The effect of experimental pain on motor training performance and sensorimotor integration

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Abstract:

Sensorimotor integration (SMI) is the ability of the central nervous system (CNS) to integrate afferent (incoming) information from different body parts and formulate appropriate motor output to muscles. Effective sensorimotor integration is essential when learning new skills and when performing tasks at home and in the workplace (Rothwell &Rosenkranz, 2005). The overall aim of this thesis is to investigate the effect of acute experimental pain on sensorimotor processing. The primary outcome is the effect of acute experimental pain on somatosensory evoked potential (SEP) peaks. Secondary outcomes include the effect of pain on motor performance and the interactive effect of pain and motor training on SEP peaks. As expected for the placebo condition, no significant differences were found in any of the post-placebo peaks. Contrary to what was expected for the placebo condition, the only peak to be significantly different post-motor learning was the N24 peak. Contrary to what was expected, there were no significant differences for any of the peaks following capsaicin application. One of the secondary outcomes was the interactive effect of pain and motor learning on SEP peaks. The only peak to show any significant differences post-intervention/post-motor learning was the N24 peak. Another secondary outcome was the effect of pain on motor performance. In terms of accuracy, no significant differences were found for either condition following motor learning. However, the data does show a trend towards improved accuracy for the subjects in the intervention group while the subjects in the placebo show a trend towards decreased accuracy. As expected, there was a significant decrease in reaction time for both conditions post-motor

learning. However, contrary to what was expected, reaction time decreased to a greater extent in the intervention condition as compared to the placebo condition. It was anticipated that the reaction time would decrease to a greater extent in the placebo condition as it was hypothesized that pain would negatively impact motor performance. It is suspected that the effect of the pain induced by the capsaicin made the motor training task more difficult and participants would have had to focus greater attentional resources to learn the task which lead to the enhanced performance following motor training.

Statement of Originality

I hereby declare that this thesis is, to the best of my knowledge, original, except as acknowledged in the text, and that the material has not been previously submitted either in whole or in part, for a degree at this or any other University.

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Abbreviations:

ADM: Abductor digiti minimi

AMH: Aδ mechano-heat nociceptors ()

ANOVA: Analysis of variance

APB: Abductor pollicis brevis

ARAS: ascending reticular activating system

BDNF: brain-derived neurotrophic factor

CaMK II: calmodulin-dependent kinase II

CMH: C mechano-heat nociceptors

CNS: Central nervous system

CSP: Cortical silent period

DCC: dorsal column

EEG: Electroencephalography

EIP: Extensor indices proprius

EMG: Electromyography

EP: Evoked potential

EPSPs: Excitatory postsynaptic potentials

FDI: First dorsal interosseous

GABA: γ- aminobutyric acid

HTM : high-threshold mechanoreceptor

ICF: Intracortical facilitation

ICI: Intracortical inhibition

ISI: Inter-stimulus interval

IwF: I-wave facilitation

LEP: laser evoked potentials

LICI: Long interval intracortical inhibition

LBP: Lower back pain

M1: Primary motor cortex area

MEG: Magnetoencephalography

MEP: Motor evoked potential

MI: Primary somatosensory cortex

NMDA: *N*-methyl D-aspartate

NT-3: Neurotrophin

NT-4: Neurotrophin

PAG: periaqueductal gray

PFC: prefrontal cortex

PMN: Polymodal nociceptors

RA: rheumatoid arthritis

SEP: Somatosensory evoked potential

SICF: Short interval intracortical facilitation

SICI: Short interval intracortical inhibition

SMA: Supplementary motor area

SmI: Primary somatosensory area

SmII: Secondary somatosensory system

SP: Substance P

STT: Spinothalamic tract

TENS: transcutaneous nerve stimulation

TMS: Transcranial magnetic stimulation

UDP: Use-dependent plasticity

Relevant Terminology:

Acute pain: is that physiological sensation of hurt that results from the activation of nociceptive pathways by peripheral stimuli of sufficient intensity to lead to or to threaten tissue damage (noxious stimuli)

A delta or group III: thin myelinated primary afferent fibres with conduction velocities of 2–33 m/s

Analgesic: (also known as a painkiller) is any member of the group of drugs used to relieve pain (achieve analgesia).

Association areas: do not have a primary sensory role but are involved in higher order processing of sensory information necessary for perception and movement initiation.

Ascending reticular activating system (ARAS): system that regulates sleep and wakefulness

Allodynia: pain that can be elicited by normally innocuous stimuli

Brainstem: is the posterior part of the brain, adjoining the spinal cord The brain stem provides the main motor and sensory innervation to the face and neck via the cranial nerves.

Broca's area: is a notable part of the operculum, which plays a key role in conversation or speech production, reading and writing.

BDNF (Brain derived neurotropin factor): helps to support the survival of existing neurons, and encourage the growth and differentiation of new neurons and synapses.

Brodman's maps: cytoarchitectural maps which equate the functional organization of the brain structure into motor sensory and association areas, as evidenced by the laminar organization of the cortex

C or group IV: non-myelinated primary afferent fibres with conduction velocities of 0.4–1.8 m/s

Central Sensitization: where nociceptive neurons in the dorsal horns of the spinal cord become sensitized by peripheral tissue damage or inflammation. This type of sensitization has been suggested as a possible causal mechanism for chronic pain conditions

Cerebellum: (Latin for *little brain*) is a region of the brain that plays an important role in motor control. It is also involved in some cognitive functions such as attention and language, and probably in some emotional functions such as regulating fear and pleasure responses.

Cerebral cortex: outer region of the cerebrum that plays a key role in memory, perceptual awareness, attention, thought, language, and consciousness.

Chronic pain: is thought to arise from damage to the peripheral or central nervous system or chronic inflammatory states

Cingulate cortex: is a part of the brain situated in the medial aspect of the cortex. It is an integral part of the limbic system, which is involved with emotion formation and processing, learning, and memory, and is also important for executive function and respiratory control

Cortical plasticity: is the modulation of cortical activity and is defined as any enduring morphological or functional change in cortical properties

Deafferentation which occurs when there is an elimination or interruption of sensory nerve fibres leading to the elimination or interruption of afferent sensory nerve impulses

Decussate: cross the midline

Degrees of freedom problem: states that there are multiple ways for humans or animals to perform a movement in order to achived the same goal.

Diencephalon: is the region of the brain that includes the thalamus, metathalamus, hypothalamus, epithalamus, prethalamus or subthalamus and pretectum. The diencephalon is located near the midline of the brain, above the mesencephelan (midbrain).

Dorsal column–lemniscal system: subserves touch, pressure, localization of skin contact, detection of vibration and proprioception

Dystonia: is a neurological movement disorder in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures

Fibromyalgia: is characterized by chronic pain and allodynia which is a heightened and painful response to pressure and is hypothesized to be the result of abnormal sensorimotor integration

GABA (γ- aminobutyric acid): is one of the main inhibitory neurotransmitters of the CNS and is found throughout the CNS

Glutamate: is the most abundant excitatory neurotransmitter in the vertebrate nervous system.

Glycine: an inhibitory neurotransmitter

Gyrus: is a ridge on the cerebral cortex. It is generally surrounded by one or more sulci.

Hyperalgesia: is an increased sensitivity to pain, which may be caused by damage to nociceptors or peripheral nerves.

Insular cortex: GH(often called insula, insulary cortex or insular lobe) is a portion of the cerebral cortex folded deep within the lateral sulcus between the temporal lobe and the frontal

lobe. The insulae play a role in diverse functions usually linked to emotion or the regulation of the body's homeostasis.

Ipsilateral: doesn't cross the midline

Laser evoked potentials (leps): have emerged in the last decade as a potentially useful tool for evaluating, objectively, nociception and the nociceptive pathways

Limbic system: involved with emotion formation and processing, learning, and memory, and is also important for executive functions and respiratory control

Long term depression: is an activity-dependent reduction in the efficacy of neuronal synapses.

Long term potentiation: enhances synaptic transmission and improves the ability of two neurons, one presynaptic and the other postsynaptic, to communicate with one another across a synapse.

Mesencephalon: (midbrain) comprises the tectum (or corpora quadrigemina), tegmentum, the ventricular mesocoelia (or "iter"), and the cerebral peduncles, as well as several nuclei and fasciculi

MI: crucial in sensorimotor integration and control and in the learning of new motor skills

Neuropathy: is the term for damage to nerves

Neurotrophin: NT-3 and NT-4 are protein growth factors which have activity on certain neurons of the peripheral and central nervous system and helps to support the survival and differentiation of existing neurons, and encourages the growth and differentiation of new neurons and synapses.

N-methyl-D- aspartate: NMDA is an amino acid derivative which acts as a specific agonist at the NMDA receptor mimicking the action of glutamate.

Nociception: perception of pain

Nociceptors: are the receptors for pain and are free nerve ending found in every tissue of the body except the brain and conduct information about noxious events to the dorsal horn of the spinal cord.

Parabrachial nucleus: is a region in the pons human brain that is related to the ascending reticular activating system (ARAS).

Periaqueductal gray (PAG): is the gray matter located around the cerebral aqueduct within the tegmentum of the midbrain.

The prefrontal cortex (PFC): is the anterior part of the frontal lobes of the brain, lying in front of the motor and premotor areas. This brain region has been implicated in planning complex cognitive behaviours, personality expression, decision making and moderating correct social behaviour

Proprioception: joint position sense

Prostaglandins: are mediators and have a variety of strong physiological effects, such as regulating the contraction and relaxation of smooth muscle tissue

Rheumatoid arthritis (RA): have some persistent or intermittent joint pain for much of the time that their disease is active. Pain is the most significant symptom in patients with RA and is most closely related to medication use.

Seps: used to measure sensory processing.

Somatotopic arrangement: is the maintenance of spatial organisation within the central nervous system. For example, sensory information maintains its structure (i.e. sensory information on the hand remains next to sensory information on the arm) throughout the spinal cord and brain. Densely innervated areas of the body occupy large regions of the cortex.

Somatosensory system: the part of the nervous system that is involved in the process of temperature, pain perception, touch, pressure, and proprioception (joint position sense).

Secondary hyperalgesia: when light touch outside the immediate area of cutaneous damage Leads to pain and is not explained by changes in the periphery

Sensory transduction: is the process by which stimuli from the external environment are converted into electrical signals for transmission through the nervous system

Short interval intracortical inhibition short interval intracortical facilitation: which are measures of cortical inhibition/facilitation that are obtained in a paired-pulse TMS protocol.

Smi: is the primary region implicated in the utilization of sensory inputs in limb motor control.

Spinal nucleus pars caudalis: which receives the fibres of the sensory root of the trigeminal nerve that descend along its lateral border as the spinal tract of trigeminal nerve

Spinothalamic tract system: subserves thermoreception (temperature), and nociception (pain)

Spinoreticular tract: is an ascending pathway positioned closely to the lateral spinothalamic tract which extends from the spinal cord to the reticular formation to the thalamus

Sulcus: is a depression or fissure in the surface of the brain. It surrounds the gyri, creating the characteristic appearance of the brain in humans and other large mammals.

Superior colliculus: is a paired structure that forms a major component of the vertebrate midbrain

Substance P: is a neuropeptide that functions as a neurotransmitter and as a neuromodulator.

Supraspinal means *above the spine*, and refers to above the spinal cord.

Thermoreception: perception of temperature.

Trigeminal neuralgia: is a neuropathic disorder characterized by episodes of intense pain in the face originating in one of the three trigeminal nerves.

1 INTRODUCTION

Sensorimotor integration (SMI) is the ability of the central nervous system (CNS) to integrate afferent (incoming) information from different body parts and formulate appropriate motor output to muscles. In the healthy brain, there is a highly organized relationship between sensory input from one part of the body and the motor cortical output to muscles acting on that same part (Rothwell &Rosenkranz, 2005). Impaired sensorimotor integration may explain why pain becomes chronic and why workers are predisposed to mechanical injury. The body of research shows that both cortical and subcortical somatosensory evoked potential (SEP) peaks of the CNS increase after deafferentation (elimination of sensory nerve impulses) and decrease after increased afferent input (repetitive movement) demonstrating that altered afferent input induces cortical plasticity which outlasts the period of altered input (Murphy et al., 2003a; Murphy et al., 2003b; Taylor & Murphy, 2008; Tinazzi et al., 1998). This is relevant to the study of pain and sensory processing as it is hypothesized that pain also results in central plastic changes that outlast the period of altered input which over time may result in syndromes which lack a discernible peripheral pathology (chronic pain, dystonia, fibromyalgia, phantom limb pain). Several studies have shown that pain affects sensory processing as demonstrated through elevated SEP peaks (Tinazzi et al., 2000a; Tinazzi et al., 2004) and functional reorganization (Knecht et al., 1998; Soros et al., 2001).

Several animal studies have shown novel motor training results in MI reorganization (Boudreau et al., 2007). In humans, plasticity has been reported in association with novel motor training (Svensson et al., 2003). Furthermore, acute experimental pain has been shown to affect neuroplasticity that would normally occur after novel motor training (Boudreau et al., 2007). There is a gap in the research as to how sensorimotor processing is affected when motor training occurs while in pain. This study will examine the effect of pain on SEP peaks and the interactive

effect of pain and motor training on SEP peaks. Experimental pain will be induced by applying capsaicin cream and SMI will be measured by recording selected early somatosensory evoked potentials (SEPs) in Humans. We will assess the effect of central sensitization on signal transmission in the nervous system of Human subjects by investigating changes in both the amplitude and latency of SEPs from baseline, post capsaicin, and post capsaicin/post motor training.

The relevant literature is reviewed in Chapters 2 - 7. Chapter 2 discusses background information on the sensory systems, motor control, pain, capsaicin as an experimental pain model and SEPs. Chapter 3 reviews the known literature on altered afferent input. Chapter 4 reviews the known literature on pain. Chapter 5 discusses the literature on motor learning and pain. Chapter 6 describes the practical and scholarly significance of the research respectively. Chapter 7 describes the overall experimental protocols and the techniques used to explore sensorimotor integration.

The methodology specific to this experiment is described in Chapters 8. The key experimental results are summarized in Chapter 9. These findings are discussed in Chapter 10, and some future research directions are suggested.

Hypotheses:

1. Experimental pain will result in elevated cortical SEP peaks.
2. Motor learning will result in elevated cortical SEP peaks related to sensorimotor integration (N18, N24, N30).
3. The interactive effect of experimental pain and motor training will also result in elevated cortical SEP peaks.
4. Experimentally induced pain will result in decreased accuracy as compared to the placebo condition, and increased reaction time as compared to the placebo condition.

2 LITERATURE REVIEW

Background Information

For the purpose of this research, background information and terminology related to the somatosensory system, motor control, pain, capsaicin cream, and SEPs, will be discussed.

2.1 The somatosensory system

The peripheral nervous system (PNS) consists of nerves that lie outside of the brain and spinal cord that connects the limbs and organs to the central nervous system (CNS) (Tortora & Derrickson, 2009). The central nervous system (CNS) consists of the brain and the spinal cord and integrates the information received from the PNS. The adult human brain consists of four major parts: brainstem, diencephalon, cerebellum, and the cerebrum (Tortora & Derrickson, 2009). The brain is divided into left and right cerebral hemispheres and at the outer region of these hemispheres is the cerebral cortex. The cerebral cortex plays a key role in memory, perceptual awareness (including pain), attention, thought, language, and consciousness (Tortora & Derrickson, 2009). The cortex is divided into four lobes: frontal, parietal, occipital, and temporal. The laminar organization of the cortex is organized into Brodman's maps which are cytoarchitectural maps which equate the functional organization of this structure into motor, sensory, and association areas (Barker & Barasi, 2008).

The somatosensory system provides conscious perception of sensory information from the skin, the musculo-skeletal system, and the viscera to the cortex to produce the sensations of temperature, pain, touch, pressure, and proprioception (joint position sense). Sensory transduction is the process by which stimuli from the external environment are converted into electrical signals and transmitted through the CNS (Barker & Barasi, 2008). The somatosensory system has been used to study stimulus information processing and the general principles of the

functional organization of the brain (Hoshi & Tanji, 2004). The somatosensory system can be divided into two systems which carry ascending information to the contralateral cerebral hemisphere: the dorsal column–system (DCCs) and the spinothalamic system (STT) (See Figure 1-1) (Barker & Barasi, 2008; Cruccu et al., 2008).

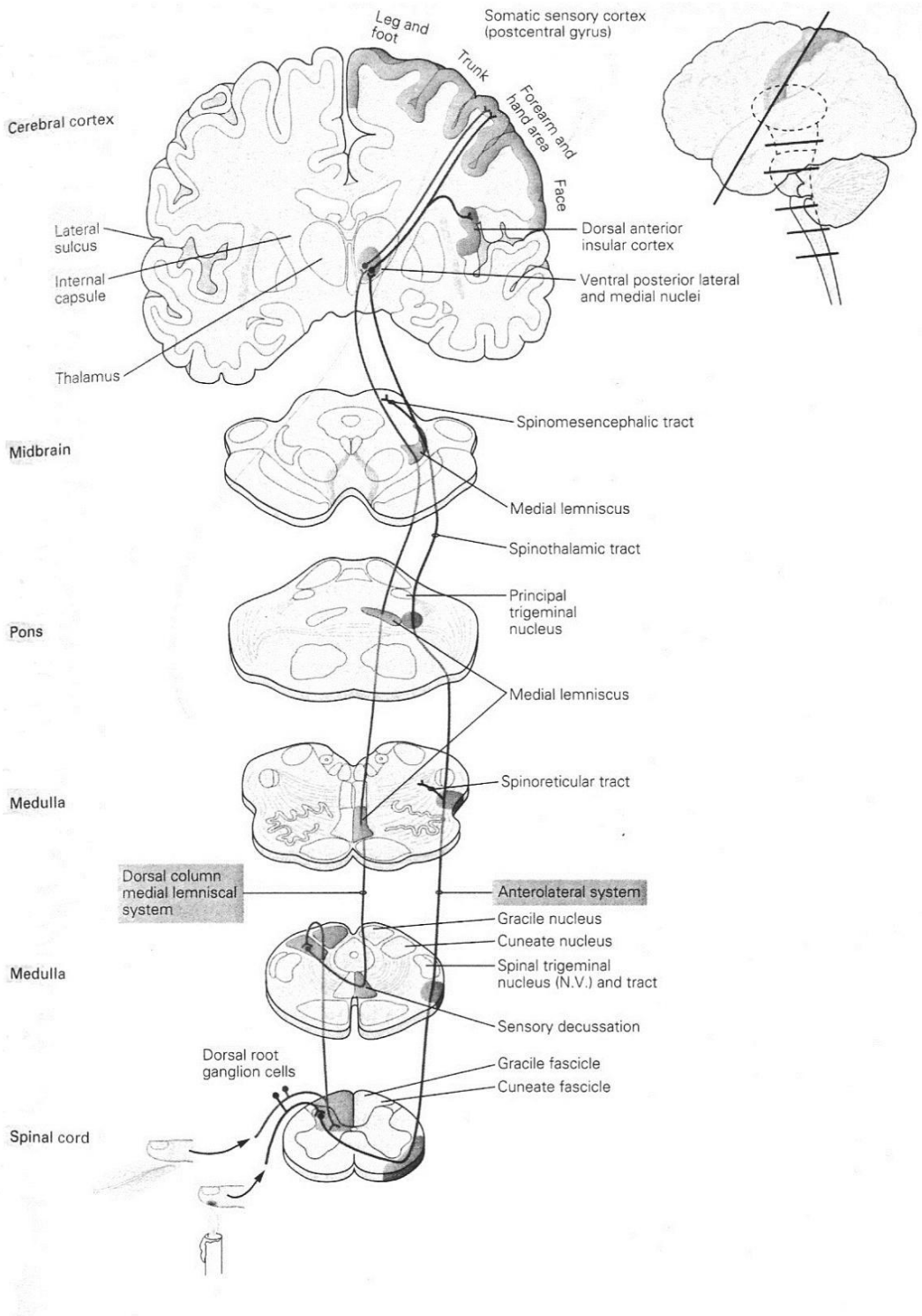

Figure 1-1: The Dorsal Column Medial Lemniscal system (left) and the Anterolateral system (right) pathways (Kandel, et al., 2000) on page 447.

The dorsal column system transmits touch, pressure, vibration and proprioception as discrete neural impulses arranged in transmission pathways. The spinothalamic tract system transmits neural impulses of thermoreception (temperature), and nociception (pain) (Cruccu et al., 2008). Both transmission pathways include three neurons which ascend to the cortex. The specialized sensory receptor, afferent axon, and cell body, together with the synaptic contacts in the spinal cord are known as the primary afferent. This first order neuron is situated in the dorsal root ganglia and connects a receptor of the limbs, trunk, neck, or posterior head with the spinal cord. The first order neuron synapses with the second order neuron and the axons of the second neuron cross the midline (decussate) and ascend to the thalamus (See Figure 1-1). From there the third order neurons ascend into the network of the somatosensory cortex areas, which include the primary somatosensory area (SmI), secondary somatosensory area (SmII), posterior parietal cortex, posterior and mid-insula and the mid-cingulate cortex (Cruccu et al., 2008; Romo et al., 2002).

The SmI is located in the postentral gyrus of the parietal lobe of the cerebral cortex and is subdivided into four different areas (Brodmann's area 3a, 3b, 1 and 2) (see Figure 1-2). The SmI plays a critical role in processing somatosensory information and is important in somatosensory acuity, detection and discrimination (Sessle et al., 2005). Specific areas of the SmI receive somatic sensory input from particular parts of the body with each area containing a topographic - somatotopic representation of the contralateral body surface with the tongue represented laterally and the feet medially (See Figure 1-2). Somatotopic arrangement is the maintenance of spatial organisation within the CNS. Within the SmI, densely innervated areas of the body such as the hands and face occupy larger regions of the cortex (Sessle et al., 2005). We are using Brodman's classification to define the cortical territories of interest. A Brodmann area is a region of the

cerebral cortex defined based on the structure and organiation of cells. For example, Brodmann areas 1, 2, and 3 represent the primary somatosensory cortex, and area 4 represents the primary motor cortex (Cruccu et al., 2008; Romo et al., 2002). The secondary somatosensory area (SmII), receives projections from the SmI and projects to the association areas: the posterior parietal cortex (Brodmann's area 39, 40) the prefrontal cortex (Brodmann's area 9-12 and 44-47) and the temporal cortex (Brodmann's areas 21, 22, 37, and 41-43) which do not have a primary sensory role but are involved in higher order processing of sensory information necessary for perception and movement initiation. The association areas then project to the motor and limbic systems (Cruccu et al., 2008; Romo et al., 2002).

