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Task-dependent Modulation of Cortical Excitability and Balance Control in Individuals with Post-concussion Syndrome

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TASK-DEPENDENT MODULATION OF CORTICAL EXCITABILITY AND BALANCE CONTROL IN INDIVIDUALS WITH POST-CONCUSSION SYNDROME

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Abbreviations

AP: anterior-posterior

BOS: base of support

COM: centre of mass

COP: centre of pressure

CSP: cortical silent period

EMG: electromyography

FDI: first dorsal interosseous

GABA: gamma-aminobutyric acid

ICF: intracortical facilitation

ISI: inter-stimulus interval

LICI: long-interval intracortical inhibition

M1:   primary motor cortex

MEP: motor evoked potential

ML: medial-lateral

mTBI: mild traumatic brain injury

MVC: maximal voluntary contraction

PCS: post-concussion syndrome

SICI: short-interval intracortical inhibition

TMS: transcranial magnetic stimulation

TS: test stimulus

Abstract

      In most cases, symptoms resolve between 7-10 days post-concussion. However, in 10-15% of the concussed population, symptoms can remain unresolved for months to years following the head injury. The purpose of this thesis was two-fold, and was broken up into two studies, where the same individuals participated in both studies. The purpose of the first study was to quantify the differences in balance control between individuals with PCS (i.e., had been experiencing symptoms for <30 days) and non-concussed individuals during a lower-limb reaching task. Participants completed a static balance assessment before and after a lower-limb reaching task, which incorporated a Go/No-Go paradigm. Results from this study revealed no differences in the static stability assessments, however, individuals with PCS demonstrated increased medial-lateral COP displacement as well as greater trunk pitch during the reaching task. Overall, the findings reveal persistent balance impairments in individuals with PCS, which may put this population at an increased risk of further injury. The purpose of the second study was to assess task-dependent modulation of cortical excitability prior to planned index finger abduction contractions comparing a non-concussed population to a population with PCS. The protocol in this study consisted of both single and paired-pulse transcranial magnetic stimulation (TMS) which was applied prior to the beginning of 3 different tasks (i.e., a rest condition with no plan to contract, a precision contraction, and a powerful contraction). In addition to the three tasks, participants also had to respond to a Go/No-Go cue. The results of this study revealed an increase in excitability prior to a precision contraction in both non-concussed and PCS groups.

No differences in task-dependent modulation were found between the two groups with respect to intracortical facilitation and inhibition, however a negative correlation between number of symptoms reported (SCAT3 symptom evaluation) and intracortical facilitation was revealed. The increase in corticospinal excitability prior to a precision contraction was not explained by the two cortical mechanisms we assessed and may therefore be due to spinal modulation or a different cortical mechanism. Overall, based on the results from this thesis, it appears that individuals with PCS have balance impairments, which may be a result of an inability to maximally activate their postural muscles. Furthermore, it appears that those individuals who reported a higher number of symptoms had greater reductions in intracortical facilitation, likely reflecting the heterogeneity of this clinical group.

Introduction

A concussion is a brain injury induced by biomechanical forces, resulting in a complex pathophysiological process affecting the brain (McCrory et al., 2013). While clinical symptoms arise following a concussion, it does not have to involve loss of consciousness. Symptoms that may present post-concussion include, physical, somatic and cognitive deficits, behavioural changes, and sleep disturbances. In most cases symptoms resolve between 7-10 days following the concussion, however, in some cases symptoms persist beyond this time frame (McCrory et al., 2013). Post-concussion syndrome (PCS) is the term used when symptoms remain unresolved for months to years following concussion (Ryan & Warden, 2003). However, the development of PCS appears to be dependent on a combination of factors, including pre-injury and post-injury neuropathological and psychological factors (Daneshvar et al., 2011; Ryan & Warden, 2003). While symptoms arise in the somatic, cognitive, and emotional domains, deficits in balance control and motor control have also been revealed post-concussion.

Previous research has demonstrated balance impairments 2 days post-concussion, as well as at return-to-play stage 6, and 30 days post-concussion when athletes reported an abatement of symptoms (Guskiewicz, Perrin, & Gansneder, 1996; Powers, Kalmar, & Cinelli, 2014b; S Slobounov, Slobounov, & Newell, 2006). These studies suggest that balance impairments were a result of sensorimotor integration deficits within individuals with a history of concussion. Furthermore, visuomotor and neurocognitive deficits have been revealed up to one year post-concussion (Bohnen, Jolles, Twijnstra, Mellink, & Wijnen, 1995; Collins et al., 1999;

Heitger et al., 2006), however, few studies have investigated visually controlled movement and balance control using the lower limbs in a PCS population. In addition to balance impairments, deficits in motor control and cortical excitability have been established in a concussed population. However, limited research has been conducted investigating balance control and cortical excitability in a PCS population.

The activation and inhibition of the pyramidal tract begins during the preparation period of voluntary movement, such that the muscle activation required to perform a task is set prior to movement (Hoshiyama et al., 1997). This has been established using specific paradigms in conjunction with transcranial magnetic stimulation to investigate the effect of "Go/No-Go" cues as well as task-dependent modulation on corticospinal excitability in a non-concussed population (Hasegawa, Kasai, Tsuji, & Yahagi, 2001; Hoshiyama et al., 1997; Leocani, Cohen, Wassermann, Ikoma, & Hallett, 2000; Schieppati, Trompetto, & Abbruzzese, 1996; Tinazzi et al., 2003). However it is unclear how these paradigms affect cortical excitability in a PCS population. Furthermore, cortical hypoexcitability was found to continue even after physical symptoms resolved in a recently concussed population of varsity athletes (Powers, Kalmar, et al., 2014b). However, it is unclear whether the same changes in cortical and corticospinal excitability exists in individuals with PCS.

Although there is research suggesting different reasons for the onset of PCS and the domains where symptoms exist, few studies have investigated cortical excitability and balance control as other domains, which may reveal impairments in individuals with PCS. If individuals with PCS demonstrate balance control

impairments and cortical excitability similar to recently concussed asymptomatic individuals, then it can be assumed that PCS is a continuum of the acute phase of a concussion. If not, then individuals with PCS can be considered an entire different population. Measurements of cortical excitability can provide information about the integrity of the pathway from brain to muscle, as well as networks within the brain. Assessing balance control can provide insight into the efficiency of the central nervous system to corral the centre of mass (COM) within the base of support (BOS). Therefore, the purpose of this thesis was to quantify neurophysiological and behavioural deficits relating to motor function in individuals with persistent post concussion syndrome.

Chapter 1: Review of Literature

Concussions

Mechanisms of Injury

It has been suggested that brain deformation or strain is the main cause of concussion (Zhang, Yang, & King, 2001). However, strain measurements are difficult to accomplish during impact situations and in living individuals. Therefore, alternate measurements such as head acceleration, are used to describe the mechanism of concussion. There are two primary mechanisms of head injury (Zhang et al., 2001). Translational acceleration occurs when the surface of the brain makes contact with the bony protuberances on the base of the skull (i.e., direct impacts to the head) (Graham, Adams, Nicoll, Maxwell, & Gennarelli, 1995; Zhang et al., 2001). This type of injury may be associated with a depressed fracture or deformation of the skull and is often accompanied by swelling (Graham et al., 1995). The second mechanism is rotational acceleration (i.e., inertial loading of the head), which results in rotation between the skull and brain. This injury can be caused by direct or indirect impact to the head, with the primary mechanism being shear stress (Zhang et al., 2001). Concussion generally occurs from either direct impact to the head or indirect impact to the head and neck when the body is suddenly stopped. Consequently, both translational and rotational acceleration mechanisms cause injury to the head (Zhang et al., 2001).

Pathophysiology

Deficits and symptoms associated with sustaining a concussion occur with minor changes in anatomical pathology. However, these changes usually completely

resolve over time, which suggests that the deficits can be attributed to temporary neuronal dysfunction rather than cell death (Giza & Hovda, 2001). The resulting neuronal dysfunction can be caused by ionic shifts, altered metabolism, damaged connectivity, or changes in neurotransmission (Giza & Hovda, 2001; Willer & Leddy, 2006). Immediately following a concussion, the brain enters a hypermetabolic state (Yoshino, Hovda, Kawamata, Katayama, & Becker, 1991). This is accompanied by an ionic shift of potassium and calcium, a decrease in cerebral blood flow, and an increase in the neurotransmitter, glutamate (Yoshino et al., 1991). These changes in neuronal functioning may make the brain incapable of responding appropriately to a second injury, which may lead to persistent symptoms (Giza & Hovda, 2001).

Following the initial hypermetabolic period, the brain enters a state of metabolic depression, which may last for weeks (Giza & Hovda, 2001; Willer & Leddy, 2006). This hypometabolic state is characterized by persistent calcium ion influx, resulting in impairments in mitochondrial oxidative metabolism leading to insufficient brain energy demand (Lifshitz, Sullivan, Hovda, Wieloch, & McIntosh, 2004). Additionally, increased calcium levels can signal cellular pathways that lead to death of neurons in the brain (Giza & Hovda, 2001). This pathophysiological cascade post-concussion leaves neural tissue more vulnerable to re-injury. Therefore, it has been suggested that individuals with a history of concussions are more susceptible for recurrent concussion as well as developing post concussion syndrome (PCS) (Willer & Leddy, 2006).

Post-concussion syndrome

Persistent post concussion syndrome (PCS) is one of the secondary complications of sustaining a concussion. PCS develops in 10-15% cases post-concussion (McCrory et al., 2013). The etiology of PCS has become a controversial topic based on the origin of symptoms. It is unclear whether the symptoms are a result of changes in neurophysiology and neuropathology secondary to the injury or if they are due to pre- or post-injury psychological factors (Ryan & Warden, 2003). Axonal injury following concussion may result from a delayed pathophysiological response that occurs over several hours. Therefore, this mechanism has been suggested to be responsible for the onset of PCS (Ryan & Warden, 2003). However, researchers define PCS as a condition which develops following head injury, producing deficits in three areas of central nervous system (CNS) functioning: 1) somatic, 2) psychological, and 3) cognitive (Hall, Hall, & Chapman, 2005).

Somatic deficits refer to neurological deficits, such as headaches and being easily fatigued (Hall et al., 2005). Headaches are the most common complaint, followed by dizziness, of individuals who have sustained a concussion and those who experience PCS (Lane & Arciniegas, 2002; Seifert & Evans, 2010). In the acute phase post-injury period, tension-type pain is the most common however, as time progresses, a mixture of persistent tension-type headaches with sporadic migraines can occur (Lane & Arciniegas, 2002). True diagnosis of post-traumatic headache suggests that the individual did not have a diagnosable headache disorder prior to the injury. However, if the individual had a history of headaches, an increase or worsening of the headaches after concussion is indicative of aggravating an existing

headache disorder (Lane & Arciniegas, 2002). Although posttraumatic headaches generally resolve within the first 3 months, some individuals develop chronic headaches (Seifert & Evans, 2010). These individuals with PCS report that the headaches are longer in duration and occur more often than those headaches they experienced before the head injury (Seifert & Evans, 2010).

Many individuals who sustain a concussion experience psychological deficits, including personality change, irritability, anxiety and/or depression (Hall et al., 2005). Additionally, individuals with PCS frequently report apathy, which is characterized by reduced motivation with decreased emotional, cognitive, and/or behavioural drive. Researchers have suggested that individuals with diagnosed affective disorders, generalized anxiety disorder, somatoform disorders, and personality disorder prior to head injury have a higher rate of diagnoses of PCS than those without pre-existing mental disorders (Hall et al., 2005). However, it is important to determine the concussed individual's pre- and posttraumatic levels of functioning as many affective disorders have similar symptomatology as PCS (Evans, 2010; Hall et al., 2005).

Cognitive deficits are characterized by a decreased ability to concentrate, to process information, to integrate thought processes and word-finding difficulties (Hall et al., 2005). Research has demonstrated that individuals with PCS have deficits in sustained attention tasks (Bohnen et al., 1995), tests of reasoning, information-processing speed and verbal learning (Leininger, Gramling, Farrell, Kreutzer, & Peck, 1990). However, it appears that deficits in short-term memory such as misplacing items, difficulty remembering conversations, and poor attention

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to detail, is the most common deficit observed in individuals with PCS (Hall et al., 2005).

In addition to the deficits already mentioned, other factors have been suggested to contribute to the development of PCS. Female gender appears to be associated with a higher chance of developing PCS, as women often experience more severe symptoms and take longer to recover post-concussion (Hall et al., 2005; Rutherford, Merrett, & McDonald, 1979). Societal influences, malingering, as well as compensation and litigation have also been shown to play a role in PCS (Bianchini, Curtis, & Greve, 2006; Binder & Rohling, 1996; Ferrari et al., 2001). Research has reported that the extent and length of injury in the US is greater since financial compensation is available, compared to countries where compensation is less accessible(Ferrari et al., 2001). Similarly, sociocultural factors are suggested to be associated with the onset of PCS as some countries have little or no cases of PCS despite the frequent minor head injuries associated with motor vehicle accidents (Ferrari et al., 2001). However, it is possible that the prolonged and intense symptoms due to PCS are a result of the individual being involved in litigation (Binder & Rohling, 1996). It has been suggested that the potential for financial compensation may reinforce PCS behaviour (Bianchini et al., 2006).

Cortical Excitability

Motor Pathways

The primary motor cortex is arranged somatotopically as a motor homunculus, where more resources are allocated to certain regions of the body that

require greater control of movement (Metman, Bellevich, Jones, Barber, & Streletz,

1993). The primary motor cortex is involved in controlling voluntary movement,

where it sends a signal down the corticospinal tract which inputs to the alpha motor

neuron, resulting in muscle contraction (Wilson, Thickbroom, & Mastaglia, 1993).

