Experimentally Evoked Central Sensitization Does Not Modulate Dynamic Postural Responses to Medial-Lateral Perturbations in Healthy Young Adults

by:

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ABSTRACT

EXPERIMENTALY EVOKED CENTRAL SENSITIZATION DOES NOT MODULATE DYNAMIC POSTURAL RESPONSES TO MEDIAL-LATERAL PERTURBATIONS IN HEALTHY YOUNG ADULTS

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This thesis is an investigation of the neuromuscular mechanisms associated with postural modulation after experimentally-induced central sensitization during dynamic movement. Central sensitization is an important mechanism in the development and maintenance of chronic pain and there’s evidence to suggest that it has the ability to modulate muscle activity and resulting balance. Our hypothesis states that capsaicin-induced central sensitization at the C4/C5 spinal segments leads to delayed leg muscle onset and time-to-peak amplitude following platform perturbations. Participants stood on a robotic motion platform and these outcome measures were quantified using surface electromyography during platform perturbations. The findings suggest that central sensitization does not change leg muscle onset and time-to-peak amplitude during medial-lateral perturbations compared to non-sensitized controls. Although some muscles showed significance in these outcome measures, overall, the findings suggest that capsaicin-induced central sensitization does not have a significant impact on leg muscle activity required to maintain balance during medial-lateral perturbations.
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Cervicogenic disequilibrium is often observed in conditions of chronic pain associated with the neck/cervical spine and is commonly seen in association with cervical spine degeneration (Chaibi & Tuchin, 2011) or following flexion-extension injuries such as whiplash (Wrisley et al., 2000). Previous studies have demonstrated that neck pain has the ability to modulate balance (Michaelson et al., 2003; Poole et al., 2008). It is thought that cervicogenic disequilibrium is an important contributor to falls, especially in the elderly (Wyke, 1979; Johansson & Andersson, 2006). Falling caused by balance disorders is one of the leading causes of unintentional injury and subsequent death among older adults in both Canada and the United States, and these rates have risen steadily since 1993 (Gorina et al., 2006; Stinchcombe et al., 2014). In middle-aged adults (aged 40-60), decreased proprioception, postural stability, and balance disorders are common contributors to the increased incidence of falling (Isles et al., 2004; Nitz et al., 2003). In older adults (aged 65-82) presenting with chronic neck pain, balance may be impaired beyond that caused by normal aging, suggesting that the balance in younger adults with neck pain could potentially be impaired as well (Poole et al., 2008). While cervicogenic pain has been associated with balance disorders, the underlying mechanisms facilitating this are still poorly understood.

Chronic or persistent pain in the cervical spine, arising from injury and/or disease, can lead to central sensitization. Central sensitization is a neuroadaptive process whereby neurons in the central nervous system (CNS) become hypersensitive through enhanced membrane excitability and synaptic efficacy (Latremoliere & Woolf, 2009), which can lead to a broad range of physiologic effects in the human body. Central sensitization is an important physiologic mechanism that has been linked to a variety of clinical manifestations associated with chronic pain including fibromyalgia (Woolf, 2011; Coppieters et al., 2016) and osteoarthritis (Woolf, 2011; Arendt-Nielsen et al., 2011; Schaible et al., 2002). Previous research has shown that experimentally-induced central sensitization at the cervical spine segments leads to a tightening balance strategy during quiet standing (Huntley et al., 2015). Quiet standing balance outcomes
post-sensitization are biologically and clinically relevant, however, they do not adequately explain the effects of central sensitization on postural adjustments during dynamic balance recovery. Understanding the effect of central sensitization on dynamic postural responses is an important next step in this field, as optimizing these postural responses is clinically relevant to understanding the mechanisms of falls and developing effective preventative strategies.

No group to date has investigated the role and impact of underlying neurophysiologic mechanisms on postural modulation of dynamic balance responses. The purpose of this study was to advance this line of research by specifically investigating the role of central sensitization on dynamic balance recovery during postural responses to a platform perturbation. The findings of this research will contribute greater insight into the fundamental neuromuscular mechanisms driving postural modulation post-sensitization. Enhancing our understanding of these mechanisms will inform future research aimed at advancing both diagnostic and therapeutic interventions for those suffering from cervicogenic disequilibrium, as well as in developing strategies to aid in fall prevention in those suffering from chronic pain.

A significant delay in muscle onset and time for these muscles to reach their peak amplitude in the centrally sensitized condition would be indicative of central sensitization adding an additional set of afferent input to the CNS, resulting in more noise in the system. In this study, the leg muscles of interest were specifically chosen as they are main contributors to balance control and postural modulation in humans (Boonstra et al., 2009; de Freitas et al., 2010; Donath et al., 2016). Muscle onset and time to peak amplitude are important outcome measures to consider during dynamic balance recovery as leg muscle activity is essential in executing the appropriate postural response when balance is disturbed.
CHAPTER 2
BACKGROUND AND LITERATURE REVIEW

2.1 CENTRAL SENSITIZATION

2.1.1 Definition

Central sensitization is a neuroadaptive phenomenon that is caused by persistent input from peripheral nociceptors (Schaible & Grubb, 1993). It has been associated with the development and maintenance of chronic pain and hypersensitivity through enhanced synaptic efficacy (Latremoliere & Woolf, 2009). In this condition, the neurons of the CNS become hyperexcitable to both noxious (hyperalgesia) and innocuous (allodynia) stimuli (Woolf, 2011; Ingraham, 2016). Central sensitization is believed to be a primary contributing factor to various conditions associated with chronic pain. The excitability of neurons within the CNS are altered by constant peripheral inputs, which is the main way in which central sensitization is both initiated and sustained (Schaible & Grubb, 1993). Previous studies have also found evidence to suggest that central sensitization has the ability to alter the excitability of motor neurons, which in turn may affect the resulting neuromuscular response (Woolf, 2007).

2.1.2 Manifestations of Central Sensitization

Allodynia, hyperalgesia, and expansion of receptive fields (referred pain) are the three primary clinical manifestations of central sensitization (Woolf, 2011). Allodynia is characterized as a painful response to normally non-painful (innocuous) stimuli, while hyperalgesia is characterized as increased pain sensation to a normally painful (noxious) stimuli (Yunus, 2007; Woolf, 2011). Hyperalgesia can be further classified into primary and secondary hyperalgesia. Primary hyperalgesia is observed at the site of injury in response to both mechanical and heat stimuli, whereas secondary hyperalgesia is manifested remote to the site of injury (Treede et al., 1992; Meng-Tzu et al., 2015). Central sensitization also manifests by way of expansion of receptive field of dorsal horn neurons, in which larger areas of increased sensation to peripheral
stimuli are observed (Latremoliere & Woolf, 2009). This phenomenon is illustrated in the dorsal horn neurons by reduced activation threshold, increased spontaneous activity, and/or elevated responsiveness to suprathreshold stimulation (Latremoliere & Woolf, 2009).

Chronic pain often alters the way in which the central nervous system (CNS) processes neural signals. Patients who suffer from chronic pain typically become more sensitive and experience pain with less aggravating stimuli (Ingraham, 2016). Central sensitization is a major factor in most difficult pain problems. While it may not be the initial cause of pain, it perhaps may be what classifies the pain as being chronic as it maintains the pain even after the initial injury is healed (Ingraham, 2016). In a study by Smart et al., the researchers characterized pain associated with central sensitization as unpredictable and disproportionate patterns of pain in response to non-specific aggravating factors. In addition, this type of pain is often disproportionate to the nature and extent of injury or pathology, it demonstrates expanded regions of pain/tenderness on palpation, and commonly presents with maladaptive psychosocial factors (Smart et al., 2011). Previous research has linked central sensitization to pain hypersensitivity associated with a variety of clinical conditions including fibromyalgia (Woolf, 2011; Coppieters et al., 2016), temporomandibular joint disorders (Woolf, 2011; Hara et al., 2016), cervicogenic disequilibrium (Wrisley et al., 2000), headache (Woolf, 2011; Hara et al., 2016), osteoarthritis (Woolf, 2011; Arendt-Nielsen et al., 2011; Schaible et al., 2002), among others. Being able to identify the mechanisms that cause chronic pain and central sensitization may help to improve both the treatment and patient outcomes for such clinical conditions. This can be achieved by understanding the most effective treatment regimen and clinical interventions by which to treat each individual case and targeting the main underlying neurophysiological mechanisms that are responsible for the generation and maintenance of pain (Smart et al., 2011).

2.1.3 Experimental Induction of Central Sensitization

Central sensitization can be induced experimentally by several methods, including noxious thermal stimuli (Coronado et al., 2014; Dirks et al., 2003), chemical stimuli (Terkelsen et al., 2014), electrical stimuli (Vo & Drummond, 2013), and capsaicin (Dirks et al., 2003; Terkelsen et al., 2014; Martucci et al., 2012). Topical capsaicin cream (Zostrix, 0.075%; Hi-Tech Pharmacal,
Amityville, NY, USA) is a commonly employed experimental technique which evokes central sensitization by stimulating C-fibers within the region of application (Petersen, 1999). Capsaicin is an ingredient found in hot chili peppers and activates the release of inflammatory substances, such as substance P, by targeting the C-fiber nociceptors (Winter et al., 1995). The capsaicin cream technique is widely used to experimentally evoke central sensitization as it is easy to use and is minimally invasive to tissues compared with more invasive approaches such as injections (Petersen, 1999). This model was initially developed as a non-invasive way to produce stable regions of secondary hyperalgesia in order to study central sensitization (Petersen, 1999; Dirks et al., 2003). Although it is a comparatively mild stimulus, the topical capsaicin is often a preferred approach to experimentally induce central sensitization based on it’s ability to evoke secondary hyperalgesia without causing long-term adverse effects (Arendt-Nielsen & Andersen, 2005) to enable researchers to safely and reliably induce transient central sensitization in humans.

2.2 PERTURBATION

2.2.1 Definition

Platform perturbation studies are widely used to measure centre of pressure, centre of mass, postural and muscular reactions and recruitment, and joint angular changes following sudden movement of the support surface. Platform perturbation studies involve participants standing on a force plate mounted to a robotic motion platform that can be programmed to move anterior, posterior and/or sideways. As the platform moves, responses can be quantified using force plate, EMG, and/or kinematic data to assess balance recovery responses. Healthy muscles are activated quickly and in an appropriate order during platform movement in order to counteract the movements of the platform and enable the subject to maintain an upright, standing position (de Freitas, 2010). Modulation of force generated is required in many daily tasks, especially during unexpected postural disruptions in order to maintain balance and prevent falling (Stokes et al., 2006). Preventing excessive centre of mass displacement during perturbations reduces the likelihood of falling. This is achieved by either increasing the base of support by stepping (Zettel et al., 2008) or maintaining the same base of support by quickly activating the appropriate leg and postural muscles to maintain the standing position (de Freitas, 2010). In our study, subjects were
asked to adopt the second method to counteract the movement of the platform by maintaining the same base of support but activating their muscles to maintain their initial standing position.

2.2.2 Stepping Reaction

Researchers have previously investigated the first strategy of stepping as a fall avoidance strategy during perturbation trials (Zettel et al., 2008). They also included a cognitive component to investigate whether any features of the forward stepping reaction were affected by the dual-task attentional split and compared these responses between older and younger adults. Their results demonstrated increased lateral excursions of the centre of mass during the stepping action in older versus younger adults. These findings supported the hypothesis that the stepping reaction of young adults was not significantly impaired by the concurrent cognitive tasks, however, older adults showed impaired anticipatory ability to generate the stepping action during the platform perturbations with the concurrent cognitive task. The older adults also showed a delay in step onset time, which could be due to the dual-task interference of planning the step initiation while also engaged in the cognitive task itself (Zettel et al., 2008). These findings are supported by other dual-task studies, which demonstrate that the switch in attention typically occurs before the foot is raised during the initiation of the stepping reaction in response to a perturbation (Zettel et al., 2005). These observations suggest that some phases of the stepping reaction may require the use of cognitive functions to plan and execute the task effectively. Previous work has also shown that the ability to quickly reallocate cognitive resources is an age-related impairment and may be a possible explanation for the observed disruption in anticipatory postural adjustments observed in older adult cohorts (Zettel et al., 2008). It has been speculated that these findings could be related to pain, whereby the pain could simply act as a distraction to delay neuromuscular responses necessary for the maintenance of balance.

