Marker of Physiological Postconcussion Syndrome in Female Athletes. *The Journal of Head Trauma Rehabilitation*, 31(3), 215–224. <https://doi.org/10.1097/HTR.0000000000000145>
- Conder, R. L., & Conder, A. A. (2014). Heart rate variability interventions for concussion and rehabilitation. *Frontiers in Psychology*, 5.  
<https://doi.org/10.3389/fpsyg.2014.00890>
- Cook, D. B., O'Connor, P. J., Lange, G., & Steffener, J. (2007). Functional neuroimaging correlates of mental fatigue induced by cognition among chronic fatigue syndrome patients and controls. *NeuroImage*, 36(1), 108–122.  
<https://doi.org/10.1016/j.neuroimage.2007.02.033>
- Critchley, H. D., Mathias, C. J., Josephs, O., O'Doherty, J., Zanini, S., Dewar, B.-K., Cipolotti, L., Shallice, T., & Dolan, R. J. (2003). Human cingulate cortex and

- autonomic control: Converging neuroimaging and clinical evidence. *Brain: A Journal of Neurology*, 126(Pt 10), 2139–2152.  
<https://doi.org/10.1093/brain/awg216>
- Epps, C.T. & Allen, M.D. (2017). Neurovascular Coupling: A Unifying Theory for Post-Concussion Syndrome Treatment and Functional Neuroimaging. *Journal of Neurology & Neurophysiology*, 08(06). <https://doi.org/10.4172/2155-9562.1000454>
- Sosin, D.M., Sniezek, J.E. & Thurman, D.J. (1996). Incidence of mild and moderate brain injury in the United States, 1991. *Brain Injury*, 10(1), 47–54.  
<https://doi.org/10.1080/026990596124719>
- da Costa, L., van Niftrik, C. B., Crane, D., Fierstra, J., & Bethune, A. (2016). Temporal Profile of Cerebrovascular Reactivity Impairment, Gray Matter Volumes, and Persistent Symptoms after Mild Traumatic Head Injury. *Frontiers in Neurology*, 7. <https://doi.org/10.3389/fneur.2016.00070>
- Dallman, M. F., Pecoraro, N. C., La Fleur, S. E., Warne, J. P., Ginsberg, A. B., Akana, S. F., Laugero, K. C., Houshyar, H., Strack, A. M., Bhatnagar, S., & Bell, M. E. (2006). Glucocorticoids, chronic stress, and obesity. In A. Kalsbeek, E. Fliers, M. A. Hofman, D. F. Swaab, E. J. W. van Someren, & R. M. Buijs (Eds.), *Progress in Brain Research* (Vol. 153, pp. 75–105). Elsevier.  
[https://doi.org/10.1016/S0079-6123\(06\)53004-3](https://doi.org/10.1016/S0079-6123(06)53004-3)
- de Boussard, C. N., Lundin, A., Karlstedt, D., Edman, G., Bartfai, A., & Borg, J. (2005). S100 AND COGNITIVE IMPAIRMENT AFTER MILD TRAUMATIC BRAIN INJURY. *Journal of Rehabilitation Medicine*, 37(1), 53–57.  
<https://doi.org/10.1080/16501970410015587>
- de Guise, E., Bélanger, S., Tinawi, S., Anderson, K., LeBlanc, J., Lamoureux, J., Audrit, H., & Feyz, M. (2016). Usefulness of the rivermead postconcussion symptoms questionnaire and the trail-making test for outcome prediction in patients with mild traumatic brain injury. *Applied Neuropsychology. Adult*, 23(3), 213–222. <https://doi.org/10.1080/23279095.2015.1038747>
- de la Torre, J. C. (2017). Are Major Dementias Triggered by Poor Blood Flow to the Brain? Theoretical Considerations. *Journal of Alzheimer's Disease: JAD*, 57(2), 353–371. <https://doi.org/10.3233/JAD-161266>
- Dean, P. J. A., Sato, J. R., Vieira, G., McNamara, A., & Sterr, A. (2015). Multimodal imaging of mild traumatic brain injury and persistent postconcussion syndrome. *Brain and Behavior*, 5(1), e00292. <https://doi.org/10.1002/brb3.292>
- DeMarchi, R., Bansal, V., Hung, A., Wroblewski, K., Dua, H., Sockalingam, S., & Bhalerao, S. (2005). Review of Awakening Agents. *Canadian Journal of Neurological Sciences*, 32(1), 4–17.  
<https://doi.org/10.1017/S0317167100016826>
- Dewan, M. C., Rattani, A., Gupta, S., Baticulon, R. E., Hung, Y.-C., Punchak, M., Agrawal, A., Adeleye, A. O., Shrime, M. G., Rubiano, A. M., Rosenfeld, J. V., & Park, K. B. (2018). Estimating the global incidence of traumatic brain injury. *Journal of Neurosurgery*, 130(4), 1080–1097.  
<https://doi.org/10.3171/2017.10.JNS17352>
- Dirnberger, G., Duregger, C., Lindinger, G., & Lang, W. (2004). Habituation in a simple repetitive motor task: A study with movement-related cortical potentials. *Clinical Neurophysiology*, 115(2), 378–384.  
[https://doi.org/10.1016/S1388-2457\(03\)00328-6](https://doi.org/10.1016/S1388-2457(03)00328-6)
- Drake, C. T., & Iadecola, C. (2007). The role of neuronal signaling in controlling cerebral blood flow. *Brain and Language*, 102(2), 141–152.  
<https://doi.org/10.1016/j.bandl.2006.08.002>
- Drew, P. J., Shih, A. Y., & Kleinfeld, D. (2011). Fluctuating and sensory-induced vasodynamics in rodent cortex extend arteriole capacity. *Proceedings of the*