The lateral corticospinal tract can be studied through stimulation of the motor

cortex. Early cortical stimulation studies in cats and primates have demonstrated

the importance of investigating the pathway from cortex to muscle (Kernell & Chien-

Ping, 1967; Patton & Amassian, 1954) however, these studies used direct

stimulation of the motor cortex, making the procedures limited in their applicability

in humans due to their invasive nature (Wilson et al., 1993). Fortunately, the

development of non-invasive cortical stimulation techniques have allowed for

further investigation of the functional anatomy of the motor cortex (Wilson et al.,

1993). One technique, transcranial magnetic stimulation (TMS), targets specific

areas of the primary motor cortex in order to measure and modulate cortical

excitability (Hallett, 2000b). Measurements obtained from TMS are important in

order to understand the physiological changes in the brain associated with cortical

plasticity and brain disorders (Hallett, 2000b). This technique uses magnetic coils of

different shapes. Round coils are more powerful in comparison to figure-eight

shaped coils, which are more focal (Hallett, 2000b). To stimulate the brain, a rapid,

high-current pulse is produced in a magnetic coil, which is placed over the scalp. The

electrical current is converted to a magnetic field as it passes through the coil. The

magnetic field then passes through the scalp and induces an electric current again in

conductive tissue (i.e., electromagnetic induction). If the current is sufficient, it will

activate pyramidal (i.e., lateral corticospinal) tract neurons trans-synaptically through corticospinal volleys with indirect waves (I-waves) (Hallett, 2000b; Wilson et al., 1993). This activity is then recorded as a motor evoked potential (MEP) by surface electromyography (EMG) in the muscle of interest. The resultant MEP amplitude is affected by changes in the balance of excitatory and inhibitory synaptic inputs to the corticospinal neurons (Stinear, Barber, Coxon, Fleming, & Byblow, 2008). Furthermore, MEP amplitude is also a product of excitability and latency of the pathway downstream to the motor cortex. An increase in the number of spinal motoneurons recruited will decrease the MEP variability (Kiers, Cros, Chiappa, & Fang, 1993). The primary motor cortex (M1) is most often used for TMS studies, as the effects of stimulation are easy to quantify by measuring the size of motor evoked potentials (MEP) produced in the muscles of interest (Siebner & Rothwell, 2003).

Single-Pulse TMS

Single-pulse TMS is used to determine the excitability of the pathway between the primary motor cortex and the recording site of the muscle of interest (Auriat, Neva, Peters, Ferris, & Boyd, 2015; Rossini et al., 2015; Sharples & Kalmar, 2012). Threshold values are used to establish stimulation intensities when assessing and modulating cortical excitability. The resting motor threshold is the lowest percent of stimulator output that is needed to generate a motor-evoked potential (MEP) that has a peak-to-peak amplitude >50μV during five of ten trials while the individual is in a resting state (i.e., no plan to contract) (Auriat et al., 2015; Rossini et al., 2015; Sharples & Kalmar, 2012). In addition, the cortical silent period (CSP) can

be assessed using singe pulse TMS. The CSP is evoked while holding a slight

contraction in a contralateral muscle following the application of single-pulse TMS.

This is observable on surface EMG recordings as the absence of EMG activity

(Rossini et al., 2015; Werhahn, Kunesch, Noachtar, Benecke, & Classen, 1999). The

cortical silent period occurs following the activation of inhibitory cortical and spinal

interneurons (Werhahn et al., 1999). Therefore, single-pulse TMS also provides

information concerning inhibitory circuit activity within the corticospinal system

(Auriat et al., 2015).

Paired-Pulse TMS

Paired-pulse TMS is used to measure intracortical inhibition and facilitation

(Auriat et al., 2015; Sharples & Kalmar, 2012; Siebner & Rothwell, 2003). This

method involves applying pairs of magnetic pulses to the primary motor cortex (i.e.,

a conditioning stimulus prior to a test stimulus) and measuring the motor response

in the muscles of interest using surface EMG (Kujirai et al., 1993). The duration of

the interstimulus interval (ISI) will activate separate groups of inhibitory and

excitatory interneurons within the cortex, which can be demonstrated by the

varying MEP amplitude following stimulation (U Ziemann, Rothwell, & Ridding,

1996).

Corticospinal output is influenced by inhibitory and facilitatory intracortical

circuitry within the primary motor cortex (M1). There are two inhibitory circuits:

short-interval intracortical inhibition (SICI) and long-interval intracortical

inhibition (LICI) (Auriat et al., 2015). The two circuits differ in the time between the

two pulses (i.e., interstimulus interval) used to quantify inhibition. SICI is evoked

when two pulses, one subthreshold conditioning stimulus followed by the second

suprathreshold test stimulus, are delivered to the primary motor cortex with an

interstimulus interval between 1-6ms. The two pulses produce decreased MEP

amplitudes in comparison to a single TMS pulse (Kujirai et al., 1993). In contrast,

LICI is produced using a suprathreshold-conditioning stimulus applied before the

test stimulus with an interstimulus interval between 50-200ms (Rossini et al., 2015;

U Ziemann et al., 1996). The conditioning pulse produces a small descending

corticospinal volley, however it is insufficient to depolarize spinal motoneurons,

thus resulting in a reduction of MEP amplitude (U Ziemann et al., 1996). Synaptic

inhibition in the brain is primarily mediated by the neurotransmitter, γ-

aminobutyric acid (GABA) (Werhahn et al., 1999). GABA receptors have an

important function in the modulation of intracortical inhibition. Specifically, based

on the differences in the timing of activation of the receptor-mediated circuitry, it

has been suggested that SICI is mediated by GABA-A and LICI is mediated by GABA-

B (Rossini et al., 2015; Werhahn et al., 1999).

   In order to assess the facilitatory circuits in the primary motor cortex, the same

subthreshold conditioning stimulus and suprathreshold test stimulus protocol used

in SICI is used in ICF. The only difference is a longer interstimulus interval of 6-30ms

is used (Kujirai et al., 1993; Rossini et al., 2015). In comparison to SICI and LICI,

different neural circuitry mediates ICF. Glutamate appears to play a role in

mediating ICF (Rossini et al., 2015; Ulf Ziemann, 2004). It is important to assess the

integrity of these intracortical circuits following neurological injury.

Cortical Excitability Following a Concussion and in Post Concussion Syndrome

A variety of studies investigating cortical excitability have been conducted at various time points following a concussion. A recent study assessed the intracortical mechanisms that contribute to altered corticospinal excitability in asymptomatic varsity football players 1-4 weeks post-concussion (Powers, Cinelli, & Kalmar, 2014). This study used both single and paired-pulse TMS to assess the integrity of the corticospinal tract as well as SICI and LICI at rest. Results of the study demonstrated that hypoexcitability continues even after physical symptoms have resolved. The authors suggest that the persistence of cortical hypoexcitability may impair the ability to maximally activate muscle, possibly leading to risk of further injury (Powers, Cinelli, et al., 2014). Another study, which evaluated asymptomatic varsity football players at least 9 months after their last concussion found that sports concussions resulted in chronic subclinical motor system deficits demonstrated by an increase in duration of the cortical silent period (CSP) (De Beaumont, Lassonde, Leclerc, & Théoret, 2007). The alteration in CSP duration was enhanced when these athletes sustained successive concussions, suggesting that intracortical inhibitory interneurons in the primary motor cortex may be negatively affected by sports concussions (De Beaumont et al., 2007). In agreement with previous studies, varsity athletes who sustained their last concussion more than 9 months before testing also demonstrated a lengthened CSP, enhanced LICI as well as increased interhemispheric inhibition in the primary motor cortex (De Beaumont et al., 2011). Since LICI is mediated by GABAb receptors, these results suggest that sport concussions induce persistent alterations of interhemispheric inhibition (De

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Beaumont et al., 2011). Similar results were found in athletes who sustained their last concussion on average 2 years before testing (Tremblay, de Beaumont, Lassonde, & Théoret, 2011). In comparison to the non-concussed group, the athletes with a history of concussions had a significantly prolonged CSP and LICI was significantly enhanced. This further suggests that specific neurophysiological abnormalities of intracortical inhibitory mechanisms in the primary motor cortex persist in individuals who have sustained multiple sports concussions (Tremblay et al., 2011). To further test brain function in healthy, retired athletes, former varsity level athletes were tested 30 years since their last sports concussion and were compared to a cohort of the same age with no history of concussion (De Beaumont et al., 2009). These individuals demonstrated motor system changes that are similar to the changes observed when testing took place 3 years post concussion (De Beaumont et al., 2007). The CSP was significantly prolonged in the formerly concussed athletes compared to the non-concussed control group, however, intracortical inhibition and facilitation values were normal (De Beaumont et al., 2009). These findings provide further insight into the specific cortical mechanisms that are affected long-term by concussions. Although these studies investigated cortical excitability at various time points post-concussion, the individuals tested only had a history of concussions and were not experiencing prolonged symptoms. Therefore, it is of interest to investigate cortical excitability in individuals with PCS to determine if some of the intracortical changes exist in this population.

Go/No-Go Tasks and Cortical Excitability

Research has demonstrated that the activation and inhibition of the pyramidal tract begins during the preparation period of voluntary movement (Hoshiyama et al., 1997). Therefore, the muscles needed to appropriately respond to the movement have already been selected prior to the movement. Intending to produce no movement, or stopping movement is an important component of motor control (Hoshiyama et al., 1997). Intracortical and corticospinal activity in the primary motor cortex (M1) can be assessed during the prevention of movement by combining TMS with specific experimental paradigms (Stinear, Coxon, & Byblow, 2009). One such paradigm, the Go/No-Go task, is used in combination with TMS to investigate corticospinal excitability. The paradigm requires a response for a Go cue (e.g. a green light), and no response for a No-Go cue (e.g. a red light). The Go/No-Go paradigm has been used in both single-pulse and paired-pulse TMS studies (Stinear et al., 2009). Following single-pulse TMS, MEP amplitudes were significantly increased in the agonistic muscles, but reduced in the antagonistic muscles 100-200ms following the go cue. However, after the no-go signal, both agonistic and antagonistic muscles had decreased MEP amplitudes (Hoshiyama et al., 1997). Similar results were found where bilateral inhibition of MEP amplitudes in homologous muscles occurred following no-go tones (Leocani et al., 2000). These studies suggest that reduced MEP amplitudes following No-Go signals are representative of inhibition of the corticospinal pathway. However, the change in MEP amplitude cannot be solely attributed to increased inhibition of corticospinal neurons, as these studies only used single-pulse TMS. Therefore, paired-pulse TMS

is used to determine if both excitatory and inhibitory mechanisms are involved in the prevention of movement (Stinear et al., 2009).

Single and paired-pulse TMS were used to investigate the effects of volitional inhibition on cortical inhibitory networks (Sohn, Wiltz, & Hallett, 2002). During the No-Go trials short interval intracortical inhibition (SICI) was enhanced, where long-interval intracortical inhibition (LICI) was reduced. These results suggest that the inhibitory networks act differently during the prevention of voluntary movements (Sohn et al., 2002). Similarly, Hallet and colleagues (2000) also showed increased intracortical inhibition following the No-Go signal (Hallett, 2000a). These studies demonstrate that cortical excitability is suppressed during a No-Go task in healthy individuals. Therefore, it is of interest to investigate the effects of movement prevention on cortical excitability in individuals with PCS, as these individuals experience persistent motor and cognitive deficits.

Power vs. Precision Tasks and Cortical Excitability

Single-pulse TMS was used to investigate cortical excitability in both proximal and distal muscles of the upper limb, while the participants performed a precision grip or a power grip task (Schieppati et al., 1996). There was an increase in the amplitude of the MEPs in the prime mover muscles during the precision task compared to the power task (Schieppati et al., 1996). Similar results have been reported when single-pulse TMS produced greater MEP amplitudes and decreased the length of the CSP during a pincer and power grip (i.e., complex task) than during finger abduction (i.e., simple task) (Tinazzi et al., 2003). However, with respect to

the complex tasks, pincer gripping (i.e., precision task) yielded increased MEP amplitudes than power gripping (Hasegawa et al., 2001; Tinazzi et al., 2003). It has been suggested that the difference in MEP amplitudes during the precision and power grip tasks may be a result of the difference in contribution of synergistic muscles during the two tasks (Tinazzi et al., 2003). In addition, these findings may reflect the involvement of different neural mechanisms during grip tasks (Hasegawa et al., 2001). Therefore, investigating task-dependent changes using paired-pulse TMS will provide insight into the cortical mechanisms that are responsible for the changes observed in cortical excitability. Furthermore, since the Go/No-Go task introduces a greater cognitive demand on the participants, it is likely that errors will be made, which can be detected using surface EMG.

Postural Stability

Static Balance Control

Balance is a general term which describes the dynamics of body posture in order to prevent falling (Winter, 1995). However, balance can be further described by the three primary components of balance control: 1) centre of mass (COM) is the weighted average of the COM of each body segment; 2) centre of pressure (COP) refers to the weighted average of all the pressures over the surface of the area in contact with the ground; and 3) the base of support (BOS) is the area of the body that is in contact with the support surface (Winter, 1995).

Static stability allows the body to remain upright during stance. Although referred to as static, upright standing is accompanied by postural sway. This can be explained by the relationship between the COM, COP, and BOS. In order to achieve quiet standing, the position of the COM must be maintained within the BOS (Winter, Patla, Frank, & Walt, 1990). This is accomplished by constantly moving the COP further than the location of the COM to keep it within the BOS. To determine where the COM is moving, there is a slight delay in COP movement in order to corral the COM, resulting in postural sway. The central nervous system accomplishes this through (CNS) controlling the COP by ankle plantarflexor and dorsiflexor torque in the sagittal plane. Winter and colleagues (1998) proposed that the torque is established by joint stiffness, whereby the CNS sets joint stiffness through appropriate muscle tone to control the body's COM during stance (Winter, Patla, Prince, Ishac, & Gielo-Perczak, 1998). Postural sway can occur in the anterior/posterior direction as well as in the medial/lateral direction (Winter, 1995).

Furthermore, three main sensory systems, visual, vestibular, and somatosensory, are involved in maintaining balance and posture (Winter, 1995). The visual system provides information about the environment as well as the orientation and movement of the body. Visual inputs are used to maintain upright stance when the reference surfaces are fixed or when surface movements can be predicted in advance (Nashner, Black, & Wall, 1982). The vestibular system is responsible for responding to linear and angular acceleration, as well as controlling the position of the head in space with respect to gravity. Vestibular inputs are

crucial in maintaining balance in instances where support surfaces and/or visual

surfaces are irregular or in motion (Nashner et al., 1982). Finally, the

somatosensory system is comprised of a variety of sensors, which respond to the

position and velocity of body segments, contact with external objects, as well as the

body's orientation in space (Winter, 1995). The somatosensory system is an

important source of information for static balance control as the ankle muscle

spindles respond very quickly to muscle length changes. Conflicts within these

sensory systems make it difficult for the postural control system to identify the

correct orientation in space as well as to determine the appropriate motor response.

Static Balance Control Following a Concussion

After sustaining a concussion, one or more sensory systems may be

compromised. However, it is likely that concussed individuals may experience

deficits in sensory integration as well. A study by Guskiewicz (2001) investigated

the effect of concussion on postural stability and neurocognitive function in varsity

athletes. Concussed athletes demonstrated postural stability deficits during the first

two days post-concussion. The authors suggest the deficits are likely related to a

sensory interaction problem preventing the concussed athletes from using and

exchanging sensory information accurately (Guskiewicz, Ross, & Marshall, 2001).