2.2.3 Muscle Onset

Muscle activation onset plays an important role in the maintenance of balance. In the study by de Freitas et al., subjects adopted the second strategy of activating their leg and postural muscles while maintaining the same base of support in order to avoid falling post-perturbation. The researchers specifically investigated the latency in muscle onset, time-to-peak amplitude,
magnitude of peak amplitude, and level of co-activation of four main left leg muscles (the tibialis anterior, gastrocnemius, rectus femoris, and biceps femoris) during anterior-posterior platform perturbations among different age groups. Based on the findings from their main outcome measures of EMG onset, time-to-peak, EMG amplitude, and level of agonist-antagonist muscle co-activation, they concluded that changes in neuromuscular function, namely those listed above as their outcome measures, occur in the fifth decade. They specifically found that the tibialis anterior and rectus femoris show a delay in both muscle onset and time-to-peak amplitude in older adults compared to younger adults (de Freitas et al., 2010).

In addition to leg muscle onset during platform perturbations, the onset of postural muscles is equally as important to maintaining balance and preventing falls. Neck muscle onset has been shown to be delayed in those with chronic neck pain as these individuals demonstrate altered neuromuscular control of the neck muscles in response to platform perturbations (Boudreau & Falla, 2014). Similarly, those with chronic neck pain associated with whiplash-related disorders, demonstrate impairments, such as larger areas of sway, that contribute to difficulties in maintaining body posture and balance during platform perturbations (Michaelson et al., 2003). The underlying neurophysiologic mechanisms mediating these responses are still poorly understood.

2.3 PAIN PERCEPTION

An individual’s expectation of pain can largely influence how that pain is perceived. Anticipation of increased pain elevates both the subjective experience of pain as well as the activation of pain-related regions of the brain (Koyama et al., 2004). This is also influenced by past memories and experiences with pain where the hippocampus and amygdala, brain structures involved in retrieval of past memories, project to regions of the brain that become active during the expectation of pain (Murray & Mishkin, 1983). An illustration of this would be if someone has previously experienced a burn, they will be able to not only remember what that pain felt like, but may also be able to feel that pain again by just thinking about it. This phenomenon is supported by the evidence demonstrating that regions of the brain involved in processing afferent sensory information overlap with brain regions involved in processing expectations (Kosslyn et al., 2001). Thus, an individual’s subjective experience of pain is strongly influenced by the brain regions
governing the expectations of pain and how they interact with other brain regions responsible for processing nociceptive input (Koyama et al., 2004).

The degree to which pain is perceived to be controllable can be determined based on both the neural and behavioural responses to nociceptive stimulation. The way in which nociceptive input is processed in the brain is largely influenced by perceived controllability, as it affects a wide array of cognitive functions, including the ability to cope with chronic pain (Jensen et al., 2001). Previous neural imaging studies have identified three areas of the brain that appear to be predominantly involved in pain processing, including the anterior cingulate cortex, the insular cortex, and the secondary somatosensory cortex (Peyron et al., 2000). These structures have been identified as important components of the neural circuit informing the organism about the body’s current state, including both the intensity and location of peripheral nociceptive input, in order to facilitate the generation of appropriate responses (Craig, 2003).

A study by Salomons et al. looked at how perceived controllability modifies the patterns of activation that are produced during peripheral stimulation. During the controllable condition, subjects were able to reduce the thermal stimulus to a non-painful duration, however, in the uncontrollable condition, they were asked to perform the same task, but their response had no effect on the duration of the thermal stimulus. Researchers used fMRI to image which brain regions were activated during the thermal stimulus during both the controllable and uncontrollable conditions. Consistent with previous brain imaging studies, researchers found bilateral activation of the insular, anterior cingulate, and secondary somatosensory cortices during the painful stimulus in the controllable condition. In addition, areas linked to cognition and affect processing were activated during the controllable pain condition, including the cerebellum, hippocampus, amygdala, prefrontal cortex, and the thalamus. These findings demonstrate that activation of these neural areas associated with pain are vast and can be modulated by an individual’s perceived controllability on the duration of the painful stimulus. The findings further suggest that cognitive factors, specifically perceived controllability, have a strong influence on an individual’s response to painful stimuli through the patterns of activation of the anterior cingulate cortex, the insula, and the secondary somatosensory cortex (Salomons et al., 2004). If an individual perceives they can control the pain, then this may lessen the influence that the pain would have on motor control as
they would be able to produce the appropriate postural response and motor actions required for a particular task (De Coster et al., 2014).

2.4 ELECTROMYOGRAPHY

2.4.1 Definition

Electromyography (EMG) is a technique used to measure and record the electrical activity of skeletal muscles. There are two types of electrodes, surface and indwelling, that can be used to record muscle activity by measuring the action potentials that are generated during muscle contractions travelling along the muscle fibres. EMG electrodes are commonly placed in a bipolar configuration over each muscle of interest to record its activity. Additionally, a reference electrode is placed over a bony landmark in order to record biological signals that are not muscle activity in order to be able to differentiate muscle activity from other biological noise (Kamen & Gabriel, 2010).

Non-invasive surface electrodes are placed on the skin over the superficial muscles to capture an overall representation of activity within the muscle of interest. Indwelling electrodes are inserted directly into the muscle of interest and are more effective at measuring the activity of deep and small muscles and specific motor units (Merletti & Farina, 2009; Soderberg & Cook, 1984). When using surface electrodes, the tissue (i.e. fat, skin, etc.) that the signal must pass through to reach the surface electrode has low-pass filtering properties, so the recorded signal at the skin surface has a lower amplitude and frequency than if it were recorded directly at the level of the muscle using indwelling electrodes (Kamen & Gabriel, 2010). Thus, indwelling electrodes preserve the signal content better than surface EMG as these filtering properties would not be a consideration when measuring the activity directly at the level of the muscle fiber (Merletti & Farina, 2009). In both cases, as the muscle contracts, the electrodes detect this action potential generated by the muscle and convert it into an analog signal. This information about muscle activity is then transferred to an amplifier and then to computer software for further analysis. This process of signal conversion is more commonly known as signal transduction (Kamen & Gabriel, 2010).
Our primary interest in this study was to employ surface EMG to investigate the overall patterns of the larger muscles of the leg involved in balance recovery response. We employed surface EMG to investigate the onset time and time-to-peak amplitude of leg muscles, including the tibialis anterior, gastrocnemius, rectus femoris, and biceps femoris bilaterally during platform perturbations after experimentally induced central sensitization versus non-sensitized control subjects.

2.4.2 Muscle Onset and EMG

One common use of EMG is to measure muscle onset during a particular task. Determining muscle onset time has been previously done by measuring the difference in time between the initiation of an action/movement and the time at which the muscle of interest is activated to perform the task (Sekir et al., 2015). Similarly, visual inspection of the EMG trace has been used in many studies to determine muscle onset latency (Oku et al., 2011; Voight & Wieder, 1991). Some studies suggest muscle onset time as the earliest detectable rise in EMG activity that deviates 1 or 1.5 standard deviations above steady state baseline activity (Hodges & Bui, 1996). Since this is not a definitive value, we identified muscle onset time as 3 standard deviations above steady state within a 10ms interval in order to ensure that we were capturing actual muscle onset and not simply noise artifact. Three standard deviations above baseline has been previously employed as a cutoff value in platform perturbation research using surface EMG (DiFabio, 1987; Rusaw et al., 2013; Kuo et al., 2011) because it reduces the likelihood of making a type I error, which assumes that a muscle was on when it actually was not (DiFabio, 1987). Muscle onset time is an important determinant in motor control given that the longer it takes a muscle to activate, the greater the difficulty in performing a task. In the context of balance, increased latency of postural and leg muscle onset during a platform perturbation increases the likelihood of falling (Fujio et al., 2016). Surface EMG has the capacity to detect the muscle onset time following a movement/perturbation and has been reported to be a highly repeatable and reliable method of determining muscle onset latency (Hodges & Bui, 1996).
2.4.3 Muscle Amplitude and EMG

In addition to muscle onset, muscle amplitude can also be determined from EMG signals. This can be done using visual inspection of the EMG tracing to identify the peak force generated by the muscle. Alternatively, this can be done using data processing tools such as Matlab or Microsoft Excel. We used the visual inspection method in order to ensure that the correct data points for the peak amplitude were being captured as these computer programs can sometimes pose technical errors. Accurately determining the maximum muscle EMG amplitudes using surface electrodes, however, presents a challenge due to skin impedance and its filtering properties, as well as relative electrode placement on the muscle of interest (Kamen & Gabriel, 2010; Ng et al., 1998). In addition to measuring the peak muscle amplitude, it is also interesting to note the time at which this peak was reached relative to muscle onset (latency in time to peak amplitude).

Several previous studies have looked at various measurements based on muscle amplitude such as the percent change in amplitude for each muscle (Vickers, 2001), co-contraction of antagonist muscles (Maeo & Kanehisa, 2014; de Freitas et al., 2010; Melzer et al., 2001), and the time at which the muscle reached peak amplitude (Murley et al., 2014). However, to date, very few studies have investigated the time for muscles to reach peak amplitude relative to muscle onset, especially following platform perturbations, and how this outcome measure is affected by the induction of central sensitization. In order to maintain balance, especially following a support surface perturbation, it is critical that postural and leg muscles reach their peak amplitude quickly. If this is impaired by central sensitization, then this may lead to adverse outcomes such as falling. Further understanding the mechanisms of how central sensitization influences the time-to-peak amplitude can aid in developing fall prevention strategies in a clinical population.

2.5 CENTRAL SENSITIZATION AND QUIET STANDING BALANCE

Huntley et al., was the first group to investigate the immediate (30-minutes) effect of experimentally induced central sensitization on postural stability during a quiet standing balance task (Huntley et al., 2015). His group induced central sensitization in the cervical spine region using the topical heat capsaicin technique and assessed postural stability by having participants perform a quiet standing balance task on a force plate. Pain in the cervical neck region was
measured by self-report measures, while the induction of central sensitization was validated using the brush allodynia technique to identify regions of secondary hyperalgesia. The brush allodynia technique is performed by lightly brushing the skin to identify dysesthesia (allodynia) within regions of secondary hyperalgesia (Ashkenazi & Young, 2004). Control trials without capsaicin cream were also performed by each participant as a means to compare the effects of the pre- and post-capsaicin trials. The primary outcome variables that were measured included the centre of pressure (COP) variability, sway range of COP, and the mean power frequency of COP and horizontal ground shear force. Results showed that inducing central sensitization via capsaicin in normal healthy young adults decreased COP variability and sway range, while increasing mean power frequency of COP displacement and shear force. These findings demonstrated reduction in postural sway, suggesting that experimental induction of central sensitization within the cervical spine region evokes tightening postural strategies during quiet standing. These findings appear in contrast to previous research, however, as it has been suggested that a longer duration of neck pain (>30 minutes) may be necessary to elicit the destabilizing impact on postural control during quiet standing (Corbeil et al., 2004; Vuillerme & Pinsault, 2009). While other research groups have established that experimentally-induced neck pain is able to destabilize standing balance (Vuillerme & Pinsault, 2009), no one has previously investigated the underlying neurophysiologic mechanisms contributing to these observations.

2.6 CLINICAL APPLICATIONS

2.6.1 Cervicogenic Disequilibrium

Dizziness and vertigo are two of the most common balance disorders (Neuhauser et al., 2008; Yardley et al., 1998). Dizziness and vertigo that arise from cervical spine disorders can be classified as cervicogenic disequilibrium, and are commonly observed after cervical spine flexion-extension injuries, such as whiplash (Wrisley et al., 2000) or cervical spine degeneration (Chaibi & Tuchin, 2011). Alterations in CNS processing has been shown to contribute to the clinical manifestation of dizziness, disequilibrium, and vertigo post-whiplash (Van Oosterwijck et al., 2013). The cervical dorsal roots and vestibular nuclei have strong connections with the proprioceptors and joint receptors of the neck, playing a large role in the perception of balance and
posture (Wrisley et al., 2000). Previous studies have reported a link between central sensitization and whiplash, suggesting that central sensitization may contribute to the clinical manifestation of ongoing symptoms observed with whiplash (Van Oosterwijk et al., 2013). Huntley et al. hypothesized that central sensitization may be an important fundamental mechanism mediating the clinical manifestation of cervicogenic disequilibrium (Huntley et al., 2015).

The chronic pain that lingers after whiplash injuries is associated with lower pain thresholds in these individuals (Curatolo et al., 2001). A meta-analysis by Van Oosterwijk et al. suggests that the chronic whiplash injuries cause the CNS to become hypersensitive and this maladaptive neurophysiologic response is believed to play a significant role in the lingering pain of those suffering from whiplash injuries. This maladaptive response may also underlie the pathophysiology of cervicogenic disequilibrium commonly experienced by those suffering from whiplash injuries (Van Oosterwijk et al., 2013). Similarly, Michaelson et al. determined that those with chronic neck pain subsequent to whiplash injury, showed larger areas of sway and impaired ability to maintain body posture/balance during platform perturbations (Michaelson et al., 2003). While this demonstrates that chronic neck pain could impair postural stability, it is important to understand the underlying neuromuscular mechanisms that contribute to specific muscle activity, including onset and time-to-peak amplitude in both postural and leg muscles that are required to maintain stability when balance is disturbed.