- National Academy of Sciences of the United States of America*, 108(20), 8473–8478. <https://doi.org/10.1073/pnas.1100428108>
- Eierud, C., Craddock, R. C., Fletcher, S., Aulakh, M., King-Casas, B., Kuehl, D., & LaConte, S. M. (2014). Neuroimaging after mild traumatic brain injury: Review and meta-analysis. *NeuroImage: Clinical*, 4, 283–294. <https://doi.org/10.1016/j.nicl.2013.12.009>
- Ellis, M. J., Leddy, J. J., & Willer, B. (2015). Physiological, vestibulo-ocular and cervicogenic post-concussion disorders: An evidence-based classification system with directions for treatment. *Brain Injury*, 29(2), 238–248. <https://doi.org/10.3109/02699052.2014.965207>
- Ellis, M. J., Leiter, J., Hall, T., McDonald, P. J., Sawyer, S., Silver, N., Bunge, M., & Essig, M. (2015). Neuroimaging findings in pediatric sports-related concussion. *Journal of Neurosurgery: Pediatrics*, 16(3), 241–247. <https://doi.org/10.3171/2015.1.PEDS14510>
- Ellis, M. J., Ryner, L. N., Sobczyk, O., Fierstra, J., Mikulis, D. J., Fisher, J. A., Duffin, J., & Mutch, W. A. C. (2016). Neuroimaging Assessment of Cerebrovascular Reactivity in Concussion: Current Concepts, Methodological Considerations, and Review of the Literature. *Frontiers in Neurology*, 7. <https://doi.org/10.3389/fneur.2016.00061>
- Falkenstein, M., Hohnsbein, J., Hoormann, J., & Blanke, L. (1990). *Effects of errors in choice reaction tasks on the ERP under focused and divided attention*. /paper/Effects-of-errors-in-choice-reaction-tasks-on-the-Falkenstein-Hohnsbein/c976d4e951e2031c87379eb9d1e6ae7a3afc1194
- Freeman, R. D., & Li, B. (2016). Neural-metabolic coupling in the central visual pathway. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 371(1705). <https://doi.org/10.1098/rstb.2015.0357>
- Freygang, W. H., & Sokoloff, L. (1958). Quantitative measurement of regional circulation in the central nervous system by the use of radioactive inert gas. *Advances in Biological and Medical Physics*, 6, 263–279. <https://doi.org/10.1016/b978-1-4832-3112-9.50011-6>
- Friedrich, H., Hänsel-Friedrich, G., & Seeger, W. (1980). [Intraoperative doppler sonography of brain vessels (author's transl)]. *Neurochirurgia*, 23(3), 89–98. <https://doi.org/10.1055/s-2008-1053867>
- Fries, E., Hesse, J., Hellhammer, J., & Hellhammer, D. H. (2005). A new view on hypocortisolism. *Psychoneuroendocrinology*, 30(10), 1010–1016. <https://doi.org/10.1016/j.psyneuen.2005.04.006>
- Gall, B., Parkhouse, W., & Goodman, D. (2004). Exercise following a sport induced concussion. *British Journal of Sports Medicine*, 38(6), 773–777. <https://doi.org/10.1136/bjism.2003.009530>
- Gehring, W. J., Goss, B., Coles, M. G. H., Meyer, D. E., & Donchin, E. (1993). A Neural System for Error Detection and Compensation. *Psychological Science*, 4(6), 385–390. <https://doi.org/10.1111/j.1467-9280.1993.tb00586.x>
- Gehring, W. J., Goss, B., Coles, M. G. H., Meyer, D. E., & Donchin, E. (2018). The Error-Related Negativity. *Perspectives on Psychological Science*, 13(2), 200–204. <https://doi.org/10.1177/1745691617715310>
- Giulio, C. D., Daniele, F., & Tipton, C. M. (2006). Angelo Mosso and muscular fatigue: 116 years after the first congress of physiologists: IUPS commemoration. *Advances in Physiology Education*, 30(2), 51–57. <https://doi.org/10.1152/advan.00041.2005>
- Giza, C. C., Kutcher, J. S., Ashwal, S., Barth, J., Getchius, T. S. D., Gioia, G. A., Gronseth, G. S., Guskiewicz, K., Mandel, S., Manley, G., McKeag, D. B., Thurman, D. J., & Zafonte, R. (2013). Summary of evidence-based guideline update: Evaluation and management of concussion in sports: Report of the

- Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*, 80(24), 2250–2257.  
<https://doi.org/10.1212/WNL.0b013e31828d57dd>
- Giza, Christopher C., & Hovda, D. A. (2001). The Neurometabolic Cascade of Concussion. *Journal of Athletic Training*, 36(3), 228–235.
- Giza, Christopher C., & Hovda, D. A. (2014). The new neurometabolic cascade of concussion. *Neurosurgery*, 75 Suppl 4, S24-33.  
<https://doi.org/10.1227/NEU.0000000000000505>
- Gold, P. W., & Chrousos, G. P. (2002). Organization of the stress system and its dysregulation in melancholic and atypical depression: High vs low CRH/NE states. *Molecular Psychiatry*, 7(3), 254–275.  
<https://doi.org/10.1038/sj.mp.4001032>
- Goldstein, B., Towell, D., Lai, S., Sonnenthal, K., & Kimberly, B. (1998). Uncoupling of the autonomic and cardiovascular systems in acute brain injury. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 275(4), R1287–R1292. <https://doi.org/10.1152/ajpregu.1998.275.4.R1287>
- Gottshall, K. R., & Hoffer, M. E. (2010). Tracking Recovery of Vestibular Function in Individuals With Blast-Induced Head Trauma Using Vestibular-Visual-Cognitive Interaction Tests. *Journal of Neurologic Physical Therapy*, 34(2), 94–97. <https://doi.org/10.1097/NPT.0b013e3181dead12>
- Grillon, C., Quispe-Escudero, D., Mathur, A., & Ernst, M. (2015). Mental fatigue impairs emotion regulation. *Emotion (Washington, D.C.)*, 15(3), 383–389.  
<https://doi.org/10.1037/emo0000058>
- Hall, C. N., Reynell, C., Gesslein, B., Hamilton, N. B., Mishra, A., Sutherland, B. A., O'Farrell, F. M., Buchan, A. M., Lauritzen, M., & Attwell, D. (2014). Capillary pericytes regulate cerebral blood flow in health and disease. *Nature*, 508(7494), 55–60. <https://doi.org/10.1038/nature13165>
- Han, Y., Ciuffreda, K. J., & Kapoor, N. (2004). Reading-related oculomotor testing and training protocols for acquired brain injury in humans. *Brain Research Protocols*, 14(1), 1–12. <https://doi.org/10.1016/j.brainresprot.2004.06.002>
- Hancock, P. A., Desmond, P. A., & Desmond, P. A. (2000). *Stress, Workload, and Fatigue*. CRC Press. <https://doi.org/10.1201/b12791>
- Hanna-Pladdy, B., Berry, Z. M., Bennett, T., Phillips, H. L., & Gouvier, W. D. (2001). Stress as a diagnostic challenge for postconcussive symptoms: Sequelae of mild traumatic brain injury or physiological stress response. *The Clinical Neuropsychologist*, 15(3), 289–304.  
<https://doi.org/10.1076/clin.15.3.289.10272>
- Hart, T., Brenner, L., Clark, A. N., Bogner, J. A., Novack, T. A., Chervoneva, I., Nakase-Richardson, R., & Arango-Lasprilla, J. C. (2011). Major and Minor Depression After Traumatic Brain Injury. *Archives of Physical Medicine and Rehabilitation*, 92(8), 1211–1219. <https://doi.org/10.1016/j.apmr.2011.03.005>
- Heyer, G. L., Fischer, A., Wilson, J., MacDonald, J., Cribbs, S., Ravindran, R., Pommering, T. L., & Cuff, S. (2016). Orthostatic Intolerance and Autonomic Dysfunction in Youth With Persistent Postconcussion Symptoms: A Head-Upright Tilt Table Study. *Clinical Journal of Sport Medicine*, 26(1), 40–45.  
<https://doi.org/10.1097/JSM.0000000000000183>
- Hill, R. A., Tong, L., Yuan, P., Murikinati, S., Gupta, S., & Grutzendler, J. (2015). Regional Blood Flow in the Normal and Ischemic Brain Is Controlled by Arteriolar Smooth Muscle Cell Contractility and Not by Capillary Pericytes. *Neuron*, 87(1), 95–110. <https://doi.org/10.1016/j.neuron.2015.06.001>
- Hilz, M. J., DeFina, P. A., Anders, S., Koehn, J., Lang, C. J., Pauli, E., Flanagan, S. R., Schwab, S., & Marthol, H. (2011). Frequency Analysis Unveils Cardiac