Similarly, upon return to play, balance control of concussed athletes was not

completely recovered which was demonstrated by increased velocity of COP

(Powers, Kalmar, et al., 2014b). This deficit was apparent even though the athletes

had reported a decrease in symptoms. Specifically, the balance deficits were more

significant in the A/P direction, which may be caused by damage to the vestibular system (Powers, Kalmar, et al., 2014b). In addition, postural deficits were demonstrated 30 days post-concussion, which may be associated with perceptual motor disintegration as a result of conflicting visual field motion (S Slobounov et al., 2006). Another study by Slobounov et al., (2012) demonstrated persistent balance deficits produced by mild traumatic brain injury that did not return to pre-injury levels despite clinical symptom resolution and neurospsychological testing that had returned to baseline levels (Semyon Slobounov, Sebastianelli, & Hallett, 2012). Finally, balance control changes were measured during a gait initiation task in response to the illumination in symptomatic concussed varsity athletes. Results of this study revealed an increase in posterior displacement of COP in the concussed group in comparison to the control group (Harper, 2014). The authors suggest that the increase in displacement during the loading phase can be attributed to instability during static stance and the need to overcome the instability in order to initiate gait (Harper, 2014). The results from these studies suggest that symptom evaluation may not be sensitive enough to identify deficits in balance control that persist in asymptomatic concussed athletes. Furthermore, prolonged dysfunction of the neuronal network involved in performing postural movement may lower the threshold for subsequent brain injury (S Slobounov et al., 2006).

Response Inhibition

Response inhibition is the cognitive process that is required to stop a planned movement (Aron, Robbins, & Poldrack, 2004). This process can be tested

using Go/No-Go paradigm, where the subjects are asked to respond to the task on the Go trials (e.g., pressing a button in response to a circle, triangle and square) and to inhibit responding on No-Go trials (e.g., to the letter X). Inhibitory control is then quantified by the numbers of errors the participants make on No-Go trials (i.e., responding to the stimulus when they should not) (Aron et al., 2004). Incorporating the Go/No-Go task into a paradigm where balance must be maintained can provide sensitive measures in understanding postural control in both healthy and special populations. Since some individuals with PCS have persistent motor and cognitive deficits, it is likely that these individuals would perform worse than non-concussed individuals.

Visuomotor Processing Following a Concussion & in Individuals with PCS

It is important to assess visuomotor integration and processing following a concussion as it may identify further subclinical deficits as a result of the head injury. Following a concussion, tests were administered to varsity athletes, which assessed concussion-related symptoms as well as verbal memory, visual memory, visual-motor speed and reaction time. Thirty-eight percent of athletes demonstrated impaired test performance in comparison to their baseline assessments even though these athletes self-reported being asymptomatic (Broglio, Macciocchi, & Ferrara, 2007). A similar study using the same combination of assessments, which were administered at baseline and within 2 days post-concussion, found that the symptomatic concussed group had significantly greater impairments than the asymptomatic-concussed group as well as the control group (Fazio, Lovell, Pardini,

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& Collins, 2007). Additionally, results demonstrated that the asymptomatic group continued to perform worse on the tests compared to the control group. This suggests that cognitive processing impairments persist after symptoms have resolved (Fazio et al., 2007). Non-concussed, recently concussed, and individuals with post concussion syndrome performed a choice reaction time task at rest and after exercise to determine if deficits in cognitive function would arise in asymptomatic recently concussed individuals. Results demonstrated that individuals with PCS benefitted from exercise but the recently concussed group was incapable of performing at a similar cognitive level compared to the non-concussed group. The results of this study emphasized visuomotor deficits in the concussed group and the effect of exercise on performance. These studies suggest that when determining return-to-play status, health professionals should not solely rely on symptom report/assessment, and the stress of physical activity should be taken into account for both asymptomatic and PCS populations.

Studies investigating the relationship between concussion and neuropsychological performance in varsity athletes (football and hockey) using a variety of neurocognitive and visuomotor tests found that a history of concussions is significantly related to long-term deficits in executive functioning and the speed of information processing (Collins et al., 1999). In addition, Covassin and colleagues (2008) found that athletes with a history of concussion take longer to recover on measures of verbal memory and reaction time in comparison to athletes without a history of concussions (Covassin, Stearne, & Elbin, 2008). It appears that neuropsychological deficits continue to linger even 12 weeks after mild head injury,

as impairments were revealed in both auditory attention as well as visuomotor speed as the performance of varsity athletes did not improve over time (Macciocchi, Barth, Alves, Rimel, & Jane, 1996). Furthermore, varsity athletes with as few as 1 previous concussion may show cumulative effects, where these athletes have an increased chance of subsequent concussive injuries with each previous concussion (Guskiewicz et al., 2003). These subsequent injuries generally occur between 7-10 days after the initial concussion. Occulomotor testing, upper-limb visuomotor testing, and neuropsychological tests were used in order to investigate the motor deficits and recovery during the first year after sustaining a mild head injury (Heitger et al., 2006). Persistent deficits were apparent on many of the motor tasks at 6 and 12 months post-injury, as the injured group continued to perform worse than the control group. Based on these results, the authors suggest that it may be valuable to assess both eye and arm motor function in individuals who are experiencing persistent post concussion symptoms as a means of confirming prolonged cerebral dysfunction (Heitger et al., 2006). Although many of these studies were conducted during the acute phase or up to 1 year post-concussion, they provide evidence of the cumulative effects of concussion and the possible visuomotor integration deficits that may persist in individuals who have PCS.

Purpose

The purpose of this thesis was two-fold, where each purpose was investigated in separate studies, which are explicitly outlined below in their respective chapters. Overall, the purpose of this thesis was to determine if

persistent balance control and motor control deficits exist in a population of individuals with post-concussion syndrome.

Hypotheses

It was hypothesized that individuals with PCS would behave similarly to a population of recently asymptomatic concussed athletes, where they would experience similar balance and cortical excitability impairments. Specifically, we hypothesized:

1) The difference between the COP-COM error signal would be greater in the PCS group as a result of sensorimotor impairments.

2) Individuals with PCS would demonstrate a decrease in overall corticospinal excitability in comparison to the non-concussed group.

3) Individuals with PCS would demonstrate a decrease in intracortical facilitation, specifically prior to a precision contraction.

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Chapter 2: Visuomotor go/no-go task and balance control in post-concussion syndrome

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Abstract

Post-concussion syndrome develops as a secondary complication of concussion, where deficits persist in three areas of central nervous system functioning: somatic, psychological and cognitive. Balance control impairments have been revealed in asymptomatic concussed athletes using independent analyses of centre of pressure (COP) and centre of mass (COM); however, the duration of these balance impairments is unknown. The purpose of this study was to examine the effects of post-concussion syndrome on balance control during a single-support lower-limb reaching task. Ten individuals (1 male) with post-concussion syndrome (PCS) and ten age-, gender- and activity-matched non-concussed individuals (CONT) participated in the study. All participants performed static stability assessments with eyes open and eyes closed before and after the lower-limb reaching task. The reaching task required participants to stand in single-support and reach their free limb out to deactivate three lights positioned in front of them at 30˚ on either side of the midline. The PCS group demonstrated no differences in the static stability assessments, but they displayed increased medial-lateral (M/L) COP displacement and increased trunk pitch during the reaching task. These results suggest that individuals with PCS became unstable in the M/L direction and made compensatory adjustments upstream to the support surface (i.e., the trunk) in order to complete the forward reaching task. Overall, the findings reveal persistent balance impairments in individuals with PCS, which may put this population at an increased risk of further injury.

Introduction

Individuals commonly report a combination of somatic, cognitive, and emotional/behavioural symptoms after sustaining a concussion (McCrory et al., 2013). While symptoms typically resolve within 10 days post-concussion, in some cases, symptoms may persist for months to years following the brain injury (McCrory et al., 2013; Ryan & Warden, 2003). Researchers define these persistent symptoms as post-concussion syndrome (PCS). However, the etiology of PCS remains unclear, as pre-injury psychological disorders and neurological deficits may play a contributing factor in the development of PCS. Additionally, the effects of PCS on sensorimotor integration and balance control remain unclear.

Balance control is comprised of three primary components: 1) centre of mass (COM), which is the weighted average of the COM of each body segment, 2) centre of pressure (COP), which refers to the weighted average of all the pressures over the surface area that is in contact with the ground, and 3) the base of support (BOS), which is the body that is contact with the ground (Winter, 1995). To successfully achieve quiet standing, the position of the COM must be maintained within the BOS, which is accomplished by constantly moving the COP further than the location of the COM. To determine where the COM is moving, there is a slight delay in COP movement in order to corral the COM, resulting in postural sway. The central nervous system (CNS) accomplishes this through controlling the COP by producing ankle plantarflexor and dorsiflexor torque in the sagittal plane (Winter et al., 1998). The torque is established by joint stiffness, whereby the central nervous system sets joint stiffness through appropriate muscle tone to control the body's COM during

stance (Winter et al., 1998). Quantifying centre of pressure (COP) movements during static tasks has provided comparisons in balance control between neuro-typical individuals and populations that are inherently unstable (Powers, Kalmar, et al., 2014b; Rocchi, Chiari, Cappello, Gross, & Horak, 2004). However, the COP is an indirect measure of the centre of mass (COM), therefore, it has been suggested that it may not provide the most accurate measure of postural stability (Hass, Waddell, Fleming, Juncos, & Gregor, 2005; Winter, 1995). Calculating the difference between the COP and COM movements during static and dynamic tasks has been suggested to provide better insight into balance assessments than analyzing the variables alone, as it provides a trajectory of the COM over the course of time (Hass et al., 2005; Winter, 1995). If previous research has investigated balance control post-concussion using independent analyses of the COP, then using the error signal produced by the difference between COP-COM should theoretically provide a better indication of balance control in a PCS group.

After sustaining a concussion, one or more sensory systems may be compromised, possibly leading to sensory integration deficits. Previous research has demonstrated that concussed athletes exhibit postural instability up to 3 days post-injury, where instability was greatest when somatosensory input was altered (Guskiewicz et al., 1996). Furthermore, balance impairments have been demonstrated during quiet stance in concussed athletes upon return-to-play (RTP6), although athletes had reported an abatement of symptoms (Powers, Kalmar, et al., 2014b). This balance deficit was indicated by increased COP velocity in the anterior-posterior direction, which may be a result of an impairment in the

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vestibulospinal tract's ability to control postural muscles (Powers, Kalmar, et al., 2014b). Likewise, postural deficits have also been reported 30 days post-concussion in asymptomatic athletes as a result of conflicting visual field motion (S Slobounov et al., 2006). These results suggest that sensorimotor integration deficits exist in concussed athletes and continue to persist even after symptoms have resolved.

While these studies assessed balance control during static tasks, it is important to determine whether dynamic instability persists beyond the resolution of symptoms. Concussed athletes exhibit slower walking speeds, and decreased COP movements during gait in order to maintain balance (Basford et al., 2003; Parker, Osternig, van Donkelaar, & Chou, 2008). This conservative gait strategy has been observed up to 28 days post-injury (Parker et al., 2008). Furthermore, asymptomatic concussed athletes who had been cleared to return to play displayed an increase in swing-time variability and segmental re-orientation during a dynamic steering task (Powers, Kalmar, & Cinelli, 2014a). Therefore, dynamic as well as static tasks have revealed balance impairments in symptomatic and asymptomatic concussed athletes. However, it is unclear how long these balance impairments exist, specifically in a population that has persistent concussion symptoms.

In addition to persistent balance impairments, visuomotor integration deficits and neuro-cognitive deficits have also been revealed up to 1 year post-concussion (Heitger et al., 2006). Athletes with a history of concussion have demonstrated deficits in motor task performance, executive functioning, speed of information processing, and sustained attention tasks in comparison to non-concussed individuals (Bohnen et al., 1995; Collins et al., 1999; Heitger et al., 2006).

However, these studies performed the visuomotor and neuro-cognitive assessments

independently, and only assessed visually controlled movement using the upper

limbs. In addition, one such study found an overall decrease in performance speed

in a pointing task that was not attributable to changes in speed-accuracy trade offs

in individuals with a history of concussion (Locklin, Bunn, Roy, & Danckert, 2010).

These results suggest that research should focus on challenging the constraints of

the visuomotor system in order to identify lingering deficits in a concussed

population (Locklin et al., 2010). Since individuals with PCS have prolonged

cognitive deficits, assessing visuomotor processing in this group may provide

further insight into motor planning and movement execution performance of this

clinical group.

Therefore, the purpose of this study was to assess balance control in

individuals with PCS (i.e., symptoms persisting > 30 days) and non-concussed

individuals during a single-support lower-limb reaching task using a Go/No-Go

paradigm. Quantifying the difference between the COP and COM movements should

demonstrate differences in balance control between the groups, and the Go/No-Go

task should cause an increased cognitive challenge, as it required the participants to

be more attentive during a choice reaction time task, which may exploit deficits in

the visuomotor system. We hypothesized that the difference between the COP and

COM (i.e., error signal) would be larger in the individuals with PCS due to persistent

balance impairments and the inability of the CNS to effectively activate the ankle

and hip muscles to control the COP and COM, ultimately leading to poorer balance

control. Furthermore, we also hypothesized that if balance impairments were

shown during the reaching task, static balance control may also be affected when re-assessed after the reaching task, more specifically during the eyes closed condition.

Methods

Participants

Ten individuals (1 male) with post-concussion syndrome (PCS) and ten non-concussed individuals (CONT) participated in this study. Each individual with PCS was age-, gender-, and activity-matched with another participant to serve as a control. Activities ranged from hockey, soccer, swimming, figure skating, and curling. Exclusion criteria for the control group included diagnosis of a concussion or post-concussion syndrome within the past 2 years. Individuals with PCS were eligible to participate in the study as long as they had been experiencing PCS for more than 30 days, and had also received clearance to return to work and/or school at least part-time. Exclusion criteria for all participants included any biomechanical injuries that would affect balance measurements (e.g., chronic ankle instability). All participants completed a health history questionnaire, which included a SCAT3 symptom evaluation (see appendix A), and provided written informed consent to participate. This study was approved by the Institutional Research Ethics Board.

Experimental Set-Up

Kinematic data was collected using the OptoTrak camera system (Northern Digital Inc., Waterloo, ON, Canada) at a sampling frequency of 100Hz. Participants were outfitted with 4 rigid bodies, each containing 3 infrared emitting diodes,

(IREDs). The rigid bodies were placed on the front of the head, one on the sternum, and one on each ankle. The rigid bodies were used as reference points for 12 digitized points on the body to track each marker's location in space and time. The digitized points were located bilaterally on the body and included the ears, glenohumeral (GH) joints, anterior superior iliac spines (ASIS), 1st and 5th metatarsals, and heels (Figure 1-A). Kinetic data was collected using the Nintendo Wii Board (Redmond, WA, USA) at a sampling frequency of 100Hz. Software created by Simon Jones allowed for the extraction of data from the Wii in order to calculate the Centre of Pressure displacement over time. A flexible wireless training system, FitLight Trainer, was laid out on the floor in a semicircular pattern. Three REB LED lights were placed symmetrically on the right and left side at 0° and 30° (Figure 1-B). The proximity of each FitLight was normalized to each participant's leg length, whereby the distance from the leg to the ankle was measured and the FitLight was placed at this distance from the centre of the Wii board. Due to the nature of the task, the foot markers were not used because they were constantly obscured throughout the experimental protocol.