2.6.2 Fall Prevention

Chronic pain is often an ongoing distraction. Those suffering from chronic pain often spend much time focusing on their pain which may contribute to slower reaction times and impaired function (McCracken, 1997; Troche et al., 2015). Engaging in this distraction could be compared to dual-task assessments in which individuals are simultaneously focusing on both the pain and maintenance of balance during platform perturbations. Similarly, older adults show a delayed stepping reaction in response to platform perturbations during dual-task performances (Zettel et al., 2008). This mechanism could also be an important consideration when evaluating patients with chronic pain as their attentional resources to maintaining balance responses may be diminished. While postural stability is expected to decline with normal aging, Poole et al. investigated the
question whether the presence of neck pain contributes to this decline and found that chronic neck pain in this population can contribute to impaired balance beyond that caused by normal aging (Poole et al., 2008). Similarly, it is possible that younger adults experiencing chronic neck pain could also exhibit impaired balance and slower stepping reaction compared to that of older individuals not experiencing pain.

2.7 CONCLUSION

Previous research has reported both biologically and clinically relevant outcomes postsensitization during quiet standing balance trials after experimentally-induced central sensitization. However, the mechanisms of how central sensitization can impact dynamic postural adjustments during postural perturbations is still unclear. Improved understanding of these mechanisms will contribute important insight into the development of new diagnostic and therapeutic interventions for fall prevention, as well as patients suffering from conditions such as cervicogenic disequilibrium subsequent to chronic neck pain and whiplash.
The overall purpose of this research project was to investigate the underlying neuromuscular mechanisms of dynamic postural responses to disturbed balance in healthy controls and those with experimentally-induced central sensitization. As this is the first study to investigate the relationship between central sensitization and dynamic postural responses, we aimed to study these mechanisms in a young healthy cohort free of comorbidities that could impact baseline levels of central sensitization, such as degenerative spine and/or joint disease (Schaible et al., 2002). The objective of this thesis is to investigate the role of central sensitization on the dynamic postural responses in young healthy humans following a platform perturbation.

We tested the following hypotheses:

- Our primary hypothesis states that capsaicin-induced sensitization at the C4/C5 spinal level leads to delayed muscle onset in four leg muscles of interest (tibialis anterior, gastrocnemius, rectus femoris, and biceps femoris bilaterally) during postural responses after a platform perturbation when compared to non-sensitized controls.
- Our second hypothesis states that capsaicin-induced sensitization at the C4/C5 spinal level leads to a delay in the time-to-peak amplitude relative to muscle onset in four leg muscles (tibialis anterior, gastrocnemius, rectus femoris, and biceps femoris bilaterally) during postural responses after a platform perturbation when compared to non-sensitized controls.

The two primary outcome measures assessed in this study were muscle onset and time to peak amplitude relative to muscle onset. Two secondary outcome measures were subsequently analyzed to further help explain some of the findings of the primary outcome measures. These included magnitude of peak amplitude and time to peak amplitude relative to platform perturbation.

This study builds on previous literature that has demonstrated that chronic pain increases the latency of muscle onsets in the leg and postural (neck) muscles (de Freitas et al., 2010;
Boudreau et al., 2014; Michaelson et al., 2003). The findings of this study will provide important novel insight into the effects of central sensitization on neuromuscular responses to dynamic postural movement in young healthy populations and will inform further research into these mechanisms in older and clinical populations. The clinical endpoint of translating this line of basic research into practice is focused on the improvement of diagnostic, therapeutic, and preventative strategies in the management of cervicogenic disequilibrium and falls.
CHAPTER 4

METHODS

This study was approved by the Research Ethics Board at the University of Guelph (REB# 16MR007). It was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki (2008)) for experiments involving human subjects. Prior to participating in the study, participants provided written informed consent.

4.1 PARTICIPANTS

A total of sixteen healthy young adults (8 males (22.25 ± 1.8 years) and 8 females (21.5 ± 1.2 years)) were randomly recruited from the student population at the University of Guelph (Guelph, Ontario, Canada). No subjects withdrew from the study. A priori power analysis (effect size 1; alpha = 0.05) determined that 16 subjects per group were necessary for 80% power to detect a main effect of 1, at an alpha of 0.05 (Hodges et al., 2003).

Participants were pre-screened by being asked to complete a health questionnaire to exclude those with pre-existing somatosensory, neurological, or musculoskeletal conditions that could impact normal balance and somatosensory processing. Additional exclusion criteria included history of recurrent dizziness/unsteadiness, recent history of falling, use of medication affecting balance, hip or knee joint replacement, medical conditions interfering with normal daily activities, and/or functional limitations of limb use. Inclusion criteria included subjects with the ability to independently stand and walk without an aid, have a minimum Snellen visual acuity of 20/40, and be right-side dominant. Each subject acted as their own control, participating in both control and treatment trials.
4.2 EXPERIMENTAL SETUP

Subjects were provided with an information and consent package detailing the procedures and risks associated with participation in this study. They were provided an opportunity to read the package in its entirety and ask any questions for clarification before signing the consent form. All participants then completed a health history profile questionnaire of their current health status to identify any exclusionary conditions.

Subjects were then asked to stand barefoot on top of a force plate (AMTI ACG, Watertown, MA, USA) on a robotic motion platform that was computer programmed to move unpredictably in one of four directions: anterior, posterior, left, or right. The platform perturbations were programmed to move at a moderate magnitude based on previously published standard values in order to disrupt balance, but not to the extent of causing a stepping response or a fall. In the anterior direction, values were set at an acceleration of 1.3 m/s², a velocity of 0.39 m/s, and a displacement of 0.12 m. In the posterior and lateral directions, values were set at an acceleration of 2 m/s², a velocity of 0.6 m/s, and a displacement of 0.18 m (Perry et al., 2000). The perturbations were designed to cause subjects to lose their balance. As a safety precaution, subjects were secured to a safety harness in order to avoid a fall and/or injury (Methods Figure 1; Appendix B Figure 1). The safety harness did not provide body weight support. Prior to the start of the trial, subjects were connected to an EMG apparatus (Bortec Biomedical Ltd. Calgary, AB, Canada), with surface electrodes placed on both legs in a bipolar configuration on the belly of the muscles of interest, including the tibialis anterior, gastrocnemius, rectus femoris, and biceps femoris bilaterally. A reference electrode was placed on the right lateral malleolus (Methods Figure 2; Appendix B Figure 2). Muscles were identified by asking the subject to flex the muscle of interest so as to ensure that the electrodes were placed in the proper location on the bellies of the muscles, where they could capture whole muscle activity.
4.3 PROTOCOL

This study was a cross-over design whereby subjects received both test and control interventions. Subjects completed twelve practice trials (three perturbations randomly in each direction) to familiarize themselves with the motion of the platform and decrease the likelihood of observing a learning curve between the control and treatment trials. Subjects were asked to maintain an upright standing position throughout the duration of the trial and to use their best
efforts not to take a step during perturbations. The control trials consisted of a total of sixteen platform movements (four perturbations in each direction). The order of the perturbations (i.e. which direction the platform moved) was randomized for each subject for both the control and treatment conditions. Upon completion of the control trial, the subject was able to rest for fifteen minutes before beginning the treatment trial (Methods Figure 3; Appendix A).

For the treatment trial, 5 mL of a topical capsaicin cream (Zostrix, 0.075%; Hi-Tech Pharmacal, Amityville, NY, USA), was applied to the skin over the C4/C5 dermatomes to induce central sensitization in the C4/C5 spinal segments (Methods Figure 4; Appendix B Figure 3). Topical capsaicin has been shown to tonically stimulate peripheral nociceptors and induce central sensitization (Dirks et al., 2003). The platform perturbations for the treatment trial began fifteen minutes after the capsaicin cream was applied. This time frame was chosen because previous studies have reported that the sensitizing effects of capsaicin peak around 15-20 minutes post-application (Huntley et al., 2015; Srbely et al., 2010). The same protocol utilized for the control trial was repeated for the treatment trial, consisting of sixteen platform perturbations in an unpredictable pattern. Both the control and treatment trials were completed on the same day and were non-fatiguing. We ensured that these trials were non-fatiguing as subjects were given breaks and time to rest in between trials and asked if they were ready before each perturbation.
4.4 DATA MEASUREMENT AND ANALYSIS

EMG data was collected using a custom Labview program (National Instruments Corporation, TX, USA) and sampled at 1000 Hz with a gain of 2000X. The primary outcome measures for this study were the onset time (ms) and time to reach peak amplitude (ms) of each targeted muscle (tibialis anterior, gastrocnemius, rectus femoris, and biceps femoris bilaterally) during platform perturbations both with and without induced central sensitization. Two secondary outcome measures were subsequently assessed which included the magnitude of peak amplitude and the time to peak amplitude relative to perturbation. A custom MATLAB program (Version 2014b, Mathworks, Natic, MA, USA) was used to process the data for each subject in order to determine the muscle onset and time to reach peak amplitude. The time to reach peak amplitude was measured in relation to both muscle onset and the onset of platform movement. Raw EMG data was high pass filtered at 50Hz, rectified, and then low pass filtered at 30Hz. Muscle onset was determined as the point at which the EMG activity exceeded 3 standard deviations above steady state muscle activity after muscle onset and platform perturbation. This cutoff of 3 standard deviations above baseline reduces the likelihood of making a type I error, assuming a muscle was on when it actually was not, and this cutoff has been previously used in platform perturbation research using surface EMG (DiFabio, 1987; Rusaw et al., 2013; Kuo et al., 2011).
4.5 STATISTICAL ANALYSIS

All values are reported as mean ± standard deviation (SD). The measured variables and primary outcome measures of leg muscle onset (ms) and the time to reach peak muscle amplitude (ms) during platform perturbations were tested for significant differences (p ≤ 0.05) between the pain and control conditions using a paired t-test. To determine the muscle onset, the average onset time was taken for each muscle in each direction for each participant. These values from all participants were averaged together to determine the mean onset time for each muscle in all four directions and a paired t-test statistical analysis was conducted on these values. This sequence was done for both the control and treatment conditions. A paired t-test analysis was used for analysis as we were looking at each muscle individually, not the entire system as a whole. To determine time to peak amplitude relative to muscle onset, the time at which the muscles activated was subtracted from the time at which the peak amplitude was reached to yield a measurement of time-to-peak. The time to peak amplitude relative to muscle onset was analyzed in the same fashion as muscle onset, whereby the mean was determined for all participants for individual muscles in each perturbation direction, followed by a paired t-test. Again, this analysis was done for both the control and treatment conditions. For the secondary outcome measures, the magnitude of peak amplitude was determined as the highest peak value captured by the EMG, measured in mV. The time to peak relative to perturbation was the time that the peak amplitude was reached, as the perturbation onset was set as time 0. Analysis of these secondary outcome measures were analyzed the same way by pooling the mean for each muscle in each direction and used a paired t-test analysis to determine any significance.
CHAPTER 5

RESULTS

Data from a total of sixteen subjects (21.9 ± 1.5 years; 8 males, 8 females) were analyzed; no one withdrew from the study. Since subjects acted as their own control, there were no conflicts between the centrally sensitized and control groups that could have impacted the results found. Anterior-posterior platform perturbations were included in the protocol and the results are presented, but the data collected from these trials are not discussed as all of the subjects took a step to prevent falling during these trials and this was not the response we were interested in measuring (Appendix C). This represents the muscle responses of a stepping reaction rather than the muscle activity of maintaining the same base of support, which was the focus of this thesis. The anterior-posterior perturbations were still included in the protocol, however, because they acted as catch trials to prevent the subjects from becoming accustomed to the movement of the medial-lateral perturbations. For all graphs and tables, the following abbreviations are used: left (L), right (R), tibialis anterior (TA), gastrocnemius (Gastroc), rectus femoris (RF), biceps femoris (BF).

