Investigating the long-term effects of concussion on sensory gating

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

The prefrontal cortex (PFC) is a brain region critical for an abundance of neural processes. A vast amount of research employing both behavioural and neurophysiological methods has demonstrated significant impairments in prefrontal function following a concussion. Concussions are the result of biomechanical forces acting on the brain, resulting in diffuse neural disruption and often produce symptoms associated with altered perceptual experiences. Relevancy-based sensory gating is a phenomenon whereby incoming sensory information is selectively inhibited or facilitated based on its relevance to a given task. This process is thought to spare the nervous system from unnecessarily processing non-relevant information from the environment. Critically, the PFC is hypothesized to be largely responsible for this effect. This investigation sought to better understand the consequences of sustaining a concussion on the ability to effectively gate sensory information based on its specific relevance. Electroencephalography (EEG) was used to measure the cortical response to electrical stimulation of the median nerve while participants completed tasks that altered the relevance of somatosensory feedback generated by passive movements of the stimulated wrist. Results suggest that concussions may lead to altered sensory gating abilities. Relative to healthy controls, previously concussed participants demonstrated a delayed ability to selectively enhance specifically relevant somatosensory information. Additional findings from a wrist position matching task suggest that these effects may result in an early cost to performance, which quickly adapts to preserve overall sensorimotor function. Further research should aim to uncover the mechanisms producing these effects following a concussion, as well as the links between altered sensory gating and behaviour.

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1.0 Introduction

Our understanding of the consequences of sustaining a concussive brain injury is constantly evolving. Despite producing diffuse effects to the nervous system, an abundance of research over the past few decades suggests that the prefrontal cortex (PFC) may be particularly sensitive to concussive forces (Belanger, Spiegel, & Vanderploeg, 2010).

A critical function of the PFC is to filter incoming sensory information based on its relevance to a given task. This process, also known as sensory gating, is thought to spare the nervous system from processing unnecessarily large quantities of sensory information, giving precedence to that which is most important (Brooke, Staines, Cheng, & Misiaszek, 1996; Knight, Staines, Swick, & Chao, 1999; Staines, Graham, Black, & McIlroy, 2002).

Thus, sensory gating is a prime candidate for post-concussive impairment. Furthermore, altered perceptual experiences represent a ubiquitous subjective experience following a concussion (McCrory et al., 2017). However, the literature on sensory gating post-concussion is sparse and the few investigations that have been employed suffer from several critical flaws.

Broadly, this thesis aimed to further our understanding of concussive injuries by measuring their impact on gating within the somatosensory system. A neurophysiological approach was taken, using electroencephalography (EEG) to record neural activity produced by early processing stages within the modality specific cortex. Performance on a tracking task that placed specific emphasis on somatosensory feedback was also employed, in an attempt to gather information relating sensory gating to behaviour.

2.0 Literature Review

2.1 Concussion

2.1.1 Definition and epidemiology. A recent consensus statement put forth by a panel of experts defined concussion as a traumatic brain injury (TBI) induced by biomechanical forces. Although direct blows to the head often cause concussions, they may also be induced by forces acting elsewhere on the body, which are impulsively transmitted to the head. Although loss of consciousness is common, it is not necessary to result in a concussion (McCrory et al., 2017).

Concussions typically result in the rapid onset of short-term impaired neurological function, however in some cases these deficits may be long lasting. Symptoms are typically widespread and may affect several different domains and processes. Cognitive function is often impaired, including slowed reaction time, amnesia, and difficulty concentrating. Physical signs and symptoms are also common such as balance impairments, sleep disturbances, and pain (such as a headache). Although symptoms may be severe, concussions are thought to largely reflect functional disturbances, as structural abnormalities are undetectable using conventional neuroimaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT; McCrory et al., 2017).

A systematic review conducted by the World Health Organization (WHO) found that the rate of hospital treatment for concussion ranges from 100 to 300/100,000 person years (py). However, discrepancies in clinical criteria and the fact that a large proportion of head injuries go untreated suggests the incidence is likely in excess of 600/100,000 py (Cassidy et al., 2004). Perhaps more worrisome, is the fact that recent attempts to capture the epidemiology of concussion are suggesting that the annual incidence may be rising (CDC, 2016; Donovan, Cancelliere, & Cassidy, 2014; Voss, Connolly, Schwab, & Scher, 2015).

Although popularized by the media, sports-related head trauma is not the most common cause of concussion. In fact, motor vehicle accidents and falls are reported as the most common causes (Cassidy et al., 2004; Donovan et al., 2014). In terms of risk factors, teenagers and young adults represent the most at-risk age groups, with males at a higher risk for concussion than females (Cassidy et al., 2004).

2.1.2 Neurophysiological effects in humans. Historically, studying the neurophysiological consequences of concussion has been limited to animal models (Giza & Hovda, 2001; MacFarlane & Glenn, 2015), where feasibility and ethical dilemmas that exist when conducting research with humans could be circumvented. Although this research provided critical information regarding the neurophysiological cascade of concussion, questions still lingered with regard to the generalizability of these results to human populations. Fortunately, recent advances in technology, coupled with an enhancement in media coverage and general interest in the topic has resulted in a surge of research efforts over the last two decades (Broglio, Moore, & Hillman, 2011; Cassidy et al., 2004; Donovan et al., 2014) aimed at identifying the neurophysiological underpinnings of concussive injuries in humans.

Although not sensitive enough to diagnose concussion on an individual basis, functional magnetic resonance imaging (fMRI) has been successful in identifying group level differences in blood-oxygen-level dependent (BOLD) signal. Task-based studies, commonly using the 'n-back' task to assess working memory, have consistently shown that concussions cause disruptions to the dorsolateral prefrontal cortex (DLPFC). The exact size and direction of this effect is less consistent however, as some studies have shown hyperactivation in the DLPFC following concussion, while others have suggested hypoactivation (Gosselin et al., 2010;

Mayer, Bellgowan, & Hanlon, 2015; Shin, Bales, Edward Dixon, & Hwang, 2017). Another common finding comes from resting-state fMRI, which has shown hypoconnectivity within the default mode network (DMN). The DMN consists of a series of nodes that are more active during self-reflective mental activity relative to attentionally demanding tasks. Although this finding has been well replicated, the behavioural consequences of DMN hypoconnectivity are less known (Mayer et al., 2015; Shin et al., 2017).

A somewhat related technique known as arterial spin labelling (ASL) has recently been used to measure changes in cerebral blood flow (CBF) post-concussion. Whole brain blood flow has been shown to increase immediately following a concussion, which is hypothesized to meet the increased energy and metabolic demands of damaged tissue (Williams & Danan, 2016). Despite the initial increase in CBF, research investigating later time points following concussion suggests that blood flow is significantly decreased relative to non-injured controls and may remain low for an extended period. A recent study by Churchill et al. (2016) found that CBF was reduced in frontal brain regions in a group of previously concussed individuals with an average of 26 months post-injury. Furthermore, the degree of CBF decrease was correlated with the number of sustained concussions (Churchill et al., 2016). Together, these results provide further evidence that frontal brain regions are particularly susceptible to concussions, and that the effects on blood flow may be both long lasting and sensitive to repeated trauma.

Although concussion is generally thought of as a functional rather than structural injury (McCrory et al., 2017), diffusion tensor imaging (DTI) has recently shown promise with its ability to detect white matter integrity. Several studies have shown that frontal tracts are particularly susceptible to concussive forces, supporting the previously discussed fMRI findings (Chong & Schwedt, 2015; Eierud et al., 2014). As with the fMRI work however, the precise effects that concussions have on white matter tracts requires further investigation.

Some research suggests that concussions cause demyelination and loss of axonal integrity, as evidenced by a decrease in anisotropy and an increase in diffusivity of hydrogen ions (Dimou & Lagopoulos, 2014). However, this has been contradicted by other work that has found the opposite effect (Eierud et al., 2014). To complicate things further, one longitudinal study found both increases and decreases in anisotropy throughout recovery (Chong & Schwedt, 2015). Although it is clear that DTI possesses the sensitivity necessary to detect post-concussive white matter damage, further investigation is required to better quantify these effects.

Magnetic Resonance Spectroscopy (MRS) is another technique that has been employed to quantify the neural consequences of concussion. Specifically, MRS is used to measure the concentration of neural metabolites in specific brain areas. The most consistent evidence from this technique suggests alterations in *N*-acetylaspartate (NAA) concentration following concussion. Specifically, NAA was shown to decrease relative to non-concussed controls in frontal brain regions, most drastically in the DLPFC (Dimou & Lagopoulos, 2014; Gardner, Iverson, & Stanwell, 2014; Williams & Danan, 2016). Furthermore, this effect has been shown both acutely and chronically, suggesting that concussions may result in long-term changes to neurotransmitter systems. Generally, NAA concentration is thought to represent a marker of neuronal integrity, where reduced concentrations typically reflect neuronal loss, metabolic dysfunction, or myelin repair (Dimou & Lagopoulos, 2014). Although an abundance of MRS studies have investigated changes in NAA concentration, there has been much less research quantifying other metabolites and neurotransmitters such as glutamate or γ-aminobutyric acid (GABA), despite being likely candidates for disruption following a concussion (Dimou & Lagopoulos, 2014).

Evidence to support the claim that GABA may be disrupted post-concussion has been provided from work using transcranial magnetic stimulation (TMS). Despite the abundance of stimulation techniques that have been employed on post-concussion populations, measures of cortical inhibition appear to be the most reliable. Long interval intra-cortical inhibition (LICI) and cortical silent period (cSP) duration have consistently shown that intra-cortical inhibition is enhanced following concussion (Lefebvre, Tremblay, & Théoret, 2015; Major, Rogers, & Pearce, 2015). Furthermore, these effects have been shown at various time points post-injury, and some evidence suggests that the inhibition may be chronically elevated. De Beaumont et al., (2009) found significantly enhanced intra-cortical inhibition in a group of individuals who sustained their last concussion at least 25 years prior to testing. Other work from this group has also shown that the degree of inhibition is correlated with the number of previously sustained concussions. The exact mechanism underlying these findings is currently unknown. One possibility is that GABA enhancements would play a neuroprotective role against subsequent concussions, as glutamate excitotoxicity occurs acutely following TBI. However, it may also represent a consequence of incomplete recovery from the initial head trauma (Lefebvre et al., 2015). Although this finding has been well replicated within the motor cortex, it is currently uncertain whether enhanced intra-cortical inhibition exists in other brain areas. The TMS techniques used to obtain these findings can only be conducted in the motor cortex, where muscular responses to the stimulation can be reliably measured (Lefebvre et al., 2015; Major et al., 2015). As previously discussed, MRS studies have yet to investigate concentrations of neurotransmitters such as GABA and glutamate in non-motor cortical regions (Dimou & Lagopoulos, 2014).

Electroencephalography (EEG) is another technique that has been used to study the neurophysiological effects of concussion. The vast majority of studies using this modality have

focused on event-related potentials (ERPs), generated in preparation for or in response of an event. The P300 cortical potential has received considerable attention in the post-concussion population and is generally thought to represent neural processing related to stimulus evaluation and categorization. Several studies have shown both a decrease in amplitude and a prolonged latency of the P300, most commonly elicited via an 'oddball paradigm'. This has loosely been interpreted as a deficit in attentional resource allocation, and delays in cognitive processing speed as a result of previous concussion(s). Furthermore, this effect has been shown for both the P3a and P3b subcomponents of the P300, suggesting deficits in both the orienting of attention and the allocation of attentional resources, respectively. These findings have been shown in both acutely concussed subjects, as well as individuals who sustained their last concussion more than 30 years prior to testing, possibly suggesting chronic deficits (Broglio et al., 2011; Gosselin et al., 2010). Another cognitive ERP that has been studied post-concussion is the error-related negativity (ERN). Research has shown reduced ERN amplitudes following concussion, possibly indicating a comprised ability to evaluate response conflict (Broglio et al., 2011). Many fewer investigations have evaluated the effects concussion may pose to sensory processing. One study investigating sensory ERPs post-concussion used an auditory 'oddball paradigm' and found a reduced N1 amplitude relative to non-injured controls, however this finding was limited to unattended stimuli only (Gosselin, Thériault, Leclerc, Montplaisir, & Lassonde, 2006). This result suggests that concussions may also affect the encoding of auditory stimuli.

It is evident that a wide variety of methods and techniques have been employed to study the neurophysiological consequences of concussions. Emerging from these findings are a few notable patterns. First, several modalities have shown that frontal brain regions, particularly the PFC, appear to be especially sensitive to the effects of a concussion. Furthermore, it is

evident that concussions result in chronic alterations to both brain structure and function, which may persist long after symptoms and other subjective measures of recovery have resolved. Despite these findings however, it is clear that further research is necessary to provide a more complete understanding of the neurophysiological effects of concussions, and how these findings can be used to explain clinical and behavioural observations.

2.1.3 Neurocognitive effects in humans. A vast amount of research has been aimed at addressing the neurocognitive effects of concussion. As a result, several meta-analyses have been conducted, which have consistently found detriments in executive function post-concussion, across a broad spectrum of tasks and conditions. Specifically, the domains of working memory and attention show the greatest deficits, with effect sizes (Cohen's *d*) ranging from 0.25-0.33 and 0.05-0.63 respectively (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Belanger et al., 2010; Frencham, Fox, & Maybery, 2005; Rohling et al., 2011; Zakzanis, Leach, & Kaplan, 1999). Furthermore, Belanger et al. (2010) used the number of concussions sustained as a moderator and concluded that executive function appears to be particularly susceptible to repeated injuries. Although the majority of this research has been conducted on acutely injured subjects, some recent findings suggest that these impairments may linger for several years or longer post-injury (Howell, Osternig, Van Donkelaar, Mayr, & Chou, 2013; Tapper, Gonzalez, Roy, & Niechwiej-Szwedo, 2016).

Although there is some debate regarding the exact definition of attention, Petersen & Posner (2012) offer a well accepted framework for the function of attention, which is composed of three distinct networks. Briefly, the Alerting network is responsible for preparing and maintaining arousal in order to process information of specific relevance. The Orienting network is responsible for prioritizing sensory input from a particular modality or spatial

location. Finally, the Executive network is involved in detecting targets while simultaneously interfering with other cognitive processes, lending support to the notion that attention is focal and has a limited capacity (Petersen & Posner, 2012; Posner & Petersen, 1989).