Experimental Protocol

Participants were initially instructed to stand on a Nintendo Wii balance board in Romberg stance (i.e., feet together and arms by their side) for 60 seconds to determine static balance control. The participants first performed a trial with their eyes open, followed by a trial with their eyes closed. These static balance assessments were performed both before and after the experimental trials (i.e.,

visuomotor protocol). The visuomotor task required participants to stand in single support with the non-support limb freely hanging, but not touching anything in front of the three FitLights. While in single support, the participants responded to any illuminated (green) FitLight, by moving their free limb over top of the light to turn it off. The lights illuminated in a randomized sequence, where green lights represented a "Go" signal, and red lights represented a "No-Go" signal. The participants moved to either respond to the lights or prevent movement according to the colour of the light, for approximately 40 seconds per trial. For each trial, each LED light illuminated 6 times, where 30% of all trials were No-Go trials. The timing between the lights was variable, such that participants could complete the trial faster if they responded to the lights quicker. However, if the participant did not respond to the lights fast enough, the light would time-out 0.90s. After the lights were deactivated, there was a 1.20s delay before the next light illuminated. Participants completed 5 trials per leg in alternating fashion, for a total of 14 trials including the static balance assessments at the beginning and end of the protocol. The entire protocol took approximately 30 minutes to complete.

Data Analysis

All variables for which RMS was calculated used the following formula:

$x_{\text{rms}} = \sqrt{\frac{1}{n}(x_1^2 + x_2^2 + \cdots + x_n^2)}$. Each variable was calculated in both the anterior-posterior and medial-lateral directions.

COP RMS Displacement (dCOP)

COP displacement is used to determine how far the COM is moving within the base of support, and is indicative of the neuromuscular control of the ankle dorsiflexors/plantarflexors during quiet stance (Winter, 1995). If the participants made errors throughout the experimental protocol (i.e., responded to the red lights) the RMS of the COP would be greater in both A/P and M/L directions. The equation used to calculate COP displacement was as a weighted average from the four quadrants of the Wii board.

COP_{ML}=(21 * (TopRight + BottomRight -(TopLeft + BottomLeft)) / (TopLeft + TopRight + BottomLeft + BottomRight)

COP_{AP}= (12 * (BottomLeft + BottomRight - (TopLeft + TopRight)) / (TopLeft + TopRight + BottomLeft + BottomRight)

COP RMS Velocity (vCOP)

COP velocity represents the rate of change of the COP during a given task, and how well the postural control system is able to corral the COM. This measure provides insight into the neuromuscular control in a concussed group during a challenging single-support task.

Trunk Pitch and Roll RMS

Trunk pitch and roll were included in this analysis as they provide a measure of the proficiency in which the postural muscles are able to maintain the body in an upright position during both static and single-limb tasks. Trunk pitch and roll were calculated using the following equations (adapted from Winter, 1995).

Trunk pitch: $\tan \theta = \frac{A/P\ trunk\ position}{vertical\ trunk\ position}$, Trunk sway: $\tan \theta = \frac{M/L\ trunk\ position}{vertical\ trunk\ position}$.

COP-COM Error

In order to measure COM and COP displacements over time, both kinematic (Optotrak) and kinetic (Wii board) signals were time-locked to allow for synchronization between the two signals. To do so, participants began each trial off the Wii board and at the start of the trial the stepped up onto the Wii board with their stance foot. This allowed us to match the vertical displacement of the COM with the vertical force from the Wii board. The position of the COM over time was calculated using a weighted average of the digitized points of the torso.

COM=0.25*(Left Shoulder)+0.25*(Right Shoulder)+0.5*(Torso)

COP and COM positions were calculated relative to the centre of the Wii board (i.e., removed the bias), and then the COM displacement was subtracted from the COP displacement in both medial-lateral (M/L) and anterior-posterior (A/P) directions at each instant in time throughout a trial. These values were then converted to absolute values, followed by calculating the average over the trial.

Error = ABS(COP_{ra} – COM_{ra}), where ra = COP and COM locations relative to the ankle. This equation represented the error signal as the COP tracked the COM (Winter, 1995).

Statistical Analysis

Statistical analyses were performed using Statistica 13.2 (TIBCO Software Inc., Palo Alto, CA). Four mixed measures 2x2 (group x time) ANOVAs were performed to assess the changes in static balance in both A/P and M/L directions between groups before and after the experimental protocol, with eyes open and

closed. Tukey's HSD post-hoc analysis was performed to assess differences between means when the ANOVAs revealed a main effect or interaction ($p < 0.05$).

To assess the effect of the visuomotor task on balance control between groups (controls vs. PCS), independent samples t-tests were performed using the average of each dependent measure. To assess the variability between groups, independent samples t-tests were also performed using the Standard Deviation of the dependent measures of each group. The dependent measures included average trunk pitch and roll positions, RMS trunk pitch and roll, RMS COP displacement, RMS COP velocity, and average error in both M/L and A/P directions. Cohen's d was calculated for results that yielded significance to determine the importance of the difference.

Simple regressions and Pearson's correlations were carried out between the number of total symptoms reported (SCAT3) and each dependent measure listed above in order to determine whether symptom severity (number of reported symptoms) was related to the balance impairments.

Results

The results from the PCS group include only 9 participants as one participant was excluded from the analyses due to ankle instability and concussion history.

COP RMS Displacement

COP displacement (dCOP) provides an indication of how well the COM is being controlled throughout a task. Previous research found that concussed football

players displayed greater A/P dCOP in the acute phase, which recovered by RTP (Powers, Kalmar, et al., 2014b). Similar to the RTP phase in the previous study, no significant differences were revealed between groups in dCOP displacement during the static stability assessments in the current study (Table 2). However, individuals with PCS exhibited greater M/L COP excursions (M = 0.94cm, SD = 0.21cm) than the control individuals during the experimental protocol (M = 0.77cm, SD= 0.07cm), $t_{(17)}$ = -2.44, p = 0.03, d= 1.09) (Figure 3-A).

COP RMS Velocity

Previous research has demonstrated persistence of increased COP velocity (vCOP) in the A/P direction during quiet stance in a recently asymptomatic concussed population (Powers, Kalmar, et al., 2014b). A mixed measures analysis of variance revealed no differences during the static stability assessments in A/P or M/L vCOP for pre and post testing eyes open (F (1, 17)= 0.57cm/s, p= 0.46cm/s) and eyes closed conditions (F (1, 17)= 2.91cm/s, p= 0.11). For further details see Table 2. Results from the independent t-tests revealed no significant groups differences during the experimental protocol in A/P vCOP (CONT M = 1.57cm/s, SD = 0.31cm/s; PCS M =1.70cm/s, SD = 0.30cm/s) or M/L vCOP (CONT M = 4.77cm/s, SD = 0.76m/s, PCS M = 5.01cm/s, SD = 0.73cm/s).

Trunk Pitch and Roll

Trunk pitch and roll measures (RMS and Average) were subjected to both mixed measures analysis of variance, as well as independent t-tests for the static

stability protocol and experimental protocol respectively. Results from the static

stability assessment revealed no significant differences between groups, condition

or time. However, the PCS group had a significantly increased RMS trunk pitch angle

(M = 2.71°, SD =0.73°) compared to the control group during the experimental

protocol (M = 1.98°, SD = 0.51°), $t_{(17)}$ = -2.56, p = 0.02, d = 1.16) (Figure 4).

COP-COM Error

The error signal as the COP tracked the COM in both M/L and A/P directions

was compared between groups during the static and lower-limb reaching task. The

statistical analyses revealed no significant differences between groups during either

protocol (Figure 2A and B).

Balance control and total number of symptoms

A moderate correlation was revealed between M/L vCOP and the total

number of symptoms reported in the post-concussion group (p = 0.077, r =0.62).

While this value is not statistically significant, it is trending towards significance and

may be a result of low power. Furthermore, Pearson's correlation revealed a

moderate correlation, which suggests that although the p-value is not significant, the

relationship is still important to report.

Discussion

The purpose of this study was to quantify differences between individuals

with post-concussion syndrome (PCS) and non-concussed (CONT) individuals

during a single support lower-limb visuomotor reaching task that challenged both

the balance control system and the individuals' cognitive functioning. It was
hypothesized that individuals with PCS would exhibit a larger COP-COM error signal
during the lower-limb reaching task due to persistent balance deficits. However, the
findings from the study demonstrated that individuals with PCS had increased
medial-lateral COP displacement as well as greater trunk pitch during the reaching
task, while no differences were observed between groups in the COP-COM error
signal.

COP-COM Difference

The combined analysis of COP and COM movements during quiet stance and
dynamic tasks has been suggested to provide better insight into balance
assessments and postural control compared to analyzing each variable alone
(Corriveau, Hébert, Raıche, Dubois, & Prince, 2004; Hass et al., 2005; Winter, 1995).
Therefore, we chose to use this analysis with the idea that differences in balance
control between non-concussed individuals (CONT) and individuals with PCS may
be captured better. Three possible outcomes could have emerged from this analysis,
1) the COM position increased and the COP position decreased, 2) the COP position
increased and the COM position decreased, or 3) the COM and COP positions
underwent similar changes, thus creating no difference between the two variables.
During both the static standing and lower-limb reaching task, we found no
differences between groups in the error signal between the COM and the COP
(Figure 2). This suggests that the COP displacements (through ankle muscle
activation) and COM displacements (trunk control) were coupled similarly for both
groups throughout the tasks and the COP can effectively act as an indirect measure

of the COM (Winter, 1995). The movements in the reaching task used in the current study could be considered similar to that of gait initiation, whereby individuals had to move into single support, followed by successive reaching movements of the free limb in the sagittal plane. Previous research has suggested that during gait initiation, in order to produce forward momentum, there is purposeful uncoupling of the COP and COM (Hass et al., 2005). However, larger distances between the COP and COM, places greater demands on the postural control system. It has been demonstrated that the separation between the COP and COM is decreased as a function of age, sensory deficits, and disease (i.e., Parkinson's disease) in order to enhance stability during gait initiation (Hass et al., 2005; Hwa-ann & Krebs, 1999; Martin et al., 2002). Therefore, it is possible that the PCS group may exhibit similar changes in the distance between the COP and COM as these groups during the preparatory phase of gait initiation. Future work should evaluate the magnitude of the COP-COM distance during a single step gait initiation task to determine whether a PCS group makes adjustments as a result of poor balance control. Since there was no difference in the error signal between the two groups, we sought to analyze the COP and COM variables independently. The COP was used in the independent analysis, as it is an indirect measure of the COM.

COP Displacement

Observationally, the PCS group did not appear much different from the control group, as they were able to complete the entire experimental protocol. However, when the components of balance control were analyzed separately,

differences emerged, which may suggest subclinical deficits exist in individuals with PCS. During the reaching task, individuals with PCS displayed greater displacement of their COP in the medial-lateral (M/L dCOP) direction in comparison to the CONT individuals (Figure 3), suggesting that this PCS population has balance impairments. Previous research with concussed athletes who had been cleared to return to play (RTP6) demonstrated balance control deficits, as indicated by increased COP velocity during quiet stance. This deficit was more pronounced in the A/P direction, likely due to impairments of the lateral vestibulospinal tract (Powers, Kalmar, et al., 2014a). In comparison, the current study demonstrated that individuals with PCS showed greater COP excursions in the M/L direction. It is not surprising that there were no differences between groups in the A/P dCOP because the distance of the lights was normalized to each participant's leg length, and the task promoted A/P movement. Although the experimental task was performed in single-support, we thought that if group differences emerged, it would be evident in A/P COP velocity. However, it appears that in order for the PCS group to have efficiently completed the reaching task in single-support, they may have become unstable in the M/L direction. The somatosensory system is the primary sensory system involved in static balance control, as it is comprised of a variety of sensors that respond very quickly to muscle length changes (Winter, 1995). In a bright environment with a stable surface, individuals rely heavily on the somatosensory system (70%) (Horak, 2006). Since no differences emerged in M/L trunk control (i.e., trunk roll), this balance control deficit evident in people with PCS is likely due to somatosensory deficits resulting in poor control of the ankle musculature.

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Since COP velocity (vCOP) is the rate of change of dCOP, it was expected that the individuals with PCS would be more cautious in the A/P direction during the reaching task and have a lower vCOP than the CONT group and that both groups would have similar M/L vCOP because that COP movement orthogonal to that of the intended movement direction would be minimized. Both groups demonstrated similar vCOP values during the reaching task. However, the results of this study indicated that increased M/L vCOP in the PCS group was associated with a higher number of reported concussion symptoms (i.e., greater severity). This finding may reflect the heterogeneity of this group, suggesting that only the most symptomatic PCS participants (who most closely resemble acutely concussed individuals) demonstrate greater balance impairments.

Trunk Angular Displacement

Poor balance control was revealed at the level of the support surface (i.e., ankle muscles) therefore, we wanted to determine if balance control was also affected at a distal location to the support surface (i.e., the trunk). While no differences emerged between groups in the control of trunk rotation about the anterior/posterior axis (roll), individuals with PCS demonstrated an increase in trunk pitch during the experimental protocol (Figure 4). All individuals in the PCS group completed the lower-limb reaching task, suggesting that the lower limb muscles needed to generate movement in the A/P direction were not impaired. Consequently, in order to accomplish the lower-limb reaching task, A/P trunk control was affected (i.e., PCS group had greater trunk pitch RMS, see Figure 4). In

certain disorders and some elderly individuals, the limits of stability are abnormally represented (Horak, 2006). For instance, when leaning in the forward direction in double-support, flexion at the hips occurs to limit forward COM motion rather than using the ankle strategy (i.e., rotation about the ankle joint only). Individuals with smaller limits of stability are associated with an increased incidence of falls (Horak, 2006). This suggests that individuals with PCS may have reduced stability limits, as they make more compensatory movements at the trunk in order to maintain upright. In turn, this group may be at an increased risk of falls. As mentioned previously, the protocol used in this study was similar to gait initiation. Previous research has demonstrated that swing time variability is greater in concussed athletes at return to play during a dynamic task (Powers, Kalmar, et al., 2014a). This may suggest that persons with PCS may also display similar variability in the swing phase during locomotion as a result of poor trunk stability. Furthermore, swing time variability has also been suggested as a marker of fall risk in older adults (Hausdorff, Rios, & Edelberg, 2001; Springer et al., 2006). Therefore, an increase in trunk pitch may result in greater swing time variability and place these individuals at an increased risk of falling when challenged dynamically (Powers, Kalmar, et al., 2014a).