- Autonomic Dysfunction after Mild Traumatic Brain Injury. *Journal of Neurotrauma*, 28(9), 1727–1738. <https://doi.org/10.1089/neu.2010.1497>
- Hinds, A., Leddy, J., Freitas, M., & Willer, B. (2016). The Effect of Exertion on Heart Rate and Rating of Perceived Exertion in Acutely Concussed Individuals. *Journal of Neurology & Neurophysiology*, 7(4). <https://doi.org/10.4172/2155-9562.1000388>
- Hiploylee, C., Dufort, P. A., Davis, H. S., Wennberg, R. A., Tartaglia, M. C., Mikulis, D., Hazrati, L.-N., & Tator, C. H. (2017). Longitudinal Study of Postconcussion Syndrome: Not Everyone Recovers. *Journal of Neurotrauma*, 34(8), 1511–1523. <https://doi.org/10.1089/neu.2016.4677>
- Holroyd, C. B., & Coles, M. G. H. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychological Review*, 109(4), 679–709. <https://doi.org/10.1037/0033-295X.109.4.679>
- Hulst, M. V. D., & Geurts, S. (2001). Associations between overtime and psychological health in high and low reward jobs. *Work & Stress*, 15(3), 227–240. <https://doi.org/10.1080/026783701110.1080/02678370110066580>
- Iadecola, C. (2013). The Pathobiology of Vascular Dementia. *Neuron*, 80(4), 844–866. <https://doi.org/10.1016/j.neuron.2013.10.008>
- Iadecola, C. (2017). The Neurovascular Unit Coming of Age: A Journey through Neurovascular Coupling in Health and Disease. *Neuron*, 96(1), 17–42. <https://doi.org/10.1016/j.neuron.2017.07.030>
- ICD-10: International statistical classification of diseases and related health problems*. (2011). World Health Organization.
- Iverson, G. L. (2005). Outcome from mild traumatic brain injury. *Current Opinion in Psychiatry*, 18(3), 301–317. <https://doi.org/10.1097/01.yco.0000165601.29047.ae>
- Janelidze, S., Lindqvist, D., Francardo, V., Hall, S., Zetterberg, H., Blennow, K., Adler, C. H., Beach, T. G., Serrano, G. E., van Westen, D., Londos, E., Cenci, M. A., & Hansson, O. (2015). Increased CSF biomarkers of angiogenesis in Parkinson disease. *Neurology*, 85(21), 1834–1842. <https://doi.org/10.1212/WNL.0000000000002151>
- Job, R. F. S., & Dalziel, J. (2001). Defining fatigue as a condition of the organism and distinguishing it from habituation, adaptation, and boredom. *Stress, Workload, and Fatigue*, 466–475.
- Johansson, A. (2009). Modeling and Simulation of Cone Crushers. *IFAC Proceedings Volumes*, 42(23), 13–18. <https://doi.org/10.3182/20091014-3-CL-4011.00004>
- Jose, S., & Gideon Praveen, K. (2010). Comparison between Auditory and Visual Simple Reaction Times. *Neuroscience & Medicine*, 2010. <https://doi.org/10.4236/nm.2010.111004>
- Kempf, J., Werth, E., Kaiser, P. R., Bassetti, C. L., & Baumann, C. R. (2010). Sleep-wake disturbances 3 years after traumatic brain injury. *Journal of Neurology, Neurosurgery & Psychiatry*, 81(12), 1402–1405. <https://doi.org/10.1136/jnnp.2009.201913>
- Kim, K. J., Ramiro Diaz, J., Iddings, J. A., & Filosa, J. A. (2016). Vasculo-Neuronal Coupling: Retrograde Vascular Communication to Brain Neurons. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 36(50), 12624–12639. <https://doi.org/10.1523/JNEUROSCI.1300-16.2016>
- Kim, T. J., Lee, J. S., Hong, J. M., & Lim, Y. C. (2012). Intracerebral steal phenomenon: A potential mechanism for contralateral stroke after carotid artery stenting. *The Neurologist*, 18(3), 128–129. <https://doi.org/10.1097/NRL.0b013e318253f8b5>