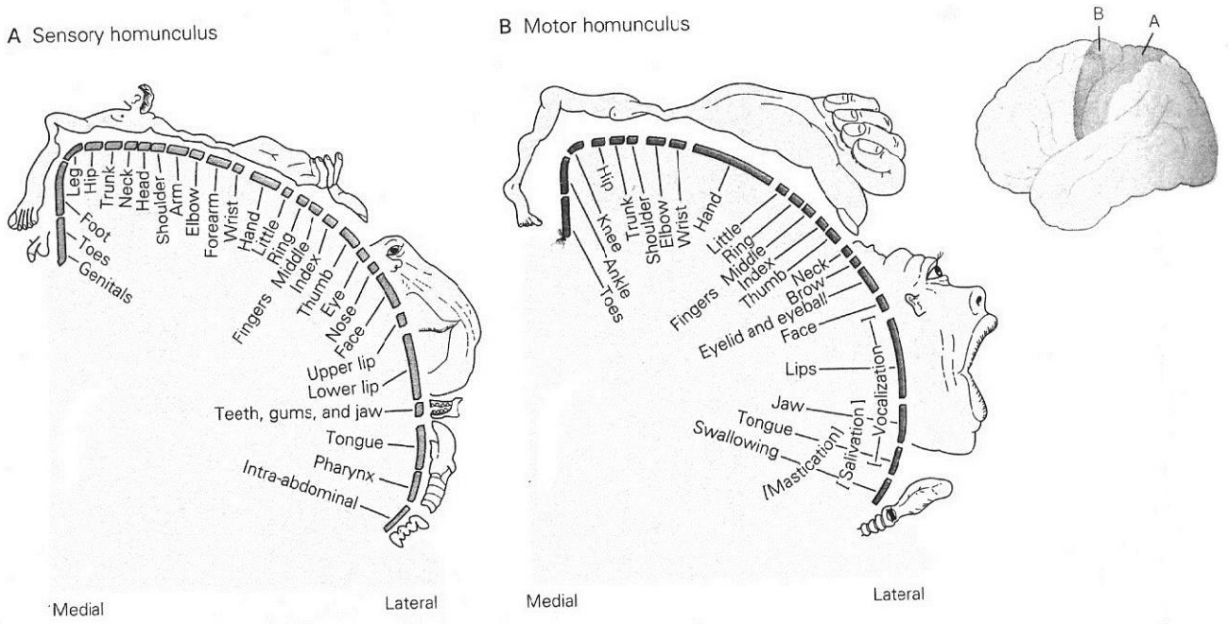

Figure 1-2: The sensory and motor homunculi. The location of limb representation within the cortex is seen here. The amount of cortical area dedicated to a certain region is represented by the size of the image, reflecting their degrees of innervations (Kandel, et al., 2000) on page 343.

2.2 Motor Control

The somatosensory pathway has evolved in association with the corticospinal tract which has a selective role in the control of fine movements. The corticospinal tract is a two neuron set in which the upper motor neuron descends from the cerebral cortex to the lower motor neuron which then innervates a muscle (Barker & Barasi, 2008). The primary motor cortex (MI) is located in the precentral gyrus of the frontal lobe and is crucial in sensorimotor integration and control and in the learning of new motor skills (Sessle et al., 2005). Similar to the SmI, the MI contains a somatotopic representation of the contralateral body surface with the tongue represented laterally and the feet medially. A range of other cortical areas are involved in the control of movement including the supplementary (SMA) (located in the lateral part of Brodmann's area 6) and premotor cortex (PMC) (located in the medial part of Brodmann's area 6), a number of motor areas centered on the anterior cingulated cortex on the medial aspect of the frontal lobe, the frontal eye fields and the posterior parietal cortex (Brodmann's area 7). Research indicates that the SMA and the PMC are separate motor areas with distinct structural and functional capabilities (Hoshi & Tanji, 2004). The supplementary motor cortex (SMA) receives direct inputs from the posterior parietal cortex and the lateral somatosensory areas. The output of the SMA is directed to M1and to the spinal cord (Romo et al., 2002). The PMC has an input directly to the spinal motor neurons via the corticospinal or pyramidal tract (Barker & Barasi, 2008).

2.2.1 Significance of the Hand

The Human hand can take on a huge variety of functions with a complex interplay of skeletal and muscular degrees of freedom which provide an enormous dexterity. Lesion data, neurophysiological studies, and modern functional imaging experiments have shown that

primates have evolved extensive cortical systems for controlling the hand (Nowak, 2008). The corticospinal tract has direct connections between neurons in the primary motor cortex and the spinal motoneuron pool and plays a critical role in controlling movement. Therefore, the cerebral cortex controls spinal motoneurons which directly connect with the muscles in the hand. In addition, the hand is also influenced by other cortical areas as well as from subcortical structures such as the cerebellum and basal ganglia (Nowak, 2008).

2.3 Pain

In this study, capsaicin will be used to induce acute pain in healthy volunteers. Pain, in its most elementary representation as a spinal reflex, is a fairly uncomplicated system. However, within the brain, pain is a complex, multi-dimensional phenomenon that influences a wide variety of nervous system functions ranging from sensory-discriminative and affective-motivational components to motor integratory responses and may extend to influences on neuro-immune function in chronic pain conditions (Tracey & Mantyh, 2007). Pain is not necessarily related linearly to the nociceptive input and is individual and subjective. Pain is influenced by memories, emotions, genetic, and cognitive factors and has different qualities and temporal features depending on the modality and locality of the stimulus (Dubin & Patapoutian, 2010). There are three forms of pain: nociceptive, inflammatory, and neuropathic. Nociceptive pain refers to the processing of brief noxious stimuli, inflammatory pain is the consequence of prolonged noxious stimulation leading to tissue damage, and neuropathic pain is the consequence of neurological damage, including peripheral neuropathies and central pain states (Bushnell et al., 2008, p. 8). The highly individual and subjective nature of pain makes it difficult to define and treat clinically (Kandel et al., 2000, p. 472).

2.4 Capsaicin

Capsaicin is a widely used pain model and can be applied topically as it provides a pain stimulus with minimal contributions from other somatosensory modalities and allows the comparison of painful stimuli (Iadarola et al., 1998). Capsaicin is used as an alternative to painful hot thermal stimuli as it circumvents the potential for tissue damage (Iadarola et al., 1998). Capsaicin binds to the TRPV1 receptor (a heat activated protein channel that resides on the membranes of nociceptive and heat neurons) which open between 37 and 45 °C. When capsaicin binds to TRPV1, it causes the channel to open below 37 °C, which explains why capsaicin is linked to the sensation of heat (Caterina et al., 1997).

Capsaicin initially leads to a sensitization of C-fiber nociceptors by triggering cation influx, and through the release of inflammatory substances, including vasoactive peptides (e.g., substance P) and through inhibiting the reuptake of substance P from the C fibers (Beydoun et al., 1996; Soros et al., 2001; Valeriani et al., 2005). Capsaicin induces peripheral sensitization due to excitability changes of the nociceptor and central sensitization through ongoing nociceptor discharge (Seifert & Maihofner, 2009). Capsaicin provides a strong acute pain stimulus, induces central sensitization, and transiently induces a variety of sensory abnormalities including hyperalgesia and allodynia (Iadarola et al., 1998). Allodynia and hyperalgesia are changes in sensory sensitivity associated with tissue inflammation or injury and are defined as an increased pain sensation to non-painful and painful stimulation, respectively (Bushnell et al., 2008, p. 8). Capsaicin results in vasodilatation leading to a flare reaction, increased blood flow, and elevated temperature (Iadarola et al., 1998).

2.5 SEPs

Evoked potentials (EPs) are electrical responses of the nervous system to sensory stimulation and can be evoked in the visual pathway, auditory pathway, or peripheral nerves in the arms or legs

(somatosensory evoked potential, SEPs) (Cruccu et al., 2008). EPs involve stimulating the peripheral receptor (eye, ear, or median/tibial nerve) and measuring the cortical response. This gives a measure of conduction along the pathway that has both a peripheral and central nervous system component (Yamada et al., 2004). SEPs are evoked by bipolar transcutaneous electrical stimulation applied on the skin over the selected nerve and are an objective and direct method of assessing the integrity of the sensory pathways of the central and peripheral nervous systems (Cruccu et al., 2008). The potentials are recognized by their distributions, reflecting the activation of their generators. They are named N or P, followed by an integer which indicates the polarity and the post-stimulus latency (ms) of the recorded wave from the time of peripheral nerve stimulation (Cruccu et al., 2008). The amplitude of the peak represents the degree of activity of each neural structure that the peaks represent, and latency represents the transmission time between point of stimulation and the neural structures responsible for generating the peak (Mauguière, 1999). Any alterations are believed to be alterations in the amount of activity of the same assumed neural structures (Mauguière, 1999).

3 LITERATURE REVIEW - ALTERED AFFERENT INPUT

This chapter reviews how altered afferent input in the form of deafferentation and repetitive movement effects plasticity in the CNS. This is relevant to the study of pain and sensory processing as it is hypothesized that pain also results in central plastic changes that outlast the period of altered input.

3.1 Deafferentation

Plasticity means the capacity for pliancy and malleability (Rossini & Dal Forno, 2004). Cortical plasticity is the modulation of cortical activity and is any enduring morphological or functional change in cortical properties (for review, Boroojerdi et al., 2001). Body parts are represented in the SmI and the MI. These cortical maps are dynamic networks which are capable of reorganization through practice, skill acquisition, and injury (Boroojerdi et al., 2001; Soros et al., 2001). Research has shown that mature CNS does have a degree of capacity for self-repair and reorganization after injury, even though a demonstration of the linkage between functional recovery and plastic reorganization is lacking (Rossini & Dal Forno, 2004). Plasticity usually includes the potential for change and all the mechanisms of self-repair or of reorganization of neural connections. Cortical maps can be modified by sensory input, experience, and learning, and go through continuous changes in response to stimuli during routine life experiences, movement patterns, and cognitive tasks. Plasticity is the basis of learning and rehabilitation (Rossini & Dal Forno, 2004). The enlargement of cortical representation areas over a few days has been shown after repeating a skilled movement pattern, such as the learning of a piano exercise (Rossini & Dal Forno, 2004). These changes can become stable, depending on the duration of the stimulus or motor pattern. This is exemplified by the permanent enlargement of the cortical representation area of the left fingers in string players (Rossini & Dal Forno, 2004).

The topography and excitability of cortical maps in response to altered afferent input is thought to contribute to chronic pain and also constitute the basis of learning and recovery of function following an injury (Boroojerdi et al., 2001). Research indicates that chronic pain is associated with changes in cortical organization. For example, the presence and severity of phantom limb pain is associated with reorganization of the SmI. Flor et al. (1995) found that activation in primary somatosensory cortex was correlated with clinical pain among persons with phantom limb pain. With phantom limb pain, the SmI area associated with the perception of sensations from the mouth area shifts into the area that used to process sensory information from the amputated limb (Jensen, 2010). Additionally, in individuals suffering from phantom pain, stimulation of the skin of the forearm produces sensations in specific parts of the phantom hand (for review, Melzack et al, 2001). As the hand and forearm are somatotopically close within the SmI, it is hypothesized that a somatotopic map of the phantom hand is revealed on the forearm which reflects neuroplastic changes in representations of the hand and forearm in the CNS. Similar cortical reorganization is thought to occur in other chronic pain conditions (Jensen, 2010).

Plasticity can be expressed in different ways including cellular and anatomic alterations. The anatomy of a neural network is much larger than the area of its usual functional influence. There are multiple representations of each muscle and joint area in the cortex. Modifications of the synaptic efficacy within neuronal networks are thought to underlie learning and memory, and this also occurs in response to deafferentation and pain. The distribution and function of a network depends on excitation and inhibition. Some areas are silent through active GABA tonic inhibition which can be altered or removed, called unmasking, which can cause a rapid change in size or distribution of the functional network (Rossini & Dal Forno, 2004). While modulation is

a reversible change, modification represents long-lasting alterations in the expression of transmitters/receptors/ ion channels or in the structure, connectivity and survival of neurons, such that the system is grossly modified. Deafferentation is an elimination or interruption of sensory nerve fibres leading to the elimination or interruption of afferent sensory nerve impulses (Tinazzi et al., 1998). Several studies have examined plasticity in the CNS in response to deafferentation (Tinazzi et al., 2000a; Tinazzi et al., 1997; Tinazzi et al., 1998). These studies demonstrate plasticity in the CNS in response to deafferentation (Tinazzi et al., 2000a; Tinazzi et al., 1997; Tinazzi et al., 1998) which is relevant to my thesis as it is proposed that pain as a form of altered afferent input also leads to cortical plasticity in the CNS.

Research shows that the mature human cortex displays a plastic capacity to reorganize itself in response to changes in sensory input (Tinazzi et al., 2000a; Tinazzi et al., 1997; Tinazzi et al., 1998; Weiss et al., 2004). Studies in sensory processing demonstrate that deafferentation leads to cortical plasticity (Tinazzi et al., 2000a; Tinazzi et al., 1997; Tinazzi et al., 1998). However, there have been contradictory findings on the effect of deafferentation on subcortical versus cortical structures of the CNS (Tinazzi et al., 1997; Tinazzi et al., 1998). Tinazzi et al. (1997) found that the N20/P20, P27 and N30 cortical peaks showed increases in amplitude while no significant differences in any of the subcortical peaks during temporary anaesthesia of the ulnar nerve. N20, P20, and P27 are generated from the primary somatosensory cortex in the posterior wall of the central fissure (SmI area) (Mauguière et al., 1999) and the N30 is thought to originate from the frontal lobe and the posterior wall of the central sulcus and reflects sensorimotor integration (Tinazzi et al., 2000). This study (Tinazzi et al., 1997) supports the hypothesis that the cortical structures play a primary role in sensory processing. In contrast, Tinazzi et al. (1998) found increased amplitudes of the cortical and subcortical SEP peaks following stimulation of

the ulnar nerve ipsilateral to the deafferented median nerve. However, Tinazzi et al. (1998) found that the differences in subcortical amplitudes were not as pronounced as the cortical SEPs. The findings of this study are in contrast to Tinazzi et al. (1997) who didn't find changes at the subcortical level. However, Tinazzi et al. (1998) was studying individuals with chronic deafferentation while Tinazzi et al. (1997) was studying individuals with acute deafferentation. These results (Tinazzi et al., 1997; Tinazzi et al., 1998) suggest that that chronic exposure to altered afferent input may result in long term cortical modulation which then modifies the subcortical structures and sets up a maladaptive loop circuit (Tinazzi et al., 1998). Further research in this area is required. These results added to the body of evidence that the somatosensory system of humans is capable of undergoing reorganization and the primary importance of cortical structures in sensory processing (Tinazzi et al., 1997; Tinazzi et al., 1998). Pain is also a form of altered afferent input and it is hypothesized that there may be a similar mechanism involved through the development of chronic pain. Long term exposure to pain (a form of altered afferent input) may result in cortical modulation which then modifies the subcortical structures. Chronic pain is ongoing pain that occurs from damage to the peripheral or central nervous system (Barker & Barasi, 2008). Apart from peripheral nociceptors and the spinal cord, morphological and functional plastic changes also take place in subcortical and cortical areas that participate in pain processing (Jensen, 2010). The evidence suggests that long term plastic modifications in cortical networks may represent a possible basic mechanism underlying chronic pain. In addition to functional changes, morphological alterations at spinal and supraspinal levels have been reported in chronic pain (Jensen, 2010). Neuropathic pain is accompanied by apoptosis of spinal cord cells and sprouting of nerve terminals in the SmI (Flor

et al., 2006), and grey matter density decreases in PFC which is associated with reduced cognitive and thalamic atrophy (Jensen, 2010).

Tinazzi et al. (2003a) found that the amplitude of cortical SEPs showed an increase of amplitudes with anaesthesia. In contrast to Tinazzi et al. (1998) who found increases in subcortical structures in sensory processing, Tinazzi et al. (2003a) found that spinal N13 and brainstem P14 potentials did not change throughout their deafferentation study on healthy subjects. These researchers found for the first time that stimulation of muscle afferents originating in the anaesthetic territory can induce rapid modulation of cortical activity (Tinazzi et al., 2003a). This study transformed the research field as Tinazzi et al. (2003a) discovered that deafferentation can induce cortical plasticity across somatic submodalities which are likely to occur within the SmI.

Other studies have investigated deafferentation, cortical plasticity, and the roles played by cortical and subcortical structures. Weiss et al. (2004) established that after deafferentation of the radial and median nerves, the cortical representation of the little finger and the skin beneath the lower lip moved closer together. Within an hour of abolishing afferent information there is an invasion of the deafferented region of the brain by the cortical representation zones of the adjacent portions of the brain (Weiss et al., 2004). The hand and lip are somatotopically close in the topography of the SmI, and therefore this study provides evidence that plasticity in response to deafferentation is occurring at the cortical level.

Murphy et al. (2003a) investigated the modulation of cortical processing of median nerve input and output by studying the role of temporary anaesthetic deafferentation of the radial nerve at the elbow and found that the N30 peak showed a significant increase in amplitude. In addition, the MEP amplitude of the median nerve innervated APB muscle was significantly decreased during

the radial nerve block suggesting that deafferentation not only has an impact on the topography of the SmI, but on the subsequent motor output as well (Murphy et al., 2003a).

3.2 Repetitive movement

While deafferentation is reduced afferent input, repetitive activity is an increase in afferent input. Murphy et al. (2003b) added to the body of evidence in support of the role of cortical structures in somatosensory processing by demonstrating that a repetitive activity leads to attenuations in the amplitudes of subcortical and cortical SEP complexes. These results support the growing body of evidence that both increased and decreased afferent inputs lead to plastic changes in the somatosensory and corticomotor systems (Murphy et al., 2003b). Research demonstrates that both cortical and subcortical components of the CNS increase after deafferentation and decrease after increased afferent input (repetitive movement) demonstrating that altered afferent input induces cortical plasticity (Murphy et al., 2003a; Murphy et al., 2003b; Tinazzi et al., 1998). The literature demonstrates that the cortical structures play a primary role in sensory processing as it has been shown that acute altered afferent input leads to rapid cortical modulation and chronic altered afferent input results in cortical changes which subsequently modulate subcortical structures (Murphy et al., 2000a; Murphy et al., 2003b; Tinazzi et al., 1997; Tinazzi et al., 1998). The studies in deafferentation (Murphy et al., 2000a; Murphy et al., 2003b; Tinazzi et al., 1997; Tinazzi et al., 1998) established that the adult human central nervous system (CNS) retains its ability to reorganize itself in response to altered afferent input and that by affecting the CNS these plastic changes outlast the period of the altered input.

The literature shows that both cortical and subcortical SEP peaks of the CNS increase after deafferentation (elimination of sensory nerve impulses) and decrease after increased afferent input demonstrating that altered afferent input induces cortical plasticity which outlasts the

period of altered input (Murphy et al., 2003a; Murphy et al., 2003b; Taylor & Murphy, 2008; Tinazzi et al., 1998). The literature demonstrates the primary role played by cortical structures in sensory processing as it has been shown that acute altered afferent input leads to rapid cortical modulation with no effects observed at the subcortical level (Murphy et al., 2000a; Murphy et al., 2003b; Tinazzi et al., 1997; Tinazzi et al., 1998). This is relevant to the study of pain and sensory processing as it is hypothesized that pain also results in central plastic changes that outlast the period of altered input which over time may result in syndromes which lack a discernible peripheral pathology (chronic pain, dystonia, fibromyalgia, phantom limb pain).

4 THE SIGNIFICANCE OF THE RESEARCH

4.1 The scholarly significance of the research

This chapter will discuss the scholarly significance of this thesis. Plasticity has been observed in response to acute and chronic pain. The literature reveals that there are subcortical and cortical changes in excitability in response to pain (Boroojerdi et al., 2001; Cook et al., 1996; Dostrovsky & Guilbaud, 1990; Hardy et al., 1950; for review, Hodges et al., 2003; Livingston, 1943; MacKenzie, 1893; Maihofner et al., 2010; Neugebauer &Li, 2003; Wei & Zhuo, 2001; Woolf, 1983). Plasticity of function is seen with changes in the dorsal horn of the spinal cord and alterations in the thalamus and the cortex (Borsook, 2007). Seminal studies reveal that pain in the absence of deafferentation induces plasticity at the cortical level (Knecht et al., 1998; Soros et al., 2001; Tinazzi et al., 2000; Tinazzi et al., 2004). Soros et al. (2001) found that acute pain in the hand caused a reorganization of the SmI. The size of the cortical hand representation and the distance between the hand and the ipsilateral lip representations decreased. The hand and the lip are somatotopically effectively encoding sites and neuron populations close, suggesting that acute nociceptive pain induces rapid neuroplastic changes at the cortical level (Soros et al., 2001). Knecht et al. (1998) investigated the application of experimental acute pain to the hand followed by non-noxious tactile stimulation of the ipsilateral lip in healthy humans. Subjects reported perceiving phantom-like sensations in the hand synchronously to the non-noxious lip stimulation indicating that acute pain induces neuroplastic changes in healthy humans likely due to a disinhibition between their respective neural regions. This expanded on the previous studies by Knecht et al. (1995, 1996) which indicated that cortical reorganization occurs in individuals with phantom limb pain.

Tinazzi et al. (2004) stimulated the right median nerve ipsilateral to facial pain in individuals with trigeminal neuralgia resulting in greater amplitudes of cortical potentials which showed a positive correlation with the magnitude of pain. This demonstrates that pain in the absence of deafferentation results in elevated cortical SEP peaks (Tinazzi et al., 2004). Tinazzi et al. (2000) assessed the relationships between pain and central sensitization by recording SEPs in patients who were experiencing chronic pain in the right thumb in the absence of deafferentation. Amplitudes of subcortical and cortical potentials after stimulation of the painful right thumb were significantly larger than when compared to the stimulation of the non-painful left thumb and showed a positive correlation with the magnitude of pain. Tinazzi et al. (2000) did not find a significant correlation between the subcortical and cortical SEP components and therefore proposed that cortical plasticity is not simply a linear reflection of subcortical plasticity (Tinazzi et al., 2000). The results of Tinazzi et al. (2000) are also in alignment with the study conducted by Tinazzi et al. (1998) who showed that subcortical SEP peaks increased in response to chronic deafferentation but did not increase to the same extent as the cortical SEP peaks. Other studies in deafferentation and spinal manipulation have found a modulation of the cortical peaks and no change in subcortical peaks in response to altered afferent input (Murphy et al., 2003a; Murphy et al., 2003b; Taylor & Murphy, 2007; Taylor & Murphy, 2009; Tinazzi et al., 1998; Tinazzi et al., 2003). Therefore, the results of Tinazzi et al. (1998, 2000) suggest that in response to chronic deafferentation and chronic pain, there may be a modulation of processing in subcortical structures by the cortex.

Studies have demonstrated increased SEP peak amplitudes from the non-deafferented, but nearby upper limb nerves when massive deafferentation co-exists with pain (Taylor & Murphy, 2007; Taylor & Murphy, 2008; Tinazzi et al., 2000; Tinazzi et al, 2004; Tinazzi et al., 1997; Tinazzi et

al., 1998). Reduced cortical SEP peak amplitudes have been observed following spinal manipulation reflecting a normalization of the pain-induced central plastic changes (Taylor & Murphy, 2007; Taylor & Murphy, 2008; Taylor & Murphy, 2009). The historical context of the field suggests that pain in the absence of deafferentation may play a pivotal role in determining cortical somatosensory rearrangements in the adult brain (Knecht et al., 1998; Soros et al., 2001; Tinazzi et al., 2000; Tinazzi et al., 2004). However, the studies by Tinazzi et al. (2004) and Tinazzi et al. (2000) have been conducted on individuals suffering from chronic pain and the spinal manipulation studies have been conducted on individuals with recurrent neck pain and stiffness (Taylor & Murphy, 2007; Taylor & Murphy, 2008; Taylor & Murphy, 2009). Although the studies by Knecht et al. (1998) and Soros et al. (2001) found cortical rearrangements in response to acute pain in healthy humans, they did not measure individual SEP peaks. The current body of evidence suggests that chronic deafferentation may result in long term cortical modulation which results in changes at the subcortical level (Tinazzi et al., 1997; Tinazzi et al., 1998). There is also evidence that chronic pain may result in long term cortical modulation of the subcortical structures (Tinazzi et al., 2000). There is a gap in our understanding of the response of specific cortical and subcortical SEP peaks to acute pain while performing a complex motor task which this thesis seeks to address.