Conclusion

The findings from the current study demonstrate that university-aged individuals with PCS demonstrate increased M/L dCOP and increased trunk pitch

during a challenging lower-limb reaching task. These balance deficits present as compensatory mechanisms necessary to maintain fluidity of movement and upright posture due to impairments of the somatosensory system. Future work with this population should assess balance control during gait initiation as well as during a dynamic task to fully expose the balance impairments that may put individuals with PCS at a greater risk of injury.

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Tables

**Table 1.** Demographic and concussion information by group (mean ±standard deviation).

	Controls	PCS Group
Age	22.4 (±4.33)	22.2 (±3.33)
Gender	1 Male, 9 Females	1 Male, 9 Females
# of concussions (last 5 years)	0	2.3 (±1.49)
SCAT3 symptom score	---	8.2 (±4.81)
Range of SCAT3 symptom score	---	1 to 15
SCAT3 symptom severity score	---	13.8 (±10.73)
Range of SCAT3 symptom severity score	---	1 to 33

Note: No significant differences between groups at time of testing

Table 2. Displacement and velocity results from static stability assessments (mean ±standard deviation).

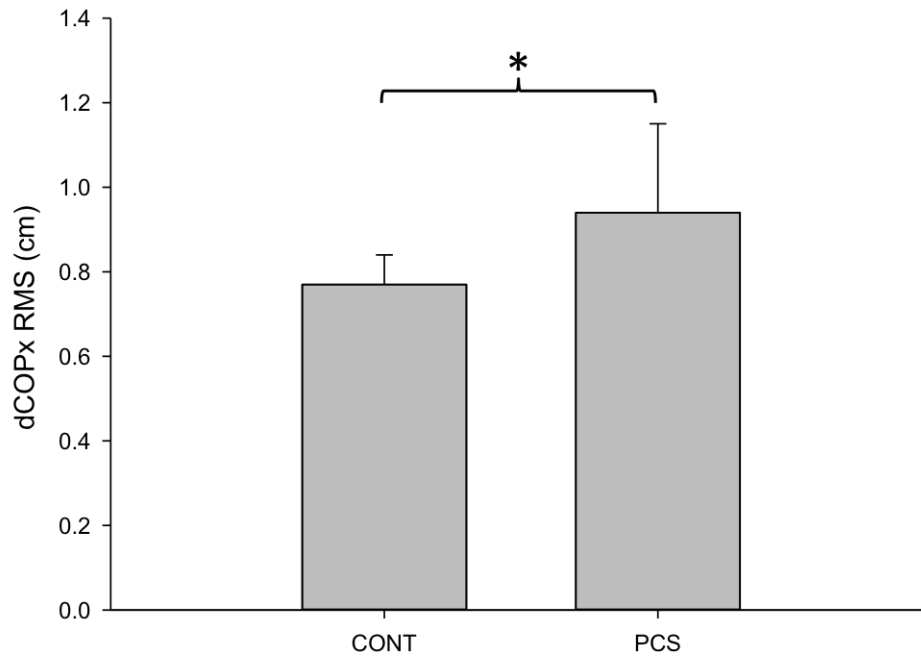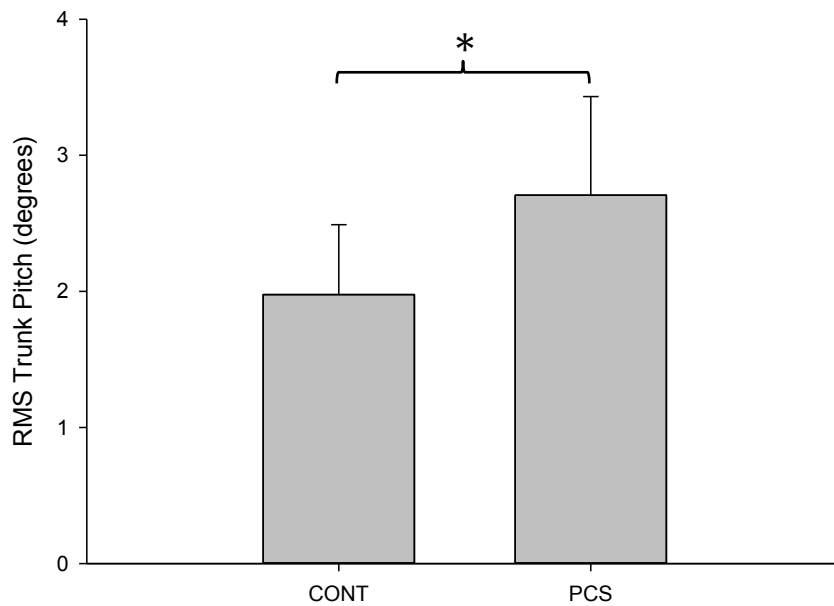|	Controls		PCS Group	
Eyes Open	PRE	POST	PRE	POST
dCOP (M/L)	0.50 ±0.10	0.50 ±0.11	0.63 ±0.27	0.62 ±0.19
(A/P)	0.82 ±0.35	0.86 ±0.45	0.60 ±0.17	0.88 ±0.30
vCOP (M/L)	1.98 ±0.15	1.97 ±0.21	1.93 ±0.32	1.85 ±0.21
(A/P)	1.43 ±0.13	1.52 ±0.17	1.71 ±0.41	1.80 ±0.52
Eyes Closed	PRE	POST	PRE	POST
dCOP (M/L)	0.56 ±0.17	0.58 ±0.19	0.74 ±0.31	0.76 ±0.25
(A/P)	0.74 ±0.19	1.04 ±0.37	0.81 ±0.29	1.18 ±0.47
vCOP (M/L)	2.30 ±0.40	2.11 ±0.39	2.26 ±0.58	2.45 ±0.45
(A/P)	1.89 ±0.32	1.81 ±0.28	2.59 ±0.94	2.52 ±0.83

Figures

A) **B)**
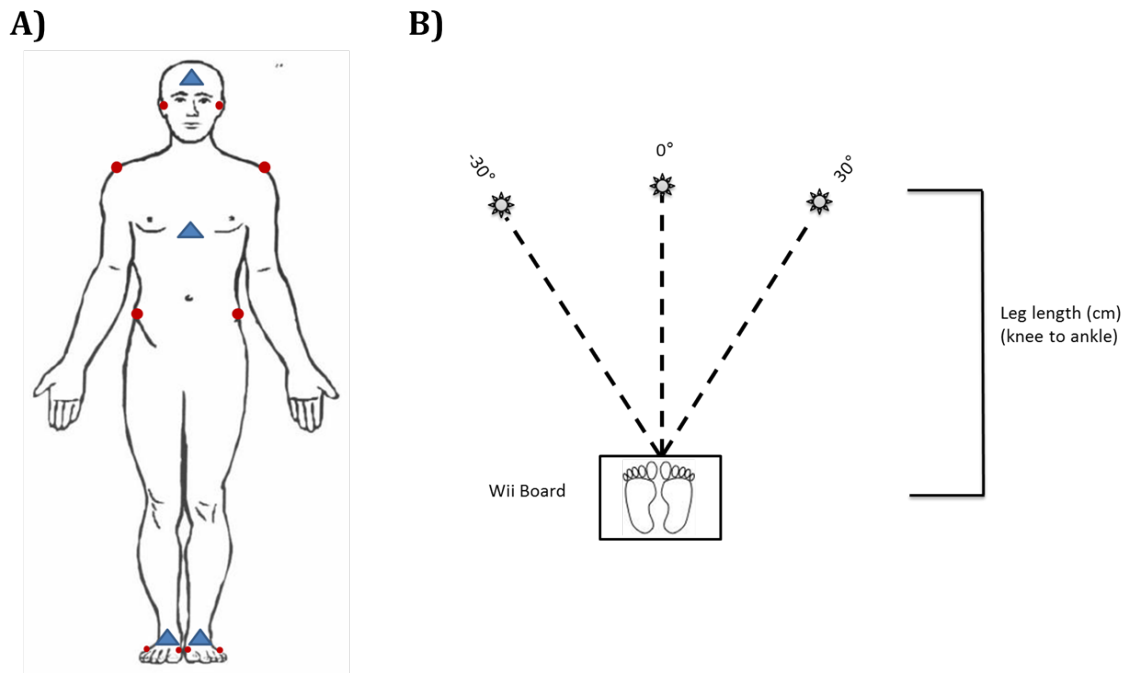
Figure 1. Experimental design. A) Optotrak set-up to collect kinematic data. Participants were outfitted with four rigid bodies (blue triangles), placed on the front of the head, the sternum, and one on each ankle. The rigid bodies were used as reference points for 12 digitized points (red dots) on the body to track each marker's location in space and time. The digitized points included the right and left ears, glenohumeral joints, anterior superior iliac spines, 1st and 5th metatarsals and heels. B) The FitLight Trainer system was arranged in a semicircular pattern. The three lights were set at -30°, 0°, and 30° at a distance from the centre of the Wii Board that was equal to the leg length (knee to ankle) of each participant. Participants stood on the Wii Board in Rhomberg stance with eyes open and eyes closed to assess static balance. Following these assessments, the visuomotor protocol began. Participants would stand on one foot and respond to the green lights (go trial) by swiping the free foot over top of the light. If the lights illuminated red, participants were instructed to withhold movement (no-go trial). Static balance was re-assessed after completion of the visuomotor protocol. Participants performed 5 trials on each leg, as well as 4 static balance trials, for a total of 14 trials.
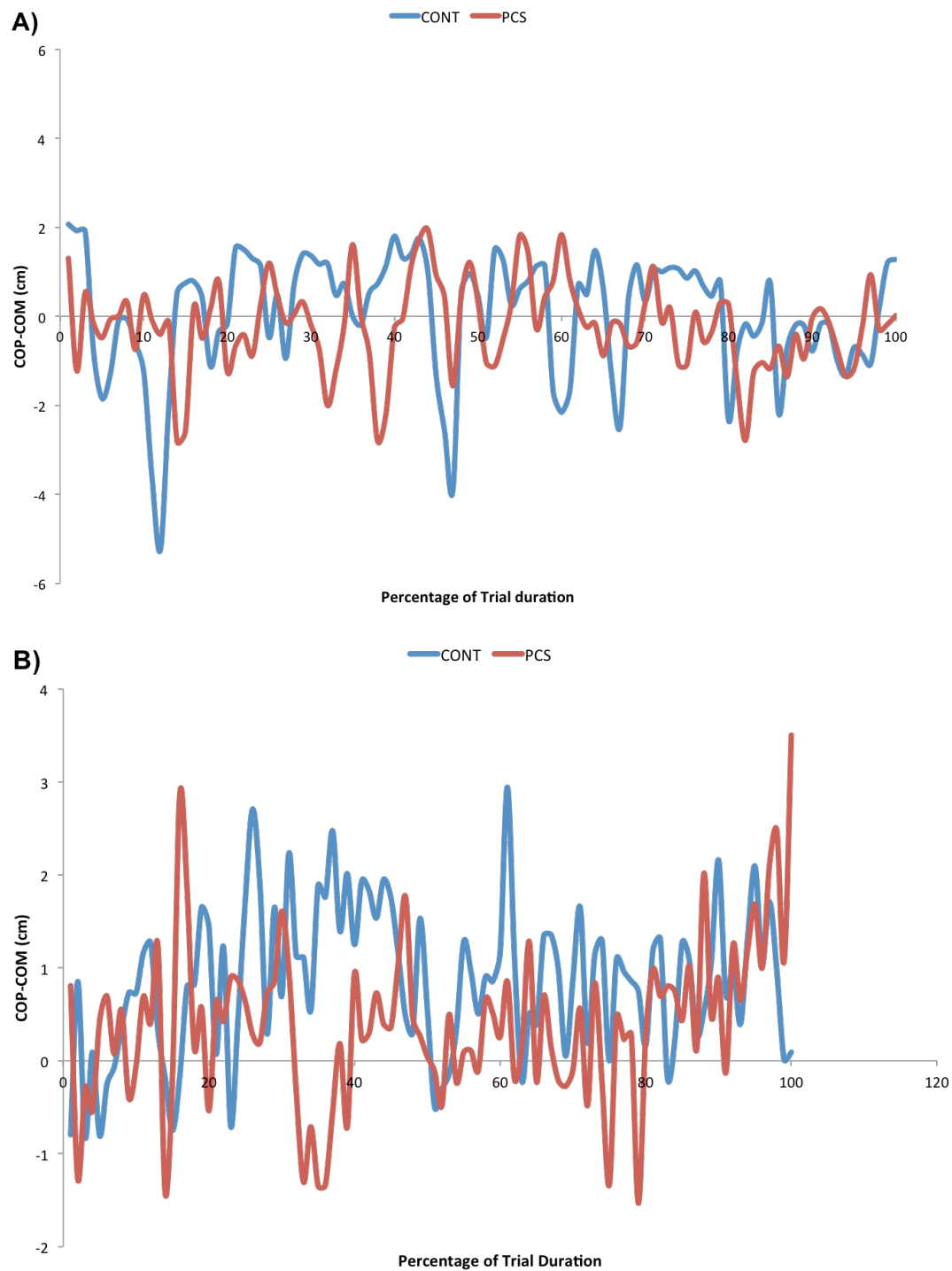
Figure 2. Sample anterior-posterior (A) and medial-lateral (B) COP-COM error signals comparing one PCS individual to one individual from the control group over one trial (i.e., 40 seconds).

Figure 3. Medial-lateral COP displacement during the lower-limb reaching task. The PCS group had greater COP displacement compared to the control group (p < 0.05). Error bars indicate standard deviation from the mean.

Figure 4. Degree of trunk pitch during the lower-limb reaching task. The PCS group had a greater trunk pitch angle compared to the control group (p < 0.05). Error bars indicate standard deviation from the mean.

Appendix A

Examples from the SCAT3 symptom evaluation. This evaluation is comprised of the most common symptoms exhibited by those with concussion. Healthcare professionals use this evaluation to assess the number of symptoms and the symptom severity that these individuals are experiencing at the time of testing.