- King, M. L., Lichtman, S. W., Seliger, G., Ehert, F. A., & Steinberg, J. S. (1997). Heart-rate variability in chronic traumatic brain injury. *Brain Injury*, 11(6), 445–453. <https://doi.org/10.1080/026990597123421>
- King, N. S., Crawford, S., Wenden, F. J., Moss, N. E., & Wade, D. T. (1995). The Rivermead Post Concussion Symptoms Questionnaire: A measure of symptoms commonly experienced after head injury and its reliability. *Journal of Neurology*, 242(9), 587–592. <https://doi.org/10.1007/BF00868811>
- Kisler, K., Nelson, A. R., Montagne, A., & Zlokovic, B. V. (2017). Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. *Nature Reviews. Neuroscience*, 18(7), 419–434. <https://doi.org/10.1038/nrn.2017.48>
- Ko, K. R., Ngai, A. C., & Winn, H. R. (1990). Role of adenosine in regulation of regional cerebral blood flow in sensory cortex. *The American Journal of Physiology*, 259(6 Pt 2), H1703-1708. <https://doi.org/10.1152/ajpheart.1990.259.6.H1703>
- Kozlowski, K. F., Graham, J., Leddy, J. J., Devinney-Boymel, L., & Willer, B. S. (2013). Exercise Intolerance in Individuals With Postconcussion Syndrome. *Journal of Athletic Training*, 48(5), 627–635. <https://doi.org/10.4085/1062-6050-48.5.02>
- La Fountaine, M. F., Gossett, J. D., De Meersman, R. E., & Bauman, W. A. (2011). Increased QT Interval Variability in 3 Recently Concussed Athletes: An Exploratory Observation. *Journal of Athletic Training*, 46(3), 230–233.
- La Fountaine, M. F., Heffernan, K. S., Gossett, J. D., Bauman, W. A., & De Meersman, R. E. (2009). Transient suppression of heart rate complexity in concussed athletes. *Autonomic Neuroscience*, 148(1–2), 101–103. <https://doi.org/10.1016/j.autneu.2009.03.001>
- La Fountaine, M. F., Toda, M., Testa, A. J., & Hill-Lombardi, V. (2016). Autonomic Nervous System Responses to Concussion: Arterial Pulse Contour Analysis. *Frontiers in Neurology*, 7. <https://doi.org/10.3389/fneur.2016.00013>
- Leddy, J., Baker, J. G., Haider, M. N., Hinds, A., & Willer, B. (2017). A Physiological Approach to Prolonged Recovery From Sport-Related Concussion. *Journal of Athletic Training*, 52(3), 299–308. <https://doi.org/10.4085/1062-6050-51.11.08>
- Leddy, J. J., Cox, J. L., Baker, J. G., Wack, D. S., Pendergast, D. R., Zivadinov, R., & Willer, B. (2013). Exercise Treatment for Postconcussion Syndrome: A Pilot Study of Changes in Functional Magnetic Resonance Imaging Activation, Physiology, and Symptoms. *The Journal of Head Trauma Rehabilitation*, 28(4), 241–249. <https://doi.org/10.1097/HTR.0b013e31826da964>
- Leddy, J. J., Kozlowski, K., Donnelly, J. P., Pendergast, D. R., Epstein, L. H., & Willer, B. (2010). A Preliminary Study of Subsymptom Threshold Exercise Training for Refractory Post-Concussion Syndrome. *Clinical Journal of Sport Medicine*, 20(1), 21–27. <https://doi.org/10.1097/JSM.0b013e3181c6c22c>
- Leddy, J. J., Kozlowski, K., Fung, M., Pendergast, D. R., & Willer, B. (2007). Regulatory and autoregulatory physiological dysfunction as a primary characteristic of post concussion syndrome: Implications for treatment. *NeuroRehabilitation*, 22(3), 199–205. <https://doi.org/10.3233/NRE-2007-22306>
- Leddy, J. J., Sandhu, H., Sodhi, V., Baker, J. G., & Willer, B. (2012). Rehabilitation of Concussion and Post-concussion Syndrome. *Sports Health*, 4(2), 147–154. <https://doi.org/10.1177/1941738111433673>
- Lee, K. A., Hicks, G., & Nino-Murcia, G. (1991). Validity and reliability of a scale to assess fatigue. *Psychiatry Research*, 36(3), 291–298. [https://doi.org/10.1016/0165-1781\(91\)90027-M](https://doi.org/10.1016/0165-1781(91)90027-M)
- Len, T. K., Neary, J. P., Asmundson, G. J. G., Goodman, D. G., Bjornson, B., & Bhambhani, Y. N. (2011). Cerebrovascular Reactivity Impairment after Sport-

- Induced Concussion. *Medicine & Science in Sports & Exercise*, 43(12), 2241–2248. <https://doi.org/10.1249/MSS.0b013e3182249539>
- Lorist, M. M., Boksem, M. A. S., & Ridderinkhof, K. R. (2005). Impaired cognitive control and reduced cingulate activity during mental fatigue. *Brain Research. Cognitive Brain Research*, 24(2), 199–205. <https://doi.org/10.1016/j.cogbrainres.2005.01.018>
- Lorist, M. M., Klein, M., Nieuwenhuis, S., Jong, R. de, Mulder, G., & Meijman, T. F. (2000). Mental fatigue and task control: Planning and preparation. *Psychophysiology*, 37(5), 614–625. <https://doi.org/10.1111/1469-8986.3750614>
- Lorist, M. M., & Tops, M. (2003). Caffeine, fatigue, and cognition. *Brain and Cognition*, 53(1), 82–94. [https://doi.org/10.1016/S0278-2626\(03\)00206-9](https://doi.org/10.1016/S0278-2626(03)00206-9)
- Lou, J.-S., Kearns, G., Oken, B., Sexton, G., & Nutt, J. (2001). Exacerbated physical fatigue and mental fatigue in Parkinson's disease. *Movement Disorders*, 16(2), 190–196. <https://doi.org/10.1002/mds.1042>
- Lyons, D. G., Parpaleix, A., Roche, M., & Charpak, S. (2016). Mapping oxygen concentration in the awake mouse brain. *ELife*, 5. <https://doi.org/10.7554/eLife.12024>
- Macciocchi, S. N., Barth, J. T., Alves, W., Rimel, R. W., & Jane, J. A. (1996). Neuropsychological functioning and recovery after mild head injury in collegiate athletes. *Neurosurgery*, 39(3), 510–514.
- Marcora, S. M. (2008). Do we really need a central governor to explain brain regulation of exercise performance? *European Journal of Applied Physiology*, 104(5), 929–931; author reply 933-935. <https://doi.org/10.1007/s00421-008-0818-3>
- Marcora, S. M., Bosio, A., & de Morree, H. M. (2008). Locomotor muscle fatigue increases cardiorespiratory responses and reduces performance during intense cycling exercise independently from metabolic stress. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, 294(3), R874-883. <https://doi.org/10.1152/ajpregu.00678.2007>
- Marcora, S. M., Staiano, W., & Manning, V. (2009). Mental fatigue impairs physical performance in humans. *J Appl Physiol*, 106, 8.
- Martin, J. A., Craft, D. K., Su, J. H., Kim, R. C., & Cotman, C. W. (2001). Astrocytes degenerate in frontotemporal dementia: Possible relation to hypoperfusion. *Neurobiology of Aging*, 22(2), 195–207. [https://doi.org/10.1016/s0197-4580\(00\)00231-1](https://doi.org/10.1016/s0197-4580(00)00231-1)
- Matthews, G., & Desmond, P. A. (2002). Task-induced fatigue states and simulated driving performance. *The Quarterly Journal of Experimental Psychology Section A*, 55(2), 659–686. <https://doi.org/10.1080/02724980143000505>
- Mayer, A. R., Toulouse, T., Klimaj, S., Ling, J. M., Pena, A., & Bellgowan, P. S. F. (2013). Investigating the Properties of the Hemodynamic Response Function after Mild Traumatic Brain Injury. *Journal of Neurotrauma*, 31(2), 189–197. <https://doi.org/10.1089/neu.2013.3069>
- McCrea, M., Broglio, S., McAllister, T., Zhou, W., Zhao, S., Katz, B., Kudela, M., Harezlak, J., Nelson, L., Meier, T., Marshall, S. W., & Guskiewicz, K. M. (2020). Return to play and risk of repeat concussion in collegiate football players: Comparative analysis from the NCAA Concussion Study (1999–2001) and CARE Consortium (2014–2017). *British Journal of Sports Medicine*, 54(2), 102–109. <https://doi.org/10.1136/bjsports-2019-100579>
- McCrea, M., Guskiewicz, K. M., Marshall, S. W., Barr, W., Randolph, C., Cantu, R. C., Onate, J. A., Yang, J., & Kelly, J. P. (2003). Acute Effects and Recovery Time Following Concussion in Collegiate Football Players: The NCAA