5.1 MUSCLE ONSETS

A primary finding of this study was that experimental induction of central sensitization does not change muscle onset times during medial-lateral platform perturbations. This was observed for all of the muscles measured in this study except for the hamstring muscle group, which demonstrated a significant delay in onset time in the treatment condition compared with controls (Table 1c & 1d; Figure 5 & 6). During right platform translations, the left biceps femoris muscle showed a significant delayed in onset time of the muscle (p=0.0372) in the sensitized group versus healthy controls (Figure 6). Similarly, during left platform translation, the right biceps femoris demonstrated significantly delayed onset of the muscle in the treatment condition (p=0.024) compared to healthy controls (Figure 5).
Table 1a. The mean onset time (ms) for each muscle from both the control and treatment conditions for the left perturbation trials with corresponding p-values. The onset time values are presented as means ± SD. *denotes a significant difference in muscle onset times between the control and treatment conditions.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Control (ms)</th>
<th>Treatment (ms)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>120.77 ± 10.46</td>
<td>122.02 ± 8.70</td>
<td>0.702</td>
</tr>
<tr>
<td>Gastroc</td>
<td>130.12 ± 15.42</td>
<td>130.12 ± 23.22</td>
<td>0.796</td>
</tr>
<tr>
<td>RF</td>
<td>130.63 ± 15.64</td>
<td>146.13 ± 23.27</td>
<td>0.059</td>
</tr>
<tr>
<td>BF</td>
<td>138.54 ± 12.03</td>
<td>158.06 ± 38.35</td>
<td>0.024*</td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>125.24 ± 10.71</td>
<td>127.25 ± 14.43</td>
<td>0.471</td>
</tr>
<tr>
<td>Gastroc</td>
<td>137.09 ± 12.56</td>
<td>175.88 ± 15.65</td>
<td>0.059</td>
</tr>
<tr>
<td>RF</td>
<td>133.81 ± 20.07</td>
<td>174.92 ± 53.18</td>
<td>0.231</td>
</tr>
<tr>
<td>BF</td>
<td>125.25 ± 22.12</td>
<td>138.85 ± 13.21</td>
<td>0.082</td>
</tr>
</tbody>
</table>

Table 1b. The mean onset time (ms) for each muscle from both the control and treatment conditions for the right perturbation trials with corresponding p-values. The onset time values are presented as means ± SD. *denotes a significant difference in muscle onset times between the control and treatment conditions.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Control (ms)</th>
<th>Treatment (ms)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>123.20 ± 10.99</td>
<td>131.25 ± 16.47</td>
<td>0.101</td>
</tr>
<tr>
<td>Gastroc</td>
<td>141.29 ± 14.95</td>
<td>161.01 ± 29.75</td>
<td>0.096</td>
</tr>
<tr>
<td>RF</td>
<td>136.62 ± 14.44</td>
<td>170.17 ± 46.89</td>
<td>0.226</td>
</tr>
<tr>
<td>BF</td>
<td>123.60 ± 13.09</td>
<td>144.91 ± 28.47</td>
<td>0.082</td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>123.40 ± 11.12</td>
<td>137.45 ± 27.94</td>
<td>0.055</td>
</tr>
<tr>
<td>Gastroc</td>
<td>124.09 ± 9.27</td>
<td>135.06 ± 18.16</td>
<td>0.095</td>
</tr>
<tr>
<td>RF</td>
<td>128.90 ± 14.10</td>
<td>130.91 ± 19.88</td>
<td>0.660</td>
</tr>
<tr>
<td>BF</td>
<td>127.93 ± 21.86</td>
<td>147.75 ± 38.50</td>
<td>0.037*</td>
</tr>
</tbody>
</table>
Figure 5 The mean onset time (ms) for each muscle (±SD) from both the control and treatment conditions for the left perturbation trials. *denotes a significant difference in muscle onset times between the control and capsaicin treatment conditions.

Figure 6 The mean onset time (ms) for each muscle (±SD) from both the control and treatment conditions for the right perturbation trials. *denotes a significant difference in muscle onset times between the control and capsaicin treatment conditions.
5.2 TIME TO PEAK MUSCLE AMPLITUDES RELATIVE TO MUSCLE ONSET

No differences in the time to peak amplitude relative to muscle onset were observed in the muscles during the treatment condition compared to the control (Table 2c & 2d; Figure 7 & 8) following medial-lateral platform perturbations. This finding held true for all muscles measured except the right tibialis anterior (p=0.045) and right rectus femoris (p=0.027), both of which reached peak amplitude significantly faster in the treatment condition following right-sided platform perturbations (Table 2d; Figure 8).

Table 2a. The mean time to peak amplitude (ms) relative to muscle onset for each muscle from both the control and treatment conditions for the left perturbation trials with corresponding p-values. The time to peak values are presented as means ± SD.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Control (ms)</th>
<th>Treatment (ms)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>TA</td>
<td>237.76 ± 226.44</td>
<td>127.16 ± 59.17</td>
</tr>
<tr>
<td></td>
<td>Gastroc</td>
<td>146.10 ± 123.07</td>
<td>193.53 ± 219.93</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>172.41 ± 141.68</td>
<td>172.09 ± 94.80</td>
</tr>
<tr>
<td></td>
<td>BF</td>
<td>571.01 ± 612.90</td>
<td>387.25 ± 453.42</td>
</tr>
<tr>
<td>Left</td>
<td>TA</td>
<td>267.89 ± 707.94</td>
<td>66.98 ± 43.80</td>
</tr>
<tr>
<td></td>
<td>Gastroc</td>
<td>628.23 ± 427.61</td>
<td>410.42 ± 246.80</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>696.53 ± 753.71</td>
<td>170.41 ± 185.80</td>
</tr>
<tr>
<td></td>
<td>BF</td>
<td>209.05 ± 231.87</td>
<td>364.41 ± 477.60</td>
</tr>
</tbody>
</table>

Table 2b. The mean time to peak amplitude (ms) relative to muscle onset for each muscle from both the control and treatment conditions for the right perturbation trials with corresponding p-values. The time to peak values are presented as means ± SD. *denotes a significant difference in time to reach peak amplitude between the control and treatment conditions.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Control (ms)</th>
<th>Treatment (ms)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>TA</td>
<td>295.15 ± 276.54</td>
<td>112.24 ± 144.05</td>
</tr>
<tr>
<td></td>
<td>Gastroc</td>
<td>903.55 ± 658.16</td>
<td>801.76 ± 495.08</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>690.70 ± 533.51</td>
<td>344.10 ± 321.56</td>
</tr>
<tr>
<td></td>
<td>BF</td>
<td>599.84 ± 779.34</td>
<td>451.47 ± 525.31</td>
</tr>
<tr>
<td>Left</td>
<td>TA</td>
<td>155.99 ± 93.30</td>
<td>128.50 ± 68.28</td>
</tr>
<tr>
<td></td>
<td>Gastroc</td>
<td>176.60 ± 159.79</td>
<td>201.98 ± 134.75</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>163.16 ± 141.31</td>
<td>176.07 ± 161.61</td>
</tr>
<tr>
<td></td>
<td>BF</td>
<td>320.37 ± 321.25</td>
<td>176.90 ± 211.71</td>
</tr>
</tbody>
</table>
Figure 7 The mean time to peak amplitude (ms) (±SD) relative to muscle onset for each muscle from both the control and treatment conditions for the left perturbation trials.

Figure 8 The mean time to peak amplitude (ms) (±SD) relative to muscle onset for each muscle from both the control and treatment conditions for the right perturbation trials. *denotes a significant difference in time to reach peak amplitude between the control and treatment conditions.
5.3 MAGNITUDE OF PEAK MUSCLE AMPLITUDE

A secondary finding of this study was that there was no significant difference in the magnitude of mean peak amplitude for each muscle during medial-lateral perturbations between treatment and control conditions (Table 3c & 3d; Figure 9 & 10). All of the muscles of interest reached the same peak amplitude during the balance response following medial-lateral perturbations in both conditions.

Table 3a. The mean peak amplitude (mV) for each muscle from both the control and treatment conditions for the left perturbation trials with corresponding p-values. The peak amplitude values are presented as means ± SD.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Control (mV)</th>
<th>Treatment (mV)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>0.57 ± 0.35</td>
<td>0.56 ± 0.33</td>
<td>0.810</td>
</tr>
<tr>
<td>Gastroc</td>
<td>0.26 ± 0.16</td>
<td>0.23 ± 0.19</td>
<td>0.444</td>
</tr>
<tr>
<td>RF</td>
<td>0.2 ± 0.10</td>
<td>0.21 ± 0.12</td>
<td>0.622</td>
</tr>
<tr>
<td>BF</td>
<td>0.14 ± 0.12</td>
<td>0.1 ± 0.06</td>
<td>0.266</td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>0.34 ± 0.16</td>
<td>0.36 ± 0.18</td>
<td>0.956</td>
</tr>
<tr>
<td>Gastroc</td>
<td>0.16 ± 0.08</td>
<td>0.11 ± 0.09</td>
<td>0.114</td>
</tr>
<tr>
<td>RF</td>
<td>0.22 ± 0.31</td>
<td>0.47 ± 0.95</td>
<td>0.406</td>
</tr>
<tr>
<td>BF</td>
<td>0.11 ± 0.09</td>
<td>0.1 ± 0.10</td>
<td>0.873</td>
</tr>
</tbody>
</table>

Table 3b. The mean peak amplitude (mV) for each muscle from both the control and treatment conditions for the right perturbation trials with corresponding p-values. The peak amplitude values are presented as means ± SD.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Control (mV)</th>
<th>Treatment (mV)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>0.37 ± 0.23</td>
<td>0.32 ± 0.19</td>
<td>0.093</td>
</tr>
<tr>
<td>Gastroc</td>
<td>0.14 ± 0.09</td>
<td>0.08 ± 0.03</td>
<td>0.254</td>
</tr>
<tr>
<td>RF</td>
<td>0.16 ± 0.12</td>
<td>0.1 ± 0.06</td>
<td>0.167</td>
</tr>
<tr>
<td>BF</td>
<td>0.15 ± 0.10</td>
<td>0.11 ± 0.08</td>
<td>0.221</td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>0.53 ± 0.25</td>
<td>0.59 ± 0.41</td>
<td>0.709</td>
</tr>
<tr>
<td>Gastroc</td>
<td>0.22 ± 0.14</td>
<td>0.22 ± 0.12</td>
<td>0.931</td>
</tr>
<tr>
<td>RF</td>
<td>0.28 ± 0.22</td>
<td>0.3 ± 0.33</td>
<td>0.654</td>
</tr>
<tr>
<td>BF</td>
<td>0.07 ± 0.07</td>
<td>0.06 ± 0.04</td>
<td>0.453</td>
</tr>
</tbody>
</table>
Figure 9 The magnitude of mean peak amplitude (mV) (±SD) for each muscle from both the control and treatment conditions for the left perturbation trials.

Figure 10 The magnitude of mean peak amplitude (mV) (±SD) for each muscle from both the control and treatment conditions for the right perturbation trials.
5.4 TIME TO PEAK MUSCLE AMPLITUDE RELATIVE TO PLATFORM PERTURBATION

No significant differences in the time at which the peak amplitude occurred relative to platform perturbation was observed between the treatment and control conditions during medial-lateral platform perturbations (Table 4c & 4d; Figure 11 & 12). This held true for all muscles except the right tibialis anterior which reached peak amplitude significantly faster (p=0.029) in the treatment condition versus the control during the right platform perturbations (Table 4d; Figure 12).