With regard to working memory, the Multicomponent Model proposed by Baddeley & Hitch (1974) has been the most influential framework. Originally, this model consisted of three main components. The Central Executive is responsible for using the attentional networks to identify relevant information while suppressing irrelevant stimuli, and to coordinate the integration of information into the slave systems. One slave system is the Phonological Loop, which stores auditory information in a rehearsal loop. The other slave system is the Visuospatial Sketchpad, which contains separate subsystems responsible for maintaining visual and spatial information (Baddeley & Hitch, 1974). More recently, a fourth element has been added to the framework, known as the Episodic Buffer. This component is thought to bind information from the slave systems together and possibly with other information not covered by the slave systems. Furthermore, the Episodic Buffer is responsible for relaying information from short into long-term memory (Baddeley, 2000).

Despite attention and working memory representing distinct functional processes, both rely heavily on neural activity in the prefrontal cortex (PFC). Broadly, the PFC is hypothesized to actively maintain patterns of neural activity that represent goals and the means to achieve them. The role of attention is critical in selecting specifically relevant sensory inputs, and consequently inhibiting those that are non-relevant. With regard to working memory, the PFC is thought to be responsible for the executive control component (the Central Executive in Baddeley's model) and must also maintain the goals or desired outcome of a task (Miller & Cohen, 2001). The neuroanatomical link between these processes may help to explain the consistently observed cognitive deficits post-concussion. The previously discussed

neurophysiological research certainly suggests that the PFC may be particularly vulnerable to concussive forces. Of greater concern is that both the cognitive deficits and neurophysiological disruptions resulting from a concussion may be chronic and persist long after the injury occurred.

2.2 Overview of the Somatosensory System

As this thesis will focus on gating of somatosensory information in the upper limb, a brief overview of the neuroanatomical components of this pathway is warranted.

Sensory afferents are initially activated by peripheral receptors. In the case of proprioceptive information, muscle spindles and Golgi tendon organs (GTOs) are activated by muscle stretch and force respectively, which open ion channels and generate an action potential. For cutaneous information, different mechanoreceptors in the skin respond to varying characteristics of touch, which open ion channels, and cause a depolarization.

The peripheral receptors transmit information to first-order neurons, whose cell bodies reside in the dorsal root ganglia of the spinal nerves. These neurons then synapse onto second order neurons at the cuneate nucleus in the medulla. Second-order neurons decussate in the tegmentum, and travel through the medial lemniscus, eventually synapsing onto neurons in the ventral posterior lateral nucleus (VPL) of the thalamus. From the thalamus, third-order neurons project through the corona radiata to layer IV of the primary somatosensory cortex (SI). SI is comprised of three functional areas: Brodmann areas (BAs) 1, 2, and 3. BA 3 is further subdivided into 3a, which in combination with area 1 receives proprioceptive information, and 3b, which receives cutaneous information. Furthermore, SI and the previously described ascending afferents are arranged somatotopically, such that each part of the body is distinctly represented.

SI also receives input from other areas of the nervous system. For example, the primary motor cortex (MI) sends projections to SI. Furthermore, it receives projections from the opposite SI via the corpus callosum. It is also postulated that the PFC sends projections to SI, either directly, or indirectly via the thalamus (see section 2.4 Sensory Gating).

In addition to the described afferents, SI also projects efferents to other areas of the brain, including the secondary somatosensory cortex (SII), where further processing and integration occurs, as well as the ipsilateral MI and thalamus, and contralateral SI.

2.3 Electroencephalography and Event-Related Potentials

2.3.1 Techniques and definitions. Electroencephalography is a neuroimaging technique capable of detecting cortical activity via electrodes placed on the scalp. When postsynaptic potentials in close proximity summate in a common orientation, the resulting fluctuations in voltage are large enough to reach the skull. The EEG technique allows the measurement of these changes in voltage, which provide a direct measure of cortical activity underlying the electrode(s) of interest. One of the major advantages of using EEG compared to other neuroimaging techniques is the high temporal resolution, which allows the measurement of changes in cortical activity on the order of milliseconds (ms). In contrast however, EEG suffers from a poor spatial resolution, and is unable to detect voltage fluctuations of subcortical structures (Luck, 2014).

Event-related potentials are positive and negative EEG components, occurring at predictable latencies, either in response or in preparation of an event. ERP components are generated via the summation of postsynaptic potentials of pyramidal cells in the cortex, which create dipoles perpendicular to the skull (Luck, 2014). Sensory ERP components represent the processing stages that sensory information undergoes once it reaches the cortex. These

processing stages and their resultant ERP characteristics are specific to each sensory modality. This thesis focuses on ERPs in the somatosensory domain, which when elicited via nerve stimulation are known as somatosensory evoked potentials (SEPs).

SEPs are elicited via electrical stimulation of a peripheral nerve, resulting in the summation of excitatory postsynaptic potentials (EPSPs) and the generation of an action potential. The afferent volley will travel along the large diameter nerve fibres of the dorsal column medial lemniscal pathway, decussating before reaching the VPL of the thalamus, and ultimately the somatosensory cortex of the contralateral hemisphere.

2.3.2 Neural generators. The first cortical stage of processing for somatosensory information is in the primary somatosensory cortex (SI). Here, two main SEPs are elicited indicative of the arrival of information to the cortex: The N20 and P27 (letters denote polarity, while numbers denote approximate latency from stimulus onset in milliseconds). The N20 is thought to represent the arrival of somatosensory information to BA 3b (Allison, McCarthy, Wood, & Jones, 1991; Allison, McCarthy, Wood, Williamson, & Spencer, 1989; Allison, 1982; Arezzo, Legatt, & Vaughan, 1979; Wood, Cohen, Cuffin, Yarita, & Allison, 1985; Yamaguchi & Knight, 1990), while the P27 is believed to represent the arrival of proprioceptive information to BA 1 (Allison et al., 1991, 1989; Allison, 1982; Arezzo, Vaughan, & Legatt, 1981; Goldring, Aras, & Weber, 1970; Kelly & Goldring, 1965; Wood et al., 1985; Yamaguchi & Knight, 1990). The P50 and N70 are two additional potentials thought to arise from SI related activity. Although less is known about the precise generators of these potentials, some evidence suggests that both are influenced largely by the type of stimulus used to evoke them (Allison et al., 1989; Allison, McCarthy, & Wood, 1992; Desmedt & Tomberg, 1989; Hamalainen, Kekoni, Sams, Reinikainen, & Naatanen, 1990; Yamaguchi & Knight, 1990).

Following processing in SI, information is passed to SII for further processing and integration, where the P100 is generated (Allison et al., 1989; Allison et al., 1992; Desmedt & Tomberg, 1989; Hamalainen et al., 1990). Evidence suggests the existence of complex interactions between SII and prefrontal cortical regions (Desmedt & Tomberg, 1989).

2.4 Sensory Gating

Broadly speaking, sensory gating refers to the filtering of incoming sensory information as it ascends to the cortex. The purpose of this process is to filter out distracting or non-relevant sensory information, such that the most relevant material results in the greatest cortical response. As Brooke et al. (1996) suggest, the significance of gating behaviour in animals is to restrict sensory transmission to achieve a just sufficient signal. Sensory gating is thought to occur at multiple levels of the nervous system, including peripheral receptors, spinal cord, thalamus, and various cortical regions. Furthermore, sensory gating has been shown to be modulated by movement (both passive and active), as well as task-relevancy. Numerous populations have shown impairments in sensory gating, including schizophrenia (Adler et al., 1998), Parkinson's disease (Kaji, Urushihara, Murase, Shimazu, & Goto, 2005), bipolar disorder (Lijffijt et al., 2009), and normal aging (Cheng & Lin, 2013).

2.4.1 Movement-related gating. Many studies have described an attenuation of SEPs during movement. Here, two main processes are thought to contribute: centripetal gating and centrifugal gating.

Centripetal gating refers to bottom-up attenuation of sensory afferents, arising from the periphery. Evidence for centripetal mechanisms comes from research showing that SEPs elicited during passive movement alone are inhibited (Brooke et al., 1996; Burke & Gandevia, 1988; Cheron & Borenstein, 1991; Gandevia, Burke, & McKeon, 1983; Jones, Halonen, &

Shawkat, 1989; Jones & Power, 1984; Nakata, Inui, Wasaka, Nishihira, & Kakigi, 2003; Rossini et al., 1989; Rushton, Rothwell, & Craggs, 1981; Seki & Fetz, 2012). The mechanism driving this attenuation has been hypothesized as presynaptic inhibition of the afferent volley via the reafference related to the passive movement itself, generated by peripheral receptors (Brooke et al., 1996; Cheron, Dan, & Borenstein, 2000; Rossini et al., 1999; Rushton et al., 1981; Seki & Fetz, 2012; Staines, Brooke, Angerilli, & McIlroy, 1998), and taking effect at the dorsal column nuclei (Brooke et al., 1996; Chapman, Jiang, & Lamarre, 1988; Cheron et al., 2000; Insola, Padua, Mazzone, & Valeriani, 2010; Seki & Fetz, 2012), the thalamic reticular nucleus (Brooke et al., 1996; Brunia, 1993; Mitrofanis & Guillery, 1993), and/or SI (Rossini et al., 1999). Further support for centripetal gating comes from Morita, Petersen, & Nielsen (1998), who demonstrated that ischemic nerve block distal to the site of stimulation resulted in a significant disinhibition of SEPs during active movement. Relative to rest however, SEPs were still significantly attenuated, indicating that centripetal mechanisms are only partially responsible for movement-related gating (Morita et al., 1998).

Centrifugal gating refers to top-down attenuation of sensory afferents, resulting from central commands. Evidence for centrifugal gating comes from multiple sources. First, as previously mentioned, peripheral gating mechanisms were only able to account for some of the SEP attenuation seen in active movement with peripheral nerve ischemia (Morita et al., 1998). Furthermore, several studies have shown that SEPs are gated prior to the onset of voluntary movement (Brooke et al., 1996; Chapman et al., 1988; Cheron et al., 2000; Cohen & Starr, 1987; Jones et al., 1989; Morita et al., 1998; Seki & Fetz, 2012; Starr & Cohen, 1985; Tinazzi et al., 1997). This pre-movement gating is argued to arise from central commands, as there is no movement to generate reafference that could inhibit the evoked potential. As with centripetal mechanisms, centrifugal gating has been shown to occur at several different sites,

and some authors argue that descending motor output can inhibit somatosensory input at any level of the ascending flow (Canedo, 1997; Chapman et al., 1988; Staines, Black, Graham, & McIlroy, 2002).

2.4.2 Relevancy-based gating. Several studies have suggested that task-relevancy plays a significant role in the gating process. Staines, Brooke, & McIlroy (2000) manipulated the relevancy of sensory information from the lower limb by requiring participants to make ankle movements (of the non-stimulated limb) that were dictated by the 'cutaneous code' of stimuli applied to the dorsum of the foot, or by the direction of passive movement induced by the experimenters. Relative to passive movement alone, the conditions where the sensory information was specifically relevant for the subsequent motor task resulted in an enhancement of cortical activity in SI.

Further research has suggested that the prefrontal cortex may play a critical role in producing the relevancy-based gating effect. For example, Yamaguchi & Knight (1990) demonstrated that patients with prefrontal lesions produced enhanced SEPs relative to healthy controls, indicating an impairment in somatosensory gating. Research using fMRI has also yielded support for a prefrontal gating mechanism. In 2002, Staines, Graham, Black, & McIlroy demonstrated that task-relevant somatosensory stimuli result in an increased BOLD signal in the contralateral SI. Critically, this functional upregulation was associated with an increased BOLD response in BA 9, corresponding to the right DLPFC (Staines et al., 2002). Further support for the PFC's role in sensory gating comes from research using TMS. Using a stimulation pattern known as continuous theta burst stimulation (cTBS), researchers have been able to transiently inhibit the DLPFC in healthy human subjects. In 2011, Bolton & Staines provided relevant and irrelevant vibrotactile stimuli to subjects' fingertips following cTBS over

the DLPFC or sham stimulation. Relative to sham, the cTBS condition resulted in an enhancement of evoked potentials for irrelevant stimuli, suggesting that the DLPFC may be at least partly responsible for gating non-relevant inputs (Bolton & Staines, 2011). Another study conducted in 2015 by Brown, Ferris, Amanian, Staines, & Boyd, used cTBS over the DLPFC while participants underwent relevant and non-relevant passive wrist movements. Compared to participants' baseline measures, cTBS resulted in significantly attenuated SEPs during relevant movement, suggesting that the DLPFC may also play a role in facilitating relevant sensory inputs (Brown et al., 2015).

Taken together, this evidence strongly suggests a relevancy-based prefrontal gating mechanism for somatosensory information. Despite being well replicated using several different techniques and modalities, the exact mechanism producing these effects is less well known. One hypothesis suggests that the PFC modulates somatosensory afferents via the thalamic reticular nucleus (TRN). Research from animal models has shown that the PFC maintains tonic suppression of thalamic inputs to SI (Cao, Wang, Bai, Zhou, & Zhou, 2008; Pandya & Barnes, 1987). Furthermore, applying a cryogenic blockade to the PFC resulted in an enhancement of early SI evoked potentials (Skinner & Yingling, 1976, 1977). Another theory is that modulation could occur via cortical connections between PFC and SI. For example, the PFC has direct bidirectional connections with BAs 5 and 7, which have reciprocal connections to SI (Jones, Coulter, & Hendry, 1978; Pandya & Barnes, 1987; Vogt & Pandya, 1978; Yamaguchi & Knight, 1990). Although both of these pathways remain prime candidates for PFC modulation of somatosensory information, their exact contributions to the effect is presently unknown.

2.5 Concussion & Sensory Gating

To date, there have been few investigations measuring the impact of concussions on sensory gating. This is particularly surprising given the ubiquity of post-concussion sensory anomalies, including feeling overwhelmed in busy sensory environments (McCrory et al., 2017).