- Concussion Study. *JAMA*, 290(19), 2556–2563.  
<https://doi.org/10.1001/jama.290.19.2556>
- McCrea, M., Kelly, J. P., Randolph, C., Cisler, R., & Berger, L. (2002). Immediate Neurocognitive Effects of Concussion. *Neurosurgery*, 50(5), 1032–1042.  
<https://doi.org/10.1097/00006123-200205000-00017>
- McCrory, P., Meeuwisse, W., Dvorak, J., Aubry, M., Bailes, J., Broglio, S., Cantu, R. C., Cassidy, D., Echemendia, R. J., Castellani, R. J., Davis, G. A., Ellenbogen, R., Emery, C., Engebretsen, L., Feddermann-Demont, N., Giza, C. C., Guskiewicz, K. M., Herring, S., Iverson, G. L., ... Vos, P. E. (2017). Consensus statement on concussion in sport—The 5th international conference on concussion in sport held in Berlin, October 2016. *British Journal of Sports Medicine*, 51(11), 838–847. <https://doi.org/10.1136/bjsports-2017-097699>
- McCrory, P. R., Ariens, M., & Berkovic, S. F. (2000). The Nature and Duration of Acute Concussive Symptoms in Australian Football. *Clinical Journal of Sport Medicine*, 10(4), 235–238.
- McEwen, B. S., & Wingfield, J. C. (2003). The concept of allostasis in biology and biomedicine. *Hormones and Behavior*, 43(1), 2–15.  
[https://doi.org/10.1016/S0018-506X\(02\)00024-7](https://doi.org/10.1016/S0018-506X(02)00024-7)
- McKeag, D. B., & Kutcher, J. S. (2009). Concussion Consensus: Raising the Bar and Filling in the Gaps. *Clinical Journal of Sport Medicine*, 19(5), 343–346.  
<https://doi.org/10.1097/JSM.0b013e3181b2c114>
- McKee, A. C., & Robinson, M. E. (2014). Military-related traumatic brain injury and neurodegeneration. *Alzheimer's & Dementia*, 10(3S), S242–S253.  
<https://doi.org/10.1016/j.jalz.2014.04.003>
- Meares, S., Shores, E. A., Taylor, A. J., Batchelor, J., Bryant, R. A., Baguley, I. J., Chapman, J., Gurka, J., & Marosszeky, J. E. (2011). The prospective course of postconcussion syndrome: The role of mild traumatic brain injury. *Neuropsychology*, 25(4), 454–465. <https://doi.org/10.1037/a0022580>
- Meglić, B., Kobal, J., Osredkar, J., & Pogačnik, T. (2001). Autonomic Nervous System Function in Patients with Acute Brainstem Stroke. *Cerebrovascular Diseases*, 11(1), 2–8. <https://doi.org/10.1159/000047605>
- Meier, T. B., Bellgowan, P. S. F., Singh, R., Kuplicki, R., Polanski, D. W., & Mayer, A. R. (2015). Recovery of Cerebral Blood Flow Following Sports-Related Concussion. *JAMA Neurology*, 72(5), 530–538.  
<https://doi.org/10.1001/jamaneurol.2014.4778>
- Meijman, T. F. (2000). The theory of the STOP-emotion: On the functionality of fatigue. *Ergonomics and Safety for Global Business Quality and Productivity*, 45–47. [https://www.rug.nl/research/portal/publications/the-theory-of-the-stopemotion\(093c3358-79a7-4e33-9d88-f59d87749427\)/export.html](https://www.rug.nl/research/portal/publications/the-theory-of-the-stopemotion(093c3358-79a7-4e33-9d88-f59d87749427)/export.html)
- Middelboe, T., Andersen, H. S., Birket-Smith, M., & Friis, M. L. (1992). Minor head injury: Impact on general health after 1 year. A prospective follow-up study. *Acta Neurologica Scandinavica*, 85(1), 5–9. <https://doi.org/10.1111/j.1600-0404.1992.tb03987.x>
- Mittenberg, W., Canyock, E. M., Condit, D., & Patton, C. (2001). Treatment of Post-Concussion Syndrome Following Mild Head Injury. *Journal of Clinical and Experimental Neuropsychology*, 23(6), 829–836.  
<https://doi.org/10.1076/jcen.23.6.829.1022>
- Mittenberg, W., Tremont, G., Zielinski, R. E., Fichera, S., & Rayls, K. R. (n.d.). *Cognitive-Behavioral Prevention of Postconcussion Syndrome*. 7.
- Miyazaki, M., & Kato, K. (1965). MEASUREMENT OF CEREBRAL BLOOD FLOW BY ULTRASONIC DOPPLER TECHNIQUE. *Japanese Circulation Journal*, 29, 375–382. <https://doi.org/10.1253/jcj.29.375>