Table 4a. The mean time (ms) at which peak amplitude was reached relative to platform movement for each muscle from both the control and treatment conditions for the left perturbation trials with corresponding p-values. The time to peak amplitude values are presented as means ± SD

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Control (ms)</th>
<th>Treatment (ms)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>TA</td>
<td>356.47 ± 226.58</td>
<td>241.43 ± 43.75</td>
</tr>
<tr>
<td>Gastroc</td>
<td>263.8 ± 118.13</td>
<td>302.43 ± 215.63</td>
<td>0.548</td>
</tr>
<tr>
<td>RF</td>
<td>296.63 ± 142.67</td>
<td>284.5 ± 97.29</td>
<td>0.754</td>
</tr>
<tr>
<td>BF</td>
<td>687.05 ± 604.02</td>
<td>501.33 ± 471.18</td>
<td>0.260</td>
</tr>
<tr>
<td>Left</td>
<td>TA</td>
<td>387.01 ± 711.65</td>
<td>177.53 ± 40.77</td>
</tr>
<tr>
<td>Gastroc</td>
<td>730.97 ± 404.75</td>
<td>560.36 ± 234.07</td>
<td>0.342</td>
</tr>
<tr>
<td>RF</td>
<td>788.81 ± 710.33</td>
<td>316.92 ± 229.19</td>
<td>0.135</td>
</tr>
<tr>
<td>BF</td>
<td>277.36 ± 264.80</td>
<td>428.22 ± 497.00</td>
<td>0.124</td>
</tr>
</tbody>
</table>

Table 4b. The mean time (ms) at which peak amplitude was reached relative to platform movement for each muscle from both the control and treatment conditions for the right perturbation trials with corresponding p-values. The time to peak amplitude values are presented as means ± SD. *denotes a significant difference in time of muscle amplitude between the control and treatment conditions

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Control (ms)</th>
<th>Treatment (ms)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>TA</td>
<td>417.04 ± 278.72</td>
<td>221.36 ± 140.92</td>
</tr>
<tr>
<td>Gastroc</td>
<td>891.19 ± 660.32</td>
<td>874.58 ± 476.27</td>
<td>0.789</td>
</tr>
<tr>
<td>RF</td>
<td>798.35 ± 519.88</td>
<td>577.42 ± 364.08</td>
<td>0.063</td>
</tr>
<tr>
<td>BF</td>
<td>704.07 ± 738.74</td>
<td>545.33 ± 541.62</td>
<td>0.615</td>
</tr>
<tr>
<td>Left</td>
<td>TA</td>
<td>274.16 ± 96.95</td>
<td>260.66 ± 97.31</td>
</tr>
<tr>
<td>Gastroc</td>
<td>306.27 ± 163.27</td>
<td>311.81 ± 134.27</td>
<td>0.940</td>
</tr>
<tr>
<td>RF</td>
<td>278.39 ± 159.40</td>
<td>319.38 ± 167.16</td>
<td>0.735</td>
</tr>
<tr>
<td>BF</td>
<td>394.79 ± 351.44</td>
<td>292.5 ± 247.56</td>
<td>0.192</td>
</tr>
</tbody>
</table>
Figure 11 The time to peak amplitude (ms) (±SD) relative to perturbation for each muscle from both the control and treatment conditions for the left perturbation trials.

Figure 12 Time to peak amplitude (ms) (±SD) relative to perturbation for each muscle from both the control and treatment conditions for the right perturbations. *denotes a significant difference in time to reach peak amplitude between the control and treatment conditions.
5.5 REPORTED SENSATIONS TO CAPSAICIN CREAM

All subjects reported the capsaicin cream to feel like a burning, hot, itchy, and prickly sensations on the back of their neck where the cream was applied. The most intense burning and painful feeling was reported by all subjects between 15-20 minutes post-cream application, which was the time at which the treatment trials were conducted. This time frame was chosen to do the treatment trials as numerous previous studies have determined this to be the time at which the capsaicin cream produces the most clinically relevant central sensitization outcomes (Huntley et al., 2015; Srbely et al., 2010). This was also further confirmed during pilot testing. Upon completion of the study, subjects reported feeling “back to normal” once they rinsed the cream off their neck.
CENTRAL SENSITIZATION IS A NEUROADAPTIVE PROCESS ASSOCIATED WITH THE DEVELOPMENT AND MAINTENANCE OF CHRONIC PAIN AND HYPERSENSITIVITY THROUGH ENHANCED SYNAPtic EFFICACY (LATREMOLIERE & WOOLF, 2009). CENTRAL SENSITIZATION HAS BEEN SHOWN TO MODULATE QUIET STANDING BALANCE BY EVOKING A TIGHTENING EFFECT IN LEG AND POSTURAL MUSCLES (HUNTLEY ET AL., 2015). HOWEVER, THE MECHANISMS BY WHICH CENTRAL SENSITIZATION MODULATES LEG MUSCLE ONSET AND TIME TO REACH PEAK AMPLITUDE DURING DYNAMIC POSTURAL CONTROL HAS NOT PREVIOUSLY NOT BEEN EXPLOR ED.


THE PRIMARY HYPOTHESES OF THIS STUDY ARE THAT CAPSAICIN-INDUCED SENSITIZATION WOULD LEAD TO DELAYED MUSCLE ONSET AND TIME-TO-PEAK AMPLITUDE IN THE LEG MUSCLES OF INTEREST DURING PLATFORM PERTURBATIONS COMPARED TO NON-SENSITIZED CONTROLS. THE RATIONALE FOR OUR HYPOTHESES IS BASED ON PREVIOUS RESEARCH REPORTING THAT CENTRAL SENSITIZATION CAUSES CHANGES IN SYNAPTIC EFFICACY (LATREMOLIERE & WOOLF, 2009). SINCE TOPICAL CAPSAICIN CAUSES A SYSTEMATIC EFFECT, WE EXPECTED THE WHOLE SYSTEM TO BE AFFECTED BY THE EXPERIMENTALLY INDUCED CENTRAL SENSITIZATION AND THEREFORE, WE WOULD EXPECT ALL OF THE MUSCLES OF INTEREST TO SHOW THESE SAME RESULTS. THE HYPOTHESIZED DELAY IN
muscle onset and time-to-peak was expected as previous studies have shown this to be true in both older adults (de Freitas et al., 2010) and in neck muscles of those with chronic pain (Boudreau & Falla, 2014). Two secondary outcome measures of magnitude of peak amplitude and time-to-peak relative to perturbation were subsequently analyzed to see if they showed any significance to further help explain some of the primary findings.

The results demonstrate that there is no overall significant change in both the primary and secondary outcome measures assessed in the treatment condition compared to the control following medial-lateral perturbations. Specifically, there was no overall significant change observed in muscle onset (Results Table 1a & 1b), time to reach peak amplitude relative to both muscle onset (Results Table 2a & 2b) and platform perturbation (Results Table 4a & 4b), and the magnitude of peak muscle activity (Results Table 3a & 3b) during medial-lateral perturbations. There were, however, some muscles that showed significance for these outcome measures and these findings will be discussed in further detail in subsequent sections. Although these findings refute both of our hypotheses, there are still some plausible explanations as to why there was little significant difference between the treatment and control conditions for these outcome measures.

6.1 STUDY FINDING 1: CENTRAL SENSITIZATION DOES NOT CHANGE MUSCLE ONSET AFTER MEDIAL-LATERAL PLATFORM PERTURBATION

The findings from our study refute our primary hypothesis indicating that during medial-lateral support surface perturbations, central sensitization does not cause an overall change in leg muscle onset. Our data shows that the biceps femoris exhibits a significant delay in onset time during contralateral platform perturbations in the treatment condition compared to healthy controls. The left biceps femoris was significantly delayed (p=0.037) during contralateral (right) perturbations in the treatment condition versus controls (Results Table 1b; Results Figure 6). Similarly, during left perturbations, the contralateral (right) biceps femoris exhibited significantly delayed onset times (p=0.024) in the treatment condition (Results Table 1a; Results Figure 5). In both of these significant results, the onset of the biceps femoris in the centrally sensitized condition was delayed by 11 milliseconds.
6.1.1 Interpretation of Study Finding 1

There are two possible explanations as to why the biceps femoris muscles showed a delayed onset time following contralateral medial-lateral perturbations in the treatment condition compared to controls. The hamstrings have been shown to be important muscles in the maintenance of balance, specifically in medial-lateral perturbations as they function as knee stabilizers (Letafatkar et al., 2015; Shultz et al., 2000) and protect the ACL from damage (Wild et al., 2013). As such, their delayed onset in the centrally sensitized condition may be detrimental to maintaining balance during medial-lateral dynamic movement.

Topical capsaicin cream evokes central sensitization by targeting C-fiber nociceptors and activates the release of inflammatory substances. By targeting the C-fibers, this leads to a prolonged feeling of pain, and the extended input of painful sensations by the capsaicin to the C-fibers leads to hypersensitivity and central sensitization (Petersen, 1999; Winter et al., 1995). A delay in leg muscle onset during platform perturbations in the treatment condition compared to healthy controls may be indicative of noise, mainly the release of excess inflammatory substances, being added to the system (Hedayatpour et al., 2011), affecting specifically the synaptic efficacy of neurons. Therefore, the topical capsaicin cream that was applied to the C4/C5 spinal segments may have altered the synaptic efficacy of the neurons branching off these spinal segments and innervating the muscles of interest (Lynn et al., 1992; Winter et al., 1995). Specifically, by targeting C-fiber nociceptors, these sensory receptors sent signals to the brain to inform it about the painful stimuli (Caterina et al., 1997). This then led to a release of inflammatory substances that add an extra level of afferent input, which may have contributed noise to the system that the CNS would have had to filter through in order to produce the appropriate postural response to maintain balance following the platform perturbations (Winter et al., 1995; Lynn et al., 1992). Although little significant difference was shown between the treatment and control conditions, it is possible that not much noise was added to the system as low-concentration capsaicin cream (0.075%) is a relatively mild technique to induce central sensitization (Anand & Bley, 2011; Derry et al., 2009; Altman & Barkin, 2009). As such, the CNS may not have had as much difficulty filtering through the noise (Winter et al., 1995) in order to initiate the appropriate postural response.
to maintain balance. This would be the case for all of the muscles except the hamstrings as the biceps femoris showed a delayed onset in the centrally sensitized condition.

A second explanation could be that the capsaicin cream on the C4/C5 spinal segments acted as a distraction to the subject (McCracken, 1997; Troche et al., 2015). The subjects may therefore be more focused on the pain on the back of their neck, which would impair their ability to switch their focus and reallocate their attention as quickly as in the control condition to be able to activate their leg muscles and produce the appropriate postural response to maintain balance (Crombez et al., 1996; Eccleston et al., 1999). While this is what would be expected for all of the muscles measured, it is unclear as to why only the biceps femoris muscles showed a significant delay in muscle onset. This is an area of research that future studies can explore.

6.2 STUDY FINDING 2: CENTRAL SENSITIZATION DOES NOT CHANGE THE TIME-TO-PEAK AMPLITUDE RELATIVE TO MUSCLE ONSET AFTER MEDIAL-LATERAL PLATFORM PERTURBATION

The findings from our study refute our secondary hypothesis that experimentally induced central sensitization delays the time-to-peak amplitude of leg muscles during postural responses after a platform perturbation. Our data demonstrates that following medial-lateral perturbations, central sensitization does not significantly change the time-to-peak of leg muscles during dynamic postural responses.

This held true for all muscles except the right rectus femoris and right tibialis anterior with the right platform perturbation. The right rectus femoris (p=0.027) and the right tibialis anterior (p=0.045) reached their peak magnitude significantly faster in the treatment condition compared to the control following right perturbations (Results Table 2b; Results Figure 8).
6.2.1 Interpretation of Study Finding 2

Although this overall finding refutes our secondary hypothesis, two muscles reached peak amplitude following muscle onset significantly faster in the treatment condition compared to controls. Aside from the right tibialis anterior and right rectus femoris muscles, there was no significant difference between conditions in the time at which the peak amplitude was reached relative to muscle onset during medial-lateral perturbations (Results Table 2a & 2b). The right tibialis anterior and right rectus femoris muscles reached peak amplitude significantly faster when the platform moved to the right in the centrally sensitized condition versus the control (Results Table 2b; Results Figure 8).

One possible explanation as to why only these muscles showed significant differences in the treatment condition could be because all of the subjects were right-side dominant, which was inclusion criteria for our study. As such, their muscles on the right may be more affected by the capsaicin cream and are more active than the left in responding to right perturbations in order to prevent them from falling as they have pre-selected to use this leg in anticipation of the perturbation (Jacobs & Horak, 2007; Marker et al., 2016). During dynamic movement, the neuromuscular function of these dominant right muscles is different than that of the non-dominant left muscles (Barbieri et al., 2015; Challoumas et al., 2017). Therefore, the dominant right muscles may be more affected by the pain (Hansson et al., 2000; Ozaras et al., 2009) Previous studies have found that subjects pre-select their supporting leg prior to perturbations, most commonly being the dominant leg (Jacobs & Horak, 2007). Since all subjects were right-side dominant, it is possible that their right leg muscles were naturally primed to fire as they pre-selected this leg and were anticipating to use this leg to maintain their balance during perturbations. Central sensitization possibly exacerbated this reaction to the anticipation of the perturbations as these muscles are ready to fire sooner (Marker et al., 2016), therefore causing the right tibialis anterior and rectus femoris to reach their peak amplitude faster following their onset than the non-dominant left muscles. However, similar to the delayed onset of the biceps femoris, it is unclear as to why specifically only the right rectus femoris and tibialis anterior reached peak amplitude significantly faster in the treatment condition compared to the control, while the other right-side muscles did not show this same significance. The right gastrocnemius and right biceps femoris reached peak...
amplitude faster in the treatment condition, but this difference was not statistically significant. Along with the biceps femoris onset, future studies should aim to determine the cause of these changes, specifically in the right tibialis anterior and rectus femoris following right perturbations.