Shaw & Cant (1984) provide one of the earliest studies investigating the effects of a concussion on the somatosensory system. The researchers experimentally induced concussions in rats and immediately measured SEPs until the animals produced spontaneous movements. Although this investigation did not explicitly measure sensory gating abilities, the results do suggest that concussions can produce amplitude reductions and prolonged latencies of early cortical potentials, which progressively recovered to baseline levels (Shaw & Cant, 1984).

Kumar and colleagues investigated sensory gating function following concussion using subjective methods (Kumar et al., 2005). The authors administered the Structured Interview for Assessing Perceptual Anomalies (SIAPA) to a group of post-concussion subjects. Their results indicate that the majority (approximately 60%) of their sample were experiencing perceptual anomalies, which was interpreted as deficits in sensory gating abilities. Although this research lacks a neurophysiological component, it does suggest that individuals who have sustained a concussion may subjectively experience disruptions in the ability to filter sensory information from the environment (Kumar et al., 2005). The lack of objectivity however, does introduce several concerning sources of bias. For example, participants were included in the study based on the presence of pre-existing sensory deficits. Furthermore, interview questions from the SIAPA are relative to pre-injury conditions (Kumar et al., 2005). More recent findings have identified the “good-old-days” bias, which suggests that individuals who have sustained a

concussion are more likely to perceive their pre-injury function as better than it may have actually been (Lange, Iverson, & Rose, 2010).

Taking a more physiological approach, Gaetz & Weinberg (2000) delivered a battery of assessments designed to evoke a number of ERP components. One task required participants to view a reversing checkerboard pattern, which evoked a number of visual components. Following a concussion, middle-aged participants' P1 peaked significantly later relative to non-concussed controls (Gaetz & Weinberg, 2000). Generated along the optic radiations, the visual P1 is thought to reflect the 'cost of attention', where amplitudes are reduced when attention is directed away from a delivered stimulus (Luck et al., 1994). Thus, this potential has been linked to gating of visual input and the prolonged latency following concussion shown by Gaetz & Wienberg may represent a delay in this process (Broglio et al., 2011). Although this represents a plausible interpretation, other mechanisms contributing to the latency shift, such as myelin damage or a loss of white matter integrity, cannot be ruled out (Gaetz & Weinberg, 2000). Another study investigated auditory sensory gating following varying severities of TBI (Arciniegas et al., 2000). The researchers elicited the auditory P50 via a paired-click paradigm. Two clicks of equivalent frequency and intensity were delivered 500 ms apart. In healthy individuals, the P50 response to the second click (also known as the test stimulus or TS) was attenuated compared to the fist click (also known as the conditioning stimulus or CS). Relative to controls, the TBI group (regardless of severity) demonstrated significantly diminished P50 responses to the CS in addition to greater P50 amplitudes following the TS. This suggests that a TBI may lead to impairments in the ability to upregulate novel information (CS), as well as downregulate or gate out repetitive information. Furthermore, the average time elapsed since the injury was approximately five years, suggesting chronic impairments to sensory gating (Arciniegas et al., 2000). Despite these findings, some issues remain with regard to the sample.

Specifically, the length of post-traumatic amnesia (PTA) was used to determine the severity of participants' TBI. This is an indirect method of determining TBI severity, and it is possible that even in the mild TBI subgroup, participants may have suffered injuries more severe than a concussion. Furthermore the PTA data was collected via self-report and may have suffered from recall bias, especially considering that an average of five years had elapsed since the injury occurred (Arciniegas et al., 2000).

3.0 Rationale

Numerous studies, from both cognitive and neurophysiological perspectives, have suggested that the PFC may be particularly susceptible to concussive forces, and that these effects may persist following clinical markers of recovery (Churchill et al., 2016; Howell et al., 2013; Tapper et al., 2016). Previous research also largely supports the PFC's involvement in relevancy based sensory gating, particularly in the early stages of cortical processing (Brown et al., 2015; Yamaguchi & Knight, 1990).

Despite these findings, limited research has investigated the effects of concussion on the ability to effectively gate incoming sensory information at early processing potentials. Collectively, the handful of studies in this area suggest that concussions may impair the ability to undergo efficient sensory gating (Arciniegas et al., 2000; Broglio et al., 2011; Kumar et al., 2005). However, this body of work also suffers from several critical limitations. Multiple studies employed questionable sampling practices such as recruiting participants with pre-existing sensory anomalies (Kumar et al., 2005) or using indirect measures to classify injury severity (Arciniegas et al., 2000). The somatosensory system has also been largely ignored in this context; in addition to the relevancy aspect of sensory gating that has specifically been shown to engage the PFC. Furthermore, the potential downstream or behavioural consequences of altered gating abilities deserves greater attention. For example, the efficient gathering of appropriate sensory feedback is suggested to comprise one of the earliest components of complex motor learning (Wolpert, Diedrichsen, & Flanagan, 2011).

This thesis aimed to further identify the effects of concussion on sensory gating. A neurophysiological approach was taken, using EEG to determine whether concussions affect gating abilities at early cortical processing potentials. Here, relevancy-based gating was of specific interest, given its ties to prefrontal areas and the fact that prefrontal cortical

processing consistently shows post-concussive deficits. Furthermore, this investigation included a strict inclusion criteria requiring medical concussion diagnosis, in an effort to improve the sampling limitations that exist in the current literature. A behavioural component was also included in an attempt to identify any potential functional consequences of impaired sensory gating following concussion.

4.0 Objective & Hypotheses

The overall objective of this investigation was to identify the effects of concussion on relevancy-based sensory gating at early cortical processing stages. Briefly, this was achieved by delivering SEPs while the relevancy of sensory information was altered. SEP amplitudes under the experimental conditions were compared between a healthy control group, and a post-concussion group.

Based on previous work (Brown et al., 2015; Staines et al., 2000), it was hypothesized that the control group would demonstrate smaller SEP amplitudes in response to task-irrelevant sensory information relative to both resting levels and task-relevant sensory information, upon arrival to SI. This would be reflective of an appropriate gating response based on relevancy, where non-relevant somatosensory information is inhibited and specifically relevant somatosensory information is facilitated.

Within the concussed group, it was hypothesized that sustaining previous head injuries would disrupt the appropriate relevancy-based gating modulations displayed in the control group at early processing potentials. This would be reflected by an impaired ability to inhibit non-relevant information, an impaired ability to facilitate relevant information, or a combination of the two.

It was also predicted that the post-concussion disruptions in sensory gating would result in behavioural consequences. More specifically, it was hypothesized that the concussed group would demonstrate poorer performance on a wrist position tracking task, where only somatosensory feedback was provided.

4.1 Exploratory Objectives & Hypotheses

Previous research has not identified the effect of attentional focus on resting SEP amplitudes. Therefore, two separate rest conditions were employed, where participants were asked to attend towards the delivered stimuli or away from them. If significant differences emerged, it was hypothesized that SEP amplitudes would be greater when attention was directed towards the stimuli relative to away from them.

Within the concussed group, it was anticipated that sensory gating disruptions and behavioural performance would be associated with certain concussion history characteristics. More specifically, these deficits were expected to worsen with a greater number of previous concussions, greater concussion severity, and shorter recovery times.

5.0 Methods

5.1 Participants

Participants in this study comprised two groups: a post-concussion group (concussed), and a control group (control). A total of 28 participants (estimated by a power analysis using data from Brown et al. [2015], $\alpha = 0.05$, and $\beta = 0.8$) were recruited, with half in each group. Inclusion criteria for the concussed group consisted of sustaining at least one medically diagnosed concussion in their lifetime. Furthermore, subjects must have been clinically cleared to return to both physical and cognitive activities, and be symptom-free at the time of testing. Apart from their concussion(s), participants must not have sustained any other central or upper limb peripheral nervous system injuries. Subjects in the control group must not have sustained or suspected to have sustained a previous concussion and must similarly have been free from any additional decrements to the nervous system. All subjects were required to be between the ages of 17 and 40, right hand dominant, and fluent in English. Although the age and handedness of participants was not expected to affect the research objectives, it is possible that differences in connectivity and electrical activity may exist for participants of different handedness, and similarly for both younger and older individuals. Fluency in English was necessary to ensure complete understanding of the instructions and accurate data collection. Subjects were recruited from the University of Waterloo via posters placed in various locations on campus.

5.1.1 Demographics. Subjects completed a modified version of the University of Waterloo Health History Questionnaire (see Appendix A), which has previously been used to gather participant characteristics following concussion (Tapper et al., 2016). This questionnaire collects information regarding previous head injuries, such as total number of concussions, time since last concussion, as well as current symptoms and their severity. For

the purposes of this study, a modification was made in order to gather data regarding other neurological conditions/disorders, or upper limb nerve injuries which may confound the results, as well as to include the number of *medically* diagnosed concussions.

5.2 Experimental Design

To measure the degree of sensory gating, a protocol based on Brown et al. (2015) was employed. Participants' left median nerve was stimulated via a bar electrode placed on the wrist. A square wave pulse (0.5 ms) was delivered (Grass SD9 Stimulator, West Warrick, RI, USA) at an intensity of motor threshold (the intensity required to evoke a just visible twitch in the abductor pollicis brevis [APB]). The interstimulus interval was randomly generated between 500 and 1000 ms to ensure that stimulation onset was not predictable. For conditions involving wrist movement, a custom device that allows for near frictionless movement within a 60° range was used (see Figures 1 and 2).

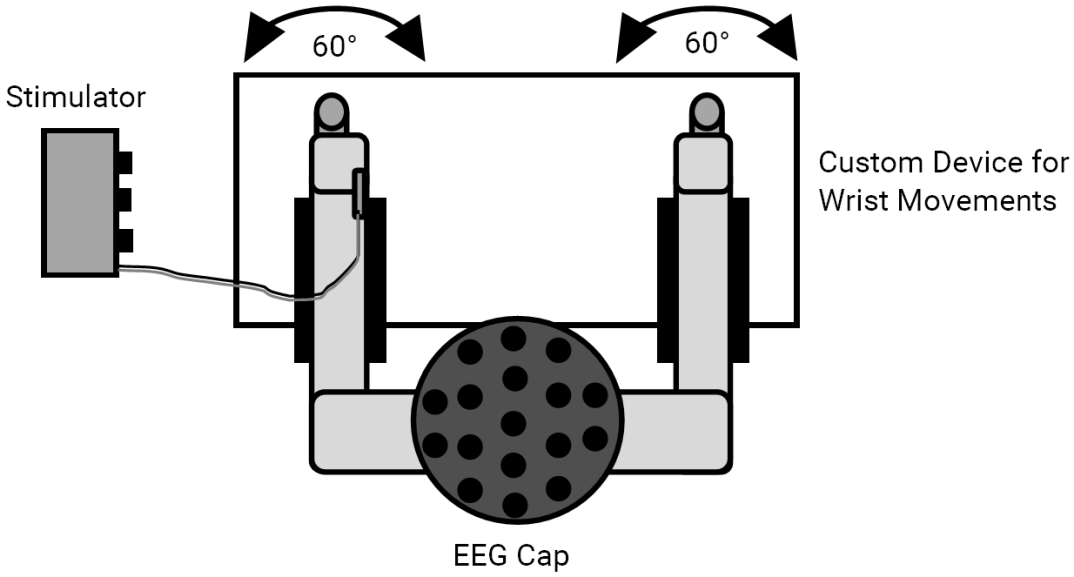

Figure 1. Schematic of experimental setup (above view).

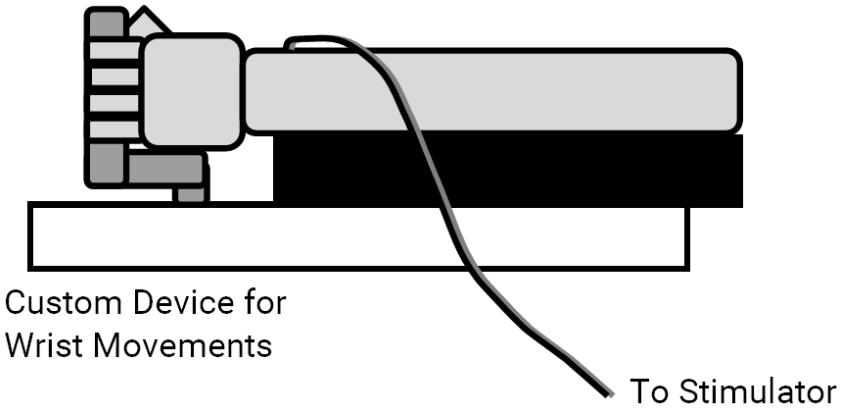

Figure 2. Schematic of experimental setup (left view).

All subjects underwent four different experimental conditions, designed to alter the relevance of sensory information. The order of the conditions were counter-balanced, and in all cases, participants' eyes remained closed.

- Rest (towards): Participants maintained a neutral wrist positon while mentally counting the number of nerve stimuli received.
- Rest (away): Participants maintained a neutral wrist position while mentally counting backwards by seven from a given starting number.
- Passive: Participants' stimulated wrist was passively moved through a series of flexion and extension movements (within 60°), while they mentally counted backwards by seven from a given starting number.
- Active: Participants' stimulated wrist was passively moved through a series of flexion and extension movements (within 60°) for seven seconds. Participants then used their non-stimulated wrist to re-create the passive movements delivered to the stimulated wrist. This comprised one block, which was repeated seven times with a different pattern of movement presented in each block.

A custom LabView (National Instruments, Austin, Texas, USA) program was used to generate the waveforms that guided the experimenter during the delivery of passive wrist movements. In each condition, over 100 nerve stimuli were delivered, although the exact number differed for each condition and participant, as the interstimulus intervals were randomly generated between 500 and 1000 ms.

5.3 Data Acquisition

EEG was collected throughout the experiment using a 32-channel cap (Quik-Cap, Compumedics Neuroscan, NC, USA), with the main electrode of interest being Cp4 (according to the International 10-20 system), which rested on the scalp directly above the somatosensory cortex contralateral to the nerve stimulation. Electrodes were referenced to linked mastoids, with all channel impedances less than 5 kΩ. This data was digitized at 1000 Hz and low-pass filtered at 200 Hz (SynAmps^2 Compumedics Neuroscan, NC, USA).

In addition to the electrophysiological data, behavioural data was also collected during the matching component of the active condition. Participants' accuracy was acquired via a custom LabView program (National Instruments, Austin, Texas, USA), which recorded voltages from potentiometers embedded in each handle of the wrist movement device at a rate of 100 Hz.