	None	Mild		Moderate		Severe	
Headache	0	1	2	3	4	5	6
"Pressure in Head"							
Neck Pain							
Nausea or vomiting							
Dizziness							
Blurred Vision							
Balance Problems							

Chapter 3: Task-dependent modulation of cortical excitability in post-concussion syndrome

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Abstract

The purpose of this research was to assess task-dependent modulation of cortical excitability prior to planned index finger abduction contractions in a population with post-concussion syndrome that had been experiencing symptoms for >30 days. It was hypothesized that post-concussion syndrome (PCS) would be associated with a reduction in corticospinal excitability prior to the motor tasks. Ten individuals with post-concussion syndrome were age-, gender-, and sport-matched with ten healthy control participants. Healthy controls had not suffered a concussion or experienced PCS within the past 2 years. Single-pulse transcranial magnetic stimulation (TMS) was used to assess corticospinal excitability, while paired-pulse TMS was used to assess short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) within the primary motor cortex. TMS was delivered 300-ms prior to the beginning of each task. Motor evoked potentials were recorded from the first dorsal interosseous muscle using surface electromyography. Concussion symptoms were recorded at the time of testing using the SCAT3 symptom evaluation. Both groups had greater corticospinal excitability prior to a target-tracing precision contraction (p= 0.003) compared to a powerful contraction with no target (p<0.05), and a rest condition with no plan to contract (p<0.01). There was no task-dependent modulation of intracortical facilitation or inhibition, however, a negative correlation was found between the number of symptoms (SCAT3 symptom checklist) and intracortical facilitation across all contraction types in the post-concussion group (r= 0.35, p= 0.055). The increase in corticospinal excitability prior to a precision contraction was not explained by the two cortical

mechanisms we assessed and may therefore be due to spinal modulation or a different cortical mechanism. While we found no differences in corticospinal excitability, SICI, or ICF in the post-concussion syndrome group overall, the most symptomatic participants had lower intracortical facilitation reflecting the heterogeneity of this clinical group.

Introduction

Post-concussion syndrome arises when concussion symptoms persist for more than 10 days (McCrory, 2013). In most cases, symptoms resolve between 7-10 days post-concussion, however, in 10-15% of cases, symptoms remain unresolved for months to years following the initial brain injury (McCrory et al., 2013). It is unclear whether persistent symptoms are a result of neuropathological changes secondary to the injury, or if they are associated with pre-or post-injury psychological factors (Ryan & Warden, 2003). However, post-concussion syndrome exhibits deficits in three areas of central nervous system functioning: somatic, psychological, and cognitive (Hall et al., 2005). While these deficits have been well established, it is uncertain whether neurophysiological deficits related to pre-motor planning and movement execution exist in this population.

Transcranial magnetic stimulation (TMS) is used to non-invasively study the integrity and excitability of the neuronal networks within the primary motor cortex in concussed populations (De Beaumont et al., 2009, 2011, 2007; Powers, Cinelli, et al., 2014; Tremblay et al., 2011). Alterations in the cortical silent period and long-interval intracortical inhibition have been reported in asymptomatic athletes, 9 months, 2 years, and 30 years since their last concussion (De Beaumont et al., 2009, 2007; Tremblay et al., 2011). In a population of recently asymptomatic athletes, reductions in intracortical facilitation were associated with a reduced ability to maximally activate muscle and an increased sense of effort to perform tasks (Powers, Cinelli, et al., 2014). It is evident that neurophysiological deficits persist in concussed athletes even after their physical symptoms have resolved, however the

cortical changes associated with persistent symptoms in post-concussion syndrome are unknown.

Activation and inhibition of the pyramidal tract begins during the preparation period of voluntary movement such that the muscle activation required to appropriately execute a task is set prior to movement (Hoshiyama et al., 1997). Furthermore, the prevention or inhibition of muscle contraction is an equally important component of motor control (Hoshiyama et al., 1997). In "Go/No-Go" task paradigms, single-pulse TMS shows increased motor evoked potential amplitudes (MEP) following a go cue, and attenuated MEP amplitudes after a No-Go cue (Hoshiyama et al., 1997; Leocani et al., 2000), demonstrating a reduction in corticospinal excitability in the No-Go condition. Similarly, intracortical excitability is also suppressed during No-Go tasks (Hallett, 2000b; Sohn et al., 2002). While these studies reveal changes in cortical excitability associated with the decision to move, the motor tasks used in these studies were always simple and consistent. Because individuals with post-concussion syndrome exhibit deficits in cognition, we sought to assess cortical excitability prior to different motor tasks with the idea that this may elucidate difficulties with pre-motor planning in this population.

Transcranial magnetic stimulation has also been used to assess task-dependent modulation of corticospinal excitability during various power and precision gripping tasks. Motor evoked potentials increase during the precision gripping tasks in comparison to power tasks (Hasegawa et al., 2001; Schieppati et al., 1996; Tinazzi et al., 2003). However, these studies only used single-pulse TMS, therefore, the changes in corticospinal excitability cannot be attributed to spinal or

cortical mechanisms. Moreover, TMS was administered during the motor tasks. This makes it difficult to discern whether the changes in motor evoked potential amplitudes were confounded by task-dependent differences in muscle activation (Sharples & Kalmar, 2012). Assessing cortical excitability with the muscle at rest, but prior to a planned contraction provides a measure of excitability during a period when premotor areas are active, but reduces the confounding effects of muscle activation (Sharples & Kalmar, 2012). Therefore, the purpose of this study was to investigate the task-dependent modulation of cortical excitability in individuals with post-concussion syndrome using a Go/No-Go task paradigm. This was carried out using single and paired-pulse transcranial magnetic stimulation, which was delivered while the hand was at rest, prior to two finger abduction tasks (precision and power) and at rest with no plan to contract. We hypothesized that there would be a task-dependent modulation of cortical excitability and that this would be impaired in individuals with post-concussion syndrome.

Methods

Participants

Ten people (9 women) with post-concussion syndrome (diagnosed previously by a physician) and ten age-, gender- and activity-matched healthy people participated in this study (see Table 1 for participant characteristics). Exclusion criteria for controls included diagnosis of a concussion or post-concussion syndrome within the past 2 years. Individuals with PCS were eligible to participate

in the study if they had been experiencing concussion symptoms for more than 30

days but had received clearance to return to work and/or school at least part-time.

All participants were screened for contraindications to TMS (Rossi et al., 2009)

completed a health history questionnaire, and provided written informed consent

prior to participation. This study was approved by the Institutional Research Ethics

Board.

Experimental Set-Up

Participants were seated in a modified automobile seat with their right arm

on a custom-built armrest with a force transducer set-up for index finger abduction.

The right arm and hand were secured to the armrest in a comfortable position with

a splint and the distal interphalangeal joint of the index finger was positioned

against the force transducer with a Velcro strap. The skin over the first dorsal

interosseous muscle (FDI) was cleaned with alcohol and a parallel bar surface EMG

sensor (10 x 1 mm Ag contacts with 1-cm interbar distance, DE-2.1, DELSYS Inc, MA,

USA) was placed over the muscle belly. A 5-cm diameter self-adhering ground

electrode (Dermatrode, Irvine, CA) was secured to the dorsal aspect of the hand. The

surface EMG signal was amplified 1000x (Bagnoli EMG, DELSYS Inc, MA, USA). Force

was amplified 10x by a custom-built amplifier. Surface EMG and force signals were

digitized at 2000 Hz using the Micro1401-3 data acquisition unit and Signal 6.0

waveform acquisition software (Cambridge Electronics Design, Cambridge, UK).

Surface EMG data was high-pass filtered at 10Hz and force was low-pass filtered at

50 Hz offline following data acquisition (Signal 6.0, Cambridge Electronics Design,

Cambridge, UK).

Transcranial Magnetic Stimulation Set-up

      A figure-eight TMS coil (Magstim Company Ltd., UK) was positioned over the

head using an articulated lighting support arm and clamp (Manfrotto Supports,

Italy). The TMS coil was moved over the hand region of the left primary motor

cortex in 1-cm increments to determine the optimal site for generating a motor

evoked potential (MEP) in the first dorsal interosseous (FDI) muscle. This was

determined by discharging the BiStim[2] stimulator (Magstim Company Ltd.,

Whitland, Carmarthenshire, UK) at suprathreshold intensities every 5 seconds, with

the handle positioned 45° posterolateral from the midsagittal line. The location that

elicited finger abduction and the largest MEP was considered the optimal FDI

hotspot. To ensure the same area was stimulated throughout the protocol, a mark

was drawn on the scalp with washable marker. To determine resting motor

threshold, the stimulator output was adjusted to find the minimum intensity that

elicited a 50 µV MEP in 5 out of 10 trials.

Single and Paired-Pulse TMS Parameters

      To assess the excitability of the corticospinal tract, a single-pulse (test

stimulus, TS) was used. The TS was set to the stimulator intensity that elicited a

peak-to-peak amplitude of 1mV. A paired-pulse paradigm (conditioning stimulus +

test stimulus, (Kujirai et al., 1993) was used to assess short-interval intracortical

inhibition (SICI) and intracortical facilitation (ICF) (Figure 1). To elicit short-interval

intracortical inhibition, a conditioning stimulus of 80% resting motor threshold intensity preceded the test stimulus by 3ms (Kujirai et al., 1993). The same conditioning stimulus preceded the test stimulus by 12ms to elicit intracortical facilitation (Kujirai et al., 1993).

Experimental Protocol

The participants began with three attempts at abducting the right index finger to produce maximal voluntary contraction (MVC) force. The highest of these three attempts was used to set 10%-MVC target for the precision contraction. Using frame-based software (Signal, Cambridge Electronic Design), the participants were shown a screen that refreshes every 5-s. Each 5-s frame was a trial during which the participant performed one of the three tasks (Figure 2). The participant was told which task they would be performing just prior to each frame. A vertical cursor prompted the participant to begin the task 1.5-s into the frame. The three tasks included: 1) a precision task for which the participant was asked to precisely trace a ramp up to the 10% target by abducting the finger), 2) a power task for which the participant was instructed to perform a very rapid and strong finger abduction contraction without a target, and 3) a resting condition for which the participant was instructed to remain relaxed (Figure 1A). It is important to note that for all tasks, the TMS stimuli were delivered while the muscle was still at rest 300-ms before the vertical cursor prompt to start the task. In this way, we assessed changes in excitability in a pre-motor period. Changes in excitability therefore reflect task-dependent modulation of cortical excitability during motor planning. Finally, we included an auditory tone presented 500-ms before the start of the task (200-ms

prior to the TMS stimulus), to inform the participant to go ahead with the task in that trial ("Go" trial) (Figure 2). In 30% of the trials, this tone did not occur. These were "No-Go" trials, when the participant should ignore the cue to begin the task and remain relaxed. Three motor tasks and three types of stimuli were pseudorandomized such that in one block of 90 frames, 10 of each type of stimulus (TS, SICI, and ICF) would be delivered at rest before each of the three motor tasks (rest, precision, and power) (Figure 1B). Thus, one block would include 90 frames. Participants completed two blocks. In between the two blocks, participants could rest and the experimenter made adjustments as necessary to ensure that the coil was positioned correctly to obtain the 1-mV test pulse prior to the second block. Each frame was visually inspected offline to ensure that there was no muscle activity present prior to the magnetic stimulus discharge, and whether participants performed the specified task on a "No-Go" trial. In the case where these situations were evident, these frames were removed from the data analysis. Waveform averages for each stimulus (TS, SICI, and ICF) were calculated for each task (rest, precision, and power) for both the Go and No-Go trials. Test stimulus MEP amplitudes are reported in millivolts (mV). Conditioned MEP amplitudes (short-interval intracortical inhibition and intracortical facilitation) are reported as a ratio between the paired-pulse (conditioned) MEP amplitude and the single-pulse (unconditioned) MEP amplitude (conditioned/unconditioned). The time between the TMS pulse and the initiation of the contraction is reported in ms and the peak force produced by participants in the power task (no target) is reported in %MVC.

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Analyses were performed using Statistica 13.2 (TIBCO Software Inc., Palo

Alto, CA). A 3x2x2 mixed ANOVA was performed to examine the effect of each of the

three tasks (power, precision, and rest), condition (Go/No-Go), and group (control

vs. PCS) on corticospinal excitability (test stimulus MEP amplitude). Separate 3x2x2

(task x Go/No-Go x group) mixed ANOVAs were performed for the intracortical

measures (short-interval inhibition and intracortical facilitation) to evaluate the

effect of each task, and Go/No-Go conditions by group. Additionally, a 2x2 (task x

group) mixed ANOVA was carried out to assess the latency between the two motor

tasks that required the participant to contract (precision and power) in both groups.

Fisher's LSD post-hoc analysis was performed to assess differences between means

when the ANOVAs revealed a main effect or interaction ($p < 0.05$). Simple regressions

were performed to assess relationships between cortical measures, total number of

symptoms, and symptom severity in the post-concussion group.

Results

Cortical measures

The post-concussion group sustained an average of 2.3 (range: 1-5)

concussions within the last 5 years. The average number of reported concussion

symptoms at the time of testing was 8.2 (range: 1-15), with an average symptom

severity of 13.8 (range: 1-33) on the SCAT3 symptom scale. Resting motor threshold

and the stimulator intensity required to evoke a 1mV peak-to-peak amplitude test

stimulus were not significantly different between the control and post-concussion group (Table 1). Corticospinal excitability assessed via single-pulse TMS was increased prior to a precision contraction compared to a power contraction ($p < 0.05$) and rest ($p < 0.01$) in both groups when the Go and No-Go conditions were collapsed (main effect of task $F_{(2, 36)} = 6.8236$, $p = 0.003$) (Figure 2). Paired-pulse TMS revealed no group or task-dependent differences in short-interval intracortical inhibition or intracortical facilitation (Figure 4). Corticospinal excitability, SICI, and ICF did not differ between the Go and No-Go trials; therefore data in figures are presented with Go and No-Go trials combined (Table 2).

Latency

Although the two motor tasks (precision and power) differed in complexity and the amount of force required, there were no significant differences in the time between the delivery of the TMS stimuli and the onset of voluntary muscle activity between the two motor tasks as or between the two groups (control precision: 0.28 ±0.05s, power: 0.30 ±0.01s; and PCS precision: 0.30 ±0.03s, power: 0.30 ±0.02s). Additionally, the amplitude of the power contractions (which had no target) did not differ between the control (11.26 ±4.79 N) and post-concussion group (13.18 ±7.69N).

Cortical measures and symptom characteristics

Intracortical facilitation was negatively correlated with the number of reported concussion symptoms ($r = 0.35$, $p = 0.055$) (Figure 4). A similar trend was

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demonstrated between intracortical facilitation and symptom severity (r = 0.33, p = 0.079) (Figure 4). There were no correlations between number of symptoms or symptom severity and corticospinal excitability (test pulse MEP amplitude) or intracortical inhibition.