As the current body of evidence suggests that there may be differences in the primary somatosensory area (SmI) processing of acute and chronic pain (Jones et al., 2003; Tinazzi et al., 2000), it would be valuable to explore the pattern and time course of subcortical and cortical SEP peaks in response to acute experimental pain through the application of capsaicin cream in healthy volunteers. This research will be conducted on healthy Humans and thus this is in contrast to those studies which have conducted their research on individuals suffering from

chronic or recurrent pain, for example, the studies by Taylor & Murphy (2007, 2008). In addition, although there have been numerous studies conducted using capsaicin cream (Beydoun et al., 1996; Simone & Ochoa, 1991), there is a gap in the knowledge concerning topical capsaicin application and the subsequent measurement of subcortical and cortical SEP peaks. SEP peaks have been previously investigated in sensory processing studies. Tinazzi et al. (1997) indicated that N20,P20, P27 and N30 cortical potentials showed increases in amplitude during temporary anaesthesia of the ulnal nerve that were intracortical in origin while the spinal N13 and subcortical P14, N18 potentials remain unchanged. Tinazzi et al. (2003a) found that the amplitudes of parietal N20 and P27 and frontal N30 somatosensory evoked potential components showed an increase in amplitude with anaesthesia while spinal N13 and brainstem P14 potentials did not change through their experiment. Murphy et al. (2003a) studied the role of temporary anaesthetic deafferentation of the radial nerve at the elbow and found that the N30 peak showed a significant increase. This study will investigate these SEP peaks as alterations in their amplitudes post-sensitization will reflect the effect of pain on sensorimotor integration. It is important to include both subcortical and cortical peaks to differentiate whether the alterations are occurring at the subcortical or cortical level. N30 is particularly important as it reflects sensorimotor integration. N18 and N24 are also important as they reflect cerebellar pathways which are important for motor processing.

Plasticity has been observed in sensory systems in response to pain, and sensory–motor integration at a reflex level such as a motor withdrawal reflex in response to noxious stimuli is well understood (Borsook, 2007). A growing body of evidence suggests that there are differing effects of experimental pain on MI excitability. Complex Regional Pain Syndrome (type I) patient's exhibit decreased MI excitability associated with the affected muscles whereas

increased MI excitability has been shown in phantom limb pain patients (Dettmers et al., 2001; Krause et al., 2006). Gronroos et al. (1993) found capsaicin produces a central facilitation of a nociceptive flexion reflex in humans. In healthy subjects, decreased MI excitability has been shown in association with capsaicin-induced skin pain and hypertonic saline- induced muscle pain of the hand (Cheong et al., 2003; Farina et al., 2001; Le Pera et al., 2001). In contrast to these results, noxious electrical stimulation of the finger has revealed an increase in the MI excitability for distal (hand) muscles and a decrease in the MI excitability for proximal (upper arm) muscles (Kofler et al., 1998). As the evidence suggests that there are differing and complex effects of experimental pain, examining the effect of acute pain on SEP peaks, and the interactive effect of pain and motor learning fills a gap in the research.

The likely mechanism behind cortical plasticity in response to pain is GABA-mediated disinhibition (Knecht et al., 1998; Soros et al., 2001). GABA plays a pivotal role in regulating the extent of rapid cortical reorganization after lesions or changes in sensory input in deafferentation (Levy et al., 2002; Marty et al., 1997; Weiss et al., 2004; Ziemann et al., 1998). Levy et al. (2002) demonstrated that GABA levels in the human sensorimotor cortex are reduced following deafferentation and is associated with an expansion of motor representations. Ziemann et al. (1998) found an up-regulation of plasticity through a deafferentation-induced down regulation of GABA related inhibitory circuits. Marty et al. (1997) demonstrated that activity dependent modulation affects GABA-containing interneurons. These finding support the hypothesis that cortical plasticity is a consequence of reduced GABA inhibition resulting in the release of latent thalamo-cortical projections (Levy et al., 2002; Marty et al., 1997; Ziemann et al., 1998). These deafferentation studies suggest that there may be a common mechanism of

GABA-mediated disinhibition in response to altered afferent input (Levy et al., 2002; Marty et al., 1997; Weiss et al., 2004; Ziemann et al., 1998).

This study will involve learning complex motor task and the likely mechanism behind the plasticity for this task is GABA-mediated disinhibition. Although there is a gap in the body of knowledge on the effects of pain on motor performance in humans, the effects of reduced sensory feedback, resulting from age, disease, or trauma for example, on motor performance of previously learned motor tasks such as gait and balance (Stumieks et al., 2008; Wolfson, 2001) or hand manipulation (Nowak, 2008) have received considerable attention. Several studies have indicated that experimental muscle pain can modulate neuromuscular control through decreases in the coordination of muscle groups, as indicated by a reorganization in muscle activity, have been shown following experimentally induced muscle pain in a shoulder flexion (Falla et al. 2007; Madeleine et al., 2006) and dynamic upper limb (Madeleine et al., 1999) and goal-directed jaw (Sae-Lee et al., 2008) motor tasks. In a seminal capsaicin and motor training study, Boudreau et al. (2007) indicated neuroplasticity of the tongue MI, as reflected in a significantly enhanced TMS–MEP stimulus–response curve and reduced MEP threshold, occurred post-placebo but not post-capsaicin. This suggests that nociceptive input modulates MI neuroplasticity associated with novel motor training and may impair the ability to learn a new motor task (Boudreau et al., 2007). Motor learning deficits have also been demonstrated with experimental pain in laboratory animals (Hook et al., 2008; Ferguson et al., 2006). The evidence suggests that pain affects sensory processing (Knecht et al., 1998; Soros et al., 2001; Tinazzi et al., 2000; Tinazzi et al., 2004) and impairs the ability to learn a new motor task (Boudreau et al., 2007). However, there is a gap in the research as to how pain impacts sensory processing

following a motor training task. This study will address this question by examining the effects of pain on sensory processing while performing a complex motor task.

Repetitive strain injury, chronic pain, fibromyalgia, dystonia, and phantom limb pain are all conditions that occur in the absence of a discernible peripheral causal pathology or appear disproportionate to the size of the injury. These conditions challenge the established peripherally based, nociceptive accounts of pain (Taylor & Murphy, 2008). However, if peripheral systems are not ultimately involved in generating and maintaining the subjective experience of pain in these conditions, how can this experience be generated and maintained in the brain? Understanding the sensorimotor processing of pain will elucidate the mechanism behind these conditions.

4. 2 The practical significance of this research

This section will discuss the practical significance of this thesis. Effective sensorimotor integration is essential when learning new skills and is important when performing tasks at home and at work. Research has underscored the plasticity of the MI and SmI, characterizing them as dynamic constructs that can change in a use-dependent manner (Sessle et al., 2005). Research in pain and sensory processing may help elucidate the mechanisms behind cortical plasticity. Impaired sensorimotor integration may partially explain why workers injure themselves and may help explain why pain becomes chronic. Work related upper limb disorders and repetitive strain injuries are a significant public health problem making a significant contribution to occupational diseases (Taylor & Murphy, 2008). Investigating information processing and the sensorimotor system may explain the mechanisms involved in the initiation of overuse injuries and chronic pain conditions.

Chronic pain, fibromyalgia, dystonia and phantom limb pain are all conditions that occur in the absence of a discernible peripheral causal pathology or appear disproportionate to the size of the injury. Most studies of patients with chronic pain indicated that there is a poor relationship between tissue damage and pain (Jones & Derbyshire, 1997). Conflict between sensory–motor central nervous processing generates somaesthetic disturbances, including pain, in healthy volunteers (McCabe et al., 2007). Such conflict has been proposed as a potential cause of pain that occurs in the absence of injury or when the pain response is disproportionate to the injury as in the instance of fibromyalgia, which is one of the most common conditions seen by rheumatologists. The wide-spread chronic pain of fibromyalgia is hard to understand due to the absence of clinical pathology. Patients suffer from widespread pain, multiple tender points, stiffness, sleep disturbances and fatigue (McCabe et al., 2007). In this study, healthy adult volunteers without a history of motor or proprioceptive disorders
performed a series of bilateral upper and lower limb movements whilst viewing a mirror/whiteboard, which created sensory–motor conflict during congruent/incongruent limb movements. Twenty-seven subjects (66%) reported at least one anomalous sensory symptom at some stage in the protocol despite no peripheral nociceptive input. The understanding gained from the study of sensory processing will elucidate how sensory-motor conflict results in fibromyalgia. By understanding the role of somatosensory processing in response to pain, and through the understanding the differences in the somatosensory processing of acute versus chronic pain, future research might eventually lead to practical applications for the rehabilitation of diseases that occur without a discernable peripheral causality such as dystonia and fibromyalgia (Tinazzi et al., 2003b). Research in the area of sensorimotor integration may also elucidate some of the mechanisms responsible for the relief of pain.

5 LITERATURE REVIEW – PAIN

This chapter reviews in detail how pain travels from the periphery to the cortex. The ascending nociceptive tracts and nociceptors will be described in detail. Changes in excitability in the spinal cord, brainstem, and supraspinal levels in response to pain will be described. Mechanisms behind this nociceptive plasticity will then be explained.

5.1 Pain: from the periphery to the cortex

Based upon the rexed lamination (division of the dorsal horn into horizontal laminae, based on the morphological properties of the cells in a Nissl-type staining) the dorsal horn can be divided into six different laminae on the basis of cytological features (see Figure 8) (Kandel et al., 2000, p. 475).

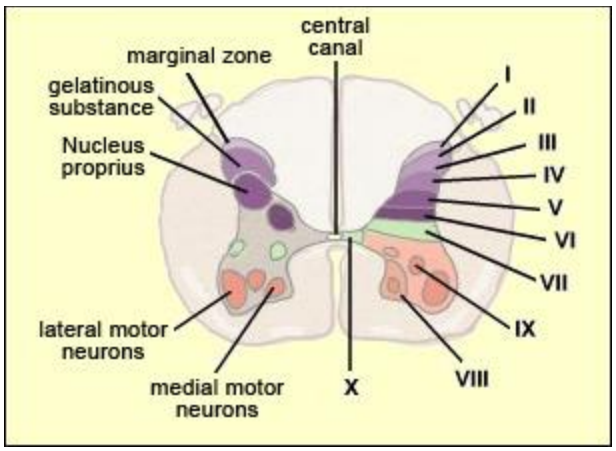

Figure 5-1: the rexed laminae system of the dorsal horn grey matter (Reproduced from http://www.thebrain.mcgill.ca)

Most pain information is transferred from the nociceptors to the surface layers (lamina I and II) and the neck (lamina V) of the dorsal horn. Beyond the peripheral nociceptor and dorsal horn, nociceptive information usually ascends to the thalamus in the contralateral spinothalamic tract (STT) and to the medulla and brainstem via spinoreticular (spinoparabrachial),

spinomesencephalic tracts and cervicothalamic tracts. These tracts serve different purposes related to their lamina origin in the dorsal horn and final central destination (Bushnell et al., 2008, p. 8).

5.1.1 The spinothalamic tract

The spinothalamic tract is the most prominent ascending nociceptive pathway and it comprises the axons of nociceptive-specific and wide-dynamic-range neurons in laminae I and V-VII of the dorsal horn (Valeriani et al., 2005). It ascends contralaterally in the anterolateral white matter terminating in the thalamus as clusters of terminals and eventually reaching the SmI, the primary somatosensory area (SmI), SmII (second somatosensory system), prefrontal cortex, posterior parietal cortex, posterior and mid-insula and mid-cingulate cortex (Jones et al., 2003; Mense, 1983). One portion of this tract ends in the ventroposterior and posterior thalamus. This lateral system projects to the SmI which mediates the sensory discriminative component of a pain sensation, such as location, texture, and intensity (Cruccu et al., 2008). Nociceptive neurons in SmI with input from the lateral system are mainly found in Brodmann area 1, but there is some evidence that Brodmann area 3a may also have some nociceptive input (Cruccu et al., 2008). Historically, thermal and pain sensations had been considered as sub served by common pathways within both the peripheral and the central nervous system through the spinothalamic pathway. However, a segregation of thermal and noxious inputs has been demonstrated (Valeriani et al., 2005). Electrical stimulation of the spinothalamic tract results in pain, and lesions of the tract result in marked reductions in pain sensation on the side opposite the spinal cord lesion. Injury to the spinothalamic tract and its targets can result in a severe pain termed central pain (Kandel et al., 2000, p. 480).

5.1.2 Spinoreticular tract

The spinoreticular tract comprises the axons of neurons in laminae VII and VIII and ascends in the anterolateral quadrant of the spinal cord and is positioned closely to the lateral spinothalamic tract terminating in both the reticular formation and the thalamus (Jones et al., 2003; Mense, 1983; Wu et al., 1999). In contrast to the spinothalamic tract, many of the axons of the spinoreticular tract do not cross the midline (Kandel et al., 2000, p. 480).

5.1.3 Spinomesencephalic tract

The spinomesencephalic tract comprises the axons of neurons in lamina I and V and it projects in the anterolateral quadrant of the spinal cord to the mesencephalic reticular formation and periaqueductal gray matter, and via the spinoparabrachial tract, it projects to the parabrachial nuclei. Neurons of the parabrachial nuclei then project to the amygdala, a major component of the limbic system, which is a neural system involved in emotion. Thus the spinomesencephalic tract is thought to contribute to the affective component of pain. Many of the axons of this pathway project in the dorsal part of the lateral funiculus rather than in the anterolateral white matter (Kandel et al., 2000, p. 480).

5.1.4 Cervicothalamic tract

The cervicothalamic tract arises from neurons in the lateral cervical nucleus, located in the lateral white matter of the upper two cervical segments of the spinal cord. The lateral cervical nucleus receives input from nociceptive neurons in laminae III and IV. Most axons in the cervicothalamic cross the midline and ascend in the medial lemniscus of the brain stem to nuclei in the midbrain and to the ventroposterior lateral and posteromedial nuclei of the thalamus. Some axons from laminae III and IV project through the dorsal columns of the spinal cord with the axons of large-diameter myelinated primary afferent fibers and terminate in the cuneate and gracile nuclei of the medulla (Kandel et al., 2000, p. 480).

5.2 Pain: Current view

Peripheral tissue damage which affects components of the PNS and CNS and increases pain sensitivity is referred to as central sensitization. Sensitization of the pain system results in persistent pain and occurs after repeated painful stimuli, so that the threshold for activation falls and subsequent inputs are amplified (Latromoliere & Woolfe, 2009). Central sensitization becomes pathological when it is maintained in the absence of peripheral pathology and persists after the injured body part is healed. This is a chronic and debilitating pain that occurs from damage to the peripheral or central nervous system. This is referred to as neuropathic pain (Latromoliere & Woolfe, 2009). Pain can occur in the absence of a noxious stimulus, in response to innocuous stimuli (allodynia), or as an exaggerated response to a noxious stimulus (hyperalgesia) (Patapoutian, 2009; Tsunozaki & Bautista, 2009). In contrast, acute pain occurs with peripheral input and is referred to as nociceptive pain. It is with central sensitization that syndromes like chronic tension-type headache, sciatica, chronic low back pain or phantom limb pain occur (Baumbauer et al., 2009).

The existence of a system that modulates pain transmission at the spinal dorsal horn was postulated by the gate control theory (Kandel et al., 2000, p. 482). The dorsal horn synapse is receiving a constant barrage of information from peripheral and central sources. The initial state of modulation is the spinal cord, where interconnections between nociceptive and non-nociceptive afferent pathways can control the transmission of nociceptive information to higher centers in the brain (Kandel et al., 2000, p. 482). Local inhibitory and excitatory interneurons in the dorsal horn and descending inhibitory and facilitatory pathways originating in the brain modulate the transmission of nociceptive signals, thus contributing to the perception of pain (Dubin & Patapoutian, 2010).

The endogenous pain control system sets up the level of excitability of spinal nociceptive second order neuron and this descending modulation is exerted by three main neurochemical systems: noradrenergic, serotonergic and opioidergic (Meyr & Steinberg, 2008). This system can exert anti-nociceptive and pronociception effects. Excitatory signals include peptides (substance P, calcitonin gene-related peptide, somatostatin, bombesin, galnin, and vasoactive intestinal peptide), amino acids (glutamate, aspartate), nitric oxide, and prostaglandins (Meyr & Steinberg, 2008). Inhibitory signals include endorphins, amino acids (GABA and glycine), serotonin, and adenosine (Meyr & Steinberg, 2008).

5.3 Pain: Brainstem

The brainstem includes the medulla oblongata, pons and midbrain and is the posterior part of the brain that is continuous with the spinal cord (Tracey & Mantyh, 2007). The motor and sensory nerve systems from the brain to the rest of the body pass through the brainstem. Sensory inputs from the brainstem are part of the ascending systems carrying pain to rostral brain centers (Tracey & Mantyh, 2007). These tracts connect to the brainstem and integrate nociceptive activity with homeostatic, arousal, and autonomic processes. These tracts convey nociceptive information to forebrain regions after brainstem processing. Projections to the brainstem can influence spinal and forebrain activity suggesting these pathways directly affect the pain experience (Tracey & Mantyh, 2007). Neurons of the brainstem receive convergent inputs from nociceptive and innocuous sources and have large receptive fields (Saadé & Jabbur, 2007). The intensity and affective quality of perceived pain is the result of the interaction between ascending nociceptive inputs and antinociceptive controls. Dysregulations in the function of these networks may underlie the development of chronic pain (Apkarian et al., 2005).Three major areas of the brainstem are components of the brainstem pain modulatory centers: the

periacqueductal gray (PAG), the locus coereuleus (LC) and the rostral ventral medulla (RVM) (Saadé & Jabbur, 2007). Research indicates that the brainstem plays a central role in mediating changes in pain perception. The brainstem can inhibit or facilitate nociception and is influenced by the diencephalon, hypothalamus, amygdala, ACC, insular, and prefrontal cortex (Tracey & Mantyh, 2007). Pain inhibition and facilitation is achieved through a descending pain modulatory system which is a well-characterized anatomical network that regulates nociceptive processing within the dorsal horn (Tracey & Mantyh, 2007).

5.4 Pain: Changes in excitability at the supraspinal level

Changes in excitability in response to pain have been demonstrated at the supraspinal level (Dostrovsky & Guilbaud, 1990; Maihofner et al., 2010; Neugebauer &Li, 2003; Wei & Zhuo, 2001). Neurons in the somatosensory thalamus of patients with neuropathic pain display high spontaneous firing rates (Dostrovsky & Guilbaud, 1990). Changes in the amygdala, (Neugebauer &Li, 2003) and anterior cingulate cortex (Wei & Zhuo, 2001) have also been described in response to pain. Further studies with humans have revealed increases in excitability corresponding to other supraspinal structures (parabrachial nucleus, periaqueductal gray (PAG), superior colliculus, prefrontal cortex) (Maihofner et al., 2010).

As with the deafferentation studies, there has been debate as to whether subcortical or cortical components play a primary role in the sensory processing of pain (Taylor & Murphy, 2007; Taylor & Murphy, 2008; Tinazzi et al., 2000a; Tinazzi et al., 1997; Tinazzi et al., 1998). Changes in excitability in response to pain have been observed in multiple components of the somatosensory system: at the spinal cord level, in supraspinal structures, and at the cortex (Melzack et al., 2001; Wall et al., 2002). Wall et al. (2002) suggested that injury initiates a progression of mechanisms that alter substrates at multiple subcortical and cortical locations.

Wall et al. (2002) suggested that peripheral injuries cause rapid changes in peripheral, spinal, and brainstem substrates which are more extensive than cortical changes (Wall et al., 2002). The result is that injuries become embodied in the CNS, from the peripheral sensory neurons to the cortex (Wall et al., 2002). PET and fMRI neuroimaging techniques have demonstrated metabolic and perfusion changes in a large number of cortical areas following painful stimuli in healthy subjects (Apkarian et al., 2005; Lorenz & Casey, 2005). Despite the differences in sensation, emotions, and behavioural responses provoked by different types of pain, individuals can easily identify each as being painful. Thus, there appears to be a common construct of pain with an underlying network of brain activity (Bushnell et al., 2008, p. 679). This network of somatosensory and associative structures receives parallel inputs from multiple nociceptive pathways suggesting that pain is processed in a distributed fashion (Apkarian et al., 2005). The presence of this network is supported by invasive and noninvasive electrophysiological studies in humans, using magnetoencephalography (MEG), electroencephalography (EEG), subdural recordings directly from the surface of the brain, and in depth recordings during stereotactic procedures (Bushnell et al., 2008, p. 670). If a stimulus is intense enough to activate nociceptors, multiple areas of the pain matrix respond to this input in a correlated manner with perceived intensity (Lorenz & Casey, 2005). These brain regions encompass a number of functionally distinct regions exhibiting activation that is closely related to perceived stimulus intensity (Jensen, 2010). These areas include the primary somatosensory area (SmI), secondary somatosensory area (SmII), posterior parietal cortex, thalamic nuclei, posterior and mid-insula and the mid-cingulate cortex (Cruccu et al., 2008; Romo et al., 2002). Other regions such as the prefrontal cortex, basal ganglia, cerebellum, amygdala, hippocampus, and areas within the parietal and temporal cortices have yielded activation by experimental pain in several studies

(Tracey & Mantyh, 2007). Iadarola et al. (1998) used PET to image regional brain activity in normal human subjects during intense pain induced by intradermal injection of capsaicin. Capsaicin produced activation in many brain regions which subserve four main functions: sensation–perception (primary somatosensory cortex, thalamus and insula); attention (anterior cingulated cortex); descending pain control (periaqueductal grey); and an extensive network related to sensory–motor integration (supplementary motor cortex, bilateral putamen and insula, anterior lobe and vermis of the cerebellum and superior colliculus). Capsaicin pain produced little or no activation in secondary somatosensory area (SmII) whereas the cerebellar vermis was strongly activated by capsaicin (Iadarola et al., 1998).

5.5 Pain: Mechanisms of nociceptive plasticity

There is plasticity of the somatosensory system in response to activity, inflammation, and neural injury (Boal & Gillette, 2004). The current pain model encompasses a dynamic enhancement in the function of neurons in nociceptive pathways due to reduced inhibition, increased excitability and synaptic efficacy (Boal & Gillette, 2004). Neuronal plasticity refers to activity-dependent changes in neuron behaviour and it is this process that is involved in pain processing (Boal & Gillete, 2004). Damage of peripheral tissue and injury to nerves produces persistent pain and hyperalgesia (Boal & Gillete, 2004). The capacity for activity dependent change has been proposed as the explanation for pain conditions that persist even after peripheral tissue damage has been resolved. Neuronal plasticity occurs in the spinal cord and throughout the CNS (Boal & Gillete, 2004). These processes help to explain pain that persists even after peripheral tissue damage has been resolved. Neuronal plasticity provides a mechanism for the CNS overreacting to normal input (Boal & Gillete, 2004; Pocket, 1995). Central sensitization is an enhancement in the neurons involved in nociceptive pathways. Changes in the functional properties of the

neurons in these pathways are sufficient to reduce pain threshold, increase the magnitude and duration of responses to noxious input, and permit innocuous inputs to generate pain sensations. Nociceptive pathways are subject to complex facilitating and inhibitory controls (Latromoliere & Woolfe, 2009).

The literature suggests that there is no single mechanism of central sensitization as there are a number of different forms of plasticity that can sensitize the central nociceptive system to produce pain hypersensitivity under normal and pathological conditions (Latromoliere & Woolfe, 2009). There are distinct changes in somatosensory processing in response to nociceptor stimuli which can increase membrane excitability, increase synaptic strength, or decrease inhibition (Latromoliere & Woolfe, 2009). Mechanisms include changes in the threshold and activation kinetics of NMDA and AMPA receptors. NMDA and AMPA are both glutamate agonists (an excitatory neurotransmitter) and thus increased amounts of these neurotransmitters leads to excitation. Mechanisms also include reductions in the release or activity of GABA and glycine activity-dependent central sensitization. GABA and glycine are inhibitory neurotransmitters and thus reductions in these neurotransmitters also lead to excitation or transient disinhibition (Latromoliere & Woolfe, 2009). GABA is the predominant inhibitory neurotransmitter in the CNS, and the most likely mechanism for cortical plasticity in response to pain is disinhibition of GABA, which is in alignment with the previously discussed deafferentation studies (Levy et al., 2002; Marty et al., 1997; Weiss et al., 2004; Ziemann et al., 1998).