5.4 Data Analysis

EEG data was analyzed using Neuroscan (Compumedics Neuroscan, NC, USA) software. Continuous data files were epoched from -100 to 500 ms of each nerve stimulus and baseline corrected to the 100 ms pre-stimulus activity. All epochs were manually inspected for noise and artifacts, which may have been produced by other generators of electrical activity including both biological (such as muscle contractions) or non-biological (from the surrounding environment) sources. Epochs were then averaged within each condition for each participant, before extracting values in microvolts (μV) for all potentials of interest. Based on previous research (Brown et al., 2015; Cheron & Borenstein, 1987, 1991; Cohen & Starr, 1987; Jones et al., 1989; Starr & Cohen, 1985; Yamaguchi & Knight, 1990) and pilot data, the amplitudes for each of the potentials of interest were determined as follows:

- N20: Greatest negativity between 17-23 ms
- P27: Greatest positivity between 24-31 ms
- P50: Greatest positivity between 40-60 ms
- N70: Greatest negativity between 60-80 ms
- P100: Greatest positivity between 80-120 ms

Since the amplitude of a given cortical potential can be influenced by the preceding potential, peak-to-peak amplitudes were used for analysis (N20-P27, P50-N70, & N70-P100). Peak-to-peak amplitudes were determined by calculating the difference in amplitude between the two potentials, and taking the absolute value of the difference. SEP waveforms for all conditions from one subject can be seen in Figure 3, with each potential of interest identified.

Participant behavioural data for the active condition was analyzed using a custom LabView (National Instruments, Austin, Texas, USA) program. The voltages measured from each of the potentiometers imbedded in the handles of the wrist movement device were plotted over time to generate two waveforms (the target and the response). Both waveforms were then parsed into individual blocks for comparison. For each block, a difference waveform was generated by plotting the voltage difference between the target and response waveforms at each sample. The root mean square (RMS) was then calculated on the difference waveform, providing a root mean square error (RMSE) value for each block. RMSE values were then averaged across all seven blocks within each participant to generate a single RMSE value for each subject.

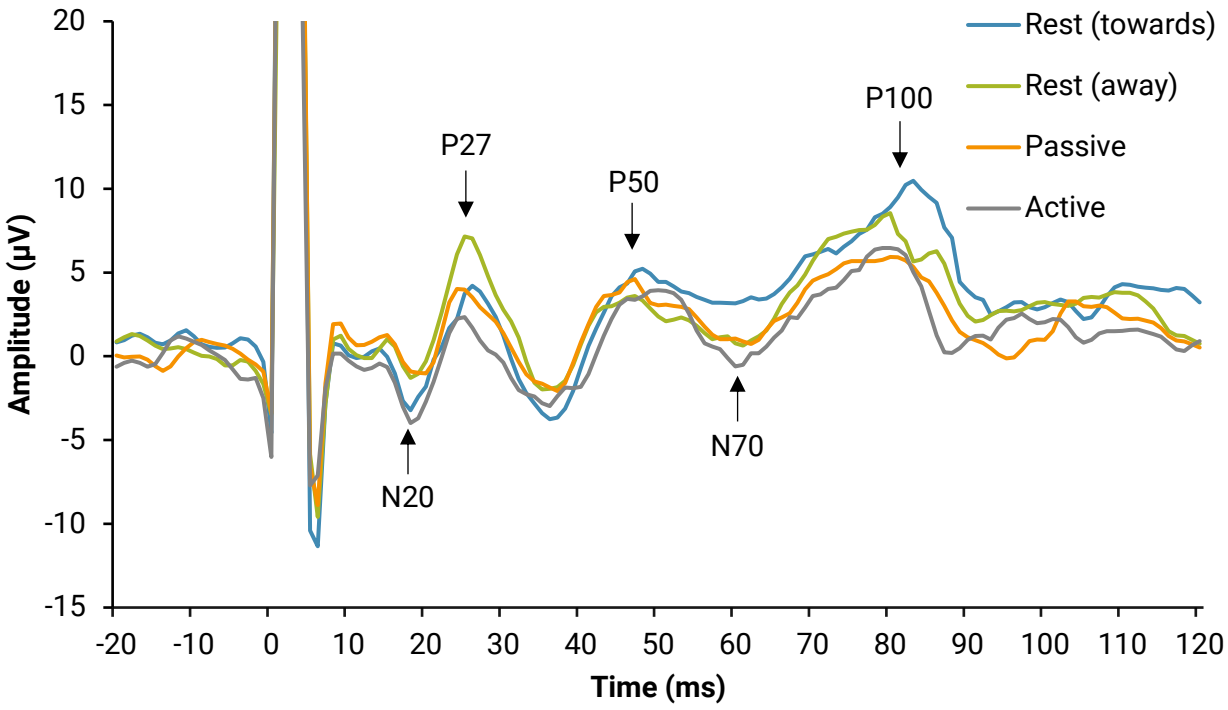

Figure 3. Individual subject waveforms showing all conditions and all potentials of interest, recorded from electrode Cp4.

5.5 Statistical Analysis

For the SEP data, a 2x4 mixed factorial Analysis of Variance (ANOVA) with group (control, concussed) as the between-subjects factor, condition (rest [towards], rest [away], passive, active) as the within-subjects factor, and SEP amplitude (in μV) as the dependent variable (DV) was conducted for each peak-to-peak potential of interest (N20-P27, P50-N70, N70-P100). At potentials where significant interactions between group and condition were revealed, one-way repeated measures ANOVAs with condition (rest [towards], rest [away], passive, active) as the factor and SEP amplitude as the DV were conducted within each group (control, concussed). Pre-planned contrasts were conducted to test the specific hypotheses, in

addition to post-hoc Tukey analyses (which correct for multiple comparisons), to elucidate any additional significant differences.

Similar 2x4 mixed factorial ANOVAs were conducted with group (control, concussed) as the between-subjects factor, condition (rest [towards], rest [away], passive, active) as the within-subjects factor, and SEP latency (in ms) as the DV for each potential of interest (N20, P27, P50, N70, P100).

The behavioural data was analyzed using an independent samples *t*-test to determine the effect of group on overall RMSE values. A post-hoc analysis compared the difference in RMSE between block one and block seven across the groups (control, concussed).

5.6 Data Screening

The EEG data was visually screened for quality prior to statistical analyses. This resulted in the removal of one concussed participants' entire ERP dataset due to excessive noise in the signal in all conditions and at all potentials of interest. Additionally, data from the N20 and P27 potentials of one subject in the control group were removed due to the peaks being indistinguishable from the baseline. ERP data from the active condition of another control participant was also removed due to the absence of all potentials of interest.

Prior to computation of the ANOVAs, residual errors were plotted and inspected to ensure that the data met the assumptions of normality and homogeneity of variances that are inherent to this type of analysis.

6.0 Results

6.1 Participant Characteristics

Participant demographics are summarized in Table 1. The control group consisted of 14 participants (nine female) with a mean age of 22.29 years (*SD* = 2.61). On the current symptoms checklist of the health history questionnaire, control participants received an average score of 1.21 (*SD* = 1.19) out of a possible 132.

The concussed group also consisted of 14 participants (11 female) with a mean age of 23.36 years (*SD* = 3.61). On the current symptoms checklist of the health history questionnaire, concussed participants received an average score of 1.50 (*SD* = 1.61). Concussed participants also reported a mean of 1.64 medically diagnosed concussions (*SD* = 0.63) and a mean recovery time of 32.86 months (*SD* = 29.28) since their most recent concussion. A total of eight participants indicated losing consciousness at least once as a result of a head injury.

Independent samples *t*-tests revealed no significant differences in age, $t(26) = 0.90$, $p = .377$, or symptom score, $t(26) = 0.54$, $p = .597$, between the groups.

Table 1
Participant Characteristics

	Control		Concussed	
Demographic	Mean	*SD*	Mean	*SD*
Age (years)	22.29	2.61	23.36	3.61
Symptom score	1.21	1.19	1.50	1.61
Medically diagnosed concussions	-	-	1.64	0.63
Recovery time (months)	-	-	32.86	29.28

Note. *SD* = standard deviation.

6.2 SEP Amplitude Analyses

Table 2 displays mean SEP amplitudes and standard deviations, separated by potential, group, and condition. Separate 2x4 mixed factorial ANOVAs (DV: SEP amplitude) were conducted for each peak-to-peak potential with group as the between-subjects factor and condition as the within-subjects factor.

6.2.1 N20-P27. For the N20-P27, a main effect of condition emerged, $F(3, 71) = 14.55$, $p < .001$, in addition to a significant interaction between group and condition, $F(3, 71) = 3.19$, $p = .029$. Mean amplitudes for each group and condition at the N20-P27 can be seen in Figure 4.

Within the control group, a one-way repeated measures ANOVA with condition as the within-subjects factor revealed a significant main effect of condition, $F(3, 35) = 13.61$, $p < .001$. *A priori* contrasts revealed larger amplitudes in the rest conditions relative to the passive condition, $F(1, 35) = 40.71$, $p < .001$, and larger amplitudes in the active condition compared to the passive condition, $F(1, 35) = 10.82$, $p = .002$. A post-hoc Tukey analysis revealed no other significant differences.

Within the concussed group, a one-way repeated measures ANOVA with condition as the within-subjects factor revealed a significant main effect of condition, $F(3, 36) = 7.00$, $p < .001$. *A priori* contrasts revealed larger amplitudes in the rest conditions relative to the passive condition, $F(1, 36) = 7.24$, $p = .011$, but no significant difference between the active and passive conditions, $F(1, 36) = 1.93$, $p = .174$. A post-hoc Tukey test also revealed significantly smaller amplitudes in the active condition relative to both rest conditions (p's < .050).

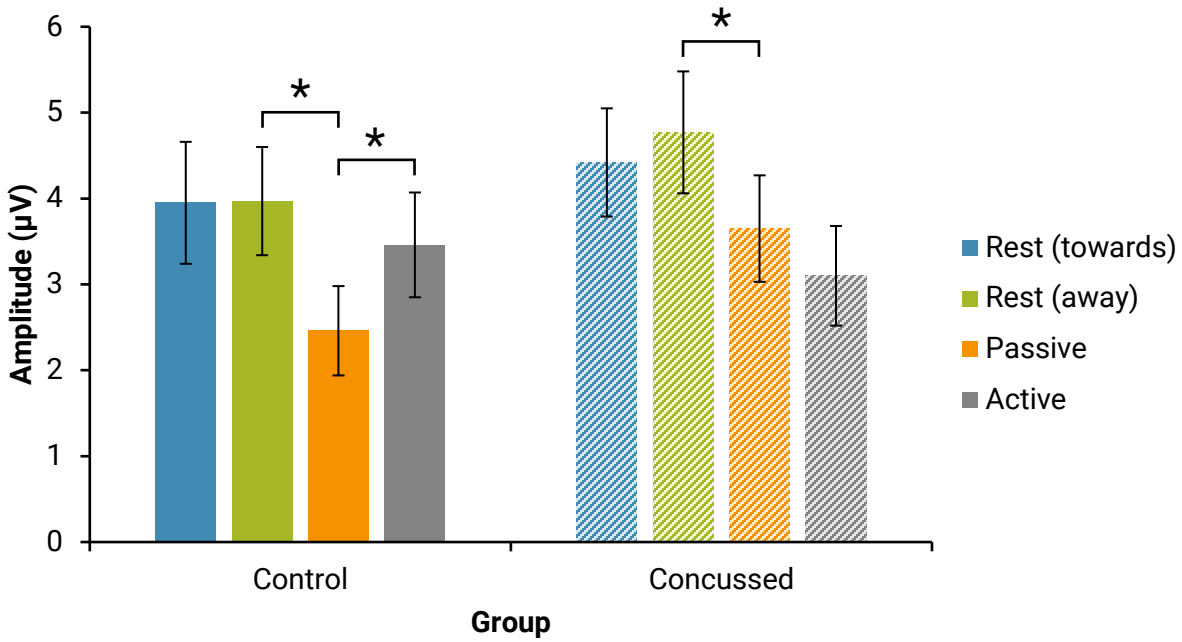

Figure 4. Mean SEP amplitudes (μV) for each condition, separated by group at the N20-P27. Recorded from electrode Cp4. Error bars represent ± 1 *SEM*. * denotes $p < .050$.

6.2.2 P50-N70. Similar to the N20-P27, a 2x4 mixed factorial ANOVA was conducted for the P50-N70 peak-to-peak potential with group as the between-subjects factor and condition as the within-subjects factor. In this analysis, both main effects and the interaction between group and condition failed to reach significance (all p's ≥ .283). Figure 5 displays the mean SEP amplitudes at this potential.

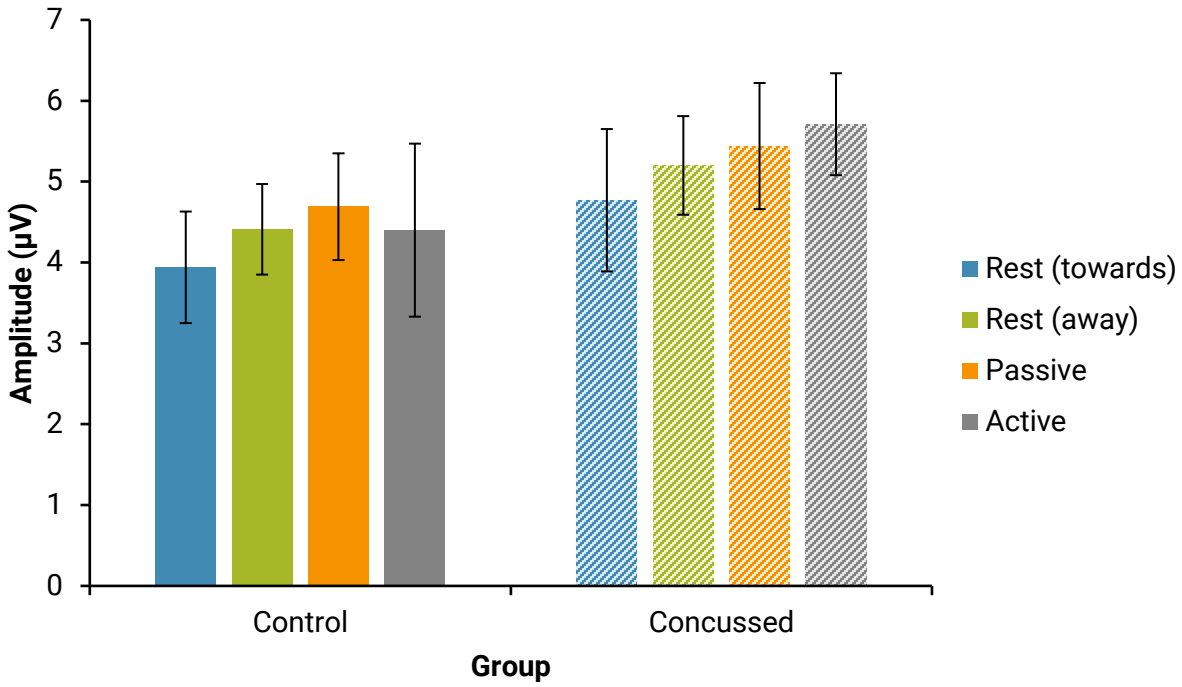

Figure 5. Mean SEP amplitudes (μV) for each condition, separated by group at the P50-N70. Recoded from electrode Cp4. Error bars represent ± 1 *SEM*.