Discussion

This study is the first to examine cortical changes based on the decision to move at rest prior to different planned contractions, and the first to demonstrate modulation of corticospinal excitability according to the demands of the planned motor task in both a healthy and concussed group. We found that corticospinal excitability was increased prior to a precision contraction compared to a power contraction and at rest. However, this was not associated with task-dependent modulation of intracortical facilitation or short-interval intracortical inhibition in either the control or the post-concussion group. Although there was no group effect of PCS on cortical excitability, PCS participants with higher total symptom scores and symptom severity scores tended to exhibit less intracortical facilitation which is consistent with the more robust reduction in intracortical facilitation we have observed previously in athletes who have sustained more recent concussions.

Previous research that has investigated task-dependent modulation using single-pulse transcranial magnetic stimulation (TMS) demonstrates greater corticospinal excitability during precision contractions. MEP amplitudes were increased in the prime mover muscles during a precision contraction, and while performing a pincer grip (precision task) compared to a power task and power

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gripping (Hasegawa et al., 2001; Schieppati et al., 1996; Tinazzi et al., 2003). Although these studies found a task-dependent modulation of corticospinal excitability associated with precision contractions, excitability was assessed while the muscle was activated during the task. In comparison, our study assessed cortical and corticospinal changes prior to planned finger abduction contractions, but while the hand was still at rest. We found an increase in corticospinal excitability at rest prior to a precision contraction, which is consistent with the earlier studies that assessed excitability during the task. Corticospinal excitability is known to increase prior to consistent voluntary movement (Rossini, Zarola, Stalberg, & Caramia, 1988; Tomberg & Caramia, 1991), and pre-movement modulation of corticospinal excitability as well as short-interval intracortical inhibition is associated with planning for different movement directions (van Elswijk, Schot, Stegeman, & Overeem, 2008). It was unclear whether corticospinal excitability would be modulated according to the type of task (precision vs. power) when the direction of the task was held constant. The results of our study conclude that corticospinal excitability is modulated before the task, according to the type of task, even though the direction of force production remained the same for both tasks.

The increase in corticospinal excitability prior to a precision contraction could not be explained by the two cortical mechanisms (SICI and ICF) that we assessed. This suggests that the increase in corticospinal excitability is due a cortical mechanism that we did not assess (e.g., LICI) or it was due to spinal modulation. It is also possible that the time between the TMS stimuli and the start of the task (300-ms) was not optimal to detect task-dependent changes in cortical

excitability. Previous research has reported that during a Go condition, MEP

amplitudes in agonist muscles were increased while antagonist muscles were

simultaneously inhibited 150-200-ms before planned voluntary movement. In the

No-Go condition, MEPs amplitudes decreased from 100-200-ms (Hoshiyama et al.,

1997) and 200-300-ms (Leocani et al., 2000) before the task. Although these studies

used single-pulse TMS only, it is possible that the changes in corticospinal

excitability can be attributed to cortical mechanisms. We found no differences in the

time between the TMS stimuli and the beginning of the contractions and no

differences in TS, SICI, or ICF in the Go and No-go trials at 300-ms. Future work with

a shorter interval between TMS stimulation and task initiation may reveal task-

dependent modulation of intracortical inhibition and facilitation. Furthermore,

previous research using Go/No-Go paradigms used more complex stimuli to signal

the different cues (i.e., Go or No-Go). For example, one study used acoustic stimuli

with different frequencies, and administered the tones using an interstimulus

interval between 6-8 s in order to reduce anticipation by the participants (Leocani).

Since differences in corticospinal excitability have been found between Go trials and

No-Go trials using more complex stimuli, it is possible that similar differences were

not observed in the current study as the Go/No-Go cues were too simple. It would

be beneficial to implement a more complex Go/No-Go paradigm (e.g., varying

acoustic frequencies) in future studies to determine if differences in cortical

excitability exist in a PCS population. Conversely, these changes may be spinally

regulated. In a study which assessed the effect of task instruction on the excitability

of spinal and supraspinal reflex pathways in the biceps brachii, an overall task-

dependent modulation of corticospinal excitability was observed during the long-latency stretch reflex (Lewis, MacKinnon, & Perreault, 2006). However, no difference was reported in the amount of short-interval intracortical inhibition between two different task instructions. This suggests that the changes in EMG activity during the long-latency stretch reflex are mediated below the cortical level (Lewis et al., 2006). Future work should include a protocol, such as transmastoid stimulation, to directly assess spinal mechanisms involved in excitability prior to different tasks.

Task-dependent modulation of corticospinal excitability did not differ between the controls and the post-concussion syndrome group. A recent study which investigated cortical changes in the early stages of concussion recovery, revealed a reduction in intracortical facilitation in the concussed athletes accompanied by a reduced ability to maximally activate muscle and an increased sense of force during submaximal contractions (Powers, Cinelli, et al., 2014). These changes were found in athletes who were no longer experiencing symptoms (i.e., asymptomatic). Thus, we hypothesized that similar alterations in cortical excitability may be evident in people with post-concussion syndrome who are characterized by a delay in the resolution of concussion symptoms. In contrast to people with more recent concussions, we found no differences in corticospinal excitability, SICI, or ICF in people with post-concussion syndrome in the present study.   Interestingly, there was a relationship between the SCAT3 symptom evaluation and intracortical facilitation in the post-concussion group. Higher total symptom scores and symptom severity scores were associated with greater

reductions in intracortical facilitation. This finding may reflect the heterogeneity of this clinical group and would suggest that only the most symptomatic PCS participants (who more closely resemble acutely concussed individuals) exhibit cortical hypoexcitability.

We found no effect of post-concussion syndrome on measures of cortical inhibition. Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the cortex (Werhahn et al., 1999), where $GABA_A$ receptors mediate short-interval intracortical inhibition, and $GABA_B$ receptors mediate long-interval intracortical inhibition (Ulf Ziemann, 2004). While $GABA_A$ receptors are unaffected by concussion (De Beaumont et al., 2009, 2007; Powers, Cinelli, et al., 2014; Tremblay et al., 2011), impairments in the $GABA_B$ receptor system as indicated by enhanced LICI and cortical silent periods, has been demonstrated even after athletes have been asymptomatic for long periods of time (De Beaumont et al., 2009, 2011, 2007; Tremblay et al., 2011). In our study, only short-interval intracortical inhibition (SICI) was measured. Consequently, changes in task-dependent modulation of cortical excitability within the post-concussion group may have been revealed if long-interval inhibitory circuits had been assessed (LICI). Furthermore, we used a 3-ms interstimulus interval in the current study to elicit SICI. Selecting a shorter interstimulus interval for SICI (e.g. 1-ms) and assessing LICI in a post-concussion group should be considered for future studies. Additionally, future work in this area should consider assessing spinal excitability to determine whether differences in spinal excitability exist between healthy people and those with post-concussion syndrome.

Conclusion

Corticospinal excitability assessed with the muscle at rest, prior to a contraction is modulated based on the nature of the planned motor task. A task that requires more precise force output is associated with greater corticospinal excitability. There was no effect of post-concussion syndrome on corticospinal or intracortical excitability, however, individuals who reported more concussion symptoms and greater symptom severity displayed reductions in intracortical facilitation. Since the effect of task on corticospinal excitability could not be isolated to a spinal or cortical mechanism, future work in this area assessing spinal excitability is warranted.

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Tables

Table 1. Cortical excitability parameters, demographic, and concussion information by group (mean ± standard deviation)

	Controls	PCS Group
Age (yrs)	22.4 (±4.33)	22.2 (±3.33)
MVC (N)	69.86 (±14.33)	66.93 (±23.58)
rMT (%MSO)	41.33 (±5.45)	45.17 (±2.79)
1mV test stimulus (%MSO)	52.44 (±6.15)	55.5 (±2.17)
# of concussions (last 5 yrs)	0	2.3 (±1.49)
SCAT3 symptom score	---	8.2 (±4.81)
SCAT3 symptom severity score	---	13.8 (±10.73)

MVC, maximal voluntary activation; rMT, resting motor threshold; %MSO, percent maximal stimulator output; SCAT3, Sport Concussion Assessment Tool3.

Table 2. Cortical excitability measures for Go and No-Go trials of the three different tasks. Values presented are the peak-to-peak MEP amplitudes (mean ± standard deviation) elicited by single-pulse TMS.

|	Control Group			PCS Group		
	Power	**Precision**	**Rest**	**Power**	**Precision**	**Rest**
Test Stimulus						
Go	0.85 ±0.51	1.06 ±0.74	0.73 ± 0.35	0.89 ±0.28	1.24 ±0.66	0.81 ±0.52
No-Go	0.73 ±0.39	0.93 ±0.41	1.14 ±0.56	1.16 ±0.56	1.02 ±0.58	0.60 ±0.31
Intracortical facilitation						
Go	1.55 ±0.75	1.98 ±1.36	1.85 ±0.82	1.36 ±1.16	1.85 ±1.23	1.57 ±1.14
No-Go	1.64 ±0.88	1.45 ±0.78	1.67 ±1.41	2.12 ±1.10	1.69 ±1.22	1.51 ±1.02
Intracortical inhibition						
Go	0.37 ±0.32	0.35 ±0.28	0.28 ±0.25	0.30 ±0.26	0.55 ±0.67	0.37 ±0.42
No-Go	0.31 ±0.37	0.34 ±0.27	0.24 ±0.24	0.57 ±0.53	0.50 ±0.38	0.41 ±0.45

Figures
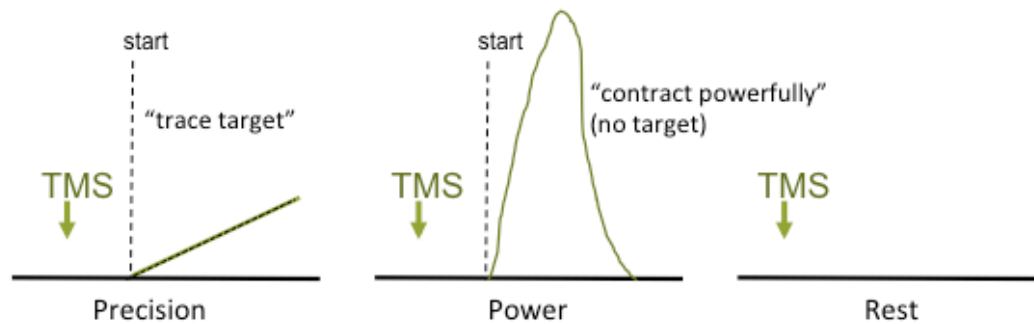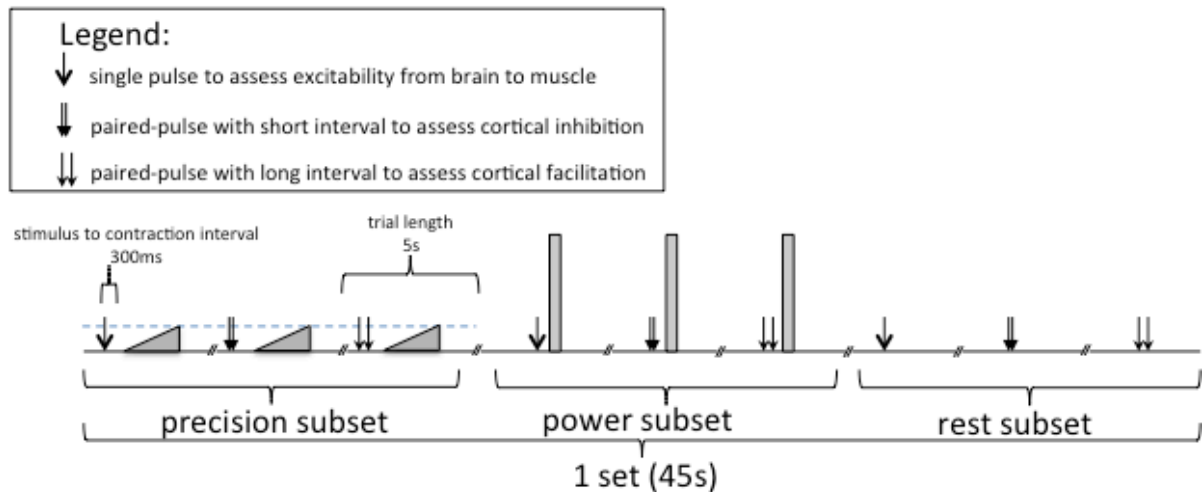