6 LITERATURE REVIEW - MOTOR LEARNING AND PAIN

This chapter will review the relevant literature on motor learning. This chapter will discuss how pain affects sensorimotor integration and motor learning and will describe some possible mechanisms for how pain affects motor learning.

6.1 Motor learning

Motor learning is a change or acquisition of a motor skill with practice or an increase in the range of motor behaviour (Manto & Bastian, 2007). The automaticity theory of movement argues that automatization occurs through separate instances of exposure to the task leads to the acquisition of a specific knowledge base (Logan, 1988, 1990). Daily tasks that are performed quickly and effortlessly with minimal conscious awareness are referred to as automatic (Logan, 1988). Automatization is important to skill acquisition as skills are thought to consist of a collection of automatic processes (Logan, 1985). The benefit gained by previous exposure to a stimulus or task is referred to as repetition priming and results in a faster response time (Grant & Logan, 1993; Logan, 1990; Richardson-Klavehn & Bjork, 1988; Soldan et. al , 2010). Repetition priming is the effects of a single to a few exposures and is the first step on the way to automaticity (Logan, 1990). In contrast, automaticity is the effect of hundreds of exposures of a stimulus or task on subsequent performance (Hauptmann & Karni, 2002; Logan, 1990). It is suggested that skill learning and repetition priming rely on common underlying mechanisms as fMRI imaging studies have demonstrated that specific neural regions exhibit changes after skill-learning and repetition priming (Logan, 1990; Poldrack & Gabrieli, 2001).

There is a positive relationship between the number of repetitions or exposures and the amount and length of knowledge retention, indicating that the experience of exposure acts as a training session which increases performance resulting in skill learning (Guadagnoli & Lee, 2004;

Hauptmann & Karni, 2002). Several studies have examined the time course of experience-dependent learning (Karni & Sage, 1993; Karni et al., 1994). These studies (Karni & Sage, 1993; Karni et al., 1994) showed performance improvements occur in two stages. Initially, fast learning occurs in which there is a within-session improvement induced by a few trials on a time scale of minutes (Karni & Sage, 1993). Fast learning occurs in our study as our study involves a limited number of trials occurring on a time scale of minutes. Following fast learning, there is slowly evolving incremental performance gains, triggered by practice but taking hours to become effective. This is referred to as slow learning (Karni & Sage, 1993). This phase in skill learning is a result of the consolidation of experience dependent changes in the cortex triggered by training.

Two mechanisms have been proposed for the changes induced in the cortex as a function of experience: the disinhibition of previously existing connections between neurons, and the growth of new connections and synapses. Disinhibition of previously existing connections between neurons can induce changes on a short time scale and subserves fast learning. The growth of new connections and synapses explains the delayed, time-dependent nature of developmental cortical plasticity and cortical reorganization compensating for injury and subserving slow learning (Karni et al., 1993). For this thesis, learning is occurring on a short time scale and likely occurs through disinhibition of previously existing lateral connections. This is the same mechanism that subserves plasticity in response to deafferentation and pain (Levy et al., 2002; Marty et al., 1997; Weiss et al., 2004; Ziemann et al., 1998).

Regardless of the stage of performance, attention plays a key role in performance (Logan, 1990). Attention is required to encode events into memory and is also required to retrieve those events from memory (Logan, 1992). When information is encoded, there is a learning mechanism

resulting in increased memory for familiar stimuli, and it is then made available for future problems through retrieval (Logan, 1992). Automaticity is often defined as processing without attention. However, automaticity is considered a memory phenomenon. Novice (nonautomatic) performance is based on a general algorithm for solving the problems the task presents, whereas automatic performance is based on single-step, direct-access retrieval of past solutions from memory. Automatic processing has the properties of well-practiced memory re-trieval and it is fast and effortless (Logan, 1988, 1990, 1992). Complex tasks are an example of retrieval interference. By presenting a key press sequence in a random order, the participant uses more attentional resources, and thus the response and reaction times will be longer and movement responses will not be automated. In addition, more exposure to a single event will result in stronger memory because each individual experience creates a separate trace that may be retrieved. Thus, as the same items are presented to an individual, they should be more easily retrieved, as demonstrated by decreased reaction time (Logan, 1988, 1992).

Research indicates that motor learning can alter the topography of movement representations within the MI through experience-dependent changes in the functional organization of the MI (Ioffe, 2004). Animal studies have shown changes in the MI during the acquisition of fine motor skills (Remple et al., 2001; Kleim et al., 2002, 2004). Other animal studies demonstrate that the increased task proficiency is correlated with increased synaptic efficacy of the MI (Monfils & Teskey, 2004) through processes such as strengthening of horizontal cortical connections in layers II/III (Rioult-Pedotti et al., 1998) and increased synapses per neuron in layer V (Kleim et al., 2002). Motor-skill learning is thought to involve the primary motor cortex (M1) especially when kinematic variables such as direction, speed, and acceleration are changed as a result of practice (Classen et al. 1998). In Humans, positron emission tomography (PET) functional

magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) studies have demonstrated changes in M1 during the acquisition of complex motor skills (Pascual-Leone et al. 1995). Several studies have shown an expansion of representations corresponding to trained movements associated with motor learning (Elbert et al., 1995; Kleim et al., 1998). These studies (Elbert et al., 1995; Kleim et al., 1998) indicate that with the development of skilled movements there is a functional reorganization within the MI. In conclusion, the MI of both humans and animals is engaged during the acquisition phase of novel motor skills (Ioffe, 2004).

In healthy individuals, novel motor-skill learning has been associated with improvements in task performance and increased representation of the muscle in the MI (Karni et al., 1998; Pascual-Leone et al., 1995; Svensson et al., 2003; Hlustik et al., 2004). Svensson et al. (2003) determined the effect of training humans in a novel tongue-protrusion task for 1 week on corticomotor excitability and found that the threshold for evoking MEPs by TMS in the tongue musculature was significantly decreased after the last training day compared with baseline and in the 2-weeks follow-up. In addition, the amplitude of the MEPs in the tongue musculature was significantly increased at higher intensities of TMS after the last training day (Svensson et al., 2003). This study demonstrated that short term motor training increases corticomotor excitability in the tongue (Svensson et al., 2003). In addition, increased cortical excitability has been demonstrated for the hand MI following 24 weeks of novel motor training (Koeneke et al., 2006). There is also evidence to suggest that neuroplastic changes in the MI occur over very short training intervals (Boudreau et al., 2007; Classen et al., 1998). Improvements in motor performance and rapid changes in cortical excitability of the tongue MI occur immediately following 15 min of novel tongue-task training (Boudreau et al., 2007) and similar findings have been reported for training of a novel hand task (Classen et al., 1998). Classen et al. (1998) used

TMS of the motor cortex to evoke thumb movements. Thumb movements were then practiced in a different direction. After this practice session, TMS evoked movements in the practiced direction for several minutes before returning to the original direction. This suggests that the training rapidly established a change in the cortical map of the thumb in the motor cortex (Classen et al., 1998). Research has shown that the performance of a complex finger-tapping task results in additional areas of cortical activation, as measured by fMRI, when compared to a simple finger-tapping task (Sadato et al., 1996). The amount of overlapping cortical territories in the MI that is altered with training is greater when training of simple finger and wrist movements are paired with fine rather than gross motor-skill training (Hlustik et al., 2004).

Other studies (Plautz et al., 2001; Remple et al., 2001) have demonstrated that movement repetition is not sufficient to produce reorganization within the motor cortex. Plautz et al. (2001) demonstrated that in the absence of motor learning, extensive repetition of digit movements did not produce reorganization within the motor cortex. Similarly, Remple et al. (2001) found that the organization of the motor cortex of rats that spent several weeks in running wheels was not significantly different from that of inactive rats. These studies demonstrate that increased movement repetition is not sufficient to drive changes in cortical movement representations (Plautz et al., 2001; Remple et al., 2001).

Marr (1969) proposed that the cerebellum plays an important role in the learning of motor skills. He supposed that during learning the cerebrum sets up and organizes the movements, and that the cerebellum is involved in the process by which the movements can be run off automatically. In his model, cerebellar inputs via the climbing fibers and mossy fibers are integrated through their connections to the Purkinje cells. The process of learning would then involve synaptic changes at this level (Marr, 1996). Additional evidence for the role of the cerebellum is provided

by animal studies (Ito, 1975; McCormick and Thompson, 1984; Yeo et al., 1992). In rabbits, lesions in the cerebellar nuclei or cortex impairs the classically conditioned response of the nictitating membrane (McCormick and Thompson, 1984; Yeo et al., 1992). In monkeys, lesions in the flocculus affects the vestibulo-ocular reflex (Ito, 1975). In addition, a clinical study demonstrates that patients with cerebellar pathology are impaired at motor learning (Sanes et al., 1990).

Cerebellar activation has been demonstrated following a motor sequence learning tasks requiring subjects to perform a sequence of motor responses using one or more fingers (Friston et al., 1992). Friston et al. (1992) examined the effect of simple repetitive motor tasks on regional cerebral blood flow (rCBF) changes using PET and demonstrated that there were CBF increases during performance of the simple repetitive motor task activations in the left sensorimotor cortex (Brodmann's Area 1-4) and bilateral activation of the cerebellar cortex as well as premotor cortex, lateral thalamus and deep cerebellar nuclei (Friston et al., 1992).

Similarly, Jenkins et al. (1994) found that when comparing the prelearned sequences to the resting state using PET, there were significant increases in activation found in the bilateral cerebellar hemispheres and bilateral ventral thalamus as well as the deep cerebellar nuclei. These results (Friston et al., 1992; Jenkins et al., 1994) indicate that the cerebellum plays a role in the automaticity of motor tasks.

6.2 Pain and sensorimotor integration

Plasticity has been observed in sensory systems in response to pain, and sensory–motor integration at a reflex level such as a motor withdrawal reflex in response to noxious stimuli is well understood (Borsook, 2007). Persistent pain generally inhibits movement, as individuals tend to limit movement in order to protect the affected region (Borsook, 2007).

Gronroos et al. (1993) examined the effect of selective activation of nociceptive primary afferent fibers by capsaicin on a nociceptive lower limb flexion reflex and found that capsaicin produced a significant decrease of the threshold for the nociceptive limb flexion reflex, and this threshold decrease was rapidly attenuated by a cool compress. In contrast, the non-nociceptive H-reflex was not modified by capsaicin (Gronroos et al., 1993). This study suggests that the activation of nociceptive primary afferent fibers of the skin by capsaicin produces a central facilitation of a nociceptive flexion reflex in humans (Gronroos et al., 1993).

Plasticity, as reflected by changes in excitability of the primary motor area (MI) of the cerebral cortex, has been reported in association with peripheral nerve lesions (Hall et al., 1990; Cohen et al., 1991), brain injury (Jenkins and Merzenich, 1987; Traversa et al., 1997), and chronic and phantom limb pain (Dettmers et al., 2001; Karl et al., 2001).

The evidence suggests that there are differing effects of experimental pain on MI excitability. For example, CRP (type I) patient's exhibit decreased MI excitability associated with the affected muscles (Dettmers et al., 2001). In healthy subjects, decreased MI excitability has been shown in association with capsaicin-induced skin pain and hypertonic saline- induced muscle pain of the hand (Cheong et al., 2003; Farina et al., 2001; Le Pera et al., 2001). Cheong et al. (2003) induced cutaneous pain through the application of capsaicin on the skin overlying the flexor carpi radialis (FCR) of the dominant limb. Amplitudes of MEPs at FCR decreased up to 40 minutes and then returned to nearly baseline value at 80 minutes supporting the hypothesis that noxious cutaneous stimulation inhibits motor cortex excitability by cortico-cortical circuits (Cheong et al., 2003). Farina et al. (2001) found a similar inhibition of motor cortex excitability after the application of capsaicin. The amplitude of MEPs from the FDI and FCR was significantly reduced from 20 to 30 min after the application of capsaicin over the FDI and FCR

muscles. In contrast, noxious electrical stimulation of the finger has revealed an increase in the MI excitability for distal (hand) muscles and a decrease in the MI excitability for proximal (upper arm) muscles (Kofler et al., 1998). In addition, increased MI excitability has been shown in phantom limb pain patients (Krause et al., 2006).

It has been shown that experimental pain in masticatory muscles has been shown to modulate motor control strategies and muscle activity of healthy subjects (Svensson et al., 1997). In painful conditions such as osteoarthritis and burns, the ability to perform skilled hand movements is impaired (Smith et al., 2006) and in individuals with rheumatoid arthritis, dexterity declines as pain increases, and this is independent of other factors (Smith et al., 2006).

Several studies have indicated that experimental muscle pain can modulate neuromuscular control through decreases in the coordination of muscle groups (Falla et al. 2007; Madeleine et al., 2006; Madeleine et al., 1999; Sae-Lee et al., 2008). There is a reorganization in muscle activity following experimentally induced muscle pain in a shoulder flexion (Falla et al. 2007; Madeleine et al., 2006) upper limb (Madeleine et al., 1999) and jaw (Sae-Lee et al., 2008) motor tasks. Falla et al. (2007) found that on the painful side, the upper trapezius showed decreased EMG amplitude and the lower trapezius showed increase EMG amplitude. Madeleine et al. (2006) found that during experimental muscle pain the EMG signal decreased and there was a caudal shift of the centre of gravity. Sae-Lee et al. (2008) found that the effects of hypertonic saline-induced pain on EMG activity varied with the task in which the muscle participated irrespective of whether the muscle was an agonist or an antagonist in the tasks. Intra-muscular injections of algesic substances have been shown to decrease the discharge frequency of low-threshold motor units (Farina et al., 2005; Farina et al., 2008) and increase the twitch amplitude of motor units (Sohn et al., 2000) during sustained muscle contractions. Farina et al. (2005)

found that experimental muscle pain reduces initial motor unit discharge rates during sustained submaximal contractions. Farina et al. (2008) found that the discharge rate decreased following injection of hypertonic saline while the peak of the spike-triggered average torque increased with pain.

6.3 Pain and motor learning

Motor learning deficits have been demonstrated in association with experimental pain in laboratory animals (Hook et al., 2008; Ferguson et al., 2006). Hook et al. (2008) administered shock to one hindleg when it is extended (controllable stimulation) and found that the rats learned to maintain the leg in a flexed position but that rats injected with capsaicin fail to learn. Similarly, Ferguson et al. (2006) administered shock to the hind leg of spinally transected rats when the leg is extended and found that the rat rapidly learns to hold the leg in a flexed position when given this controllable shock. However, if shock is independent of leg position (uncontrollable shock), the rats fail to learn and impaired future learning as it led to a learning deficit that lasts up to 48 h (Ferguson et al., 2006).

Boudreau et al. (2007) found that neuroplasticity of the tongue MI, as reflected in a significantly enhanced TMS–MEP stimulus–response curve and reduced MEP threshold, was observed post-placebo session but not post-capsaicin. This suggests that MI neuroplasticity may rapidly occur in association with successful performance in novel tongue-task training, but that intra-oral tonic pain interferes with these effects. This suggests that nociceptive input modulates MI neuroplasticity associated with novel motor training and may impair the ability to learn a new motor task (Boudreau et al., 2007). This is relevant to this thesis as it is hypothesized that the pain will lead to decreased accuracy post-motor learning. Nociceptive-induced cortical

neuroplasticity such as that which can be present in chronic pain patients (Flor, 2003; Schweinhardt et al., 2006) also interferes with motor learning.

Research demonstrates that pain may interfere with training-induced motor cortical plasticity (Boudreau et al., 2007).

6.4 Pain and motor learning: mechanism

A mechanistic understanding of how pain affects the motor cortex is not currently known. Inhibition of the motor cortex by pain is proposed to be via cortico-cortical, thalamo-cortical or striato-cortical circuits (Borsook, 2007). Pain fibers project to the SmI and may produce inhibition of motor cortex via thalamocortical or cortico-cortical inhibitory inputs. The ventrolateral and anterior thalamic regions are the main relay for cerebellar and basal ganglia (globus pallidus) to the motor cortex (Massion, 1976). Pain afferents to the globus pallidus from the spinal cord have been shown in animal studies (Braz et al., 2005) and activation in the globus pallidus to pain has been reported in fMRI studies in Humans (Becerra et al., 1999). Animal studies show that activation of the motor cortex modulates nociception (Senapati et al., 2005 Yezierski et al., 1983). In the primate, activation of the motor cortex inhibits spinothalamic neurons (Yezierski et al., 1983) and electrical stimulation to the motor cortex inhibited the response of spinal dorsal horn neurons to noxious, but not innocuous stimulation (Senapati et al., 2005).

Stimulation of the anterior thalamus produces an alteration in motor cortex excitability (Molnar et al., 2006). In addition, rTMS (Fregni et al., 2007) and application of motor cortex stimulation electrodes (Osenbach, 2006) improves chronic pain conditions. Stimulation of the primary somatosensory area and motor cortex has been used in the treatment of chronic pain (Canavero et al., 1999, Carroll et al., 2000), stroke pain (Canavero et al., 2002, Canavero et al., 2003), and

phantom limb pain (Carroll et al., 2000). The effects may be due to cortico-thalamic connections, producing inhibition on the sensory pathway (Borsook, 2007). There is currently a gap in the body of knowledge of how motor systems may be affected by pain, how pain may affect the motor systems, and how pain impacts motor learning. Although we know that pain alters the way we move we do not understand how this happens.

7 – OVERVIEW OF THE EXPERIMENTAL APPROACHES AND RATIONALE FOR THE DESIGN OF THE PROTOCOL

The following chapter will describe and discuss in detail the main techniques and protocols utilized for the experiment presented in this thesis.

7.1 Somatosensory evoked potentials

SEPs are an objective and direct method of assessing the integrity of the sensory pathways of the central and peripheral nervous systems (Cruccu et al., 2008). In Humans, SEPs are evoked by bipolar transcutaneous electrical stimulation applied on the skin over the selected nerve and are typically recorded from the surface of the skin and scalp close to the sites of the hypothesized neural generators of the various waveform components (Mauguière et al., 1999). SEPs were recorded using surface electrodes as this technique has the advantage of being non-invasive (Mauguière et al., 1999).

For the upper limb, the most commonly stimulated nerves are the median, ulnar and radial nerve and the most commonly stimulated nerves in the lower limb are the peroneal and tibial nerves (Mauguière et al., 1999). For this thesis, the median nerves were stimulated. Gandevia et al. (1984) demonstrated that muscle afferents dominate the cerebral potentials produced by stimulation of the mixed median nerve. An electrical stimulus depolarizes neurons by generating a potential difference across the nerve fiber, resulting in a depolarization close to the site of the cathode (Mauguière et al., 1999). As long as the stimulation intensity is not too high, stimulation depolarizes large diameter myelinated afferents, but not the afferents that convey pain (small myelinated Aδ or unmyelinated C afferents) (Burke et al., 1981). This is important in the design of this experiment as simulating afferents that convey pain would confound our results by putting our placebo group in pain. Therefore the stimulation intensity was not too high (i.e. not above

motor threshold). Motor threshold was defined as the lowest intensity that produced a visible muscle contraction of the abductor pollicis brevis muscle for median nerve stimulation (Taylor & Murphy, 2008). The stimulus intensity was altered as needed to maintain a constant thumb twitch throughout the test.

As opposed to direct recordings, SEPs are recorded at some distance from the neural generators which may lead to an attenuation or alteration of the actual potentials (Mauguière et al., 1999). Stimuli (at 1 × motor threshold) consisting of electrical square pulses of 1-millisecond duration were delivered at a rate of 2.47 Hz, which is a rate that does not lead to SEP peak attenuation. Stimuli were administered through 7-mm Ag/AgCl disposable adhesive electrodes (Hydrospot from Physiometrix [Physiometrix Inc, Billerica,MA]). The electrical pulses were delivered at a constant voltage through two disk electrodes connected to the negative (cathode) and positive (anode) pole of the stimulator. The anode (positive stimulating electrode) was placed on the wrist crease while the cathode (negative stimulating electrode) was placed 2 cm proximal to the wrist crease and was placed proximal to the anode in order to prevent anode block (Mauguière et al., 1999).

The potentials are recognized by their distributions, reflecting the activation of their generators. They are named N or P, followed by an integer which indicates the post-stimulus latency (Cruccu et al., 2008). There are two conventions, the first which labels upward deflections negative (N), and another convention in which upward deflections are positive (P). The International Federation of Clinical Neurophysiologists (IFCN) (Nuwer et al., 1994), and the American Clinical Neurophysiology Society (Epstein et al., 2006) utilizes the first convention. Therefore, upward deflections were labelled negative (N) for this thesis. The amplitude of each respective peak represents the degree of activity of its neural structure. Alterations are believed

to be alterations in the amount of activity of the same assumed neural structures (Mauguière et al., 1999).

7.2 SEP recording

SEP recording electrodes were placed over Erb's point bilaterally, over the skin overlying the cervical spine and in the parietal and frontal scalp regions in accordance with the International Federation of Clinical Neurophysiologists recommendations (Taylor & Murphy, 2010). The median nerve SEPs are recorded on an analysis time of 30±50 ms. As most of the clinically useful SEP components peak before 50 ms for upper limb stimulation, there is no need to recording beyond 50 ms (Mauguière et al., 1999). Most commercially available recording devices allow 500 or 1000 sampling points over analysis times of 10±100 ms, resulting in a bin width of 100 or 50 ms for an analysis time of 50 ms. These bin widths are appropriate for the recording of subcortical and short-latency cortical SEPs (Mauguière et al., 1999). All electrodes were securely fastened and held in place throughout the duration of the data recording session. A series of positive and negative potentials were recorded from Erb's point, the cervical spine, and scalp. In each case, negative electrical potentials at the first electrode were displayed as upgoing deflections or peaks (Mauguière et al., 1999). The potentials can be recognized by their typical distributions and SEP latencies were measured at the peak of the waveform of interest. For standard clinical recordings it is recommend to have at least four channels designed to highlight one or more component each: peripheral (Erb's point) channel, cervical channel, parietal channel, and the frontal channel (Cruccu et al., 2008). Therefore, this study included these four channels. The locations of scalp electrodes are specified using the 10±20 international system of EEG electrode placement. The fontal scalp electrode was placed at the Rossi site of the 10±20 system and the parietal scalp electrode was placed at the site Cc' of the 10±20 system

(Mauguière et al., 1999). Cc' and the Rossi site recording electrodes were referenced to the contralateral earlobe (Mauguière et al., 1999).

This study investigated SEP peaks as alterations in their amplitudes post-sensitization reflect the effect of pain on sensorimotor integration. It is important to include both subcortical and cortical peaks to differentiate whether changes are occurring at the subcortical or cortical level. N30 is particularly important as it reflects sensorimotor integration. N18 and N24 are also particularly relevant as they reflect cerebellar pathways which are important for motor processing.

7.2.1 Channel 1

Channel 1 is recorded at the Rossi site (located on the contralateral frontal region) and measures P14, N18, N24, and N30.

P14

In healthy adults, 3 or 4 positivities preceding the N20 potential are observed and occur with mean latencies of 9, 11, 13 and 14 ms and are labelled P9, P11, P13 and P14 respectively. The P13-P14 potentials are consistently recorded in normal individuals (Mauguière et al., 1999). In some subjects P14 is hardly visible as a notch on the ascending phase of P13, in other subjects, P13 and P14 cannot be differentiated and thus P13-P14 is usually labelled as P14. In the same individual, P14 can display some degree of side-to-side difference. The P14 peak is measured at the onset of rising negativity of N18 and arises from the lower brain-stem close to the cervico-medullary junction near the foramen magnum and thus arises above the spinal cord but below the cortex (Mauguière et al., 1999).

N18

The N18 potential is a long-lasting scalp negative shift which follows P14. Lesion studies suggest that N18 has a brain-stem origin situated below the thalamus and above the foramen

magnum (Mauguière et al., 1999). The source of the N18 is the nuclei in lower medulla (dorsal column nuclei and/or the accessory inferior olives) as well as the cuneate nucleus (Mauguière et al., 1999). The N18 reflects activity in the olivo-cerebellar pathways and alterations in N18 reflect changes in cerebellar activity (Nuwer, 1998; Yamada et al., 2004).