6.2.3 N70-P100. Consistent with the previous potentials, a 2x4 mixed factorial ANOVA with group as the between-subjects factor and condition as the within-subjects factor was performed for the N70-P100. This analysis revealed a significant main effect of condition, $F(3, 74) = 4.42$, $p = .007$, and a significant interaction between group and condition, $F(3, 74) = 3.37$, $p = .023$. Figure 6 displays mean SEP amplitudes for each condition and group at this potential.

Within the control group, a one-way repeated measures ANOVA with condition as the within-subjects factor revealed no significant main effect of condition $F(3, 38) = 1.58$, $p = .210$.

Within the concussed group, a one-way repeated measures ANOVA with condition as the within-subjects factor revealed a significant main effect of condition $F(3, 36) = 6.44$, $p =$

.001. A Tukey post-hoc analysis revealed that amplitudes in the passive condition were significantly less than all other conditions, $p < .050$. No other significant differences emerged.

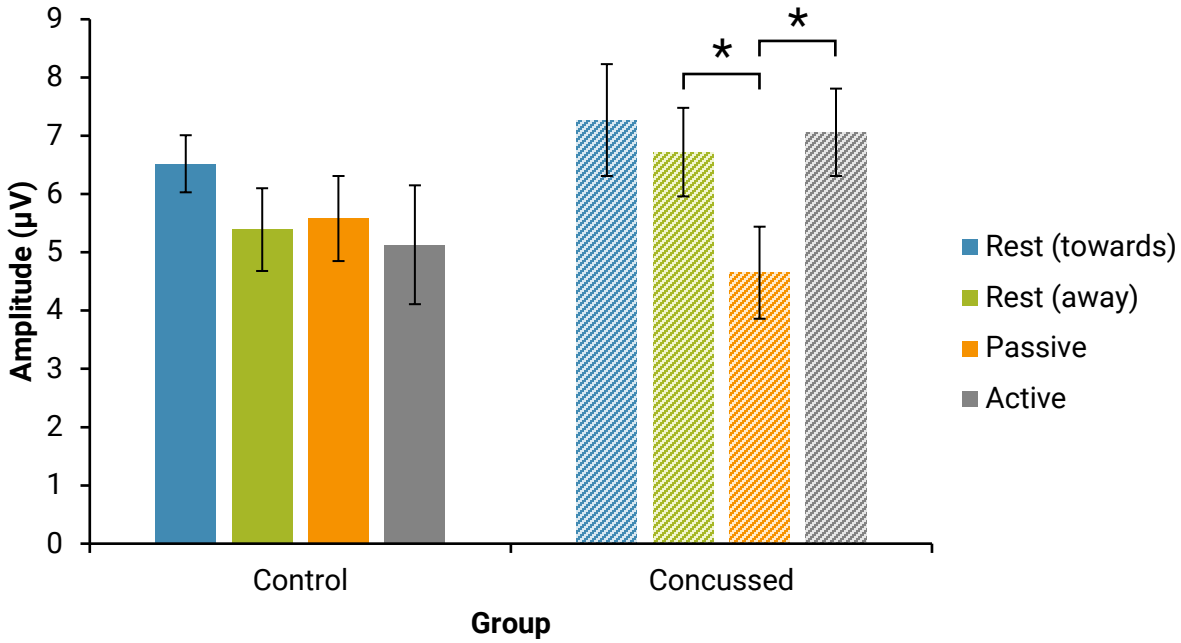

Figure 6. Mean SEP amplitudes (μV) for each condition, separated by group at the N70-P100. Recorded from electrode Cp4. Error bars represent ± 1 *SEM*. * denotes $p < .050$.

Table 2

Mean SEP Amplitudes (μV) and Standard Deviations for Each Potential, Each Group, and Each Condition

	N20-P27				P50-N70				N70-P100			
	Control		Concussed		Control		Concussed		Control		Concussed	
Condition	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
Rest (towards)	3.95	2.55	4.42	2.26	3.94	2.60	4.77	3.19	6.52	1.85	7.27	3.45
Rest (away)	3.97	2.26	4.77	2.55	4.41	2.09	5.20	2.21	5.39	2.65	6.72	2.76
Passive	2.46	1.88	3.65	2.22	4.69	2.46	5.44	2.81	5.58	2.74	4.65	2.83
Active	3.46	2.10	3.10	2.09	4.40	3.87	5.71	2.27	5.13	3.67	7.06	2.69

Note. SD = standard deviation.

6.3 SEP Latency Analysis

Separate 2x4 mixed factorial ANOVAs (DV: SEP latency in ms) were conducted for each potential (N20, P27, P50, N70, P100) with group (control, concussed) as the between-subjects factor and condition (rest [towards], rest [away], passive, active) as the within-subjects factor. No significant main effects or interactions emerged from these analyses (all p's ≥ .199).

6.4 Behavioural Analyses

Mean behavioural scores, separated by group and block can be seen in Figure 7 and Table 3. An independent samples t-test revealed no significant difference in overall behavioural performance (RMSE) between the control and concussed groups, $t(26) = 0.21$, $p = .835$. A post-hoc analysis on the difference scores between block one and block seven demonstrated a significantly greater improvement in performance within the concussed group relative to controls, $t(26) = 2.29$, $p = .031$.

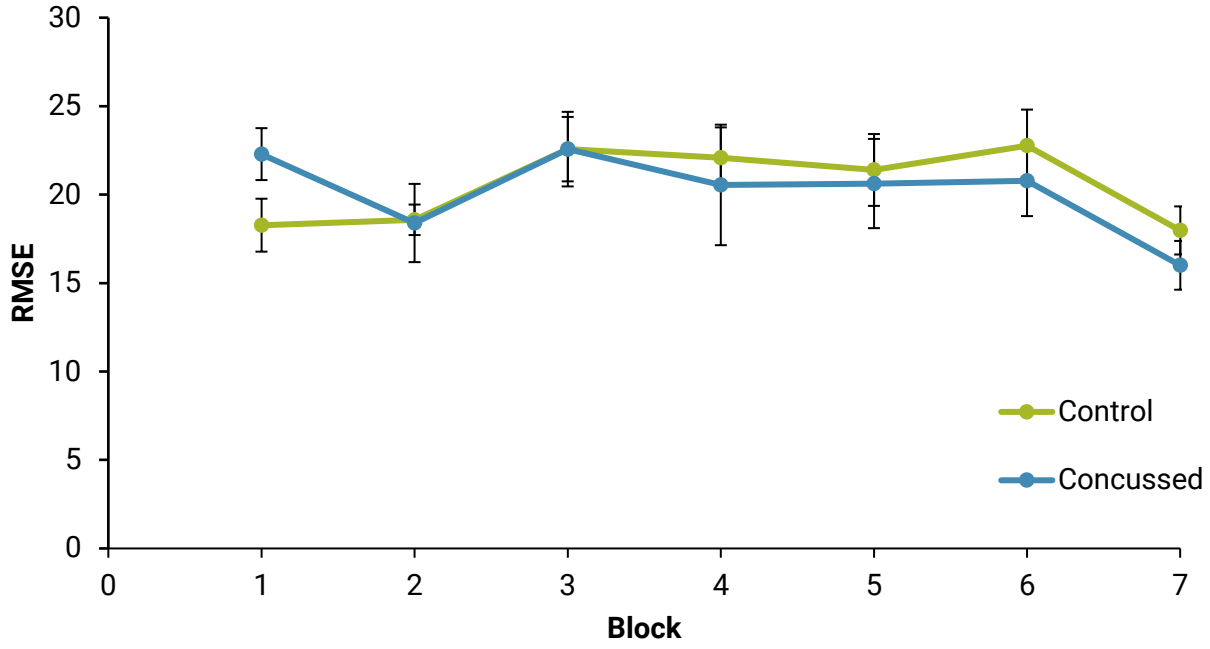

Figure 7. Mean RMSE values for each block, separated by group. Error bars represent ± 1 *SEM*.

Table 3
Mean Behavioural Scores (RMSE) and Standard Deviations for Each Group and Each Block

	Control		Concussed	
Block	Mean	*SD*	Mean	*SD*
1	18.27	5.60	22.29	5.49
2	18.58	3.22	18.39	8.27
3	22.57	7.89	22.57	6.81
4	22.08	6.42	20.55	12.74
5	21.39	7.60	20.63	9.44
6	22.76	7.64	20.78	7.47
7	17.97	5.09	16.00	5.16
Overall	20.52	3.22	20.17	5.22

Note. RMSE = root mean square error, *SD* = standard deviation.

6.5 Exploratory Analyses

Due to their exploratory nature, the analyses comparing gating efficiency and behavioural performance with concussion history characteristics are provided in Appendix B. The implications of these associations are developed more thoroughly in the discussion.

7.0 Discussion

This thesis aimed to investigate the effects of concussion on relevancy-based sensory gating at early cortical processing potentials. A total of 28 participants were recruited, comprised of 14 subjects who had previously sustained at least one medically diagnosed concussion and were no longer experiencing symptoms, as well as 14 healthy control participants with no history of head injury. Electrophysiological data was collected by measuring cortical responses in the somatosensory cortex to contralateral median nerve stimulation. The nerve stimuli served to probe the state of SI and SII under different experimental conditions designed to alter the relevancy of somatosensory feedback. The rest conditions served as a baseline, with the passive condition designed to provide non-relevant afferent information, and the active condition designed to provide relevant afferent information. Furthermore, given that the wrist movements in both the passive and active conditions were guided by the experimenter, movement-related gating would have contributed equally to both. A behavioural task, which consisted of mirroring passive wrist movements delivered by the experimenter was administered to provide a means of assessing the potential behavioural cost of impaired sensory gating.

The results of this experiment revealed that concussions have the potential to disrupt sensory gating, particularly with regard to the regulation of task-relevant afferents. Of greater concern is that concussed participants were clinically recovered and asymptomatic with an average of over 29 months since their most recent injury, suggesting these effects are long lasting.

Consistent with our hypotheses, the control group demonstrated efficient sensory gating at the N20-P27. *A priori* contrasts revealed that SEP amplitudes in the passive condition were significantly less than those at rest, as well as those in the active condition. The N20 and

P27 are potentials generated by the arrival of somatosensory information to BAs 3b and 1 within SI (Allison et al., 1991, 1989; Allison, 1982; Wood et al., 1985; Yamaguchi & Knight, 1990). Thus, these results demonstrate that the non-injured controls effectively inhibited non-relevant afferents in the passive case, in addition to facilitating the relevant sensory information in the active case. This pattern of modulation has been shown previously (Brown et al., 2015; Staines et al., 2000) and our results serve to replicate these findings. Since the N20 and P27 were the earliest cortical potentials measured, it remains uncertain exactly where the inhibition of non-relevant information occurred. Past research however, suggests that the PFC is specifically involved in this process via inhibitory connections with both the thalamus (Cao et al., 2008; Pandya & Barnes, 1987; Skinner & Yingling, 1976, 1977) and the somatosensory cortex (Jones et al., 1978; Pandya & Barnes, 1987; Vogt & Pandya, 1978; Yamaguchi & Knight, 1990).

The concussed group also demonstrated results consistent with our hypotheses at the N20-P27. Here, an *a priori* contrast revealed significantly decreased amplitudes in the passive condition relative to rest, indicating efficient gating of non-relevant sensory afferents. However, no significant difference between the passive and active conditions indicates a potential impairment in the selective facilitation of relevant sensory information at the earliest level of modality-specific somatosensory processing. The PFC has been the subject of an abundance of concussion research, which has consistently demonstrated both cognitive and neurophysiological disruptions as a result of head injuries (Belanger et al., 2010; Belanger & Vanderploeg, 2005; Broglio et al., 2011; Churchill et al., 2016; Dimou & Lagopoulos, 2014; Shinet al., 2017). Given the role of the PFC in sensory gating, specifically with regard to the upregulation of relevant sensory information (Brown et al., 2015; Staines et al., 2000), this finding supports the notion that concussions may be particularly detrimental to PFC function.

Despite impairments in the gating process at the N20-P27, the concussed group did demonstrate effective regulation of sensory information at the N70-P100. Post-hoc analyses revealed significantly reduced SEP amplitudes in the passive case relative to both rest and active. Thus, concussed participants demonstrated the same modulation pattern at the N70-P100 as control participants demonstrated earlier at the N20-P27. Given that concussed participants did demonstrate effective gating of non-relevant afferents at the N20-P27, this suggests that concussions may specifically affect the PFCs ability to release sensory inhibition in the early stages of processing relevant information. However, this upregulation was present at later processing stages (N70-P100), suggesting a delay rather than an absence of this ability. The notion of delayed sensory gating has been discussed previously within the literature. Gaetz & Weinberg (2000) demonstrated a prolonged visual P1 latency in response to a reversing checkerboard paradigm for previously concussed participants relative to controls. In their review, Broglio et al. (2011) interpreted this finding to suggest the possibility of a delay in sensory gating and preferential attention processes, although the authors did not elaborate on this interpretation. Despite the lack of group differences in the mean latency of any potentials in the current investigation, the evidence still supports a delay in the appropriate modulation of somatosensory information post-concussion.