6.3 SECONDARY STUDY FINDINGS: CENTRAL SENSITIZATION DOES NOT CHANGE PEAK MAGNITUDE OR TIME-TO-PEAK AMPLITUDE RELATIVE TO PERTURBATION ONSET

Two secondary outcome measures were assessed during data analysis. The first was the magnitude of peak muscle activity and the second was the time at which this peak magnitude was reached relative to platform perturbation onset. Similar to the two primary findings, central sensitization did not cause the muscles to reach peak amplitude faster than the control relative to perturbation onset (Results Table 4a & 4b; Figure 11 & 12) nor did the peak magnitude change (Results Table 3a & 3b; Figure 9 & 10). However, the right tibialis anterior muscle reached peak amplitude significantly earlier relative to perturbations in the right direction (p=0.029) (Results Table 4b; Figure 12).

6.3.1 Interpretation of Secondary Findings

Similar to the time-to-peak amplitude relative to muscle onset, the right tibialis anterior also showed a significant difference in the time-to-peak amplitude relative to platform movement following perturbations to the right. This muscle reached peak amplitude significantly faster in the centrally sensitized condition for both outcome measures. This finding is consistent with changes in time-to-peak amplitude relative to muscle onset as these outcome measures are very similar so they should produce comparable results. Although the right rectus femoris showed statistically significant differences for the time-to-peak relative to muscle onset, it also approached significance (p=0.063) for the time-to-peak relative to perturbation in the right direction. The right rectus femoris also follows the same trend in both time-to-peak outcome measures. One reason as to why the rectus femoris did not show the same degree of significance as the right tibialis anterior may be due to the high degree of variability. One of the main reasons for this variability is because human participants were used for this study and although they all have similar inherent
characteristics, they do respond to various stimuli differently. We tried to reduce this by having inclusion/exclusion criteria and using a priori analysis for determining adequate sample size, however, this does not completely eliminate human variability as a confounding factor. Similar to the findings from the time-to-peak relative to muscle onset, a potential explanation as to why only the right tibialis anterior showed a significant difference between the control and treatment group for this outcome measure could also be attributed to the fact that all subjects were right-side dominant. It is unclear as to why the right tibialis anterior was the only muscle that showed this significant trend, but perhaps this right-sided muscle is most involved in maintaining balance (Thain et al., 2016; Mierau et al., 2015) following perturbations in the right direction. This may be due to the fact that the tibialis anterior crosses the ankle joint, as movement about the ankle is critical in maintaining balance (Cattagni et al., 2016; Billot et al., 2010). Future studies should aim to further investigate this observation.

The ankle plantarflexors and dorsiflexors play an important role in controlling ankle movement required to maintain balance (Cattagni et al., 2016; Billot et al., 2010; Winter et al., 1998). In order to do this, the CNS must take sensory information from the body and its surroundings to generate the appropriate postural response to maintain balance, which requires generating corrective ankle motions (Winter et al., 1998). The tibialis anterior is known to play a major role in maintaining upright posture during both quiet standing and dynamic movement (Winter et al., 1998; Di Giulio et al., 2009; Gatev et al., 1999; Day et al., 2013). Among the ankle muscles, the tibialis anterior has been shown to be the best mechanical source of providing adjustments in response to proprioceptive feedback (Di Giulio et al., 2009; Day et al., 2013). In this study, that would be represented in the tibialis anterior’s response required to maintain balance following platform perturbations. Similar to the faster time-to-peak amplitude relative to muscle onset, this outcome measure could also be explained by the fact that the subjects’ right muscles were naturally primed to fire in anticipation of the perturbation in order to maintain balance. Since they were all right-side dominant, they may have naturally pre-selected to use their right leg to maintain balance (Jacobs & Horak, 2007). The induced central sensitization may have heightened/intensified this reaction to the anticipated perturbation, resulting in a faster time to reach peak amplitude. In order to further validate this plausible explanation, future research may
find relevance in investigating this outcome measure specifically in the dominant leg in response to anticipated perturbations and in centrally sensitized conditions.

6.4 STUDY FINDINGS AND THE CURRENT LITERATURE ON MUSCLE ACTIVITY AND CENTRAL SENSITIZATION

The findings of our study are not directly in line with those reported in previous literature that studied similar outcome measures. Previous literature has demonstrated that chronic neck pain results in delayed onset time for neck muscles (sternocleidomastoid and splenius capitis) (Boudreau & Falla, 2014). While both neck and leg muscles are important contributors to maintaining balance, their neuromuscular responses to neck pain and their functions as postural stabilizers are different (Freyler et al., 2015). In order to maintain balance and avoid falling during medial-lateral perturbations, the body needs to respond by activating the postural muscles (Stokes et al., 2006; Fujio et al., 2016). Our results show no overall change in leg muscle onset with induced central sensitization, while the findings by Boudreau & Falla show the opposite trend with their neck muscles of interest in those with chronic pain (Boudreau & Falla, 2014). This may be due to the fact that they studied these same outcome measures in those with subjective neck pain, while we investigated the effect of experimentally induced central sensitization in a different set of postural stabilizing muscles. Other researchers have found that other postural and spinal stabilizing muscles involved in maintaining balance exhibit delayed onset in those with chronic low back pain (Hodges & Richardson, 1996; Hodges & Richardson, 1998; Hungerford et al., 2003; Tsao et al., 2008). These different findings further emphasize that even though these neck and leg muscles are all involved in the postural response to maintain balance, their neuromuscular properties may react differently to central sensitization and chronic pain. These differences could, in part, be explained by the mechanism used to induce central sensitization as well as the subject cohorts themselves. In contrast to our study, the previous studies all used clinical populations as their treatment group and compared them to healthy controls. In our study, subjects acted as their own control and had central sensitization experimentally induced for the treatment condition. Our study also used topical capsaicin cream (0.075%) which is a technique that experimentally induces mild degrees of central sensitization (Anand & Bley, 2011; Derry et al., 2009; Altman & Barkin, 2009).
These outcome measures have also been studied in different age cohorts to see if differences exist across the lifespan. Contrary to the findings in our study, deFreitas et al. concluded that older adults, when compared to younger adults, demonstrate a delay in muscle onset and time to reach peak amplitude relative to onset of the left tibialis anterior and rectus femoris during anterior-posterior platform perturbations (de Freitas et al., 2010). While these findings contradict our observations, this could be explained by the fact that the subjects used in the deFreitas et al. study did not suffer from chronic pain or central sensitization. Further, these findings were a result of anterior-posterior perturbations and were only measured in the left leg, while we focused on medial-lateral perturbations and found differing results in the same muscles of the right leg.

Muscle onset and the time for leg and postural muscles to reach their peak amplitude are important factors in maintaining balance. Although our study did not consider the effect of age on neuromuscular responses to dynamic movement, there is evidence to suggest that older adults with chronic neck pain show impaired balance beyond that caused by normal aging (Poole et al., 2008). This may, therefore, suggest that younger adults who have chronic neck pain may have impaired balance as well.

The heat capsaicin technique is a method to evoke central sensitization by combining thermal stimulation and topical capsaicin (Dirks et al., 2003). When this technique is applied topically to the cervical spine region over a greater surface area than was done in our study, a tightening effect is observed in the leg muscles during quiet standing (Huntley et al., 2015). Alternatively, inducing central sensitization over a smaller surface area and without heat, as was done in our study, does not appear to change overall leg muscle activity during dynamic postural adjustments. This may therefore suggest that heat capsaicin may elicit a stronger sensitization response and may therefore have a greater effect on the postural responses than when heat is not applied. Further, inducing central sensitization over a smaller surface area, as was done in our study, may not add as much noise to the system, which may therefore evoke a smaller insignificant neuromuscular response (Winter et al., 1995). The study by Huntley et al., which was a precursor to this study, did not use EMG to determine leg muscle activity, rather they measured centre of
mass and centre of pressure using a force plate. The reduced area of sway in the treatment condition was interpreted as a tightening effect in the leg muscles (Huntley et al., 2015). Using EMG provides more specific representation of individual muscle activity, whereby the force plate data provide information on the overall body motion (Ramsey et al., 2016). These differences may account for some of the variance observed in the findings in our study when compared to the study by Huntley et al. Our study also looked at different outcome measures. Huntley et al. investigated postural control and its ongoing postural feedback loops during quiet standing (Huntley et al., 2015), whereas we studied instantaneous leg muscle responses to disturbed balance and dynamic postural responses.

While previous studies reported more significant differences between their treatment and control groups, our study found that central sensitization did not cause a significant change in neuromuscular activity during dynamic movement, specifically in leg muscle onset and time for these muscles to reach peak amplitude. This held true for most muscles measured in all outcome measures. These differences between study findings in the literature may be due to differences in methodology and/or subject cohorts.

6.5 ALTERNATE INTERPRETATIONS OF FINDINGS

While our overall conclusions are presented on the basis that the expected results did not occur, there are some alternate interpretations that can be considered. It is possible that these results are actually presented as a false-negative; saying something did not happen when it actually did. One main factor that must be taken into account when analyzing the results, is the action of the muscles measured, which in this study were mainly flexion and extension of the hip, knee, and ankle. These muscles are not primarily involved in the lateral response as was measured in this study. Alternatively, muscles involved in adduction and abduction of the leg joints could be a better representation of the influence that central sensitization may have on muscle activity following medial-lateral perturbations (Hof & Duysens, 2013). The fact that we still found some significant differences in muscle onset and time-to-peak amplitude in the muscles of interest shows that even muscles not directly involved in the lateral response are affected by this condition.
As flexor and extensor muscles are not primarily involved in the medial-lateral response, it is not surprising that most of these muscles did not show a significant difference between the centrally sensitized condition and the control. However, since some muscles did show significance for these outcome measures, this can provide some positive evidence that central sensitization does in fact have an impact on leg muscle activity during medial-lateral perturbations, even in muscles that are not directly involved in the lateral response. Specifically, finding statistically significant differences between the two conditions in the hamstring muscle onset following contralateral perturbations may point to some alternate positive interpretations of the overall results. In addition to flexion of the knee and extension of the hip, the biceps femoris is also involved in rotation of the hip and lower leg (Umegaki et al., 2015; Kimura, 2013; Valente et al., 2013). It’s rotational properties may therefore make it a contributor to movements about the hip and knee that are involved in medial-lateral responses. This may suggest that leg muscles involved in rotation about these joints, as well as adductor and abductor muscles with similar properties, show significance to these outcome measures as they are more heavily involved in the lateral response. Our finding of a significant delay in the biceps femoris muscle onset following contralateral perturbations, may lead future studies to look more specifically at these outcome measures in other adductor and abductor muscles.

Since the actions of the muscles measured are mainly flexion and extension of the hip, knee, and ankle, it is speculated that they would show greater activity in response to anterior-posterior perturbations (de Freitas et al., 2010). Had we reduced the magnitude of these perturbations so participants did not need to take a step to prevent falling, then perhaps these muscles would show more significant differences between the centrally sensitized condition and the control. We cannot definitively make this claim, however, since we did not analyze these outcome measures for anterior-posterior perturbations. This can be an area that future studies can more specifically investigate to learn about the influence that central sensitization has on the neuromuscular response to such perturbations in these muscles.
CHAPTER 7

CLINICAL APPLICATIONS

The results of this study may contribute to our understanding of how chronic pain and central sensitization impact dynamic balance strategies in young healthy populations. Understanding how chronic pain and central sensitization affect leg muscle activity during dynamic balance responses may inform future research advancing the diagnostic and therapeutic interventions for those suffering from various clinical conditions associated with pain and/or sensitization, such as cervicogenic disequilibrium and osteoarthritis. While central sensitization affects a wide range of clinical conditions, the ones discussed here have the most relevant applications to the neuromuscular responses that central sensitization affects during dynamic movement.

7.1 FALL PREVENTION

Falls are one of the leading causes of injury, especially among the elderly, resulting in loss of independence and potential nursing home admissions (Sattin et al., 1990; Tinetti & Williams, 1997). Impaired balance control strategies are a major contributing factor to falling (Maki et al., 2011).

Central sensitization and chronic pain have been suggested to impair balance control as they act as a distraction in that those suffering from it may focus their attention on the pain rather than the task at hand (McCracken, 1997; Troche et al., 2015). It also alters neuromuscular communication by adding more noise to the system, specifically from the excess release of inflammatory substances, which has been suggested as a potential mechanism for impairment of an individual’s ability to maintain balance. It does this by impairing communication from the brain instructing the muscles to execute the appropriate response to maintain balance. (Baron et al., 2013; Vuillerme & Pinsault, 2009; Michaelson et al., 2003).
Our findings suggest that experimentally induced central sensitization does not cause an overall change in leg muscle activity required to maintain balance in response to medial-lateral perturbations. These findings suggest that central sensitization may not significantly impair an individual’s ability to activate their leg muscles and reach peak amplitude as they achieve these neuromuscular responses at the same speed as healthy controls. These observations suggest a reduced likelihood that central sensitization and chronic pain contribute to mediating falls during medial-lateral perturbations.