N24

The N24 reflects activity in the pathway between the cerebellum and primary somatosensory cortex and has the potential to show changes in cerebellar activity (Rossi et al., 2003).

N30

The N30 peak is related to a complex cortical and subcortical loop linking the thalamus, premotor areas, basal ganglia and primary motor cortex. The N30 is thought to originate from the frontal lobe and the posterior wall of the central sulcus and reflects sensorimotor integration (Tinazzi et al., 2000). N30 changes have been reported during execution and programming of voluntary movements in normal individuals (Mauguière et al., 1999).

7.2.2 Channel 2

Channel 2 is recorded from Cc' (located on the contralateral parietal lobe) and measures N20 and P25 (Mauguière et al., 1999).

N20

N20 is localized to the parietal scalp region, showing a polarity reversal across the central fissure (Mauguière et al., 1999). N20 represents the largest early negative deflection in Channel 2, although it may have several small peaks riding on top of it. The N20 peak is usually identified as a portion of the negative potential just preceding the sharp drop-off toward the succeeding cortical positive peak P25. N20 is generated from the primary somatosensory cortex in the

posterior wall of the central fissure (SmI area) (Mauguière et al., 1999). The N20 negativity often shows a bifid configuration, with the earlier peak corresponding to N18 (Yamada et al., 2004).

P25

The P25 component is recognized as the main prominent positive peak succeeding the N18- N20 complex at Cc'. It is generated in the SmI (Mauguière et al., 1999).

7.2.3 Channel 3

N9

Channel 3 is recorded from Erb's point and measures N9 which is the maximal peripheral nerve volley arising from the brachial plexus trunks (Mauguière et al., 1999). Erb's point is located within the angle formed by the posterior border of the clavicular head of the sternocleidomastoid muscle and the clavicle, 2± 3 cm above the clavicle (see Figure 2-2). The Erb's point electrode is referenced to ipsilateral ear (Mauguière et al., 1999). When the Erb's point channel shows a double negativity, the first peak is chosen (This doubling is seen most often in children and thus is not a significant concern in the design of this experiment) (Mauguière et al., 1999).

7.2.4 Channel 4

Channel 4 is recorded from the C5 spinous segment and measures N11 and N13 (see figure 2-2). According to the International Federation of Clinical Neurophysiologists (IFCN) guidelines the N11 peak amplitude was measured to the preceding positive trough and the N13 to the succeeding positive trough (Nuwer et al., 1994).

N11

The N11 is a small negative potential which preceeds the N13 peak, and is often difficult to differentiate from the N13. N11 reflects the ascending volley in dorsal column fibers arriving at the spinal cord (Mauguière et al., 1999). The posterior spinal cervical electrode is located over

the fifth cervical spinous process (C5). C5 is found two spines above the C7 process which is the most prominent spinous process at the base of the neck when the neck is flexed. Subjects were asked to flex their neck in order to find C7 and then C5 was subsequently identified. The C5 spinous electrode was referenced to the anterior neck (tracheal cartilage). The anterior cervical electrode (AC) was attached on the skin surface of the supra-glottal region on the midline (Mauguière et al., 1999).

7.3 Subject Numbers

Subject recruitment was based on calculations performed using GPOWER statistical software (Faul and Erdfelder, 1992). The calculation of the required subject sample size was carried out with a $\alpha = 0.05$ (5% chance of type I error), $1-\beta = 0.80$ (power 80%), and resulted in a required sample size of n=12 (Faul and Erdfelder, 1992), indicating that at least twelve subjects needed to be tested before the null hypothesis could be accepted. Therefore, 12 subjects were recruited for each condition. The experiment took approximately 2 hours and we aimed to test 24 subjects in total (12 males, 12 females).

7.4 Consultation and Ethics

The University of Ontario Human Participants Ethical Committee approved the study in accordance with the Declaration of Helsinki. Under the supervision of Dr. Bernadette Murphy, this thesis utilized an existing ethics proposal (see Appendix 10.1, 10.2, 10.3). The consent form was revised and my name was added to the existing ethics application once the project was refined (see Appendix 10.4)

7.5 Statistical Analysis

Analysis of the results for the clinical study was conducted using the computer software program SIGNAL 4.03(SIGNAL), IBM SPSS Software 19(SPSS) and Microsoft Office Excel 2007 (Excel). Throughout this thesis the exact p-values were reported for statistical significance. The

10-point visual analogue scale (VAS) results, the allodynia results, the motor performance results, and the SEP peaks were used to compare the placebo group with the intervention pain group.

A repeated measures ANOVA was performed for the pain ratings and the allodynia numbers. Significant differences were expected in the level of pain as rated on the 10-point VAS between the intervention and placebo groups. Experimentally induced pain is expected to lead to central sensitization and allodynia, and it is expected that these effects will not be observed in the placebo condition.

8 METHODS

The aim of this thesis is to investigate the effect of acute experimental pain on sensorimotor processing. Experimental pain was induced by applying capsaicin cream and SMI was measured by recording selected early somatosensory evoked potentials (SEPs) in Humans. The effect of central sensitization on signal transmission was assessed in the nervous system of Human subjects by investigating changes in both the amplitude and latency of SEPs from baseline, post-intervention, and post-intervention/post-motor learning. There is a gap in the research as to how sensorimotor processing is affected when motor learning occurs while in pain. Our primary outcome is to measure the effect of acute experimental pain on SEP peaks. Specifically, the amplitudes of the SEP peaks were measured following experimental pain and were compared to their baseline values. The secondary outcomes include the interactive effect of pain and motor learning on SEP peaks and the effect of pain on motor performance.

8.1 Considerations

In order to ensure that only young and healthy subjects were included in this experiment, subjects began by filling out a health survey in order to ensure they were the appropriate age, and to identify and exclude any medical condition which may impact normal somatosensation including recent cervicothoracic injury, neurologic conditions or the concurrent use of medication, and were not suffering from a chronic pain condition (see Appendix 10.3). Following this, qualified subjects were given written and verbal explanations of the study and then randomly assigned to either the placebo or the experimental intervention.

There are some factors which can affect SEP latencies and were therefore considered in the design of this experiment. During the development of somatosensory pathways from birth until adulthood myelinogenesis occurs and there is an increase in body growth which leads to an

increase in conduction velocities and increases in latencies respectively. From birth, latencies increase until adult values are reached at the age of 15 to 17 years of age (Mauguière et al., 1999). After the age of 55, latencies begin increasing due to conduction slowing in the peripheral nerves (Mauguière et al., 1999). Therefore, we aimed to test subjects between 18 – 50 years of age. Another point to consider is that the latencies of SEPs vary according to the distance between the stimulated site and the SEP sources and thus height can impact the SEP latencies (Mauguière et al., 1999). During the SEP peak analysis, the amplitude of SEP peaks were measured from the trough to the peak of interest, the latency of which may vary from subject to subject according to their height. SEPs were measured at baseline, following the application of the placebo or capsaicin cream, and after the motor learning task. The dominant arm was used in all subjects for all SEP studies. The impedance of the electrodes was maintained at less than 5 k Ω throughout the experiment. Muscle artifact was reduced by making the subject as comfortable as possible (Mauguière et al., 1999). During the data recording sessions, the subjects were seated in a reclining chair in a quiet room and were asked to be as quiet as possible and sit still. Changes in limb temperature have been shown to slow peripheral nerve conduction velocities (Mauguière et al., 1999) and therefore the room was set at a moderate temperature and wasn't too cold. During sleep, changes in the amplitude, waveform and latency of the parietal N20 have been reported (Mauguière et al., 1999). Therefore, the state of consciousness of subjects was monitored during the recording to ensure that the subjects did not fall asleep.

8.2 Protocol

Two groups of twelve subjects were randomly assigned to either intervention (capsaicin) or placebo (lotion) conditions. SEPs were measured at baseline, and subsequently a thin layer of capsaicin or lotion (depending on whether the subject is in the intervention or placebo group)

was applied to a 50 cm^2 area of the of the C_5 dermatome ("target region") on the lateral aspect of the right elbow. Subjects in the intervention group received 0.075% capsaicin sold under the brand Zostrix and subjects in the placebo group received Life brand skin lotion. The investigator applying the cream wore wear latex gloves throughout the procedure and subjects were cautioned not to touch or scratch the treated area for up to 3 hours. There was a five minute application period in order to rub the cream in and the borders of the cream location were marked off with a marker. SEPs, allodynia, and VAS were measured at 20 minutes in both the intervention and placebo conditions. Pain was rated by using a 10-point VAS, in which "0" corresponds to no pain and "10" to the most painful sensation one may conceive. Allodynia was performed by using a soft brush and its presence confirmed central sensitization. The borders of allodynia was determined by brushing from the periphery well outside the area and gradually moving towards the application site in steps of 1 cm at intervals of 2 s. The borders were identified when the subjects reported the point at which there was a clear transition from non-painful normal sensation to pain (burning, tender or unpleasant sense). Following these tests, the motor learning task was performed. The motor learning task consisted of a repetitive typing task where it was required to press keys on an external numeric keyboard with the middle three fingers consecutively for 20 minutes. The task consisted of a complex sequencing of three numbers e.g. 9, 7, 8, 7, 9, 8, etc. In order to monitor and analyze motor learning effects, all subjects were required to press the keys in the pattern for the complex motor task for two minutes before and after the motor learning task. Reaction time and accuracy data were recorded. SEPs, allodynia, and VAS were performed immediately after motor learning. It was hypothesized that individuals in the experimental group would have decreased accuracy and that their reaction time would decrease, but that those in the placebo group will be faster post-motor

learning. In order to calculate the average accuracy and reaction time for each subject the data from e-prime was exported into excel and manipulated in order to rid the spreadsheet of the blank cells. For each subject (pre and post-motor learning) there was an excel spreadsheet showing the fifteen number combinations with the six responses. From this, the average accuracy and average reaction time for each subject can be calculated. A repeated measures ANOVA was performed for two aspects of the motor learning task; reaction time and accuracy.

For the purpose of this thesis the amplitude and latency of the following SEP components were measured: N9, N11, N13, P25, N20, P14, N18, N24, and N30. The data was continuously examined during data collection as examination of the raw data can identify artifacts, particularly continuous low amplitude artifacts that may be present (Mauguière et al., 1999). The SEP peak amplitude and latencies were all measured manually. Only trials with a stable peripheral nerve volley (N9) were included for analysis. Trials were included trials for analysis if the N9 SEP peak amplitude was within +/- 15% of baseline values. In addition, trials were only included for data analysis if the SEP peaks were of normal appearance which is a requirement of being able to accurately discern the peak to peak amplitude. SEP amplitudes were measured, from the averaged traces, from the peak of interest to the preceding or succeeding peak of opposite deflection, according to international recommendations (Nuwer et al., 1994), and past studies in this field (Cheron and Borenstein, 1987, 1991; Rossini et al., 1996; Sonoo et al., 1996).
A repeated measures ANOVA was performed for each SEP peak (N9, N11, N13, P25, N20, P14, N18, N24, and N30). In order to normalize the data to facilitate comparison between the placebo and capsaicin state, the pre-intervention/pre-placebo peaks were made = 1 by dividing it by itself. Then the post-motor learning and post-intervention/post placebo accuracy data were divided by the original pre-intervention/pre-placebo data. This allows all subjects to be compared

to each other because the different scores are compared to 1. For the experimental group, a repeated measures ANOVA was performed for all of the peaks pre and post-intervention, and pre and post-motor learning. For the placebo group, a repeated measures ANOVA was performed for all of these peaks pre and post-placebo, and pre and post-motor learning. Trials were included for analysis if they had a stable peripheral nerve volley (N9) and thus all subjects whose N9 varied by 15 % were excluded. Statistical significance was set at $p < 0.05$.

For the SEPs measured following the application of the placebo lotion, it was predicted that there would be no significant differences in any of the peaks. For the SEPs measured post-placebo/post-motor learning it was predicted that there would be significant differences in several peaks related to sensorimotor integration (N18, N24, N30). For the SEPs measured following the application of capsaicin but prior to motor learning it was predicted that pain would result in significantly higher cortical SEP peaks reflecting an alteration in the processing of cortical neural generators. SEPs are measured after motor learning (while in experimental pain) and therefore obtained data was gathered on the interactive effect of motor learning and pain on SEP peaks. It was hypothesized that these cortical SEP peaks would be significantly higher reflecting and alteration in the processing of cortical neural generators. This design gives convincing evidence of a relationship between exposure (capsaicin cream) and effect (SEPs and motor performance).

9 RESULTS

Two groups of twelve subjects were randomly assigned to either experimental (capsaicin) or placebo (lotion) conditions. However, one of the inclusion criteria was only to include trials with a stable peripheral nerve volley (N9) pre and post intervention in the final analysis. Because the N9 SEP peak amplitude was greater than +/- 15% of baseline values in a number of subjects, the number of participants was increased. In total, thirty-seven subjects, (twenty-one in the placebo group, sixteen in the intervention group) aged 20 – 41 (mean age = 24.12) with no history of neurological disorders participated in this study. Informed consent was obtained for all of these subjects and the local ethical committee approved the study. Of the twenty-one individuals in the placebo group, there were ten individuals whose N9 varied by less than 15%, and although a further five had N9 volleys that varied by less than 20 %, they were not included. Of the sixteen individuals in the intervention group, there were ten individuals whose N9 varied by less than 15 %. Of the twenty individuals whose SEP data met the inclusion criteria, there were 11 males and 9 females that participated (with a mean age of 23.95) (see Table 9-1). For nine out of the eleven individuals in the placebo group who were excluded it because their N9 SEP peak amplitude was greater than +/- 15% of baseline values post-motor learning (rather than post-capsaicin). Similarly, five of the six individuals in the intervention group were excluded because their N9 SEP peak amplitude was greater than +/- 15% of baseline values post-motor learning. In these excluded individuals, the N9 SEP peak amplitude was within +/- 15% of baseline values post-application of intervention/placebo. Subject details for the subjects that were included in the analysis are shown in Table 9-1.

9.1 Pain ratings:

There was a significantly different level of pain as rated on the 10-point VAS for the intervention

group. Post-intervention F = (19,3)123.857 (α=0.000), post-motor learning F=(19,3) 32.275 (α=0.000) and post-motor learning (45 minute mark) F = (19,3) 8.679 (α =0.001).

For the placebo condition, the average VAS rating was 0 at all three measurement times.

For the experimental group, the average VAS rating pre-intervention was 0, post-intervention was 5.10, post-motor learning was 4.15, and post-motor learning (45 minute mark) was 1.8. Details are shown in Table 9-2.

The average VAS ratings can also be graphed as shown below (Figure 9-1).

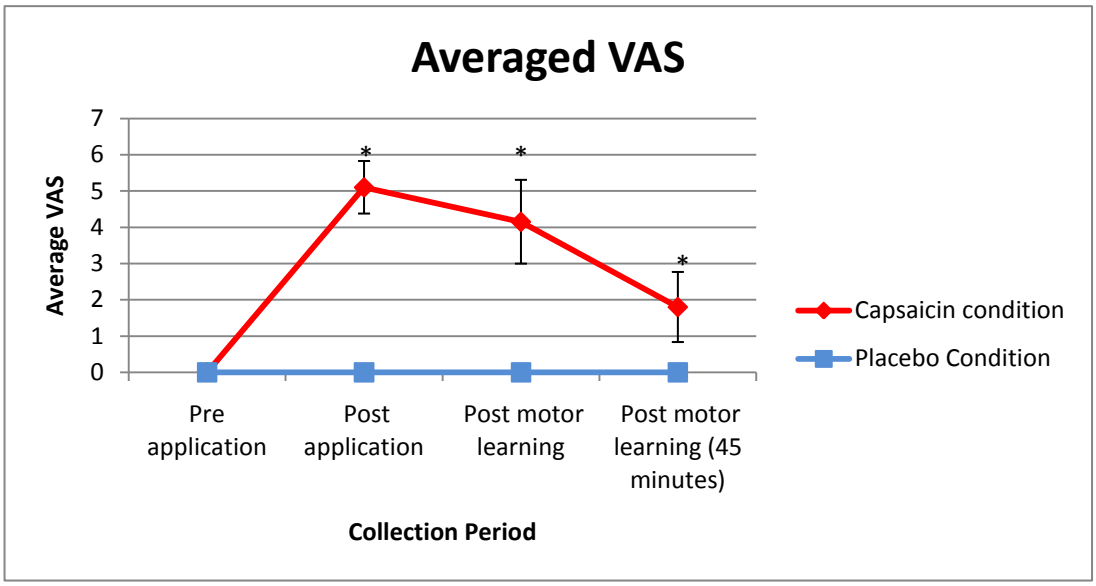

Figure 9-1: Line-graph depicting averaged VAS ratings of subjects in the placebo and the intervention conditions. Error bars represent the standard deviation. Significant differences are indicated by an asterisk.

9. 2 Allodynia:

The experimentally induced pain leads to allodynia, and these effects were not observed in the placebo condition. A repeated measures Analysis of variance with planned contrasts of each level relative to baseline indicated that the differences in allodynia were significantly different to baseline at each time point in the intervention condition. Post-intervention F = (19,3) 47.740 (α=

0.000), post-motor learning F = (19,3) 22.232 (α = 0.000), post-motor learning F = (19,3) 9.008 (α =0.015).

9.2.1 Placebo condition: allodynia results

No allodynia was found in the placebo condition for any of the subjects, at any of the measurement times.

9.2.2 Intervention condition: allodynia results

In contrast to the placebo condition, there was allodynia in every subject post-intervention in the capsaicin condition. Pre-intervention, the average upper level was 0 cm, the average lower level was 0 cm, and the total average level was 0 cm. Post-intervention, the average upper level was 2.7 cm, the average lower level was 2.1 cm, and the total average level was 4.8 cm. In the post-intervention/post-motor learning, there was allodynia in every subject. Post-intervention/post-motor learning, the average upper level was 2.8 cm, the average lower level was 2.7 cm, and the total average level post was 4.9 cm. After the last collection of SEPs (at the 45 minute mark), there was allodynia in six of the ten individuals in the intervention condition. At the 45 minute mark, the average upper level was 1.8 cm, the average lower level was 1.5 cm, and the total average level was 3.3 cm. Subject details are shown in the table below (Table 9-3).

The average total allodynia results can also be graphed as shown below (Figure 9-2).

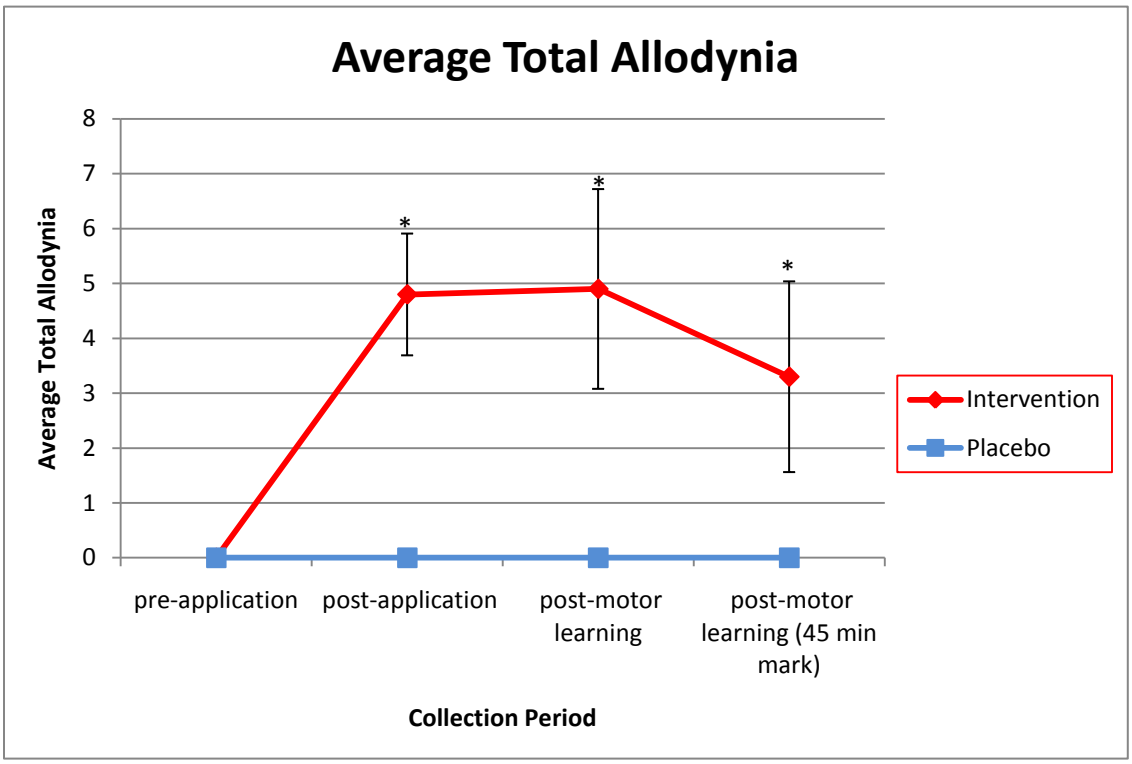

Figure 9-2: Line-graph of averaged total allodynia levels of subjects in the placebo and intervention conditions. Error bars represent the standard deviation. Significant differences are indicated by an asterisk.

9.3 Motor performance:

Thirty subjects were included in the motor performance analysis. Two of the original 32 subjects were excluded, one from the placebo group and one from the intervention group as the analysis of their results suggested that these subjects had misplaced their fingers on the keyboard which skewed their results. The remainder of the subjects in the intervention condition (fifteen subjects), and fifteen subjects from the placebo condition were included.

Pre and post-motor learning 15 number combination options, each with 6 responses. E-prime creates a set of 6 columns for each of the 15 combinations (15x6=90). Table 9-4 is an example of a single subject's accuracy and reaction time data in excel.

9.3.1 Placebo condition results:

Accuracy

For the subjects in the placebo condition, the repeated measures ANOVA revealed no significant differences in accuracy following motor learning F= (29, 1) 1.555 ($\alpha = 0.233$). However, there was a trend of decreased accuracy post-motor learning. The average accuracy pre-motor learning was 0.983, and the average accuracy post-motor learning was 0.969. Subject data is shown in Table 9-5.

Reaction Time

The repeated measures ANOVA on the reaction time found a significant decrease in reaction time post-motor learning F= (29, 1) 21.753 ($\alpha = 0.0$).

For the subjects in the placebo condition, the average reaction time decreased post-motor learning. The average reaction time pre-motor learning was 546.89 ms and the average reaction time post-motor learning was 451.98 ms. Subject data is shown in Table 9-6.

9.3.2 Intervention condition results:

Accuracy

A repeated measures ANOVA was performed on the accuracy data for the intervention group. No significant differences were found post-motor learning F= (29,1) 1.237 ($\alpha = 0.285$). However, we do see a trend towards increased accuracy post-motor learning. For the subjects in the intervention condition the average accuracy pre-motor learning was 0.969, and the average accuracy post-motor learning was 0.985. Subject data is shown in table 9-7.

Reaction Time

A repeated measures ANOVA was performed on the reaction data for the intervention group. Significant differences were found post motor learning F= (29,1) 110.122 ($\alpha = 0.0$).

For the subjects in the experimental condition, there is a decrease in the reaction time post-motor learning. For the subjects in the experimental condition the average reaction time pre-motor learning was 502.36 ms and the post-motor learning was 379.98 ms. Subject data is shown in table 9-8.

Accuracy:

The data for the placebo and intervention conditions can be graphed as shown in the figure below (Figure 9-3).