- Mollayeva, T., Kendzerska, T., Mollayeva, S., Shapiro, C. M., Colantonio, A., & Cassidy, J. D. (2014). A systematic review of fatigue in patients with traumatic brain injury: The course, predictors and consequences. *Neuroscience & Biobehavioral Reviews*, *47*, 684–716.  
<https://doi.org/10.1016/j.neubiorev.2014.10.024>
- Moore, C. I., & Cao, R. (2008). The hemo-neural hypothesis: On the role of blood flow in information processing. *Journal of Neurophysiology*, *99*(5), 2035–2047.  
<https://doi.org/10.1152/jn.01366.2006>
- Mutch, W. A. C., Ellis, M. J., Ryner, L. N., Morissette, M. P., Pries, P. J., Dufault, B., Essig, M., Mikulis, D. J., Duffin, J., & Fisher, J. A. (2016). Longitudinal Brain Magnetic Resonance Imaging CO2 Stress Testing in Individual Adolescent Sports-Related Concussion Patients: A Pilot Study. *Frontiers in Neurology*, *7*.  
<https://doi.org/10.3389/fneur.2016.00107>
- Naalt, J. van der, Zomeren, A. H. van, Sluiter, W. J., & Minderhoud, J. M. (1999). One year outcome in mild to moderate head injury: The predictive value of acute injury characteristics related to complaints and return to work. *Journal of Neurology, Neurosurgery & Psychiatry*, *66*(2), 207–213.  
<https://doi.org/10.1136/jnnp.66.2.207>
- Nauta, W. (1986). Circuitous connections linking cerebral cortex, limbic system, and corpus striatum. *The Limbic System: Functional Organization and Clinical Disorders*, 43–45.
- Ngai, A. C., Ko, K. R., Morii, S., & Winn, H. R. (1988). Effect of sciatic nerve stimulation on pial arterioles in rats. *The American Journal of Physiology*, *254*(1 Pt 2), H133-139. <https://doi.org/10.1152/ajpheart.1988.254.1.H133>
- Nornes, H., Grip, A., & Wikeby, P. (1979). Intraoperative evaluation of cerebral hemodynamics using directional Doppler technique. Part 2: Saccular aneurysms. *Journal of Neurosurgery*, *50*(5), 570–577.  
<https://doi.org/10.3171/jns.1979.50.5.0570>
- Norrie, J., Heitger, M., Leathem, J., Anderson, T., Jones, R., & Flett, R. (2010). Mild traumatic brain injury and fatigue: A prospective longitudinal study. *Brain Injury*, *24*(13–14), 1528–1538. <https://doi.org/10.3109/02699052.2010.531687>
- Omboni, S., Parati, G., Frattola, A., Mutti, E., Di Rienzo, M., Castiglioni, P., & Mancia, G. (1993). Spectral and sequence analysis of finger blood pressure variability. Comparison with analysis of intra-arterial recordings. *Hypertension (Dallas, Tex.: 1979)*, *22*(1), 26–33. <https://doi.org/10.1161/01.hyp.22.1.26>
- Paniak, C., Reynolds, S., Phillips, K., Toller-Lobe, G., Melnyk, A., & Nagy, J. (2002). Patient complaints within 1 month of mild traumatic brain injury: A controlled study. *Archives of Clinical Neuropsychology*, *17*(4), 319–334.  
[https://doi.org/10.1016/S0887-6177\(01\)00115-9](https://doi.org/10.1016/S0887-6177(01)00115-9)
- Park, J., Kim, Y., Chung, H. K., & Hisanaga, N. (2001). Long Working Hours and Subjective Fatigue Symptoms. *Industrial Health*, *39*(3), 250–254.  
<https://doi.org/10.2486/indhealth.39.250>
- Pellman, E. J., Lovell, M. R., Viano, D. C., Casson, I. R., & Tucker, A. M. (2004). Concussion in Professional Football: Neuropsychological Testing—Part 6. *Neurosurgery*, *55*(6), 1290–1305.  
<https://doi.org/10.1227/01.NEU.0000149244.97560.91>
- Pellman, E. J., Viano, D. C., Casson, I. R., Arfken, C., & Powell, J. (2004). Concussion in Professional Football: Injuries Involving 7 or More Days Out—Part 5. *Neurosurgery*, *55*(5), 1100–1119.  
<https://doi.org/10.1227/01.NEU.0000147063.12873.F5>
- Ponsford, J. L., Ziino, C., Parcell, D. L., Shekleton, J. A., Roper, M., Redman, J. R., Phipps-Nelson, J., & Rajaratnam, S. M. W. (2012). Fatigue and Sleep Disturbance Following Traumatic Brain Injury—Their Nature, Causes, and

- Potential Treatments. *The Journal of Head Trauma Rehabilitation*, 27(3), 224–233. <https://doi.org/10.1097/HTR.0b013e31824ee1a8>
- Ponsford, J., Willmott, C., Rothwell, A., Cameron, P., Kelly, A.-M., Nelms, R., & Curran, C. (2002). Impact of early intervention on outcome following mild head injury in adults. *Journal of Neurology, Neurosurgery & Psychiatry*, 73(3), 330–332. <https://doi.org/10.1136/jnnp.73.3.330>
- Ponsford, Jennie, Cameron, P., Fitzgerald, M., Grant, M., & Mikocka-Walus, A. (2011). Long-Term Outcomes after Uncomplicated Mild Traumatic Brain Injury: A Comparison with Trauma Controls. *Journal of Neurotrauma*, 28(6), 937–946. <https://doi.org/10.1089/neu.2010.1516>
- Porges, S. W. (2001). The polyvagal theory: Phylogenetic substrates of a social nervous system. *International Journal of Psychophysiology*, 42(2), 123–146. [https://doi.org/10.1016/S0167-8760\(01\)00162-3](https://doi.org/10.1016/S0167-8760(01)00162-3)
- Prins, J. B., van der Meer, J. W., & Bleijenberg, G. (2006). Chronic fatigue syndrome. *The Lancet*, 367(9507), 346–355. [https://doi.org/10.1016/S0140-6736\(06\)68073-2](https://doi.org/10.1016/S0140-6736(06)68073-2)
- Raichle, M. E., & Mintun, M. A. (2006). Brain work and brain imaging. *Annual Review of Neuroscience*, 29, 449–476. <https://doi.org/10.1146/annurev.neuro.29.051605.112819>
- Riese, H. (1999). Mental Fatigue after Very Severe Closed Head Injury: Sustained Performance, Mental Effort, and Distress at Two Levels of Workload in a Driving Simulator. *Neuropsychological Rehabilitation*, 9(2), 189–205. <https://doi.org/10.1080/713755600>
- Rose, S. C., Fischer, A. N., & Heyer, G. L. (2015). How long is too long? The lack of consensus regarding the post-concussion syndrome diagnosis. *Brain Injury*, 29(7–8), 798–803. <https://doi.org/10.3109/02699052.2015.1004756>
- Rubiano, A. M., Carney, N., Chesnut, R., & Puyana, J. C. (2015). Global neurotrauma research challenges and opportunities. *Nature*, 527(7578), S193–S197. <https://doi.org/10.1038/nature16035>
- Russell, S., Jenkins, D., Rynne, S., Halson, S. L., & Kelly, V. (2019). What is mental fatigue in elite sport? Perceptions from athletes and staff. *European Journal of Sport Science*, 19(10), 1367–1376. <https://doi.org/10.1080/17461391.2019.1618397>
- Sammons, E. L., Samani, N. J., Smith, S. M., Rathbone, W. E., Bentley, S., Potter, J. F., & Panerai, R. B. (2007). Influence of noninvasive peripheral arterial blood pressure measurements on assessment of dynamic cerebral autoregulation. *Journal of Applied Physiology*, 103(1), 369–375. <https://doi.org/10.1152/jappphysiol.00271.2007>
- Sapolsky, R. M., Romero, L. M., & Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews*, 21(1), 55–89. <https://doi.org/10.1210/edrv.21.1.0389>
- Schneider, K. J., Meeuwisse, W. H., Nettel-Aguirre, A., Barlow, K., Boyd, L., Kang, J., & Emery, C. A. (2014). Cervicovestibular rehabilitation in sport-related concussion: A randomised controlled trial. *British Journal of Sports Medicine*, 48(17), 1294–1298. <https://doi.org/10.1136/bjsports-2013-093267>
- Schoenberger, N. E., Shiflett, S. C., Esty, M. L., Ochs, L., & Matheis, R. J. (2001). Flexyx Neurotherapy System in the Treatment of Traumatic Brain Injury: An Initial Evaluation. *The Journal of Head Trauma Rehabilitation*, 16(3), 260–274.
- Shrey, D. W., Griesbach, G. S., & Giza, C. C. (2011). The Pathophysiology of Concussions in Youth. *Physical Medicine and Rehabilitation Clinics of North America*, 22(4), 577–602. <https://doi.org/10.1016/j.pmr.2011.08.002>