The exact mechanism driving these changes remains uncertain. Previous research has shown that attention is specifically affected by concussions (Belanger et al., 2005, 2010; Frencham et al., 2005; Rohling et al., 2011; Zakzanis et al., 1999), presenting the possibility of delays in the ability to decipher relevant versus non-relevant sensory information. Given that the output of the PFC is generally inhibitory (Miller & Cohen, 2001), the default response may be to vastly inhibit large amounts of incoming information until the specific relevancy can be determined. This may explain why SEP amplitudes for the concussed group in both the passive

and active conditions were similarly inhibited at the N20-P27, and the specific disinhibition of task-relevant information in the active condition was not apparent until the N70-P100. Another possibility is that the concussive effects may reflect a down-regulation of cortical activity in the PFC. A previous study by Brown et al. (2015) measured peak-to-peak N20-P27 amplitudes in neurologically intact participants before and after cTBS was applied to the DLPFC. A similar modulation pattern was present in their pre-stimulation group as control participants in the current investigation. Furthermore, their post-stimulation effects showed a strikingly similar pattern of disruption to sensory gating as the concussed group in the current study. Given that cTBS results in a transient down-regulation of cortical activity in the targeted area, it is plausible that concussions may result in similar effects, albeit for a much longer period of time. Long-term CBF reductions have been shown in frontal brain regions following concussion (Churchill et al., 2016), which could play a potential role in this down-regulation. However, this hypothesis does not account for the later gating modulation observed in the concussed group at the N70-P100. One possible mechanism to account for this is that concussions may differentially affect PFC output pathways. Research using MRS has demonstrated decreased concentrations of NAA in the frontal lobes following concussion. Reduced NAA has been suggested to reflect myelin repair, supporting the notion of damaged white-matter tracts following these types of injuries (Dimou & Lagopoulos, 2014). Furthermore, DTI research has consistently found white-matter decrements following concussion (Chong & Schwedt, 2015; Eierud et al., 2014; Williams & Danan, 2016). The N20 and P27 are generated by the arrival of afferent information to SI, while the N70 is generated by later SI-related processing (Allison et al., 1991, 1989; Yamaguchi & Knight, 1990). Furthermore, the P100 is unique in that its generator is located in SII (Allison et al., 1989; Allison et al., 1992; Desmedt & Tomberg, 1989; Hamalainen et al., 1990). Therefore, it remains possible that PFC pathways

specifically targeting the sources generating the N20 and P27 could be affected to a greater extent than those reaching the N70 and P100. However, the current evidence using the available techniques to assess this hypothesis is mixed, and research has yet to reveal differentially affected PFC pathways. Further research is necessary to identify the specific mechanism or collection of mechanisms responsible for these effects.

Regardless of the mechanism, it is likely that the prolonged relevancy modulations post-concussion reflect an adaptation to the injury. The concussed group demonstrated an impaired ability to upregulate relevant sensory information upon arrival to SI. This process is critical for extracting and integrating the appropriate sensory information while completing a task. Although delayed, this relevancy-based upregulation was preserved, occurring later at the N70-P100. The behavioural task employed in this investigation required participants to integrate somatosensory feedback generated by experimenter induced passive wrist movements, in order to mirror those movements with the opposite limb. The results from this task suggest that the adaptation following concussion may come with some initial cost, but is generally effective in maintaining performance. Overall RMSE values were not statistically different between groups, indicating that control and concussed participants completed the task with a similar degree of accuracy. However, a follow-up analysis revealed that the difference between the first and last block was larger for concussed participants than controls. As seen in Figure 7, the concussed group had worse performance on the first block, but maintained similar performance to controls on the remaining blocks. The delayed upregulation of relevant information following concussion may be responsible for the initial discrepancy in performance at block one. However, this adaptation was capable of quickly adapting to a similar level of performance observed in controls for the remaining blocks.

7.1 Exploratory Analyses

The effect of attention during the delivery of SEPs at rest has not been explored in previous research. This was of concern, given that participants are often given no explicit instructions during rest conditions, other than not moving the effector of interest, and attention may be self-directed. However, the analyses employed in this investigation suggest that specifically directing attention towards or away from the stimuli do not result in significantly different SEP amplitudes during rest at any potentials measured. Therefore, it does not appear necessary to provide explicit attentional instructions in these conditions.

Despite lacking the necessary power to conduct correlational analyses, visual inspection yielded several trends within the concussed group. A series of scatterplots were generated which compare concussion history characteristics with overall behavioural scores and a proxy measure for gating efficiency (determined by subtracting passive amplitudes from active amplitudes) at the N20-P27 and N70-P100 for individual participants. A line of best fit is provided for each dataset using the least squares method. These plots are provided in Appendix B.

When comparing the number of reported medically diagnosed concussions to gating efficiency at the N20-P27, a negative trend emerged (Figure B1). That is, the greater the number of concussions sustained, the worse gating performance appears to be. When compared to gating at the N70-P100 (Figure B2), as well as behavioural performance (Figure B3), there appeared to be little association with the number of previous concussions.

Similar plots were generated for loss of consciousness following head injury. As Figure B4 depicts, there appeared to be no association between losing consciousness and N20-P27 gating efficiency. However, Figure B5 demonstrates that there may be a slight negative relation between losing consciousness and the ability to gate information at the N70-P100. Critically,

when compared to behavioural performance (Figure B6), losing consciousness appears to be specifically detrimental to task performance. This association was followed up with an independent samples *t*-test, which revealed a statistically significant difference, $t(11) = 2.18$, $p = .051$.

Finally, recovery time since the most recent concussion was also evaluated. Figures B7 and B8 show recovery time plotted against gating efficiency at the N20-P27 and N70-P100 respectively. Both plots show the same slight trend towards improved gating performance with longer recovery times. This is supported by a comparison with overall behavioural performance (Figure B9), which also indicates improvement with longer recovery time. Together, these trends suggest the possibility of recovering gating functionality and its' associated behavioural consequences over time.

Although no concrete conclusions can be discerned from these plots, the trends observed generally support the notion that sensory gating is enhanced at the N70-P100 post-concussion to compensate for decrements in gating abilities at the N20-P27, and that this adaptation may be capable of preserving function on tasks involving the integration of somatosensory feedback. Additional research with larger samples is required to more completely characterize these associations.

7.2 Limitations

There are several limitations from this investigation that should be considered when interpreting the findings. For example, changes in SEP amplitude as a result of positional changes of the electrode used to stimulate the median nerve cannot be ruled out. However, the experimental setup used in the current investigation was modeled after the one employed by Brown et al. (2015), who monitored M-wave activity following stimulation using EMG and

found that the movements induced during the experiment did not significantly change the muscular response to the stimulation. Since the diameter of efferent nerve fibres are approximately the same size as the large-diameter fibres transmitting the afferent signal, this method can provide useful information with regard to changes in stimulation intensity. Furthermore, in the current study, participants' APB twitches were visually monitored throughout the collection to ensure stimulation at motor threshold was maintained.

The peak-to-peak approach to measuring SEP amplitudes also has its limitations. The strength of this approach is that the effect of a shift relative to baseline caused by a preceding potential is largely eliminated. However, the major disadvantage of this approach is that it precludes the ability to isolate specific potentials and confidently determine if one is driving an effect more than the other. In this case, the benefits were thought to outweigh the costs.

Another limitation comes from using nerve stimulation in general. The purpose of artificially stimulating the median nerve was to measure sensory gating at very early cortical potentials (N20-P27) which are not evoked to the same degree with natural stimuli. Although this method served as a means to probe the somatosensory cortex at these early processing stages, direct nerve stimulation is not encountered in day-to-day life and serves to reduce the external validity of this investigation.

The behavioural task employed in this study aimed to identify the potential post-concussive consequences of altered sensory gating. Although the efficient gathering of appropriate sensory information is a necessary process to accurately complete the task, other neural processes are likely to contribute to performance. Specifically, working memory, which has consistently shown post-concussive deficits, would be critically involved and may have contributed to the behavioural results obtained.

Finally, this study aimed to identify the effect of concussion on relevancy-based gating. Previous research largely supports the role of the PFC in moderating these effects, however concussions represent very diffuse injuries, affecting various brain structures and pathways. Due to the nature of these injuries, it is not possible to rule out other concussion-related deficits that could be contributing to the obtained results. For example, the thalamus (particularly the thalamic reticular nucleus) in addition to modality specific cortical regions also play a role in the gating process and may also experience damage from head injuries.

7.3 Future Directions

There are several avenues for future research to pursue based on the findings of this investigation. As discussed in the limitations, the contribution of the thalamus to the altered gating pattern observed in the concussed group is uncertain. A thalamo-cortical potential can be generated using SEPs (component P14), however a large stimulus artifact in the present study precluded the ability to detect this peak. Future experiments aimed at identifying the involvement of the thalamus to altered post-concussive gating may strengthen our understanding of prefrontal gating, or potentially uncover other contributing mechanisms to this effect.

The results suggest there may be behavioural consequences to the altered gating pattern observed post-concussion. However, directly comparing SEP amplitudes to performance on each block of the task was not possible due to the small number of stimuli delivered per block. Future research could attempt to more closely examine the link between neural activity and behaviour in this context, including whether sensory discrimination training can improve gating function. The task employed in the current study also lacks considerable external validity. Research using more ecologically valid tasks that mirror

experiences encountered in daily life may further elucidate the true cost of these disruptions, and may potentially lead to clinical recovery strategies for concussion patients.

On the topic of recovery, the data presented in Appendix B suggests a trend towards improvement of both sensory gating and behavioural decrements with longer recovery time. Further investigation of this trend with larger samples is warranted and may identify whether sensory gating function can eventually return to the level of non-injured controls. Another potential avenue is to study concussion patients who are experiencing persistent symptoms, as sensory gating disruptions may be worse in this population and at least partially account for this phenomenon.

Finally, more research is necessary to elucidate the injury mechanisms leading to the observed results. Although it is hypothesized that the PFC is involved, the exact underpinnings are unclear. Future research targeted at post-concussive changes to the PFC and the pathways leading to the thalamus and somatosensory cortex that produce relevancy-based gating is necessary. Neurophysiological techniques are continually becoming more sensitive at detecting post-concussive changes in the brain and are furthering our understanding of the mechanics of these injuries. Specifically, neurotransmitter systems such as GABA and glutamate within the PFC could be targeted using MRS, or specific output pathways probed using DTI. Furthermore, EEG could be used to test other sensory systems in greater depth, particularly the visual modality, which is heavily relied upon in daily life and may present greater functional consequences following a concussion.

8.0 Conclusion

This thesis aimed to quantify the effects of concussion on sensory gating. Specifically, early somatosensory processing potentials were measured using median nerve SEPs during passive wrist movements. Task instructions altered the relevancy of somatosensory feedback generated by the wrist movements, providing a means to assess relevancy-based sensory gating. A wrist movement tracking task was employed to gain insight into the relationship between electrophysiological measures of gating and behaviour.

The results suggest that concussions have the ability to affect the processing of relevant sensory feedback. Generated by the arrival of information to SI, the N20-P27 peak-to-peak measure demonstrated that concussed participants were unable to upregulate relevant somatosensory information in the same fashion as non-injured controls. This ability was not completely absent however, as the concussed group showed the appropriate modulation pattern at the N70-P100, which is generated via later processing in SI and SII respectively. Thus, it appears the facilitation of specifically relevant information is delayed post-concussion, and may reflect an adaptation to the earlier dysfunction caused by the brain injury. The behavioural component of the experiment revealed a potential initial cost to sensorimotor performance; however, this cost appears to be relatively small and short lived.

This area of research remains underdeveloped and several potential avenues for future work exist. The precise injury mechanisms contributing to these effects are currently unknown. Furthermore, the relationship between electrophysiological markers of dysfunctional sensory gating and its subsequent behavioural impact should be further elucidated.

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Appendix A

Modified University of Waterloo Health History Questionnaire

Participant ID_____M/F
Age_____

1. Aside from concussion, have you been diagnosed with any other neurological conditions (ADHD, depression, anxiety, etc.)?
a) _____yes _____no
b) If yes, please list:
_____

2. Have you sustained nerve damage to either of your upper limbs:
a) In the past 6 months?
_____yes _____no
b) That resulted in permanent damage?
_____yes _____no

3. At what age did you begin playing organized sport? _____

4. How many years have you played your sport? _____

5. Do you wear a mouth guard while playing?
_____yes _____no

If yes, what kind?
_____stock _____boil & bite
_____custom, front teeth _____custom, all

6. Have you suffered from neck pain within the past 6 months? _____yes _____no

7. Have you suffered a concussion?
_____yes _____no _____not sure

8. If yes to #7,
   a) How many times total? _____
   b) How many were clinically diagnosed?
   _____
   c) How many while playing sport in the past 6 months? _____
   d) Date of last concussion? _____
   e) Have you been clinically cleared to return to full physical and cognitive activity since the most recent concussion? _____yes _____no

Date_____
Sport/Position_____

   f) How long did symptoms last (for most recent concussion)?
   _____ 1-3 days _____ 4-7days
   _____ 8-10 days _____ 11-14 days
   _____ more than 14 days
   g) After the most recent concussion, how long did you refrain from physical activity?
   _____ 1-3 days _____ 4-7 days
   _____ 8-10 days _____ 11-14 days
   _____ more than 14 days

9. Have you ever been knocked unconscious?
_____yes _____no

10. If yes to #9,
    a) How many times in the past 6 months? _____
    b) What is the longest duration you've been knocked unconscious? _____

11. In the past 6 months, after being hit in the head in, have you experienced any of the following symptoms?
_____ confusion _____getting 'dinged'
_____headaches _____balance problems
_____nausea _____getting 'bell rung'
_____dizziness _____ringing in ears
_____blurry vision _____poor memory
_____other: _____