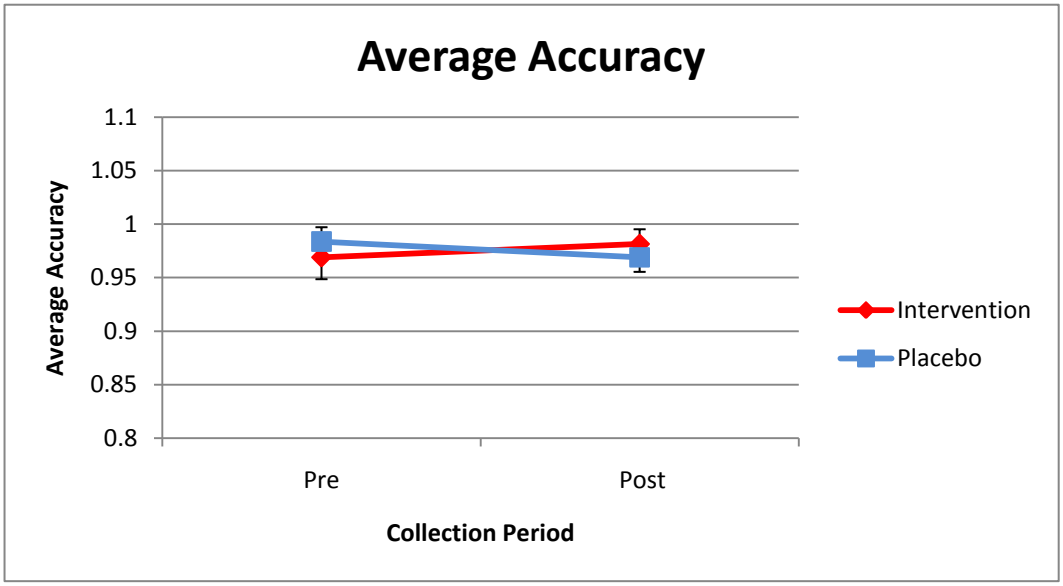

Figure 9-3: Line-graph depicting the average accuracy for the intervention and placebo groups both pre and post-motor learning. The intervention group average accuracy increases post-motor learning while the placebo group average accuracy decreases post-motor learning. The average accuracy pre-motor learning is higher for the placebo group. Error bars represent the standard deviation.

Reaction Time

The reaction time data can be graphed as shown below (Figure 9-4).

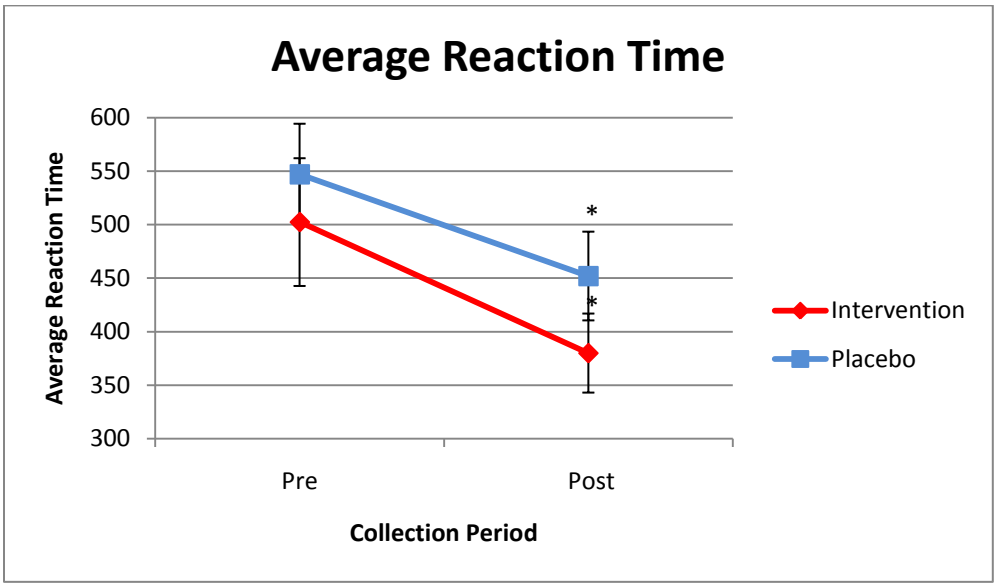

Figure 9-4: Line-graph depicting the average reaction time pre and post-motor learning for the intervention and placebo groups. Error bars represent the standard deviation. Significant differences are indicated by an asterisk.

At both collection periods (pre and post motor learning) the intervention group had a faster reaction time.

9.4 SEPs

The normalized averages for the peaks can be graphed as shown below (Figure 9-5). The only SEP peak to be significantly different was the N24 peak which was significantly increased following motor learning for both intervention and control groups $F(19,2) = 5.969$ ($\alpha = 0.037$),

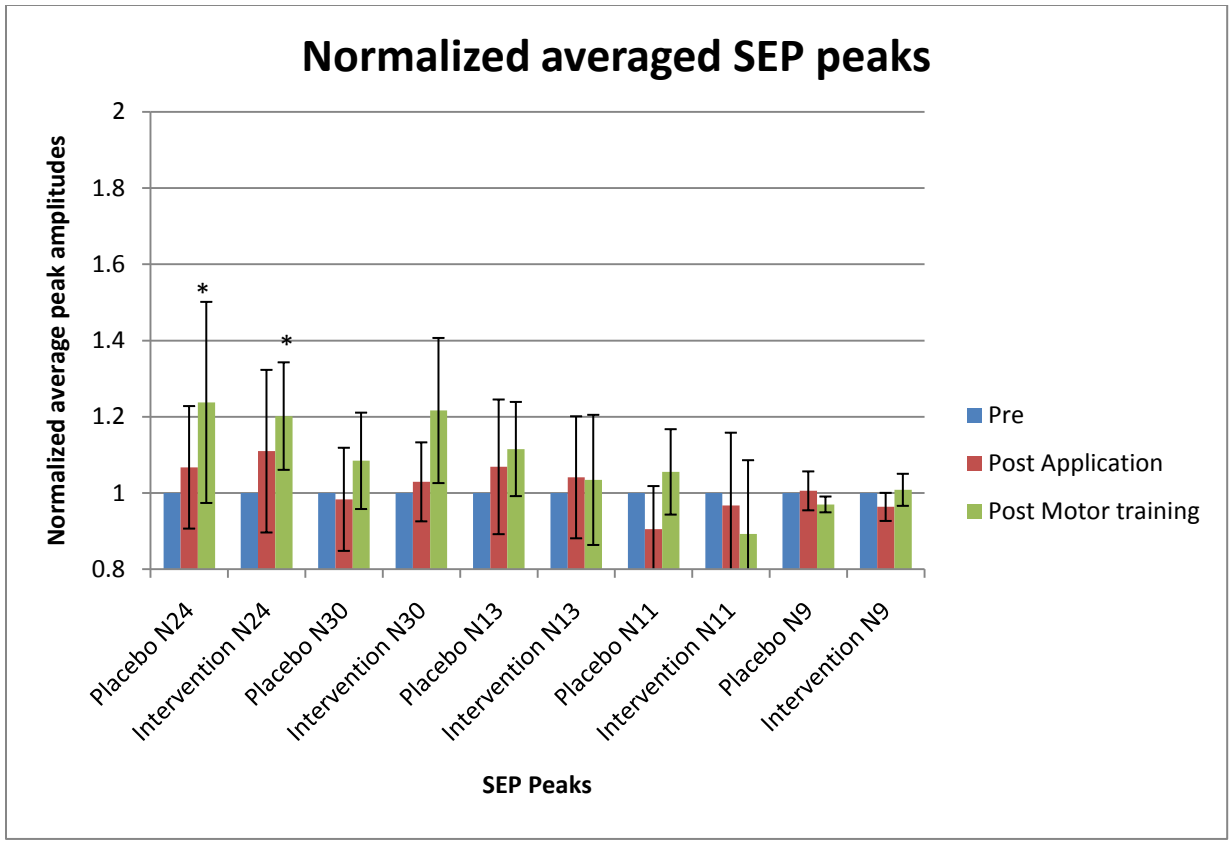

Figure 9-5: Bar-graph of averaged normalized SEP ratios showing baseline, following the placebo, and following the typing task. Error bars represent the standard deviation. Significant differences are indicated by an asterisk.

Figure 9-6 includes the raw data from a representational intervention subject indicating cortical peaks. There is a significant difference for the N24 peak post-motor learning.

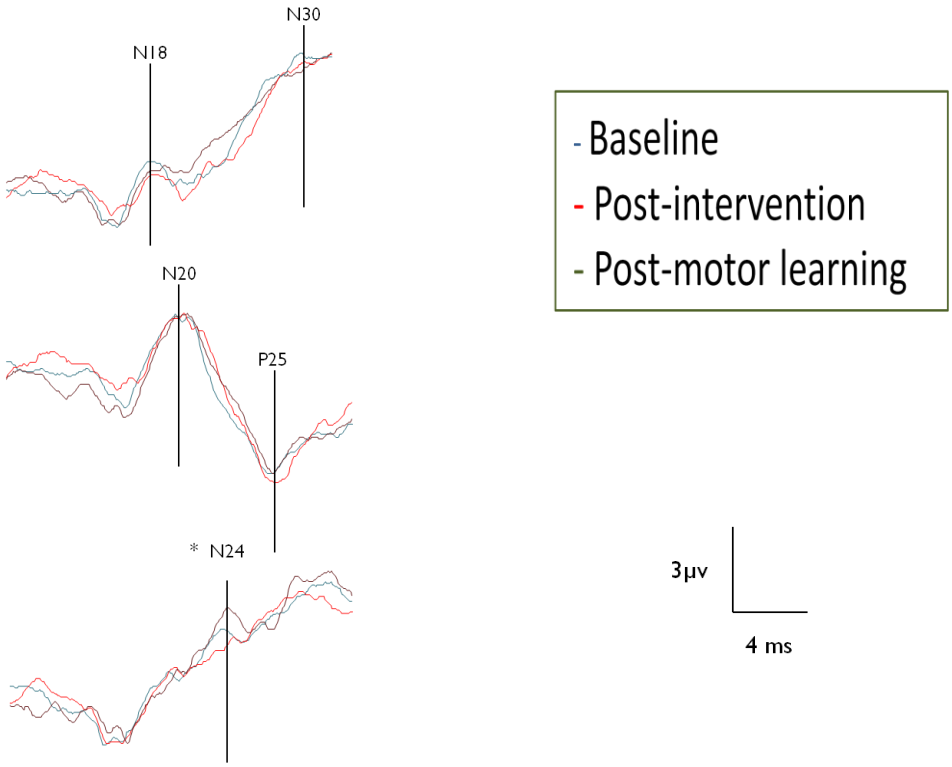

Figure 9 – 6: raw data from a representational intervention subject indicating cortical peaks. There is a significant difference for the N24 peak post-motor learning as indicated by an asterisk.

9.4.1 N24

Following application of the capsaicin cream, the N24 peak wasn't significantly different F = (19,2) 0.847 (α = 0.381). However, following motor learning, the N24 was significantly increased for both intervention and control groups F = (19,2) 5.969 (α = 0.037), however interaction of Time*Condition didn't reveal any significant differences between the degree of interest when comparing the two groups F = (19,2) 0.087 (α = 0.774) or post-motor learning F = (19,2) 0.03 (α = 0.867).

Figure 9-7 demonstrates the N24 increases following motor learning in both the placebo and intervention conditions (Figure 9-7).

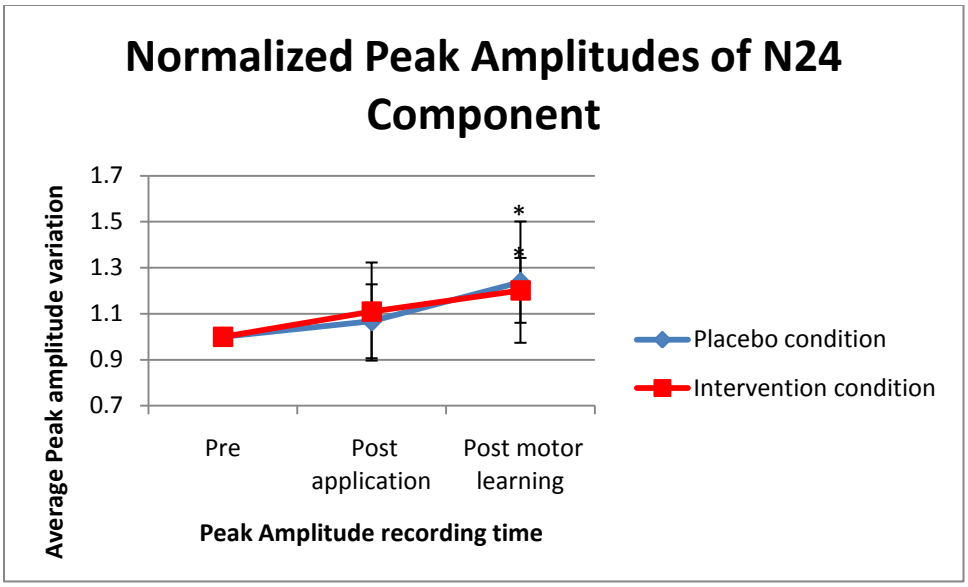

Figure 9-7: Line-graph depicting the normalized averaged N24 peak amplitude post-application and post-motor learning for the placebo and intervention conditions. Error bars represent the standard deviation. Significant differences are indicated by an asterisk.

9.4.2 N30

Following cream application, the N30 peak wasn't significantly different $F = (19,2)\ 0.022$ ($\alpha = 0.886$) for either group. Although the N30 appeared to be increased following motor training (Figure 9-8) the difference was not significant $F = (19,2)\ 2.263$ ($\alpha = 0.167$) and the interaction of Time*Condition didn't reveal any significant differences post-application $F = (19,2)\ 0.131$ ($\alpha = 0.726$) or post-motor learning $F = (19,2)\ 2.093$ ($\alpha = 0.182$).

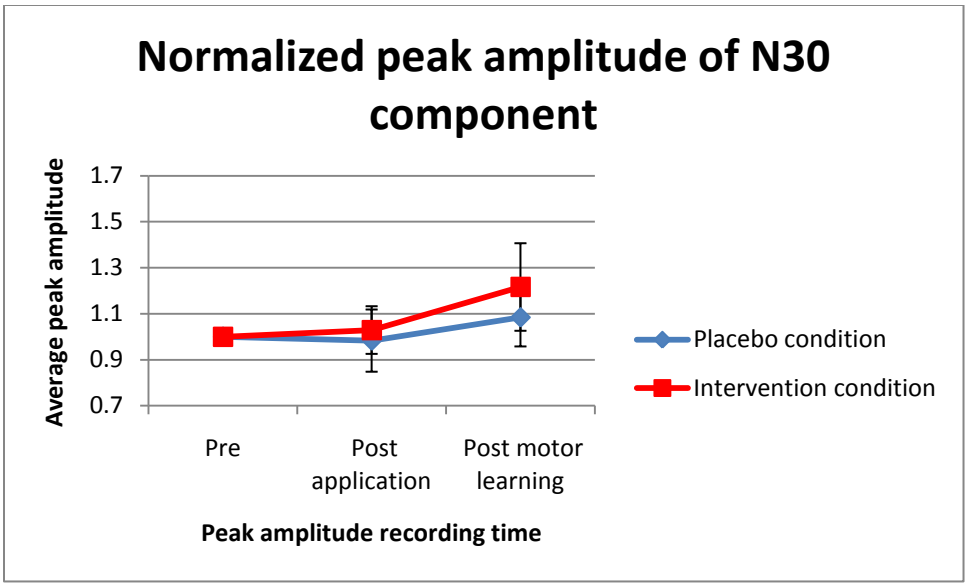

Figure 9-8: Line-graph depicting the normalized averaged N30 peak amplitude post-application and post-motor learning for the placebo and intervention conditions. Error bars represent the standard deviation.

9.4.3 N13

For the placebo condition the N13 component seemed to increase post-application and post-motor learning and for the intervention condition, the N13 component increases post-application but decreases post-motor learning (Figure 9-9), however none of the changes were statistically significant. The interaction of Time*Condition didn't reveal any significant differences post-application $F = (19,2)\ 00.039$ ($\alpha = 0.848$) or post-motor learning $F = (19,2)\ 0.383$ ($\alpha = 0.552$).

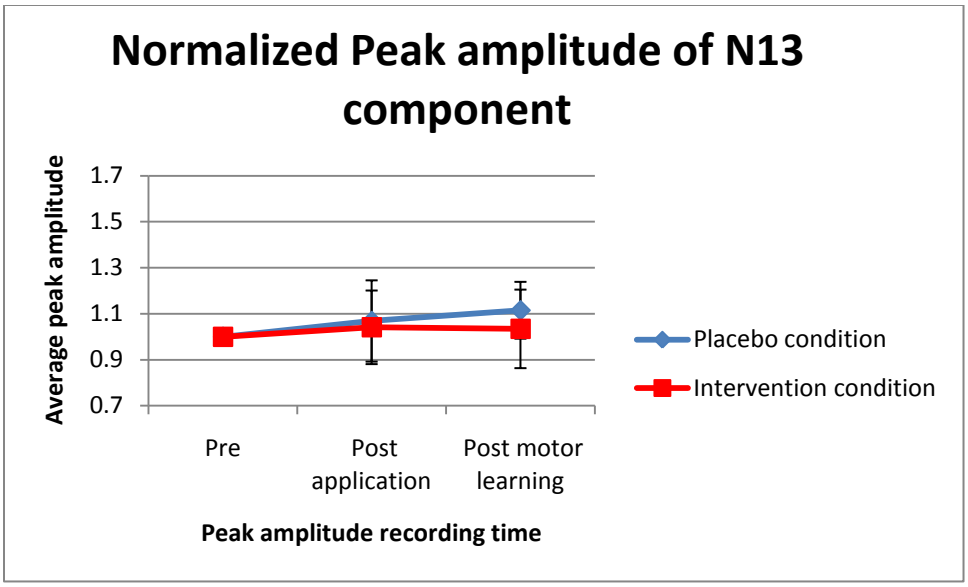

Figure 9-9: Line-graph depicting the normalized averaged N13 peak amplitude post-application and post-motor learning for the placebo and intervention conditions. Error bars represent the standard deviation.

9.4.4 N11

Post-application, the N11 peak wasn't significantly different F = (19,2) 0.756 (α = 0.407). Post-motor learning, the N11 wasn't significantly different for either condition F = (19,2) 0.150 (α = 0.708). The interaction of Time*Condition didn't reveal any significant differences post-application F = (19,2) 0.204 (α = 0.662) or post-motor learning F = (19,2) 1.199 (α = 0.302).

The N11 peak was not shown to be significantly different in any of the conditions. However, the figure below demonstrates that for the placebo condition, the N11 component decreases post-application and then increases post-motor learning. For the intervention condition, the N11 component decreases post-application and post-motor learning (Figure 9-10).

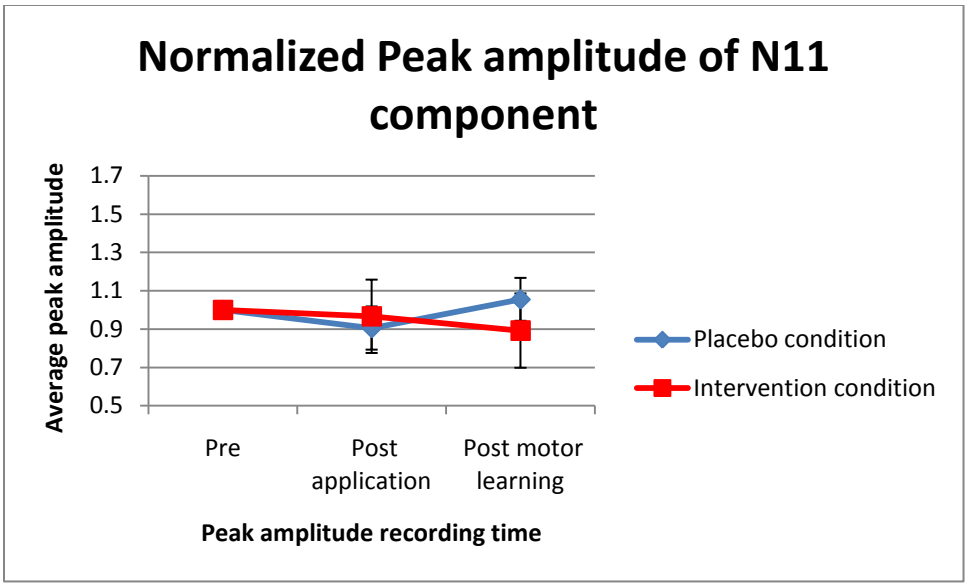

Figure 9-10: Line-graph depicting the normalized averaged N11 peak amplitude post-application and post-motor learning for the placebo and intervention conditions. Error bars represent the standard deviation.

9.4.5 N9

The N9 peak wasn't significantly different post-application F = (18,2) 0.536 (α = 0.483) or post-motor learning F = (19,2) 0.330 (α = 0.580). The interaction of Time*Condition didn't reveal any significant differences post-application F = (19,2) 1.189 (α = 0.304) or post-motor learning F = (19,2) 2.590 (α = 0.142) (Figure 9-11)

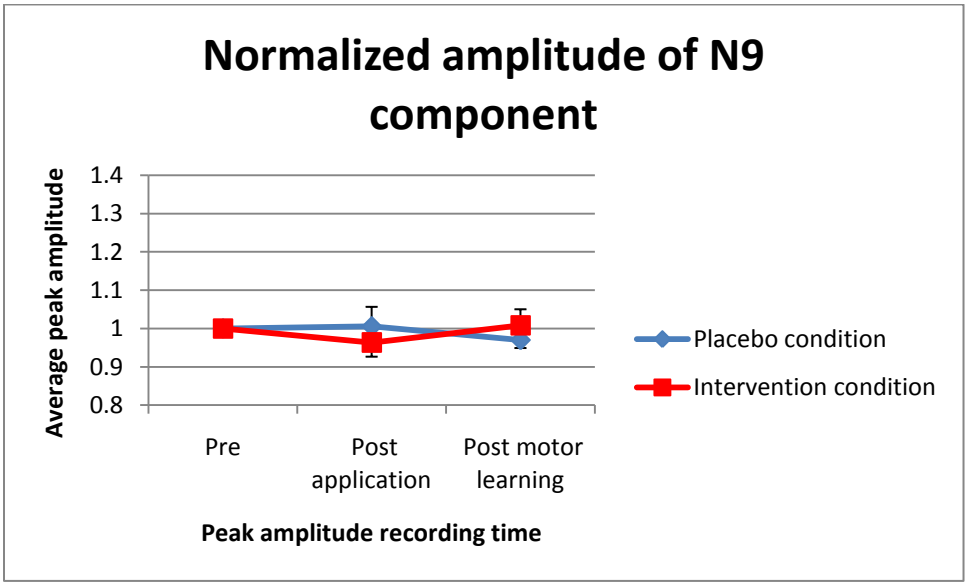

Figure 9-11: Line-graph depicting the normalized averaged N9 peak amplitude post-application and post-motor learning for the placebo and intervention conditions. Error bars represent the standard deviation.

9.4.6 N20

The N20 component appeared to increase slightly post-application and then decreases slightly post-motor learning, while for the intervention condition, it appeared to increase post-application and then stays elevated post motor learning (Figure 9-12). However, this increase was not statistically significant. The interaction of Time*Condition also was not significant post-application $F = (19,2)\ 0.202$ ($\alpha = 0.664$) or post-motor learning $F = (19,2)\ 0.118$ ($\alpha = 0.739$).