- Siegrist, J. (1996). Adverse health effects of high-effort/low-reward conditions. *Journal of Occupational Health Psychology, 1*(1), 27–41. <https://doi.org/10.1037//1076-8998.1.1.27>
- Smets, E. M., Garssen, B., Bonke, B., & De Haes, J. C. (1995). The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *Journal of Psychosomatic Research, 39*(3), 315–325. [https://doi.org/10.1016/0022-3999\(94\)00125-o](https://doi.org/10.1016/0022-3999(94)00125-o)
- Smirl, J. D., Hoffman, K., Tzeng, Y.-C., Hansen, A., & Ainslie, P. N. (2015). Methodological comparison of active- and passive-driven oscillations in blood pressure; implications for the assessment of cerebral pressure-flow relationships. *Journal of Applied Physiology (Bethesda, Md.: 1985), 119*(5), 487–501. <https://doi.org/10.1152/jappphysiol.00264.2015>
- Smit, A. S., Eling, P. A. T. M., & Coenen, A. M. L. (2004). Mental effort causes vigilance decrease due to resource depletion. *Acta Psychologica, 115*(1), 35–42. <https://doi.org/10.1016/j.actpsy.2003.11.001>
- Smith, M. R., Thompson, C., Marcora, S. M., Skorski, S., Meyer, T., & Coutts, A. J. (2018). Mental Fatigue and Soccer: Current Knowledge and Future Directions. *Sports Medicine (Auckland, N.Z.), 48*(7), 1525–1532. <https://doi.org/10.1007/s40279-018-0908-2>
- Sokoloff, L. (1996). Circulation in the Central Nervous System. In R. Greger & U. Windhorst (Eds.), *Comprehensive Human Physiology: From Cellular Mechanisms to Integration* (pp. 561–578). Springer. [https://doi.org/10.1007/978-3-642-60946-6\\_29](https://doi.org/10.1007/978-3-642-60946-6_29)
- Sparks, K., Cooper, C., Fried, Y., & Shirom, A. (1997). The effects of hours of work on health: A meta-analytic review. *Journal of Occupational and Organizational Psychology, 70*(4), 391–408. <https://doi.org/10.1111/j.2044-8325.1997.tb00656.x>
- Szechtman, H., Talangbayan, H., Canaran, G., Dai, H., & Eilam, D. (n.d.). *Dynamics of behavioral sensitization induced by the dopamine agonist quinpirole and a proposed central energy control mechanism*. 10.
- Tarasoff-Conway, J. M., Carare, R. O., Osorio, R. S., Glodzik, L., Butler, T., Fieremans, E., Axel, L., Rusinek, H., Nicholson, C., Zlokovic, B. V., Frangione, B., Blennow, K., Ménard, J., Zetterberg, H., Wisniewski, T., & de Leon, M. J. (2015). Clearance systems in the brain-implications for Alzheimer disease. *Nature Reviews. Neurology, 11*(8), 457–470. <https://doi.org/10.1038/nrneurol.2015.119>
- Tops, M., Boksem, M. A. S., Wijers, A. A., Duinen, H. van, Boer, J. A. D., Meijman, T. F., & Korf, J. (2007). The Psychobiology of Burnout: Are There Two Different Syndromes? *Neuropsychobiology, 55*(3–4), 143–150. <https://doi.org/10.1159/000106056>
- Tops, M., Peer, J. M. V., Wijers, A. A., & Korf, J. (2006). Acute cortisol administration reduces subjective fatigue in healthy women. *Psychophysiology, 43*(6), 653–656. <https://doi.org/10.1111/j.1469-8986.2006.00458.x>
- Tops, M., Riese, H., Oldehinkel, A. J., Rijdsdijk, F. V., & Ormel, J. (2008). Rejection sensitivity relates to hypocortisolism and depressed mood state in young women. *Psychoneuroendocrinology, 33*(5), 551–559. <https://doi.org/10.1016/j.psyneuen.2008.01.011>
- Van Cutsem, J., Marcora, S., De Pauw, K., Bailey, S., Meeusen, R., & Roelands, B. (2017). The Effects of Mental Fatigue on Physical Performance: A Systematic Review. *Sports Medicine, 47*(8), 1569–1588. <https://doi.org/10.1007/s40279-016-0672-0>

- van der Linden, D., & Eling, P. (2006). Mental fatigue disturbs local processing more than global processing. *Psychological Research*, 70(5), 395–402.  
<https://doi.org/10.1007/s00426-005-0228-7>
- van der Linden, D., Frese, M., & Meijman, T. F. (2003). Mental fatigue and the control of cognitive processes: Effects on perseveration and planning. *Acta Psychologica*, 113(1), 45–65. [https://doi.org/10.1016/s0001-6918\(02\)00150-6](https://doi.org/10.1016/s0001-6918(02)00150-6)
- van der Linden, D., Frese, M., & Sonnentag, S. (2003). The Impact of Mental Fatigue on Exploration in a Complex Computer Task: Rigidity and Loss of Systematic Strategies. *Human Factors*, 45(3), 483–494.  
<https://doi.org/10.1518/hfes.45.3.483.27256>
- Van Zomeren, A. (1984). Attention deficits ; The riddles of selectivity, speed and alertness. *Closed Head Injury, Psychological, Social and Family Consequences*, 74–107.
- Wang, Y., Nelson, L. D., LaRoche, A. A., Pfaller, A. Y., Nencka, A. S., Koch, K. M., & McCrea, M. A. (2015). Cerebral Blood Flow Alterations in Acute Sport-Related Concussion. *Journal of Neurotrauma*, 33(13), 1227–1236.  
<https://doi.org/10.1089/neu.2015.4072>
- Wang, Y., West, J. D., Bailey, J. N., Westfall, D. R., Xiao, H., Arnold, T. W., Kersey, P. A., Saykin, A. J., & McDonald, B. C. (2015). Decreased Cerebral Blood Flow in Chronic Pediatric Mild TBI: An MRI Perfusion Study. *Developmental Neuropsychology*, 40(1), 40–44.  
<https://doi.org/10.1080/87565641.2014.979927>
- Wei, H. S., Kang, H., Rasheed, I.-Y. D., Zhou, S., Lou, N., Gershteyn, A., McConnell, E. D., Wang, Y., Richardson, K. E., Palmer, A. F., Xu, C., Wan, J., & Nedergaard, M. (2016). Erythrocytes Are Oxygen-Sensing Regulators of the Cerebral Microcirculation. *Neuron*, 91(4), 851–862.  
<https://doi.org/10.1016/j.neuron.2016.07.016>
- Williamson, J. W., Fadel, P. J., & Mitchell, J. H. (2006). New insights into central cardiovascular control during exercise in humans: A central command update. *Experimental Physiology*, 91(1), 51–58.  
<https://doi.org/10.1113/expphysiol.2005.032037>
- Zaben, M., Ghoul, W. E., & Belli, A. (2013). Post-traumatic head injury pituitary dysfunction. *Disability and Rehabilitation*, 35(6), 522–525.  
<https://doi.org/10.3109/09638288.2012.697252>
- Zhu, M., Ackerman, J. J. H., Sukstanskii, A. L., & Yablonskiy, D. A. (2006). How the body controls brain temperature: The temperature shielding effect of cerebral blood flow. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, 101(5), 1481–1488. <https://doi.org/10.1152/jappphysiol.00319.2006>