There are two primary postural responses to preventing falls when balance is disturbed. The first is taking a step, and the second is activating leg and postural muscles while maintaining the same base of support. Previous research has found that older adults show an impaired stepping reaction to anterior-posterior perturbations when their attention is focused on another task (Zettel et al., 2008). This may be comparable to older adults who are more likely to suffer chronic pain and may show this impaired response to anterior-posterior perturbations as their attention is focused on their pain. Such an attention split could impair one’s ability to successfully complete tasks such as maintaining balance in response to a perturbation (McCracken, 1997; Troche et al., 2015). This could be an important mechanism in facilitating falls as this neck pain has been shown to impair older adults beyond that caused by normal aging (Poole et al., 2008). While this may be the case in older adult populations and following anterior-posterior perturbations, the findings from our study suggest that this does not hold true for medial-lateral perturbations in a young healthy population after experimentally induced central sensitization, as it does not appear to impair the activity of the leg muscles of interest when moving side to side. As such, central sensitization induced at this spinal level (C4/C5) using the topical capsaicin cream method may not impair balance to the point of causing a fall. Future research should investigate the effect of greater magnitudes of experimentally induced central sensitization on changes in leg muscle activity, and it’s role in balance and fall prevention strategies.
7.2 CERVICOGENIC DISEQUILIBRIUM

Two of the most prevalent balance disorders are dizziness and vertigo (Neuhauser et al., 2008; Yardley et al., 1998). These conditions are classified as cervicogenic disequilibrium when they arise from cervical spine injury or disorders. One of the most common etiologies for cervicogenic disequilibrium are flexion-extension injuries of this region, commonly observed during acceleration-deceleration injuries, such as whiplash (Wrisley et al., 2000). It has been suggested that chronic neck pain associated with whiplash injury is a common mechanism leading to central sensitization and hyperexcitability of the CNS (Van Oosterwijk et al., 2013). Patients with this type of neck pain and central sensitization arising from this spinal level show larger areas of sway and impaired ability to maintain body posture when their balance is disturbed during platform perturbations (Michaelson et al., 2003). Similarly, strong associations have been established between the cervical spine region and its role in the perception of balance and making appropriate postural adjustments necessary to maintaining balance (Boissiere et al., 2015; Stokell et al., 2011). Further, neck injury and/or neck pain may contribute to feelings of dizziness/disequilibrium (Brown, 1992).

Our results lie in contrast to these claims, showing that experimentally-induced central sensitization at the cervical spine level does not cause an overall change in leg muscle onset and time for these muscles of interest to reach peak amplitude. These observations may be the case since our study did not use a clinical population for the treatment group as did these previous studies. These outcome measures (muscle onset and time-to-peak amplitude) are important in maintaining balance because leg muscle activity is critical in executing appropriate postural responses when balance is disturbed. Since our results show no change in these outcome measures between the control and treatment conditions, it could be inferred that central sensitization induced with topical capsaicin that this cervical level (C4/C5) may not be enough to alter leg muscle activity and resulting balance. In addition to leg muscles, there are other critical muscles (such as cervical neck extensors (Gosselin et al., 2003), hip adductors/abductors (Hof & Duysens, 2013), and trunk muscles (Freddolini et al. 2014; Ganesh et al., 2015)) involved in postural modulation required to maintain an upright position in response to disturbed balance. Individuals suffering from cervicogenic disequilibrium may find relevance to the results of this study as our findings
suggest that their condition may not significantly disrupt their ability to respond appropriately when balance is disturbed in the medial-lateral directions.
CHAPTER 8
LIMITATIONS

This study should be interpreted in light of the following limitations. Firstly, there is little significant difference observed between the control and treatment conditions for most muscles for all outcome measures. This could be explained by the high degree of variability and the methodology employed in this study. One of the reasons for the high variability in the protocol is because human participants were used. Many natural biological factors play into the fact that little significance was found in the outcome measures assessed in this study. While all humans have many similar inherent characteristics, not all humans are exactly the same and they respond differently to various stimuli. Although we conducted a priori analysis to determine the necessary sample size to account for these differences, this method does not completely eliminate this variability. There are always fundamental considerations (such as age, gender, height, weight, etc.) to be made when working with humans. We accounted for this as much as possible by having inclusion/exclusion criteria (Methods 4.1 Participants) for our subject cohort.

Another methodological consideration was the use of surface electrodes to measure the activity of the muscles of interest. These electrodes come with a list of their own limitations such that they are unable to reliably detect the activity of deep muscles and are subject to picking up cross-talk from different muscles located near the muscle of interest (Kamen & Gabriel, 2010). In this study, subjects were asked to flex these muscles to make sure that the electrodes were being placed in the correct location on the bellies of the muscles of interest to be able to capture the activity of the whole muscle. Alternatively, indwelling electrodes could be used to obtain a more accurate measurement of the activity of the muscles of interest; however, these electrodes come with their own set of limitations, including level of invasiveness (Ounpuu et al., 1997) and having smaller pick-up volumes than surface electrodes (Allen et al., 2013). Indwelling electrodes were also not the optimal choice for the purpose of this study. We were interested recording whole muscle activity, which surface electrodes are ideal for, while indwelling electrodes are better for capturing the activity of small, deep muscles and individual motor units (Kamen & Gabriel, 2010).
The brush allodynia technique was not used in this study to confirm the presence of central sensitization. This is because many previous studies have already shown that 15-20 minutes post-cream application is when the effects of the topical cream reaches peak effect (Huntley et al., 2015; Srbely et al., 2010). This was further confirmed during pilot testing.

The topical capsaicin cream we used is a fairly mild technique used to induce central sensitization (Anand & Bley, 2011; Derry et al., 2009; Altman & Barkin, 2009). As such, it may not have evoked as intense a sensitization response as was expected. The low concentration of capsaicin (0.075%) used may further explain the small effect sizes observed between the control and treatment trials. Future research should investigate these mechanisms with higher concentrations of topical capsaicin. Alternatively, a more invasive approach to inducing central sensitization, such as intradermal capsaicin injection, could be used in the future to elicit a more robust sensitization response to better test neuromuscular balance responses following the platform perturbations and balance disruption. Intradermal capsaicin injections elicit greater responses and longer lasting effects compared to the topical application of capsaicin cream, but this technique comes with its own set of limitations as well such as severe initial pain and higher level of invasiveness (Dirks et al., 2003; Scanlon et al., 2006; Simone et al., 1989).

Lastly, a young, healthy population was used for this study and the findings of this study cannot necessarily be extrapolated to older and/or clinical populations. Future research should investigate these mechanisms in older and/or clinically representative populations. In experimental pain studies, it is important to consider both the age and sex of the subjects as these variables have been reported to have an effect on pain outcomes (Arendt-Nielsen & Andersen, 2005). All subjects in this study were between the ages of 17-25 and there were an equal number of males and females (8 of each). While our sample size might be considered small, our a priori power analysis determined that a sample size of 16 subjects was needed (Hodges et al., 2003). All of our subjects were right-side dominant and it is possible that there may be different neuromuscular responses to the outcome measures explored in this study following medial-lateral perturbations in those who are left-side dominant (Marker et al., 2016; Hansson et al., 2000).
CHAPTER 9

FUTURE DIRECTIONS

The findings of this study add to the growing body of literature regarding underlying neuromuscular mechanisms contributing to postural modulation post-sensitization, and shed light on specific future directions of research needed to advance this area.

As this study aimed to investigate these neuromuscular mechanisms in a young healthy cohort to minimize the potential impact of comorbidities that could impact baseline levels of central sensitization, future research should aim to investigate these outcomes in a clinical population. Such populations include those suffering from cervicogenic disequilibrium and/or conditions relating to chronic pain such as degenerative spine and/or joint diseases, osteoarthritis, and whiplash. Another important population in which these outcome measures should be assessed in light of the risk of falls, is the older aging population. In this way, researchers could aim to see if there are disparities among different age cohorts in terms of these neuromuscular postural responses post-sensitization during dynamic movement and if these responses change over the lifespan.

While this study only looked at the tibialis anterior, gastrocnemius, rectus femoris, and biceps femoris, it would be beneficial for future studies to investigate these same neuromuscular responses in a broader profile of muscles linked to balance control, including hip adductors and abductors (Hof & Duysens, 2013), trunk muscles (Freddolini et al. 2014; Ganesh et al., 2015), and cervical neck extensor muscles (Gosselin et al., 2003). Furthermore, it is still unclear why the hamstring muscles were the only muscles to produce significant differences in their onset time between the treatment and control conditions. Since the hamstrings are knee stabilizers, are there unique structural or functional properties of this muscle that impart these differences during dynamic postural responses? Similarly, future studies should also investigate why specifically only the right tibialis anterior and rectus femoris reached peak amplitude faster relative to muscle onset and platform perturbations in the right direction in the treatment condition compared to the control. This would be important in further understanding the specific mechanisms of the tibialis anterior
and rectus femoris and how pain contributes to their function. This is essential in being able to develop adequate fall prevention strategies by being able to target these muscles specifically.

Another important research direction could be to study the neuromuscular responses in control and treatment conditions during anterior-posterior perturbations. While these perturbations were included in the methodology of this study, the results are not considered as these perturbations acted as catch trials to prevent the subjects from becoming accustomed to the medial-lateral perturbations. The results from these perturbations were omitted as all subjects demonstrated a stepping response in the anterior-posterior directions. Future research could test these mechanisms using reduced magnitude and velocity of the anterior-posterior perturbations.

Finally, these outcome measures should be re-assessed with a greater magnitude of experimentally induced central sensitization. Determining the dose-response effect of these mechanisms would provide important insight into the causal relationship of central sensitization and neuromuscular function associated with balance control.
CHAPTER 10

SUMMARY AND CONCLUSIONS

Cervicogenic disequilibrium is frequently seen in conditions of chronic pain in the neck/cervical spine region and may increase the risk of falls, especially among the elderly. One of the leading causes of unintentional injury among older adults is falling caused by balance disorders (Gorina et al., 2006; Stinchcombe et al., 2014). In older adults with chronic neck pain, previous research has shown that balance control is impacted to a greater extent than that caused by normal aging, which suggests that balance control in younger adults with chronic neck pain could also be affected (Poole et al., 2008).

Central sensitization is a condition of the CNS associated with the development and maintenance of a number of clinical conditions associated with chronic pain. Previous research has demonstrated that central sensitization leads to a tightening balance strategy adopted during quiet standing (Huntley et al., 2015). However, quiet standing balance outcomes do not explain how central sensitization might affect postural adjustments during dynamic balance recovery.

This study aimed to investigate the effects of experimentally induced central sensitization on leg muscle activity and resulting postural responses during medial-lateral dynamic movement. The outcome measures of muscle onset and time to peak amplitude were specifically chosen to assess because appropriate leg muscle activity is critical during dynamic balance recovery.

While there were not many significant differences between the control and treatment conditions for all outcome measures, there were nevertheless important overall findings that emerged from the results of our study. Although no overall changes in our outcome measures were observed, the biceps femoris showed significant delay in onset time following perturbations in the opposite direction. Further, the tibialis anterior and rectus femoris demonstrated a significantly faster time to peak amplitude following right perturbations in the centrally sensitized condition compared to the control.
Although preliminary, the findings from this study suggest that central sensitization induced at the C4/C5 spinal level with topical capsaicin is not a major underlying neuromuscular mechanism that alters leg muscle activity during dynamic movement. Aside from the few significant findings, overall, leg muscle activity required to maintain balance during perturbations is not significantly altered by central sensitization induced at this level by topical capsaicin cream. Further understanding of these neuromuscular mechanisms will help in developing fall prevention strategies, particularly among those suffering from chronic pain and the elderly. Given the aging demographic, research in this field has the potential for significant impact on society.