12. In regards, to how you feel NOW, please rate the following:

	None			Mild			Severe
Headache	0	1	2	3	4	5	6
"Pressure in head"	0	1	2	3	4	5	6
Neck pain	0	1	2	3	4	5	6
Nausea/vomiting	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6
Blurred vision	0	1	2	3	4	5	6
Balance problems	0	1	2	3	4	5	6
Sensitivity to light	0	1	2	3	4	5	6
Sensitivity to noise	0	1	2	3	4	5	6
Feeling slowed down	0	1	2	3	4	5	6
"Don't feel right"	0	1	2	3	4	5	6
Hard to concentrate	0	1	2	3	4	5	6
Feeling "in a fog"	0	1	2	3	4	5	6
Trouble remembering	0	1	2	3	4	5	6
Fatigue/low energy	0	1	2	3	4	5	6
Confusion	0	1	2	3	4	5	6
Drowsiness	0	1	2	3	4	5	6
Trouble falling asleep	0	1	2	3	4	5	6
More emotional	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Nervous/anxious	0	1	2	3	4	5	6

13. Do the above symptoms get worse with physical activity? _____yes _____no

14. Do the above symptoms get worse with mental activity? _____yes _____no

Appendix B

Exploratory Analyses

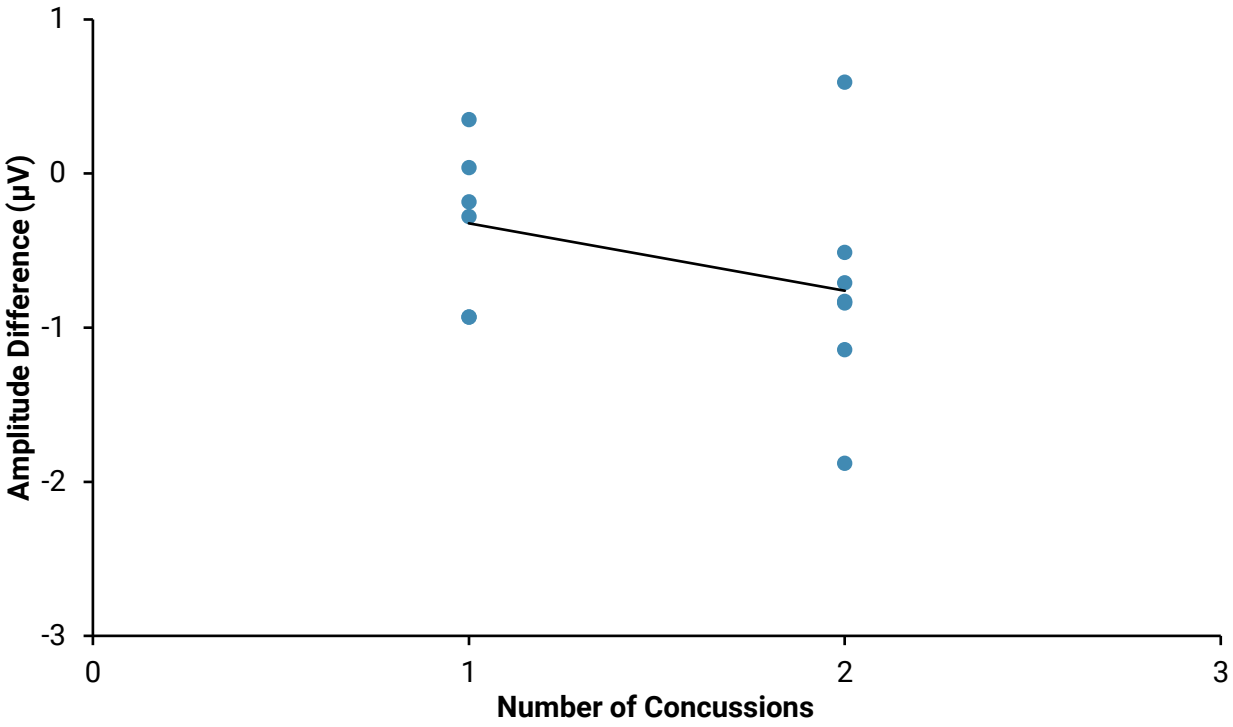

Figure B1. Amplitude difference between passive and active conditions at N20-P27 in the concussed group, by number of medically diagnosed concussions. Line of best fit $R^2 = .117$. SEPs measured from electrode Cp4.

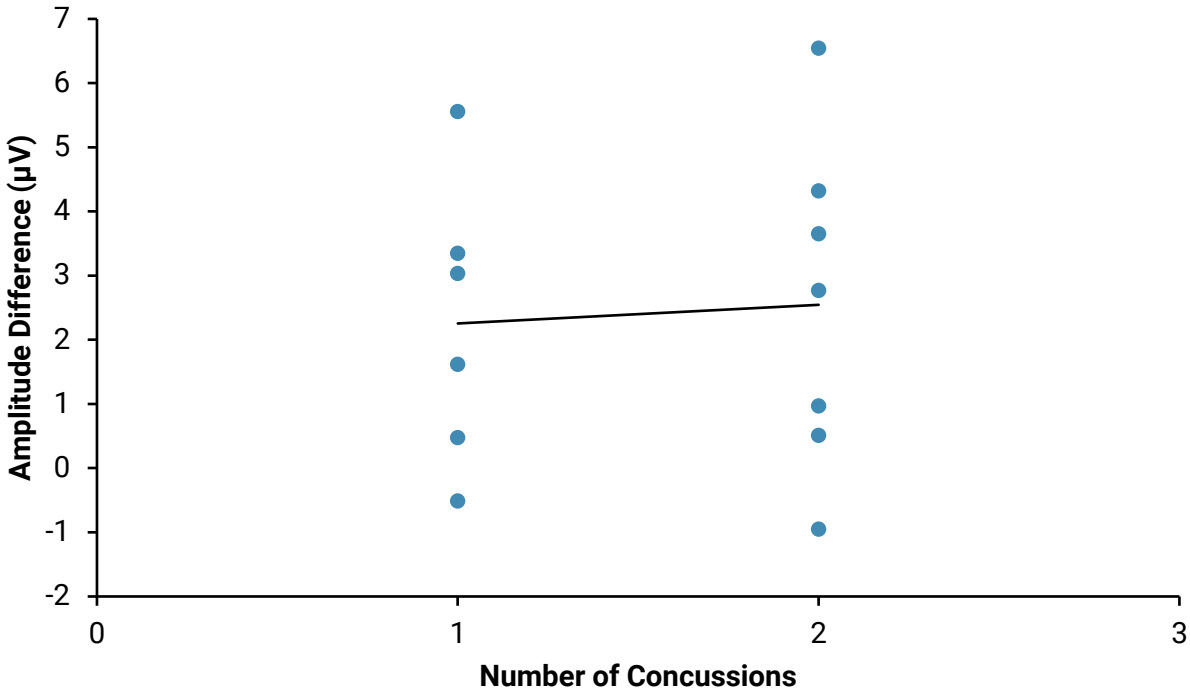

Figure B2. Amplitude difference between passive and active conditions at N70-P100 in the concussed group, by number of medically diagnosed concussions. Line of best fit $R^2 = .001$. SEPs measured from electrode Cp4.

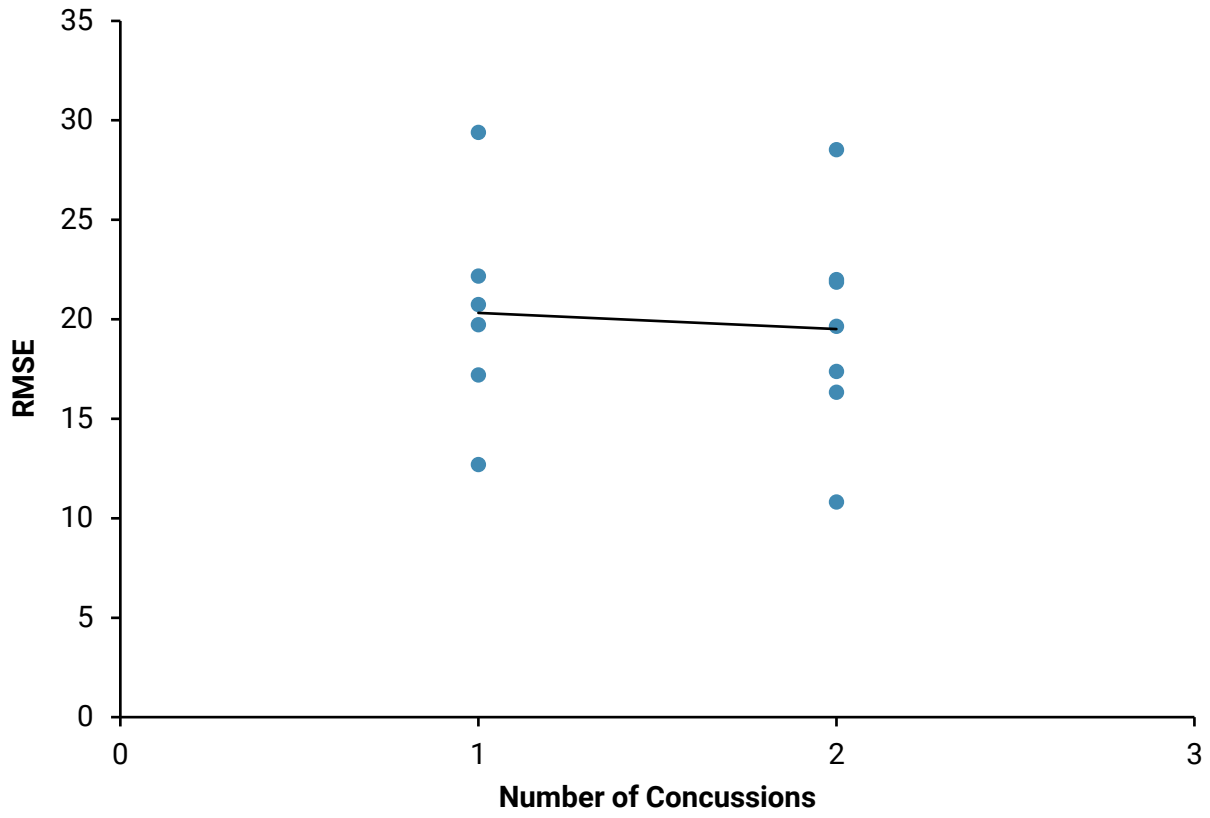

Figure B3. Behavioural performance (RMSE) in the concussed group, by number of medically diagnosed concussions. Line of best fit R^2 = .006. RMSE = root mean square error.

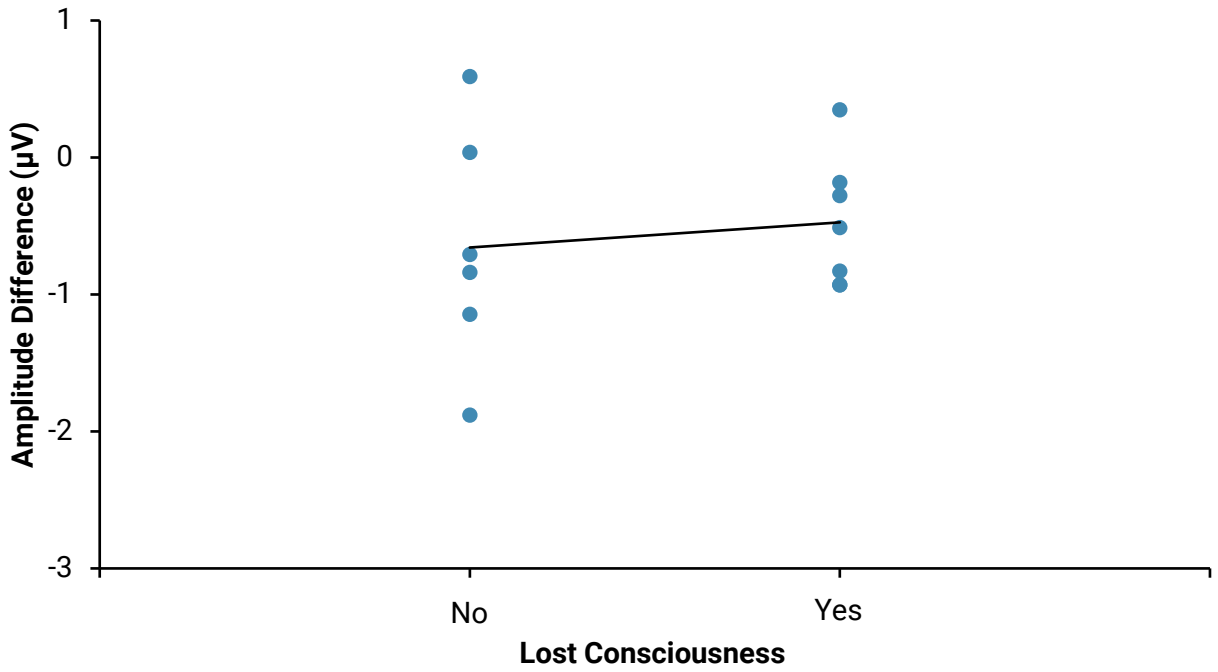

Figure B4. Amplitude difference between passive and active conditions at N20-P27 in the concussed group, by loss of consciousness following head injury. Line of best fit $R^2 = .021$. SEPs measured from electrode Cp4.