## **Appendix**

1) Modified Visual Analogue Scale – Fatigue

2) Rivermead Post-concussion Symptom Questionnaire

3) Table 1

## Visual Analogue Scale for Mental Fatigue

DIRECTIONS: You are asked to place an "X" through these lines to indicate how you are feeling RIGHT NOW. For example, suppose you had not eaten since yesterday. Where would you put the "X" on the line below?

Not at all  
hungry

---

Extremely  
hungry

NOW PLEASE COMPLETE THE FOLLOWING ITEMS.

Not at all  
tired

---

Extremely  
tired

Not at all  
sleepy

---

Extremely  
sleepy

Not at all  
drowsy

---

Extremely  
drowsy

Not at all  
fatigued

---

Extremely  
fatigued

Not at all  
worn out

---

Extremely  
worn out

Not at all  
energetic

---

Extremely  
energetic

Not at all  
vigorous

---

Extremely  
vigorous

Not at all  
efficient

---

Extremely  
efficient

Not at all  
lively

---

Extremely  
lively

Not at all  
bushed

---

Totally  
bushed

Not at all  
exhausted

---

Totally  
exhausted

Keeping my eyes  
open is no effort  
at all

---

Keeping my eyes  
open is a  
tremendous chore

Concentrating is  
no effort at all

---

Concentrating is a  
tremendous chore

Carrying on a  
conversation is  
no effort at all

---

Carrying on a  
conversation is a  
tremendous chore

I have absolutely  
no desire to  
close my eyes

---

I have a tremendous  
desire to close my  
eyes

I feel absolutely  
no motivation to  
do well in the  
assigned task

---

I feel tremendous  
motivation to do  
well in the assigned  
task

# The Rivermead Post-Concussion Symptoms Questionnaire

After a head injury or accident some people experience symptoms which can cause worry or nuisance. We would like to know if you now suffer from any of the symptoms given below. As many of these symptoms occur normally, we would like you to compare yourself now with before the accident.

For each one, please circle the number closest to your answer.

0 = Not experienced at all

1 = No more of a problem

2 = A mild problem

3 = A moderate problem

4 = A severe problem

Compared with before the accident, do you now (i.e. over the past 24 hours) suffer from:

<i>Headaches</i>	0 1 2 3 4
Feelings of Dizziness	0 1 2 3 4
<i>Nausea and/or Vomiting</i>	0 1 2 3 4
Noise Sensitivity, easily upset by loud noise	0 1 2 3 4
<i>Sleep Disturbance</i>	0 1 2 3 4
Fatigue, tiring more easily	0 1 2 3 4
<i>Being Irritable, easily angered</i>	0 1 2 3 4
Feeling Depressed or Tearful	0 1 2 3 4
<i>Feeling Frustrated or Impatient</i>	0 1 2 3 4
Forgetfulness, poor memory	0 1 2 3 4
<i>Poor Concentration</i>	0 1 2 3 4
Taking Longer to Think	0 1 2 3 4
<i>Blurred Vision</i>	0 1 2 3 4
Light Sensitivity, Easily upset by bright light	0 1 2 3 4
<i>Double Vision</i>	0 1 2 3 4
Restlessness	0 1 2 3 4

Are you experiencing any other difficulties?

1. 0 1 2 3 4

2. 0 1 2 3 4

How many concussions do you think you've had in your life?

\_\_\_\_\_

When was your most recent concussion?

\_\_\_\_\_

**Table 1**

	Pre 1	Post 1	Pre 2	Post 2	Pre 3	Post 3	Pre 4	Post 4	Pre average (±SD)	Post average (±SD)
<b>RPQ Score</b>	10		26		33		33		25.50 ±10.85	
<b>Symptoms</b>	8		10		12		13		10.75 ±2.21	
<b>VAS-F</b>	41	25	62	81	45	77	49	105	49.25 ±9.11	72.00 ±33.68
<b>SRT-V (ms)</b>	267.55	273.36	337.36	335.5	277.81	312.27	247.54	262.16	282.565 ±38.63	295.82 ±34.07
<b>SRT-A (ms)</b>	208.9	191	245.45	262	199.36	236.45	182.27	221.27	208.995 ±26.68	227.68 ±29.67
<b>PCAv increase (cm/s)</b>	8.44	7.89	7.61	6.93	9.33	8.57	11.24	9.21	9.155 ±1.56	8.15 ±0.98
<b>MCAv increase (cm/s)</b>	10.31	8.60	10.71	8.74	9.69	8.81	8.05	9.10	9.69 ±1.17	8.81 ±0.21
<b>PCA time to peak (s)</b>	9.5	28.025	23.55	21.05	14.175	16.125	15.425	19.65	15.66 ±5.84	21.21 ±4.99
<b>MCA time to peak (s)</b>	21.2	25.95	31.075	24.125	23.74	22.17	18.95	16.425	23.74 ±5.27	22.17 ±4.13
<b>PCA Curve Area (cm)</b>	24.39	83.92	53.52	36.04	32.58	61.48	64.39	75.05	43.72 ±18.45	64.12 ±20.87
<b>MCA Curve Area (cm)</b>	67.56	81.97	102.78	52.22	80.34	57.37	70.67	37.93	80.34 ±19.50	57.37 ±22.47

**Table 1.** Individual and mean scores for Rivermead Post-Concussion Symptom Questionnaire (RPQ), modified Visual Analogue Scale – Fatigue (VAS-F), simple reaction time to visual stimuli (SRT-V) and auditory stimuli (SRT-A) and cerebrovascular measures. Posterior cerebral artery (PCA) and middle cerebral artery (MCA) were measured for increase (in velocity from baseline due to stimulus), time to peak (from stimulus onset) and curve area (of velocity over time curve).

Each score is given pre and post mentally fatiguing task.