Cattagni, T., Scaglioni, G., Laroche, D., Gremeaux, V., & Martin, A. (2016). The involvement of ankle muscles in maintaining balance in the upright posture is higher in elderly fallers. Experimental Gerontology; 77: 38-45


Donath, L., Kurz, E., Roth, R., Zahner, L., & Faude, O. (2016). Leg and trunk muscle coordination and postural sway during increasingly difficult standing balance tasks in young and older adults. Maturitas; 91: 60-68


Ingraham, P. (2011). Central sensitization in chronic pain: Pain itself can change how pain works, resulting in more pain with less provocation. Pain Science


Kosslyn, S.M., Ganis, G. & Thompson, W.L. (2001). Neural foundations of imagery. Nat Rev Neurosci; 2(9): 635-642


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APPENDIX A

Schematic Outline of Protocol

A schematic overview of the protocol used for this experiment. A total of 12 randomized practice trials were completed to familiarize the participant with the movement of the platform and prevent a learning curve from being observed. This was immediately followed by the control condition, consisting of 16 randomized trials. The subject then descended the platform and had capsaicin cream applied to the skin overtop their C4/C5 spinal segments to induce central sensitization. They sat with the cream for 15 minutes before getting back up onto the platform to complete the treatment trial, consisting of 16 randomized trials.
APPENDIX B

Experimental Setup

Figure 1 Safety harness setup on the robotic motion platform

Figure 2 EMG electrode placement on front and back of subject. Surface electrodes were placed in a bipolar configuration on the bellies of the muscles of interest. These included the tibialis anterior, gastrocnemius, rectus femoris, and biceps femoris on both legs. There was one reference electrode placed on the right lateral malleolus.
Figure 3 An approximation of the area (C4/C5 region) that was targeted for applying the capsaicin cream.
APPENDIX C

Anterior-Posterior Perturbation Results

For all tables, the following abbreviations are used: left (L), right (R), tibialis anterior (TA), gastrocnemius (Gastroc), rectus femoris (RF), biceps femoris (BF).

C.1 Muscle Onsets

Table C.1a. The mean onset time (ms) for each muscle from both the control and treatment conditions for the anterior perturbation trials with corresponding p-values. The onset time values are presented as means ± SD

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Control (ms)</th>
<th>Treatment (ms)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>TA</td>
<td>115.14 ± 8.67</td>
<td>115.36 ± 8.17</td>
</tr>
<tr>
<td></td>
<td>Gastroc</td>
<td>134.31 ± 15.56</td>
<td>135.78 ± 13.44</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>131.11 ± 13.08</td>
<td>137.74 ± 11.75</td>
</tr>
<tr>
<td></td>
<td>BF</td>
<td>132.69 ± 12.62</td>
<td>138.32 ± 14.39</td>
</tr>
<tr>
<td>Left</td>
<td>TA</td>
<td>118.28 ± 11.74</td>
<td>116.90 ± 10.90</td>
</tr>
<tr>
<td></td>
<td>Gastroc</td>
<td>143.97 ± 33.32</td>
<td>137.48 ± 15.50</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>123.34 ± 13.86</td>
<td>131.56 ± 14.24</td>
</tr>
<tr>
<td></td>
<td>BF</td>
<td>135.42 ± 16.99</td>
<td>143.33 ± 17.38</td>
</tr>
</tbody>
</table>

Table C.1b. The mean onset time (ms) for each muscle from both the control and treatment conditions for the posterior perturbation trials with corresponding p-values. The onset time values are presented as means ± SD

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Control (ms)</th>
<th>Treatment (ms)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>TA</td>
<td>125.18 ± 15.65</td>
<td>124.93 ± 13.21</td>
</tr>
<tr>
<td></td>
<td>Gastroc</td>
<td>119.58 ± 25.20</td>
<td>120.96 ± 17.57</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>150.53 ± 23.17</td>
<td>170.44 ± 33.57</td>
</tr>
<tr>
<td></td>
<td>BF</td>
<td>131.41 ± 13.77</td>
<td>139.93 ± 15.66</td>
</tr>
<tr>
<td>Left</td>
<td>TA</td>
<td>122.89 ± 16.89</td>
<td>129.61 ± 26.39</td>
</tr>
<tr>
<td></td>
<td>Gastroc</td>
<td>120.16 ± 19.78</td>
<td>117.29 ± 14.91</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>130.71 ± 24.86</td>
<td>133.69 ± 42.74</td>
</tr>
<tr>
<td></td>
<td>BF</td>
<td>122.11 ± 22.06</td>
<td>130.75 ± 29.88</td>
</tr>
</tbody>
</table>
C.2 Time to Peak Muscle Amplitudes Relative to Muscle Onsets

Table C.2a. The mean time to peak amplitude (ms) relative to muscle onset for each muscle from both the control and treatment conditions for the anterior perturbation trials with corresponding p-values. The time to peak values are presented as means ± SD. *denotes a significant difference in time to reach peak amplitude between the control and treatment conditions.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Control (ms)</th>
<th>Treatment (ms)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>TA</td>
<td>190.62 ± 82.85</td>
<td>207.59 ± 120.22</td>
</tr>
<tr>
<td></td>
<td>Gastroc</td>
<td>382.42 ± 295.62</td>
<td>308.53 ± 148.63</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>275.47 ± 173.39</td>
<td>389.54 ± 403.26</td>
</tr>
<tr>
<td></td>
<td>BF</td>
<td>431.45 ± 681.15</td>
<td>264.01 ± 200.76</td>
</tr>
<tr>
<td>Left</td>
<td>TA</td>
<td>152.20 ± 71.18</td>
<td>215.10 ± 145.50</td>
</tr>
<tr>
<td></td>
<td>Gastroc</td>
<td>486.86 ± 377.34</td>
<td>365.32 ± 358.11</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>454.78 ± 328.26</td>
<td>340.25 ± 340.61</td>
</tr>
<tr>
<td></td>
<td>BF</td>
<td>251.45 ± 290.49</td>
<td>266.15 ± 325.66</td>
</tr>
</tbody>
</table>

Table C.2b. The mean time to peak amplitude (ms) relative to muscle onset for each muscle from both the control and treatment conditions for the posterior perturbation trials with corresponding p-values. The time to peak values are presented as means ± SD. *denotes a significant difference in time to reach peak amplitude between the control and treatment conditions.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Control (ms)</th>
<th>Treatment (ms)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>TA</td>
<td>489.65 ± 390.64</td>
<td>395.21 ± 363.69</td>
</tr>
<tr>
<td></td>
<td>Gastroc</td>
<td>398.21 ± 231.36</td>
<td>255.66 ± 209.81</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>356.31 ± 249.73</td>
<td>267.85 ± 183.10</td>
</tr>
<tr>
<td></td>
<td>BF</td>
<td>618.03 ± 772.59</td>
<td>310.32 ± 241.86</td>
</tr>
<tr>
<td>Left</td>
<td>TA</td>
<td>444.18 ± 290.95</td>
<td>428.96 ± 293.81</td>
</tr>
<tr>
<td></td>
<td>Gastroc</td>
<td>430.98 ± 255.29</td>
<td>264.36 ± 147.89</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>366.79 ± 237.72</td>
<td>229.60 ± 151.70</td>
</tr>
<tr>
<td></td>
<td>BF</td>
<td>379.92 ± 286.10</td>
<td>312.85 ± 248.19</td>
</tr>
</tbody>
</table>
C.3 Magnitude of Peak Muscle Amplitude

Table C.3a. The mean peak amplitude (mV) for each muscle from both the control and treatment conditions for the anterior perturbation trials with corresponding p-values. The peak amplitude values are presented as means ± SD.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Control (mV)</th>
<th>Treatment (mV)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>TA</td>
<td>0.73 ± 0.32</td>
<td>0.78 ± 0.41</td>
</tr>
<tr>
<td></td>
<td>Gastroc</td>
<td>0.3 ± 0.44</td>
<td>0.17 ± 0.13</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>0.44 ± 0.30</td>
<td>0.35 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>BF</td>
<td>0.35 ± 0.25</td>
<td>0.3 ± 0.20</td>
</tr>
<tr>
<td>Left</td>
<td>TA</td>
<td>0.77 ± 0.41</td>
<td>0.78 ± 0.49</td>
</tr>
<tr>
<td></td>
<td>Gastroc</td>
<td>0.26 ± 0.29</td>
<td>0.18 ± 0.15</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>0.63 ± 0.70</td>
<td>0.45 ± 0.34</td>
</tr>
<tr>
<td></td>
<td>BF</td>
<td>0.25 ± 0.25</td>
<td>0.26 ± 0.24</td>
</tr>
</tbody>
</table>

Table C.3b. The mean peak amplitude (mV) for each muscle from both the control and treatment conditions for the posterior perturbation trials with corresponding p-values. The peak amplitude values are presented as means ± SD. *denotes a significant difference in peak muscle amplitude between the control and treatment conditions.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Control (mV)</th>
<th>Treatment (mV)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>TA</td>
<td>0.52 ± 0.35</td>
<td>0.48 ± 0.23</td>
</tr>
<tr>
<td></td>
<td>Gastroc</td>
<td>0.522 ± 0.48</td>
<td>0.45 ± 0.27</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>0.42 ± 0.37</td>
<td>0.27 ± 0.23</td>
</tr>
<tr>
<td></td>
<td>BF</td>
<td>0.4 ± 0.30</td>
<td>0.32 ± 0.17</td>
</tr>
<tr>
<td>Left</td>
<td>TA</td>
<td>0.57 ± 0.36</td>
<td>0.47 ± 0.27</td>
</tr>
<tr>
<td></td>
<td>Gastroc</td>
<td>0.49 ± 0.38</td>
<td>0.49 ± 0.30</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>0.39 ± 0.37</td>
<td>0.27 ± 0.25</td>
</tr>
<tr>
<td></td>
<td>BF</td>
<td>0.15 ± 0.15</td>
<td>0.12 ± 0.11</td>
</tr>
</tbody>
</table>
C.4 Time to Peak Muscle Amplitude Relative to Platform Perturbation

Table C.4a. The mean time (ms) at which peak amplitude was reached relative to platform movement for each muscle from both the control and treatment conditions for the anterior perturbation trials with corresponding p-values. The time to peak amplitude values are presented as means ± SD.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Control (ms)</th>
<th>Treatment (ms)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>TA 306.27 ± 83.07</td>
<td>315.95 ± 116.15</td>
<td>0.759</td>
</tr>
<tr>
<td></td>
<td>Gastroc 502.68 ± 283.64</td>
<td>430.43 ± 167.86</td>
<td>0.196</td>
</tr>
<tr>
<td></td>
<td>RF 393.33 ± 151.53</td>
<td>510.82 ± 379.93</td>
<td>0.149</td>
</tr>
<tr>
<td></td>
<td>BF 556.95 ± 648.70</td>
<td>380.82 ± 205.89</td>
<td>0.288</td>
</tr>
<tr>
<td>Left</td>
<td>TA 268.95 ± 68.27</td>
<td>326.33 ± 144.84</td>
<td>0.277</td>
</tr>
<tr>
<td></td>
<td>Gastroc 608 ± 347.88</td>
<td>491.48 ± 369.31</td>
<td>0.508</td>
</tr>
<tr>
<td></td>
<td>RF 548.62 ± 268.79</td>
<td>459.22 ± 355.35</td>
<td>0.398</td>
</tr>
<tr>
<td></td>
<td>BF 317.13 ± 294.79</td>
<td>347.84 ± 340.12</td>
<td>0.324</td>
</tr>
</tbody>
</table>

Table C.4b. The mean time (ms) at which peak amplitude was reached relative to platform movement for each muscle from both the control and treatment conditions for the posterior perturbation trials with corresponding p-values. The time to peak amplitude values are presented as means ± SD. *denotes a significant difference in time of muscle amplitude between the control and treatment conditions.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Control (ms)</th>
<th>Treatment (ms)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>TA 613.4 ± 385.80</td>
<td>509.82 ± 340.16</td>
<td>0.135</td>
</tr>
<tr>
<td></td>
<td>Gastroc 513.16 ± 246.58</td>
<td>366.45 ± 213.53</td>
<td>0.008*</td>
</tr>
<tr>
<td></td>
<td>RF 489.46 ± 246.50</td>
<td>418.69 ± 182.96</td>
<td>0.257</td>
</tr>
<tr>
<td></td>
<td>BF 753.79 ± 742.62</td>
<td>447.04 ± 267.18</td>
<td>0.173</td>
</tr>
<tr>
<td>Left</td>
<td>TA 548.28 ± 297.52</td>
<td>542.21 ± 275.34</td>
<td>0.970</td>
</tr>
<tr>
<td></td>
<td>Gastroc 533.93 ± 262.22</td>
<td>367.62 ± 150.79</td>
<td>0.047*</td>
</tr>
<tr>
<td></td>
<td>RF 480.79 ± 246.93</td>
<td>350.4 ± 147.49</td>
<td>0.016*</td>
</tr>
<tr>
<td></td>
<td>BF 487.9 ± 266.98</td>
<td>400.38 ± 238.05</td>
<td>0.104</td>
</tr>
</tbody>
</table>