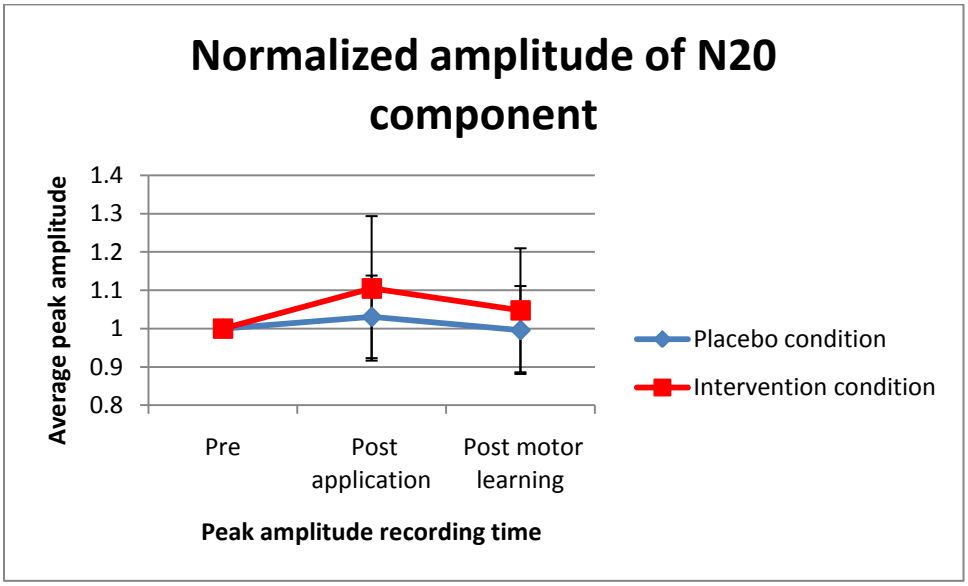

Figure 9-12: Line-graph depicting the normalized averaged N20 peak amplitude post-application and post-motor learning for the placebo and intervention conditions. Error bars represent the standard deviation.

9.4.7 P25

The interaction of Time*Condition didn't reveal any significant differences post-application $F = (19,2)\ 0.046$ ($\alpha = 0.835$) or post-motor learning $F = (19,2)\ 0.002$ ($\alpha = 0.962$).

The P25 peak was not shown to be significantly different in any of the conditions. The P25 component showed a trend to increase post-application and post-motor learning, whereas for the intervention condition, the P25 component decreases post application and then increases post-motor learning (Figure 9-13), however these differences were not significant and there was no significant interaction of time and condition.

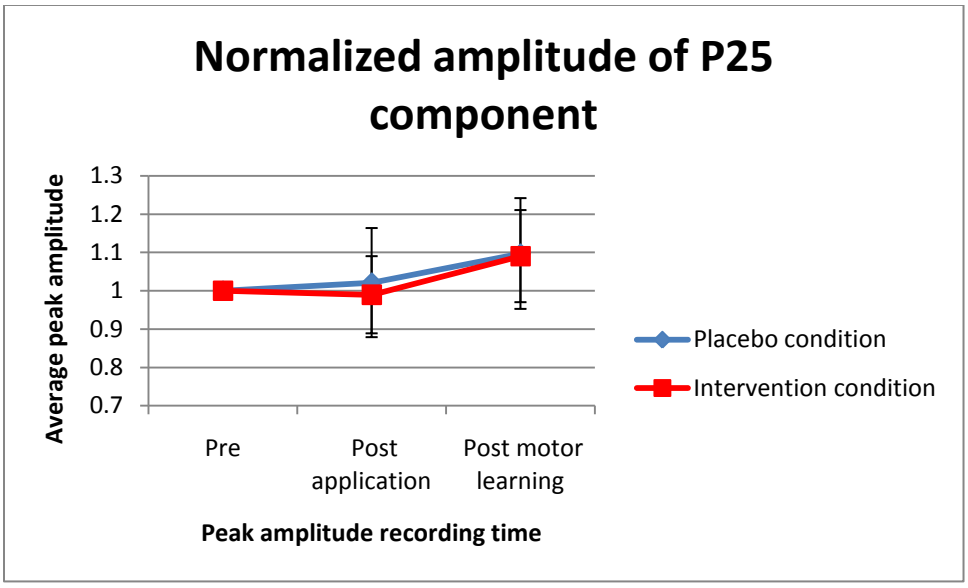

Figure 9-13: Line-graph depicting the normalized averaged P25 peak amplitude post-application and post-motor learning for the placebo and intervention conditions. Error bars represent the standard deviation.

9.4.8 N18

For the placebo condition, the N18 component increases post-application and then decreases post-motor learning while for the intervention condition, the N18 component increases post-application, and then still stays elevated post-motor learning although it decreases slightly from the post-application level (Figure 9-14) however none of these changes or the time by condition interaction were significant.

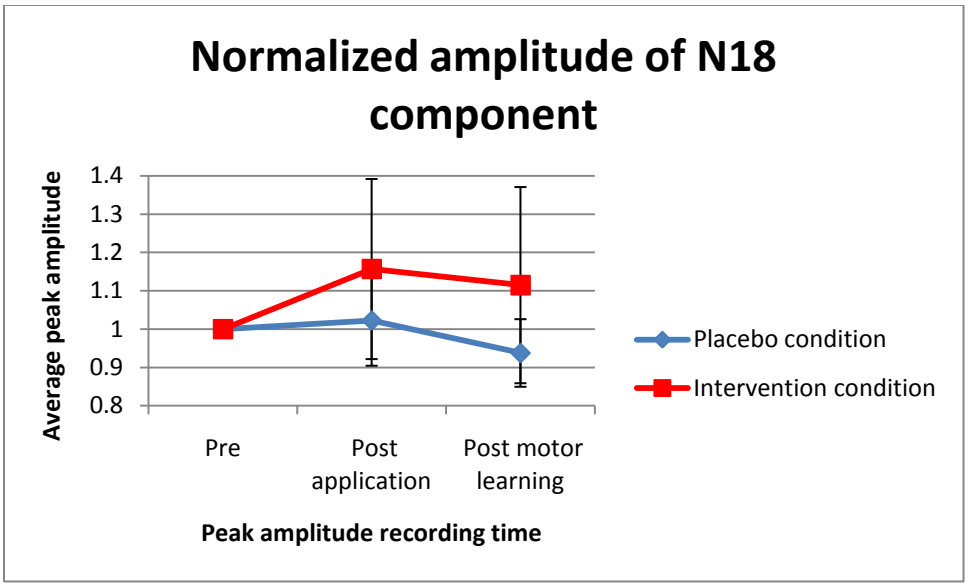

Figure 9-14: Line-graph depicting the normalized averaged N18 peak amplitude post-application and post-motor learning for the placebo and intervention conditions. Error bars represent the standard deviation.

10 DISCUSSION

10.1 Pain ratings and allodynia:

As expected, the experimentally induced pain leads to allodynia, which supports the claim that central sensitization was evoked in the target segment and indicates that the capsaicin acted as good experimental pain model.

10.2 SEPs:

The primary outcome was the effect of acute experimental pain on SEP peaks. It was predicted that for the placebo condition that there would be no significant differences in any of the SEP peaks following the application of the placebo cream. As several studies have shown an expansion of representations corresponding to trained movements associated with motor learning (Elbert et al., 1995; Kleim et al., 1998) significant differences post-motor learning in several cortical peaks related to sensorimotor integration (N18, N24, N30) for both the placebo and experimental conditions were predicted. As several studies have shown that pain affects sensory processing as demonstrated through elevated SEP peaks (Tinazzi et al., 2000; Tinazzi et al., 2004) and functional reorganization (Knecht et al., 1998; Soros et al., 2001) it was predicted that pain would result in elevated cortical SEP peaks reflecting an alteration in the processing of cortical neural generators. SEPs were measured post-motor learning and therefore data was gathered on the interactive effect of motor learning and pain on SEP peaks. It was hypothesized that these cortical SEP peaks would be elevated reflecting an alteration in the processing of cortical neural generators.

While significant differences in several peaks related to sensorimotor integration (N18, N24, N30) were expected for the subjects in the placebo condition post-motor learning, only the N24 was significantly different. For the SEPs measured following the application of capsaicin but

prior to motor training it was predicted that pain would result in elevated cortical SEP peaks reflecting an alteration in the processing of cortical neural generators. Contrary to what was expected, no significant differences were found for any of the peaks following application of the capsaicin cream. One of the secondary outcomes was the interactive effect of pain and motor learning on SEP peaks. It was hypothesized that these cortical SEP peaks will be elevated reflecting an alteration in the processing by cortical neural generators related to sensorimotor integration. Although several peaks were expected to be significantly different post-intervention/post-motor learning, the only peak to show any significant differences following motor learning was the N24 peak.

The N24 reflects activity in the pathway between the cerebellum and primary somatosensory cortex and has the potential to show changes in cerebellar activity (Rossi et al., 2003). The cerebellum is a brain region involved in motor processing as it modulates movement and is involved in the learning of motor skills and the coordination of movements (Lundy-Ekman, 2007, p. 10). Our finding of a significant difference post-motor learning is in line with several other studies in the literature. Motor sequence learning tasks requiring subjects to perform a sequence of motor responses using one or more fingers demonstrated cerebellar activation changes following learning tasks in work using PET (Friston et al., 1992). Similarly, Jenkins et al. (1994) found that when comparing the prelearned sequences to the resting state using PET, there were significant increases in activation in the cerebellum.

The cerebellum is also thought to play a role in sensory processing as tasks requiring discriminatin of sensory information lead to significant increases in cerebellar activation (Gao et al., 1996). Furthermore, a passive manipulation of limb position by an experimenter produces cerebellar activation similar to voluntary movement of the limb (Jueptner & Weiller, 1998).

These findings suggest that cerebellar activity observed during the execution of a motor task may be due in part to sensory processing.

The N24 SEP peak was the only significantly different peak post-motor learning. This is particularly interesting as the N24 SEP peak shows changes in cerebellar activity, which is a brain region involved in both the learning of motor skills and noxious processing (Moulton et al., 2010). Neuroanatomical tracers demonstrate that the cerebellum receives inputs from cutaneous primary afferents (Randic et al., 1981; Snyder et al., 1978), and electrophysiological studies demonstrate that it receives nociceptive afferents (Ekerot et al., 1987a; Ekerot et al., 1987b; Hayashi et al., 1984). Stimulation of nociceptors evokes neural activity in the cerebellum and thus afferent input from nociceptors reach the cerebellum (Ekerot et al., 1987a; Ekerot et al., 1987b; Hayashi et al., 1984). Stimulation of cutaneous A-delta and C fiber nociceptors in cats activates climbing fibers that terminate on Purkinje cells in the cerebellar anterior lobe (Hayashi et al., 1984). In addition to climbing fiber input, C-fiber nociceptors may also act through mossy fibers to reach Purkinje cells in the cerebellum (Wu and Chen, 1992). Noxious stimulation in rats activates nociceptive neurons in the lateral medullary reticular formation, which project to the cerebellar vermis (Ness et al., 1998). Nociceptive stimulation has also been shown to modulate Purkinje cell activity in the cerebellum (Saab and Willis, 2001). In addition, Iadarola et al. (1998) performed a PET study performed on healthy Humans and found that the cerebellar vermis was strongly activated by capsaicin. The cerebellum responds to noxious stimuli as most fMRI studies of pain show activation in the cerebellum (Apkarian et al., 2005; Borsook et al., 2007).

The cerebellum may be involved in processing motor control error signals in state estimation and may be a comparator for errors in somatosensory processing. Such error signals may play a role

in wrongly executed movements. This hypothesis may also apply to nociceptive inputs (Gureje et al., 2001; Haley et al., 1985). It is thought that the cerebellum is an integrator of multiple effector systems including affective processing, pain modulation, and sensorimotor processing (Moulton et al., 2010). The N24 peak reflects activity in the pathway between the cerebellum and primary somatosensory cortex and has the potential to show changes in cerebellar activity (Rossi et al., 2003) which is relevant to this study as it was the only peak to be significantly different following motor learning and the N24 can show changes in cerebellar activity. The role of the cerebellum in motor control and in response to nociceptive stimuli needs further study and such research may lead to an understanding of chronic pain states which have altered cerebellar processing (Moulton et al., 2010).

A possible explanation as to why there were no significant differences following motor learning for other peaks related to sensorimotor integration (N18, N30) was that the motor learning task was comparable to a repetitive typing task. This is supported by the high pre-motor learning accuracy and the feedback from the participants that they were bored. Studies (Plautz et al., 2001; Remple et al., 2001) have demonstrated that movement repetition is not sufficient to produce reorganization within the motor cortex that normally occurs post-motor learning. Plautz et al. (2001) demonstrated that in the absence of motor learning, extensive repetition of digit movements did not produce reorganization. Similarly, Remple et al. (2001) found that the organization of the motor cortex of rats that spent several weeks in running wheels was not significantly different from that of inactive rats. These studies demonstrate that increased movement repetition is not sufficient to drive plastic changes in cortical movement representations (Plautz et al., 2001; Remple et al., 2001). Movement repetition is not sufficient to generate plastic change and this may explain why N18 and N30 were not significantly different

post-motor learning, although this does not explain why N24 was significantly different. In addition, SEP studies have demonstrated that cortical and subcortical SEP peaks of the CNS decrease after repetitive movement (Murphy et al., 2003a; Murphy et al., 2003b; Taylor & Murphy, 2008; Tinazzi et al., 1998). Although there were no significant decreases in any of the SEP peaks, this may provide some insight as to why there were not any significant increases for most of the peaks.

For this study ten individuals in each group were included whose N9 did not vary by more than 15% (mean age =23.95). Early on in this study, the N9 was varying by more than 15 % in a number of subjects, and therefore the number of participants was increased. In the placebo group, nine of the eleven individuals in the placebo group were excluded as their N9 varied post-motor learning. Similarly, in the intervention group, five of the six individuals were excluded because their N9 varied post-motor learning. In these excluded individuals, the N9 did not vary by more than 15 % post application. This suggests that subjects had trouble returning to their original position post-motor learning. Based on this information, the subjects were subsequently carefully positioned and the subjects were asked to observe and remember their arm position so that they could reposition themselves. Subsequently, increased vigilance led to a stable N9 in our subjects. Interestingly, fewer individuals in the intervention group were excluded. A possible explanation is that the pain made it easier to remember the original position. The intensity of the pain reaction emphasizes dangerous situations which are important for survival and maintaining homeostasis (Dubin & Patapoutian, 2010). This has evolutionary importance as the ability for organisms to change their behaviour as a result of experience leads to an increased chance of survival (Baumbauer et al., 2009). Attention is required to encode events into memory is also required to retrieve those events from memory (Logan, 1992). The persistence of a

heightened responsiveness of the nervous system following a brief noxious stimulus has clear parallels with memory, where information needs to be stored and retrieved. Future studies should employ a means of stabilizing the arm in order to ensure that the arm returns to the original position in order to prevent the N9 from varying by more than 15 %. A splint could be utilized as this could be easily removed for the typing component and the arm could easily be repositioned afterwards.

10.3 Motor performance

10.3.1 Accuracy:

Another secondary outcome of this study was the effect of pain on motor performance. Boudreau et al. (2007) demonstrated that acute experimental pain impairs the ability to learn a new motor task as the mean performance score was significantly lower for the capsaicin session when compared to that of a placebo session. Thus, for the motor learning component of this study, it was predicted that the experimental pain would result in decreased accuracy reflecting the effect of pain on motor learning. This was not observed. Although not significantly different, there was a trend towards improved accuracy for the intervention group while there is a trend towards decreased accuracy for the individuals in the placebo group. An important distinction between our study and Boudreau et al. (2007) is that in this study acute pain was applied to the arm and the motor learning task involved the fingers. In contrast, Boudreau et al. (2007) applied acute pain to the tongue and the motor learning task involved the tongue. This raises the possibility that the effect of remote pain is different from that of pain applied directly to the muscle used in the motor learning task.

The individuals in the intervention group were at a lower average accuracy pre-motor learning (0.969 versus 0.984 for the placebo condition). This suggests that the pain may have affected the

pre-motor learning accuracy, resulting in a lower average. As the accuracy for both the intervention and placebo groups is very high pre-motor learning (0.969 and 0.984 respectively), there was not very much room for improvement. Individuals who were in pain had more room for improvement as they were at a lower average accuracy pre-motor learning (possibly due to their pain). Future studies should use a more complex motor task which would have a lower accuracy pre-motor learning. This would allow for greater improvements between pre and post-motor learning and it would be easier to see the effects of pain on motor learning. Subjects in both groups provided feedback that they were bored by this motor learning task. This provides an explanation as to why the accuracy declined in the placebo group post motor learning as many of the subjects were bored by this monotonous task. If the task had been more complex the subjects would likely not have been as bored and would be more focused on the learning task.

10.3.1 Reaction Time:

For the motor learning component of this study, it was predicted that the reaction time would decrease for both conditions, but that the individuals in the placebo group would be faster post-motor learning. As expected, reaction time decreased in both the intervention and placebo conditions. Decreased reaction time for both the intervention and placebo conditions can be explained by motor learning, as both groups may have become faster at the task through learning. However, another possible explanation is that the subjects may have completed the final component of the task faster than the initial component because they were bored and wanted to end this section of the experiment.

The results of the motor learning component of our study were contrary to what was expected (increased accuracy and decreased reaction time post-intervention). The literature shows that motor learning deficits are demonstrated in association with experimental pain in laboratory

animals (Hook et al., 2008; Ferguson et al., 2006) and Boudreau et al. (2007) found that neuroplasticity of the tongue MI, as reflected in a significantly enhanced TMS–MEP stimulus–response curve and reduced MEP threshold, was observed post-placebo session but not post-capsaicin. Therefore, pain interfered with training-induced motor cortical plasticity (Boudreau et al., 2007). The disruption of corticomotor plasticity during pain is thought to be possibly due to diversion of attention away from training. As outlined in the section on motor learning, attention is required to encode events into memory and is also required to retrieve those events from memory (Logan, 1992). Plasticity of the motor cortex can be moderated by changes in attention (McGaughy et al., 2002; Conner et al., 2003; Rosenkranz and Rothwell, 2004; Stefan et al., 2004) as the learning of motor actions is dependent on the availability of attentional resources (Hazeltine et al. 1997; Nissen and Bullemer 1987). For example, after stroke, recovery is dependent on the ability to attend to the dysfunctional body side (Denes et al. 1982). In addition, Stefan et al. (2004) demonstrated that there is a disruption of plasticity in the motor cortex when participants focused attention to a body region not involved in the training task.

Thus cortical regions not involved with the processing of attended tasks may interfere with the neurophysiological processes that underlie plasticity (Stefan et al., 2004). In addition, increased attention to the trained area increases plastic changes (Rosenkranz and Rothwell, 2004). In addition, studies that have disrupted the cholinergic function in the basal forebrain, which linked to attention, leads to impaired motor learning (McGaughy et al., 2002; Conner et al., 2003). As our study involved pain on the arm involved in the motor learning task, the pain may have led to increased attention to the trained area. This increased attention may have enhanced the encoding of the typing task into memory resulting in improved accuracy post-intervention.

Our findings provide support for the enhancement of knowledge transfer with the presence of non-target stimuli (pain). Under certain circumstances, the presence of additional stimuli can increase the ability to detect, or interpret a pattern of target stimuli (Verrillo & Bolanowski, 1996; Zhang et al., 2009). This has been described through summation (Vernon, 1953; Verrillo, 1965), enhancement (Verrillo, 1976; Verrillo, 1983), and negative masking (Hamer, Verrillo, & Zwislocki, 1983; Gescheider, Verrillo, & Pelli, 1991). Enhancement is the decreased threshold for stimuli to be perceived (Verillo, 1985). Several studies have compared a simultaneous target and secondary stimulus which lead to enhancement of the target stimuli (Verrillo & Bolanowski, 1996; Zhang et al., 2009). Verrillo & Bolanowski (1996) found that submersion in water increased the sensitivity of the skin. In addition, Zhang et al. (2009) found that tactile detection was enhanced by non-noxious heat when heat is delivered at a non-noxious intensity with a target stimulus. These studies (Verrillo & Bolanowski, 1996; Zhang et al., 2009) suggest that a stimulus which occurs during the acquisition of tactile information may provide improvement to knowledge transfer. Another study which is in line with these findings is a study by Passmore et al. (2009). Passmore et al. (2009) had participants attempt to recreate the components of Morse code patterns and found that when paresthesia stimulation was present under transfer conditions, performance was significantly better than for the no-stimulation group (Passmore et al., 2009). The results of Passmore et al. (2009) indicated that a secondary stimulus draws increased attentional resources toward discerning the meaningful stimulus. In this study, the paradoxical findings of increased accuracy and decreased reaction time in the intervention condition can be explained by a secondary stimulus (pain) which draws resources towards discerning the meaningful stimulus (typing task).

Limitations:

An important limitation of this study is that there were only ten subjects in each group for the SEP data analysis due to the large number of subjects whose data did not meet the inclusion criteria of a stable peripheral volley, raising the possibility of a type II error. If there had been 12 subjects in each group there may have been a statistically significant increase in the N30 peak following motor learning as Figure 9-5 indicates that the N30 peak has increased post-motor learning. More participants should be recruited in order to determine if this is a type II error.

11 CONCLUSION

This experiment demonstrated a significantly higher N24 SEP peak post motor learning. This observation provides support for the role of the cerebellum in motor learning. There were no significant differences in any of the SEP peaks following the application of capsaicin which is not in line with previous studies which demonstrated that pain affects sensory processing through elevated SEP peaks (Tinazzi et al., 2000; Tinazzi et al., 2004) and functional reorganization (Knecht et al., 1998; Soros et al., 2001). However, this study fills a gap in the research as a growing body of evidence suggests that there are differing effects of experimental pain on cortical excitability (Dettmers et al., 2001; Krause et al., 2006; Gronroos et al. 1993; Farina et al., 2001; Le Pera et al., 2001). This experiment also demonstrated significantly improved reaction time for both conditions. Although not significantly different, there was a trend towards improved accuracy post-motor learning for those in the intervention condition. These paradoxical findings of increased accuracy and decreased reaction time in the intervention condition can be explained by a secondary stimulus (pain) which draws resources towards discerning the meaningful stimulus (typing task). Future studies should use a more complex motor task which would have a lower accuracy pre-motor learning. This would allow for greater improvements between pre and post-motor learning and it would be easier to see the effects of pain on motor learning in terms of accuracy, reaction time, and SEP peaks. There remains a gap in the understanding of how pain affects sensorimotor processing and this would fill a gap in the literature. In addition, a better understanding of the sensorimotor processing of pain will help elucidate the mechanism behind conditions that occur in the absence of a discernible peripheral causal pathology or appear disproportionate to the size of the injury (e.g. dystonia, fibromyalgia).

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Appendices:

13.1 Appendix 1: REB application form – Central sensitization

Research Ethics Board (REB)
Application for Ethical Review of Research Involving Human Participants

Instructions

Note: Do not include this page in your submission to the REB

The Research Ethics Board (REB) is required to refer to the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS) and UOIT Ethics Policy and Procedures when reviewing all requests. You are also encouraged to refer to these documents prior to completion and submission of this application.

The REB meets monthly to review research requests.

There are four main sections to this application. The REB is primarily concerned with a) background information and research rationale, b) the exchange of data between research and participants, c) safeguards in place to protect participant and data and d) investigator information and signatures. This application seeks information from the researcher addressing each of these three areas.

Return **1 COPY** of your completed application and all accompanying material to the Office of Research Services, also send an electronic copy to compliance@uoit.ca. **Handwritten notes on the application form will not be accepted.** Please ensure all necessary items are attached prior to submission, otherwise your application will not be processed (see checklist below). **No research with human participants shall commence prior to receiving approval from the Research Ethics Board.**

Send your complete application and any questions to

REB Administration, Office of Research Services (U5-7)
University of Ontario Institute of Technology • 2000 Simcoe St. N. • Oshawa, ON • L1H 7L7

905-721-8668 ext. 3693 or compliance@uoit.ca

In order for us to direct your application to the appropriate Research Ethics Board, please answer the following questions.