Figure 1. Experimental design (A). TMS was delivered while the hand was at rest, but prior to 3 different tasks: 1) precision contraction (participant was shown a ramp up to their 10% MVC target which they had to trace precisely by abducting their index finger), 2) a power task (participant was instructed to perform a very brief and strong finger abduction contraction without a target as quickly as possible. 3) resting condition (participant performed no contraction). Muscle activity was recorded using surface EMG. **Tasks and stimuli in one set (B).** Three TMS stimuli (test stimulus, short-interval intracortical inhibition, intracortical facilitation) were pseudorandomized for each set of nine frames to ensure that every set contained one of each type of stimulus for each type of task. One block consisted of 10 of these sets for a total of 90 frames.
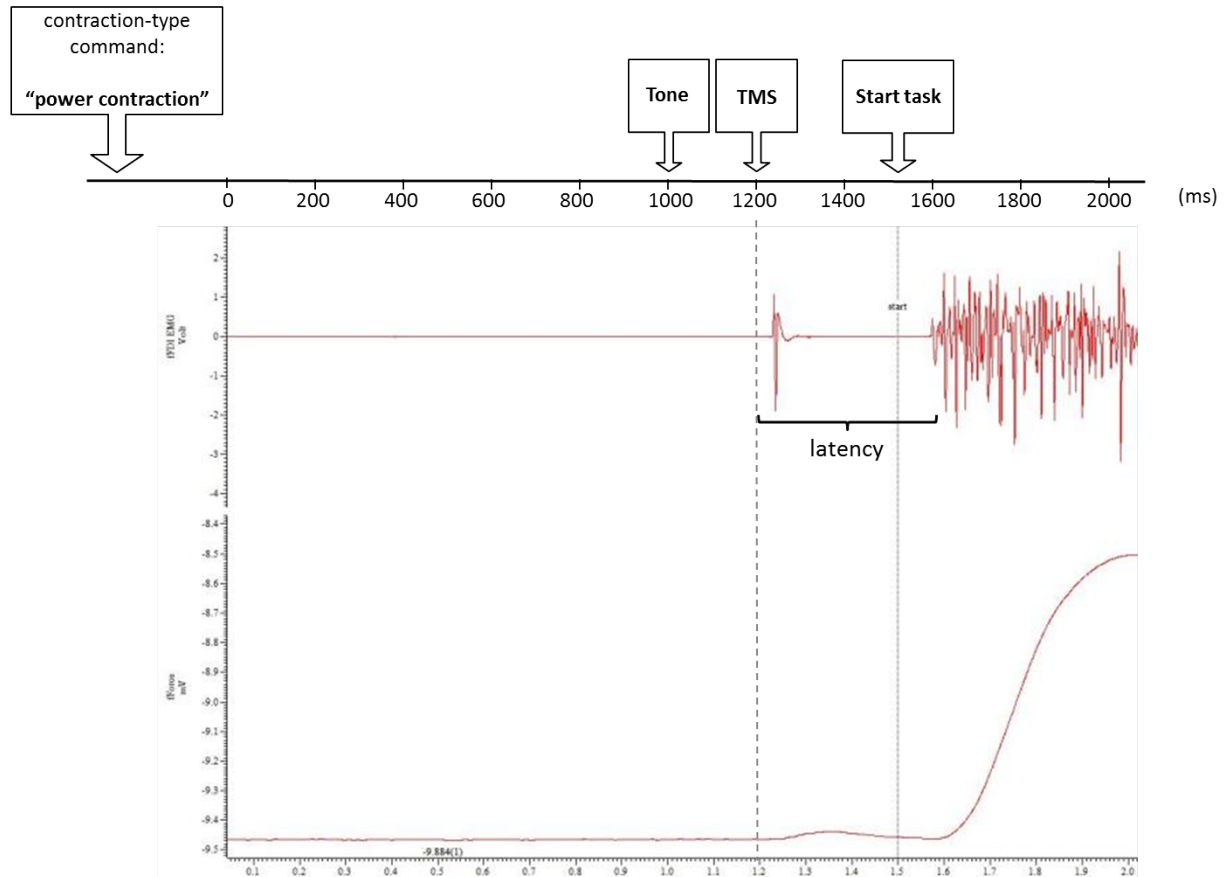
Figure 2. Timing sequence from a sample frame. Prior to the beginning of each frame participants were told what contraction they would perform next (rest, precision, or power). 1-s into the frame an auditory tone was presented, which cued the participant to perform the contraction ("Go" signal). 200-ms later, one of the TMS stimuli (TS, SICI, or ICF) was delivered to the primary motor cortex. 300-ms following stimulation, participants were cued to begin the task (vertical cursor prompt). The entire frame duration was 5-s.
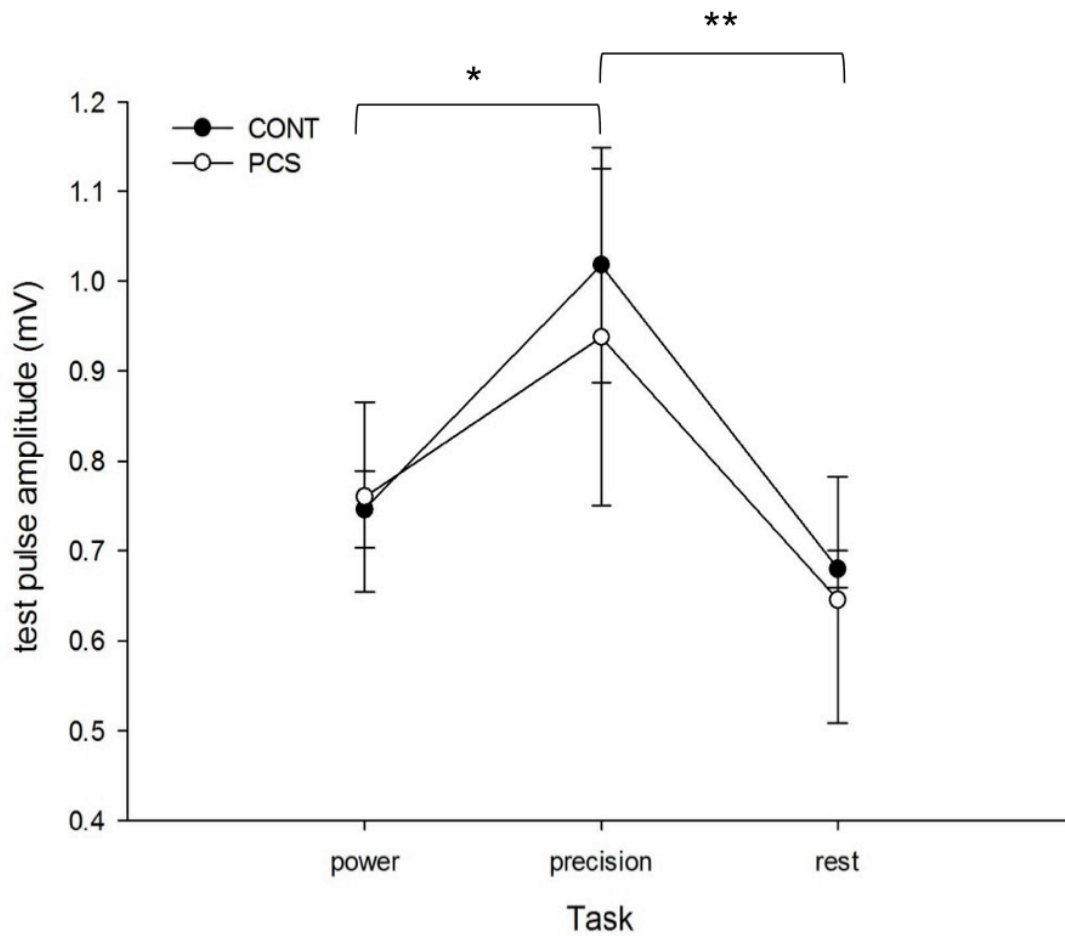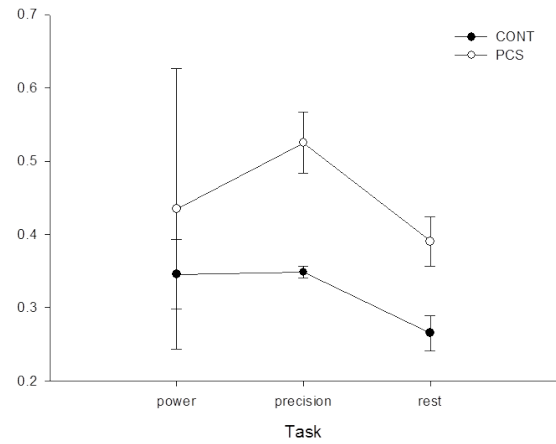
Figure 3. Corticospinal excitability measures. Mean amplitude (± standard deviation) of motor evoked potentials elicited by test stimulus (TS – 1mV). Corticospinal excitability was significantly increased in both groups prior to a precision contraction compared to a power contraction ($p < 0.05$) and at rest ($p < 0.01$) when the Go and No-Go trials were combined.
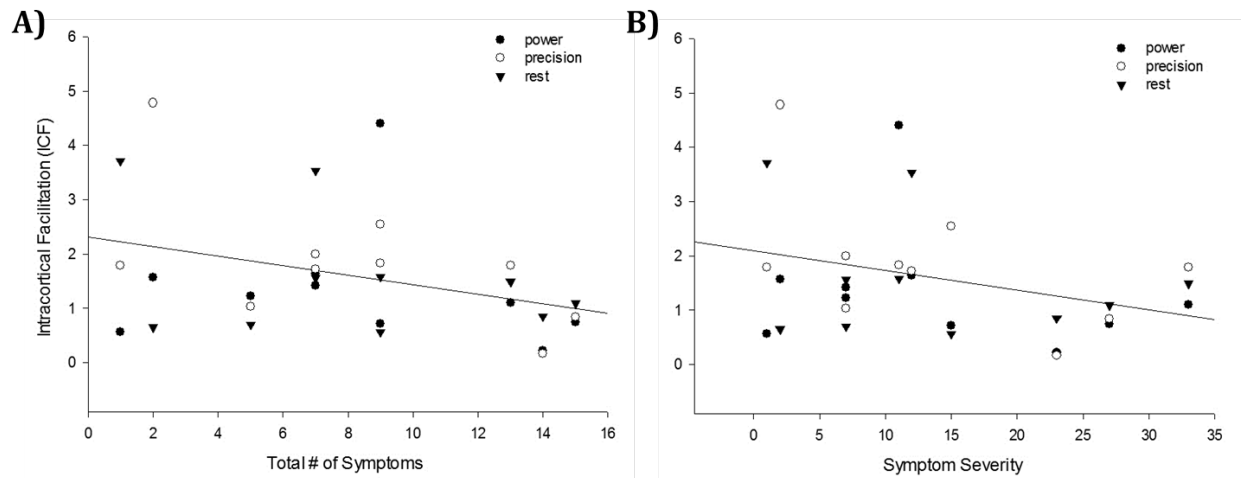
A) Intracortical facilitation
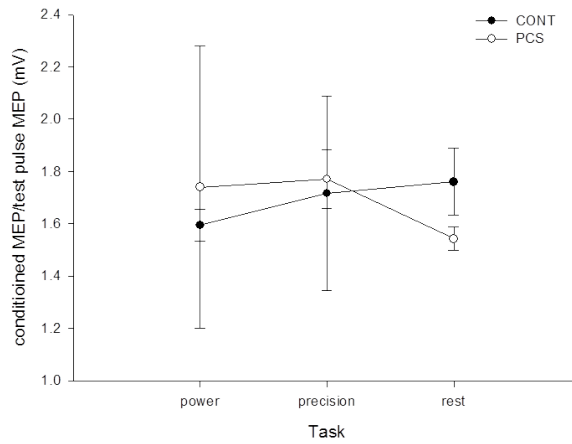
B) Intracortical inhibition

Figure 4. Intracortical excitability measures. Task-dependent modulation of A) intracortical facilitation and B) short-interval intracortical inhibition did not differ between groups or Go/No-Go trials.

Figure 5. Cortical excitability and SCAT3 symptom scores for the post-concussion group only. A) A negative correlation between intracortical facilitation and the number of reported symptoms was revealed when all tasks (power, precision, and rest) were combined (r =0.35, p = 0.055). B) A similar trend was observed between intracortical facilitation and symptom severity (r =0.33, p= 0.079).

Chapter 4: General Discussion and Future Directions

Post-concussion syndrome is a complex issue due to a variety of factors, such as pre-injury psychological disorders and monetary incentives due to ongoing lawsuits, which may confound the nature of the symptoms these individuals experience. In most cases symptoms resolve between 7-10 days post-concussion, however, diagnoses of PCS are made in 10-15% of cases following a concussion. While the diagnosis of PCS has been established based on symptomatology, it is unclear whether persistent changes in neurophysiology and balance control exist in this population. As such, the purpose of this thesis was to identify whether persistent cortical and/or balance deficits exist in individuals with PCS to provide further understanding of motor/balance control issues through measuring cortical activity in this complex population, which may eventually lead to more effective symptom management and safer return to sport decisions.

Each component of this two-part study provided further insight into PCS in a group of university-aged individuals. However, since this sample was small, results should be interpreted with caution, as they may not be representative of all individuals with PCS. Furthermore, the type of task in Chapter 3 was limited to an upper-limb task based on the feasibility of the TMS apparatus to evoke controlled responses in the upper-limbs. Since Chapter 2 used a lower-limb task to measure balance control, it would be beneficial to also use a lower-limb to investigate cortical excitability in future studies of this nature in order to better correlate the results from each study. Chapter 2 revealed that individuals with PCS expressed balance control deficits orthogonal to the intended movement (i.e., increased M/L sway) during a lower-limb reaching task, which was likely a result of sensorimotor

integration deficits. While balance impairments were revealed, the reaching task did not reveal differences in the magnitude of COP-COM movements, nor did it cause impairments to the postural control system during quiet standing post-testing. Since the combined analysis of COP-COM movements has been suggested to provide better insight into balance control than independent analyses of these variables, future work should use more challenging dynamic tasks to fully exploit balance impairments in this group. As an alternative, modifying other sensory systems (e.g., removing visual or somatosensory information) during the reaching task may also expose subclinical balance impairments.

Chapter 3 revealed no differences in corticospinal excitability or intracortical excitability between groups prior to powerful and precise finger abduction tasks. Only an overall effect of task (i.e., precision) on corticospinal excitability was revealed, which was displayed in both groups. Since previous research has reported differences in intracortical excitability between asymptomatic concussed athletes and controls, it is possible that the tasks used in this protocol may not have been challenging enough to expose neurophysiological deficits in this PCS group. Future research in this area should consider developing more difficult tasks with greater complexities, to determine if alterations in cortical excitability exist in this population.

In addition, both studies incorporated a Go/No-Go paradigm, which increased the cognitive demands of the participants, as they had to decide when to withhold movement and when to produce movement. While it was expected that the PCS group would perform worse than the control group, no differences were

revealed between the two groups in cortical excitability. This suggests that individuals with PCS are able to respond to Go/No-Go cues as effectively as those without concussion-based symptoms, which is important in sports and activities of daily living (e.g., driving and responding to traffic lights appropriately). However, the Go and No-Go trials were not independently analyzed in Chapter 2, therefore, the effect of the Go and No-Go cues on balance control cannot be ascertained. Future attempts should be made to evaluate balance control based on the specific trial instructions (i.e., Go or No-Go cue) to determine if individuals with PCS respond differently than non-concussed individuals.

Overall, individuals with PCS effectively completed both tasks during the behavioural and neurophysiological testing. Observationally, they did not appear to experience any greater difficulty when performing the tasks in comparison to the control group. However, impairments emerged when individual components of the balance measures were analyzed (Chapter 2). Furthermore, the two studies demonstrated that as a whole, the PCS group showed associations between greater symptom severity and lower intracortical facilitation and greater balance impairments. Although no differences were found in intracortical excitability between the two groups, it is possible that the more symptomatic individuals with PCS, who had greater reductions in intracortical facilitation (i.e., hypoexcitable), also had greater difficulty controlling the ankle and hip muscles by the central nervous system. In turn, these individuals experienced greater balance impairments. The findings from this thesis likely reflect the heterogeneity of this clinical group, suggesting that perhaps persistent deficits of this nature are more challenging to

expose in this complex population. However, the findings demonstrate significant impairments in this population, which may put these individuals at a greater risk of injury if they are allowed to return to play too soon. Thus, a may more conservative approach to return to play decisions should be considered for this population. Furthermore, our initial hypotheses of what we expected to see in this PCS population were based on results from studies, which investigated cortical excitability and balance control in acutely concussed or recently asymptomatic concussed athletes, as very little research of this nature has been performed in PCS. Therefore, we believed that if individuals with PCS would behave similarly to acutely concussed athletes, then PCS could be thought of as a continuum from an acute concussion. However, the results from this thesis are not in agreement with the results reported from the previous concussion studies, suggesting that individuals with PCS do not behave in the same manner or experience the same deficits as an acute concussed population. Therefore, it can be concluded that PCS does not fall on a continuum from acute concussion, rather, it is it's own separate group with distinct impairments in balance control and corticospinal excitability.