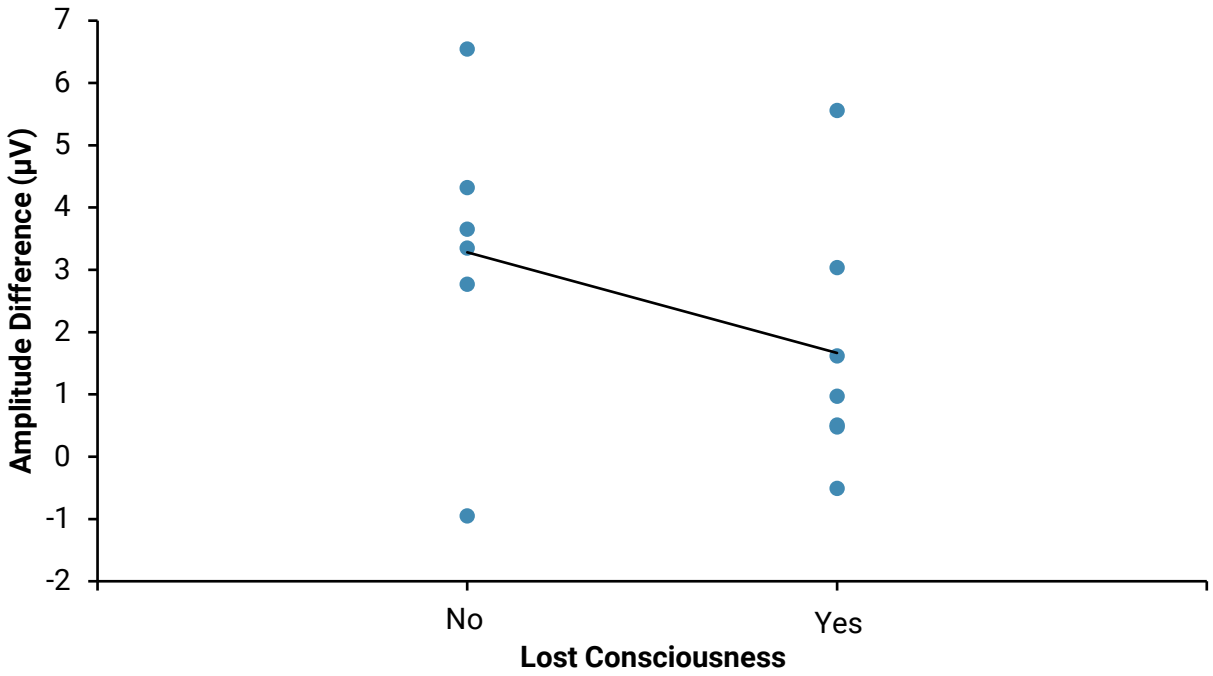

Figure B5. Amplitude difference between passive and active conditions at N70-P100 in the concussed group, by loss of consciousness following head injury. Line of best fit $R^2 = .133$. SEPs measured from electrode Cp4.

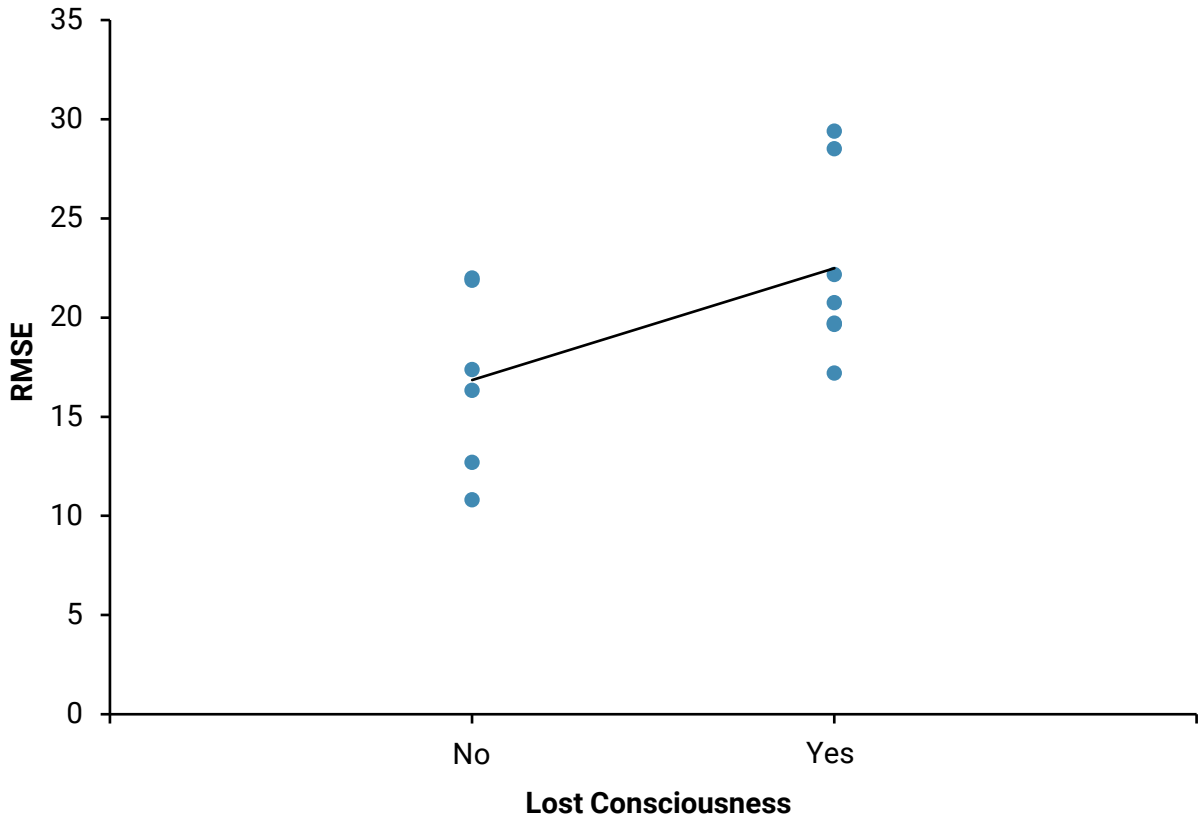

Figure B6. Behavioural performance (RMSE) in the concussed group, by loss of consciousness following head injury. Line of best fit R^2 = .303. RMSE = root mean square error.

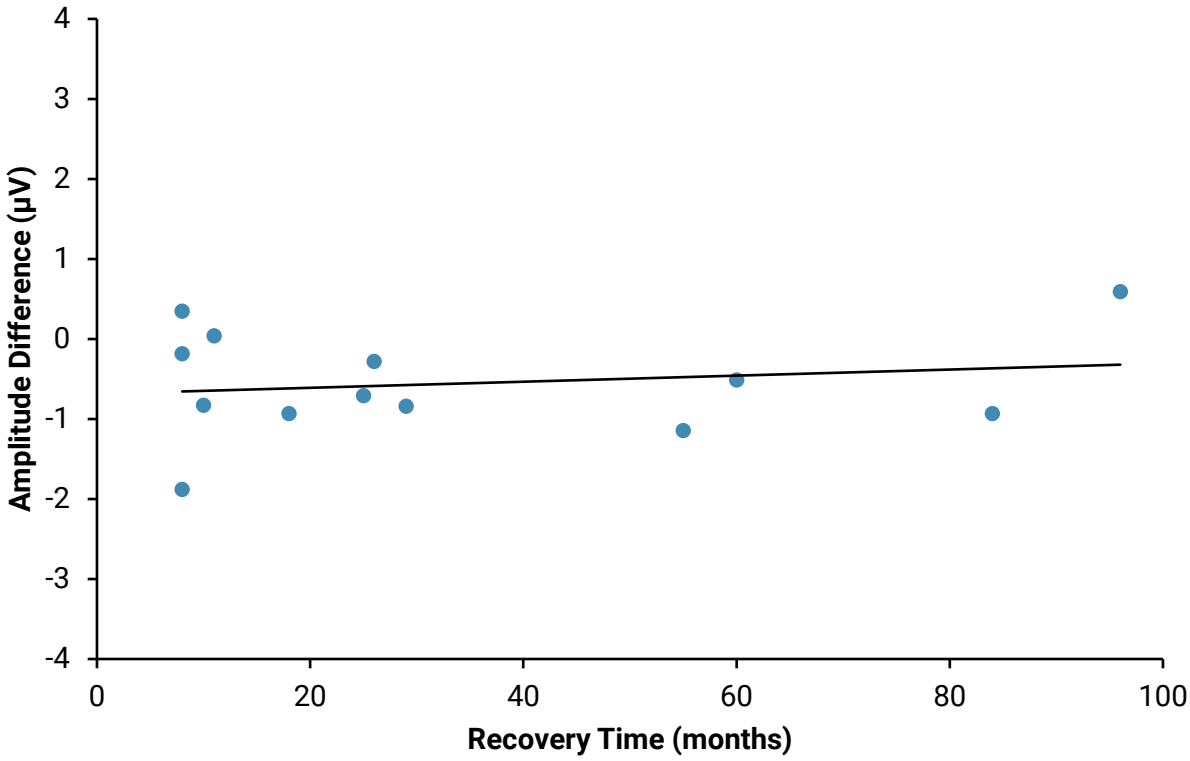

Figure B7. Amplitude difference between passive and active conditions at N20-P27 in the concussed group, by recovery time in months. Line of best fit $R^2 = .030$. SEPs measured from electrode Cp4.

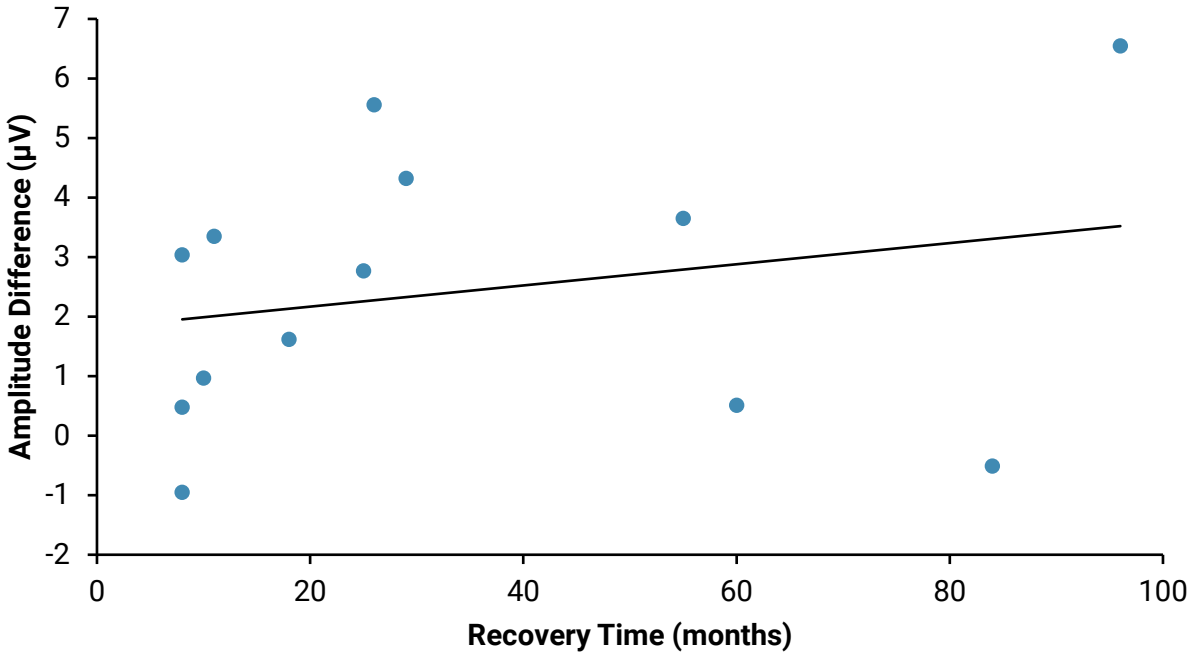

Figure B8. Amplitude difference between passive and active conditions at N70-P100 in the concussed group, by recovery time in months. Line of best fit R^2 = .055. SEPs measured from electrode Cp4.

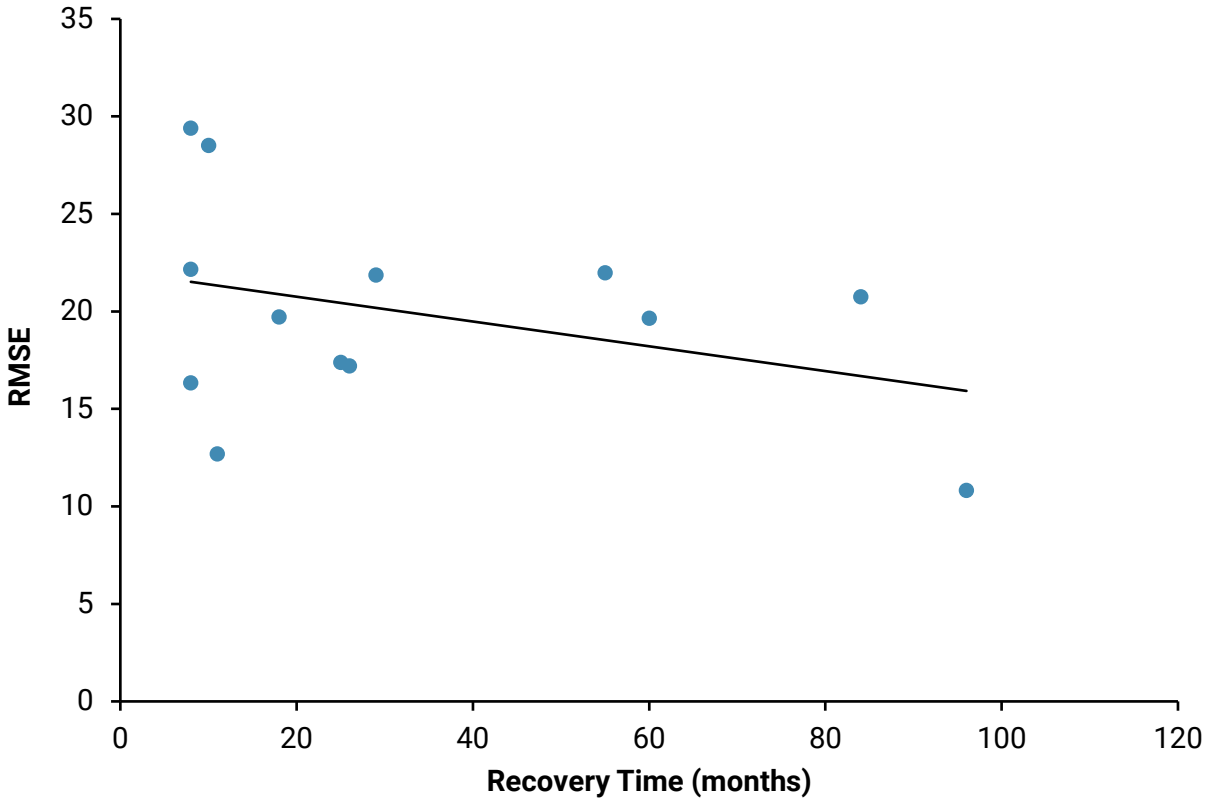

Figure B9. Behavioural performance (RMSE) in the concussed group by recovery time in months. Line of best fit $R^2 = .131$.