(☐ - may be checked by double-clicking and selecting "Checked" or entering appropriate text)

I am a(n):

☒ Faculty Researcher

☐ Graduate Student Researcher

Is this research for academic credit? ☐ Yes ☐ No

☐ Undergraduate Student Researcher

Is the research for academic credit? ☐ Yes ☐ No

☐ External (to UOIT) Researcher

In the faculty of:

☐ Criminology, Justice and Policy Studies

☐ Business and Information Technology

☐ Science

☐ Engineering and Applied Science

☒ Health Sciences

☐ Energy Systems and Nuclear Science

☐ Education

Undergraduate Student Research

UOIT has established a number of Faculty Research Ethics Boards (FREBs) for the review of course, individual and group thesis projects by undergraduate students in addition to the main UOIT Research Ethics Board (UOIT REB).

The FREBs shall review research projects conducted by undergraduate students when (1) it is conducted as part of an undergraduate course offered and (2) it is not part of a faculty member's research programme already subject to review by the UOIT REB.

The FREBs may refer an application to the UOIT REB. Examples of situations in which referral would be appropriate are research that the FREB thinks may be of more than minimal risk, research involving ethical or legal issues for which it does not have adequate expertise, and in cases for which conflicts of interest reduce its size to less than two members.

Faculty Research

All faculty and external research proposals involving human participants will be reviewed by the UOIT Research Ethics Board.

University of Ontario Institute of Technology Research Ethics Board (REB) Application for Ethical Review of Research Involving Human Participants	**File #**	

	Name	**(e.g., faculty, student, visiting professor, other affiliation)**	**Dept./Address**	**Phone No.**	**E-Mail**
Principal Investigator	Bernadette Murphy	Faculty	Health Sciences	Ext 2778	Bernadette.murphy@uoit.ca
Co-	John	Visiting	Department of Human Health	416-760-	jsrbely@rogers.com

Investigator(s)	Srebly	Professor	and Nutritional Science, University of Guelph	7418	
	Mathew Weisbrod	Visiting Professor, Family Medicine	460 Hume St Collingwood, On L9Y 1W6	705-444-7200	4weisbrod@rogers.com
All co-investigators must be listed. Attach additional investigator information/signature pages to this application.					
Faculty Supervisor(s) (for student PIs)					

Submit the application, all consent materials and instruments to the Office of Research Services (see guide below) **Hard copy: Original + 2 additional copies of the following documents, and** **Electronic: Electronic file of all documents to compliance@uoit.ca**			
Recruitment Materials • Letter of invitation • Verbal script • Telephone script • Advertisements (newspapers, posters) • Email correspondence • Other	☐ ☐ ☐ ☒ ☐	**Letter of Approval/Permission (if applicable)** *(Not letters of support)* • cooperating organizations • school board(s) • hospitals • community agencies • or other institutions (university/college) • other	☐ ☐ ☐ ☐ ☐

	☐		☐
Consent Materials • Consent form • Assent form for minors • Parental/3rd party permission forms • Transcriber confidentiality agreement • Other	☒ ☐ ☐ ☐ ☐	**Plan for Dissemination/Communication of Results to Participants** • Thank you letter • Feedback letter • Workshop • Verbal thank you • Debriefing letter • Other	☐ ☒ ☐ ☒ ☐ ☐
Data Gathering Instruments • Questionnaires • Interview guides • Tests • Other	☐ ☐ ☐ ☐ ☐	**Any previously approved protocol to which you refer**	☐
		Information/ Signatures of all investigators/co-investigators (attach additional signature pages)	☒

Considering the risks involved in the proposed research, you are applying for
Expedited Review ☒ **Full Re**

Please note Expedited Review involves review by 1 REB member and the REB Chair. Expedited review does not mean a rapid review of the application. You will be notified if your application has been sent for Full review. (See UOIT and TCPS policy for more information on risks)

Section A: General Information, Rational and Purpose of Research

A1. Title of the Research Project: CENTRAL SENSITIZATION EVOKES CHANGES IN THE PROPERTIES OF NERVE CONDUCTION

A2. Proposed Date (dd/mm/yyyy)

(a) of commencement:02/07/2010

(b) of completion:30/06/2011

(Note, please allow sufficient time for REB to review request.)

A3. Indicate the location(s) where the research will be conducted.

University of Ontario Institute of Technology	☒
Community Site(s)	☐ Specify
School Board(s)	☐ Specify
Hospital(s)	☐ Specify
Other	☐ Specify

A4. Other Ethics Approval/Permission:

(a) Is this a multi-centered study? (when several university/hospital REBs consider the same proposal from the perspectives of their respective institutions)		☒ **Yes** ☐ **No**
(b) Has any other Canadian University **Research Ethics Board** approved this research?		☐ **Yes** ☒ **No**
	If **NO**, will any other Research Ethics Board be asked for approval? *Specify university/hospital to be approached or explain why approval will not be sought*	☒ **Yes** ☐ **No** **Approval is being sought from the University of Guelph for the SEP aspect of this study**
	If **YES**, please complete Section A of the application only; unless you are accessing the UOIT student base, then you must complete the entire application. Title of the project approved elsewhere: Name of the Other Institution: Name of the Other Board:	

	Date of the Decision: A contact name and phone number for the other Board: Provide a copy of the application from the other institution together with all accompanying materials and a copy of the clearance certificate / approval. Ensure all investigator information and signature pages are attached with your submission.	
(c) Has any other **person(s) or institution(s) granted permission** to conduct this research? *Specify (e.g,. school boards, community organizations, proprietors)*		☐ **Yes** ☒ **No**
	If **NO**, will permission/approval be sought? *Specify Agency/College, Government Agency, NGO etc.*	☐ **Yes** ☒ **No**
	If **YES**, Name of the Other Institution: Date of the Decision: A contact name and phone number for the other Board: Provide a copy of the clearance certificate / approval.	
	(d) Are you signing an external agreement with an institution governing the use of data? ☐ **Yes** ☐ **No** If yes, please submit with your application.	
(e) Has this research application received a peer/scientific review?		☐ **Yes** ☒ **No**

A5. Level of the Research (determined by status of Principal Investigator):

☐ Undergraduate ☐ Masters Thesis/Project ☐ Ph.D.

☐ Post Doctorate ☒ Faculty Research ☐ Administration

☐ Course Assignment (specify) ☐ Other (specify)

A6. Professional Expertise/Qualifications:

a) Does this research require professional/specialized expertise qualifications other than your own? ☐ **Yes** ☒ **No**
If **YES**, specify:

b) Does the researcher (or your supervisor if the Principal Investigator is a student researcher), or any members of your research team have the professional expertise/recognized qualifications required to carry out this research?
☒ **Yes** ☐ **No**

If **YES**, specify: Dr. Murphy has expertise in somatosensory evoked potentials, transcranial magnetic stimulation (TMS) and H-reflexes. Dr. Srebly has been conducting the central sensitization component for the past 4 years.

A7. Funding of the Project:

a) Is this project currently being funded ☐ **Yes** ☒ **No**
b) If **No**, is funding being sought ☐ **Yes** ☒ **No**

If Applicable:

c) Period of Funding (dd/mm/yyyy): From: To:
d) Agency or Sponsor (funded or applied for)

☐ CIHR ☐ NSERC ☐ SSHRC

☐ Other (specify): Project Title:

A8. Conflict of Interest:

Will the researcher(s), members of the research team, and/or their partners or immediate family members:

a) receive any personal benefits related to this study - for example: a financial remuneration, patent and ownership, employment, consultancies, board membership, share ownership, stock options (Do not include details regarding Release Time Stipend, conference and travel expense coverage, possible academic promotion, or other benefits which are integral to the conduct of research generally). ☐ **Yes** ☒ **No**

b) if **Yes**, please describe the benefits below.

c) Describe any restrictions regarding access to or disclosure of information (during or at the end of the study) that the sponsor has placed on the investigator(s).

A9. Rationale:

Describe the purpose and background rationale for the proposed project, as well as the hypothesis(es)/research question(s) to be examined.

The objective of this pilot study is to assess whether evoking central sensitization modulates the electrophysiologic properties of segmentally related evoked potentials. To do this we plan to utilize three main techniques, namely, somatosensory evoked potentials, transcranial magnetic stimulation and surface electromyography with H-reflexes. With these techniques it is possible to non-invasively investigate various aspects of human central neural processing, to identify differences in the way the brain works between patients with chronic neck problems

and those without.

Central sensitization is defined as the hyperexcitability of neurons within the central nervous system. This hyperexcitability is expressed as an increased responsiveness of the neuron to an input stimulus. Persistent pain signals transmitted to the central nervous system will result in neurons within the central nervous system to become sensitized.

The phenomenon of central sensitization is an important consideration in the study of health and disease. Central sensitization has been linked to the pathophysiology of myofascial pain syndrome and functional gastrointestinal disorders (FGID) such as Irritable Bowel Syndrome, gastric motility disorders, however, its precise mechanisms are still unclear. Currently, there is no accurate objective measure for central sensitization. In order to elucidate the role of central sensitization in the pathophysiology of myofascial pain and FGIDs, we require a method to reliably measure and quantify changes in central sensitization.

Evoked Potentials (EPs) are the electrical signals generated by the nervous system in response to sensory stimuli. Auditory, visual, and somatosensory stimuli are used commonly for clinical evoked potential studies. Somatosensory evoked potentials (SEPs) are a series of waves that reflect the sequential activation of nerves along the somatosensory pathways. Abnormal SEPs can result from dysfunction anywhere along this pathway including the peripheral nerve, plexus, spinal root, spinal cord, brain stem, thalamocortical projections, or primary somatosensory cortex. It is, therefore, possible that changes in SEPs may also occur after central sensitization, providing a quantitative experimental measure of functional change in the nervous system.

H-reflexes measure spinal cord excitability and are elicited by stimulating sensory nerves electrically and recording the resultant reflex using electromyography (EMG) recording electrodes.

Motor evoked potentials (MEPs) are elicted via magnetic brain stimulation and measure the excitability of the pathways between the brain and a muscle in the target area of the central sensitization.

A10. Participants: The REB is mandated by the guiding principals of the TCPS. In this section we are primarily concerned with the following two principals: Respect for Vulnerable Populations and Respect for Justice and Inclusiveness. (See TCPS for more information**)** http://www.pre.ethics.gc.ca/english/policystatement/context.cfm#C

a) Is this a vulnerable population? ☐ **Yes** ☒ **No**
b) Are issues of inclusiveness being respected? ☐ **Yes** ☐ **No**
c) Describe the number of participants and any required demographics characteristics (e.g., age, gender).

This is a pilot experimental study requiring 10 to 12 healthy volunteers of both genders aged between 18 and 50.

Section B: Methodology, Data Exchange, Risk Management

B1. Methods: Are any of the following procedures or methods involved in this study? Check **all** that apply**.**

☐Questionnaire (mail)

☐Questionnaire (email/web)

☐Questionnaire (in person)

☐Interview(s) (telephone)

☐Interview(s) (face to face)

☐Participant Journals

☐Audio/video taping

☐Unobtrusive observations

☐Invasive physiological measurements (e.g., venipuncture, muscle biopsies)

☒Non-invasive physical measurement (e.g., exercise, heart rate,

☐Secondary Data

☐Computer-administered tasks

☐Focus Groups

blood pressure)

☐Analysis of human tissue, body fluids, etc.

☐Other: (specify)

B2. Data Exchange Procedures: Describe sequentially, and in detail, all procedures in which the research participants will be involved (e.g., paper and pencil tasks, interviews, questionnaires, physical assessments, physiological tests, time requirements, etc.) ***Remember to attach a copy of all questionnaire(s), interview guides, or other test instruments. Remember also to describe the procedures for all stages of the research (e.g., pre-tests, etc.) where applicable.***

This study will assess the effect of central sensitization on signal transmission in the nervous system of human subjects by comparing changes in somatosensory evoked potentials (SEPs), motor evoked potentials (MEPs) and H-reflexes pre versus post sensitization. Dr. Murphy currently has REB approval (07-073) for both SEP and TMS procedures. The study will be a pre/post experimental design with electrophysiological and self report measures

Qualified subjects will begin by filling out a health survey to identify and exclude any medical condition which may impact normal somatosensation at the fifth cervical (C5) segment, including (but not limited to) recent/acute cervicothoracic injury (whiplash, sports related), neurologic conditions (radiculopathy, neuropathy) or concurrent use of medication.

We will induce sensitization at the C5 spinal segment by employing the heat-capsaicin model previously employed in a University of Guelph REB approved study (REB# 050C011). A specified $50cm^2$ area of the C_5 dermatome ("target region") on the lateral aspect of the right elbow will be marked off and pre-treated with 45-degree heat (moist towelette heated in temperature controlled water bath) for 10 minutes. A thin layer of capsaicin (0.075%) will then be applied to the target region and massaged into the skin until visibly absorbed. The investigator applying the crèmes will wear latex gloves throughout the procedure. Subjects will be cautioned not to touch or scratch the treated area for up to 3 hours.

After the capsaicin is applied, we will evaluate changes in the nervous system using sensory evoked potentials (SEP), MEPs and H-reflexes. A SEP is an electrical potential elicited by either physiological [1] or electrical [2] stimulation of peripheral somatosensory receptors or their axons. These electrical potentials travel along peripheral nerves and ascend the nervous system via the spinal cord; accordingly, they can be recorded at sites along the peripheral nerve and/or its central projections. Typically in human work, potentials are recorded from the surface of the skin using service electrodes. This surface recording technique has the advantage of being non-invasive and is therefore applicable in both clinical and experimental studies involving human subjects[3]. The amplitude of a SEP peak is taken to represent the degree of activity of the neural structures responsible for generating the peak. Alterations to the peak amplitudes are therefore believed to represent alterations in the **amount of activity** of the neural structures, suggesting change in the function of the nerve. The latency of the SEP peak is taken to represent the neural transmission **time** between the point of stimulation and the neural structures responsible for generating the peak. Alterations in the peak latency are also believed to represent alterations in neural transmission [3]; we will be investigating changes in both the amplitude and/or latency of SEP pre versus post capsaicin, as evidence of change in neural function post-sensitization. MEPs measure changes in excitability of the motor cortex (part of the brain which controls movement) and muscle and are elicited by applying TMS over the motor cortex and recording the EMG signal from a target muscle. H-reflexes measure changes in spinal cord excitability. They are elicited by electrically stimulating a nerve and recording from a muscle supplied by that nerves. The entire experiment will take approximately 2 hours.

1. Angel, R.W., C.C. Boylls, and M. Weinrich, *Cerebral evoked potentials and somatosensory perception.* Neurology, 1984. **34**: p. 123-126.

2. Cohen, L. and A. Starr, *Vibration and muscle contraction affect somatosensory evoked potentials.* Neurology, 1985. **35**: p. 691-698.

3. Mauguiere, F., *Somatosensory evoked potentials: normal responses, abnormal waveforms and clinical applications in neurological diseases.*, in *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields.*,

B3. **Recruitment:** Describe how and from what sources the participants will be recruited, including any relationship between the investigator(s), sponsor(s) and participant(s) (e.g., family member, instructor-student; manager-employee). ***Attach a copy of any poster(s), advertisement(s) or letter(s) to be used for recruitment. Remember also to describe the procedures for all stages of the research (e.g., pre-tests, etc.) where applicable.***

We will test 12 subjects (6 males, 6 females) in the pilot of this study. Central sensitization has been linked with age, accordingly, for this trial we will aim to test normal young healthy subjects.

B4. **Compensation:** The REB is concerned with potential feelings of coercion on the part of the participant. Please provide details addressing coercion issues. (For more information see TCPS discussion regarding **compensation** under "Minimal Risk" Section C, Article 1http://www.pre.ethics.gc.ca/english/policystatement/section1.cfm#1C1 and "Voluntariness" Section B. Article 2.2 http://www.pre.ethics.gc.ca/english/policystatement/section2.cfm#2B]

(a) Will participants receive compensation for participation? ☒ **Yes** ☐ **No**

(b) If yes, please provide details.

Participants will be offered their choice of either a $10 gasoline voucher or a $10 TimCard to compensate them for their time.

B5. Possible Risks:

a) Physical risks (including any bodily contact, physical stress, or administration of any substance)? ☒ **Yes** ☐ **No**

b) Psychological risks (including feeling demeaned, embarrassed worried or upset, emotional stress)? ☐ **Yes** ☒ **No**

c) Social risks (including possible loss of status, privacy, and / or reputation)? ☐ **Yes** ☒ **No**

d) Are any possible risks to participants greater than those that the participants might encounter in their everyday life? ☒ **Yes** ☐ **No**

e) Is there any deception involved? ☐ **Yes** ☒ **No**

f) Is there potential for participants to feel coerced into contributing to this

research (e.g., because of regular contact between them and the researcher)? ☐

Yes ☒**No**

B6. **Description of Risks:** If you answered **'yes'** to any of the above, please explain the risk.

Capsaicin is a counterirritant found in chili peppers and several over the counter analgesic (pain relieving) ointments (Rub A535). For this particular study, we will use 0.075% capsaicin sold under the brand Zostrix. Topical application of capsaicin will cause a sensation of itching, prickling or burning as it activates the peripheral pain receptors. Local vasodilation and erythema (skin reddening) are also common; the magnitude of response varies with the dose applied. Systemic events are rare (Reynolds JEF, 1999). No adverse effects were reported using the identical protocol in a previously approved study (University of Guelph REB# 050C011).

Participants may experience some mild discomfort as their skin is prepared for the electrodes by rubbing them with special abrasive tape and then wiping the area with alcohol. The electrodes over the neck, shoulder and scalp are only recording electrodes and do not pierce the skin and do not run current through the body. The stimulating electrodes will be used to stimulate some of the hand and/or forearm muscles by passing mild electrical current through them. This creates a mild tingling sensation on the skin over the nerve. This is not painful but may feel quite strange. It will also make some of the hand and/or forearm muscles twitch which is not painful either, but can also feel strange. The literature indicates that TMS stimulation over the cerebellum can lead to mild transient nausea (Satow, Mima et al. 2002). We have therefore included this as a potential side effect although no one in our previous research has ever experienced this.

B7. Management of Risks: Describe how the risks will be managed (include the availability of appropriate medical or clinical expertise, qualified persons). Give an explanation as to why less risky alternative approaches could not be used. ***Remember also to describe the procedures for all stages of the research (e.g., pre-tests, etc.) where applicable.***

Patients will be asked to fill out a complete health history and systems review to identify risk factors that may be associated with adverse effects. Physical examination will be performed by either a qualified physician (Matthew Weisbrod) or a registered chirorpractor (Dr. Srebly or Dr Murphy) who will also be present during the study to monitor proceedings and provide immediate management in the event of an adverse effect.

The surface electrode techniques have low risks such as the person getting a skin irritation from the alcohol swab or electrode gel, but these again are uncommon and not serious. The electrical stimulation is not painful but participants will experience a light twitch of the muscles in their hand as the nerves at the wrist send electrical signals to make these muscles contract. Any fear or anxiety can be managed by explaining to participants what will be happening and reinforcing their right to stop the experiment at any time.

B8. **Possible Benefits:** Discuss any potential direct benefits to the participants from their involvement in the project. Comment on the (potential) benefits to the scientific community/society that would justify involvement of participants in this study.

There will be no direct benefits to the subjects for participating in this pilot trial. This is an important research thread as it will improve our understanding of how central sensitization affects the electrophysiologic properties of signal transmission in the nervous system and may provide proof of concept for further studies in the quantification of central sensitization. Participants will have the opportunity to gain insight into the mechanisms by which sensitization develops in acute pain situations.

B9. **The Consent Process:** Describe the process that the investigator(s) will be using to obtain informed consent. Include a description of who will be obtaining the informed consent. If there will be no written consent form, explain why not. See samples) ***If applicable, attach a copy of the Letter of Invitation, the Consent Form, the content of any telephone script and any other material that will be utilized in the informed***

consent process. Remember also to describe the procedures for all stages of the research (e.g., pre-tests, etc.) where applicable.

The issue of informed consent will be addressed on the written informational package given to each participant. The participant will be required to read, acknowledge and sign the informed consent portion prior to proceeding with the study. The procedure will also be explained verbally.

B10. Consent by an authorized party: If the **participants are minors or for other reasons are not competent to consent**, describe the proposed alternative source of **assent** (agreement to participant in research from minors), including any **permission form** to be provided to the person(s) providing the alternative consent.

N/A

B11. Alternatives to prior individual consent (e.g. Naturalistic Observation): If obtaining individual participant consent prior to commencement of the research project is not appropriate for this research, please explain and provide details for a proposed alternative consent process.

N/A

B12. Acknowledgement/Feedback to Participants: Explain what feedback/ information will be provided to the participants after participation in the project. Include, for example, appreciation for participation, a more complete description of the research purpose, any results that may be available, and participant access to a final results summary. Also, describe the method and timing for delivering the feedback.

Participants will be asked if they wish to receive feedback once the experiments are complete. For those that do, a lay language summary of the experimental results will be send by either email or surface mail depending on their preference.

B13. Participant withdrawal:

a) Describe how the participants will be informed of their right to withdraw from the project. Outline the procedures that will be followed to allow the participants to exercise this right. ***Remember also to describe the procedures for all stages of the research (e.g., pre-tests, etc.) where applicable.***

The participants will be informed that they can withdraw from the study at any point without reason. They will be assured that there will be no consequence of such withdrawal.

b) Indicate what will be done with the participant's data and any consequences that withdrawal might have on the participant, including any effect that withdrawal may have on participant compensation.

Their data will be withdrawn from the study. The written questionnaire will be shredded and relevant datafiles deleted from the database. If participants withdraw before commencing the study they will not be compensated but anyone who withdraws part way through the

experiment will still be compensated.

Section C) Safeguards in place to protect participant and data

Confidentiality: information revealed by participants that holds the expectation of privacy (this means that all data collected will not be shared with anyone except the researchers listed on this application).

Anonymity: information revealed by participants will not have any distinctive character or recognition factor, such that information can be matched to individual participants (any information collected using audio-taping or video recording cannot be considered anonymous).

Remember also to describe the procedures for all stages of the research (e.g., pre-tests, etc.) where applicable.

C1. Given the definitions above:

Confidentiality	
a) Will the data be treated as confidential?	☒ **Yes** ☐ **No**
b) Describe the procedures to be used to ensure the confidentiality of data both during the conduct of the research and in the release of its findings. Confidentiality will be secured by the use of ID codes throughout the process and on all documentation/correspondence.	

c) If participant confidentiality is not appropriate to this research project, explain, providing details, how all participants will be advised that data will not be confidential.

Anonymity

d) Are the data anonymous? (see below)	☐ **Yes** ☒ **No**

e) Describe the procedures to be used to ensure anonymity of participants in the release of its findings.

The data will be anonymous in any published work, but it is essential for the researchers to be able to match the data to each individual.

f) If participant anonymity is not appropriate to this research project, explain, providing details, how all participants will be advised that data will not be anonymous.

The data is anonymous with respect to everyone except the researchers.

C2. State who will have access to the data.

The researchers and students working in the lab including summer students or any graduate students assigned to the project. Currently this may include Jessica Bosse, Julian Daligadu, and Erin Dancey.

C3. Explain how written records, video/audio tapes, and questionnaires will be secured, and provide details of their final disposal or storage (including for how long they will be secured and the disposal method to be used). ***Remember also to describe the procedures for all stages of the research (e.g., pre-tests, etc.) where applicable.***

- ☑ I plan to keep raw data and aggregate data indefinitely, without identifiers.
- ☐ I plan to keep raw data and aggregate data indefinitely, with identifiers. Describe the storage method.

☐ I plan to keep raw data and aggregate data, with identifiers for the time period of (please specify date, where you are storing the data and why you are keeping the identifying data):

☐ I plan to destroy and/or dispose of the data. Please describe how and when it will be destroyed (remember this should be communicated to participants during the consent process).

C4. SECONDARY USE OF DATA

(a) I understand that if I use the data for purposes other than described in this application that consent must be sought from participants.
☒ **I agree to this statement.**

(b) If there are no plans to use the data with identifiers for secondary purposes and yet, you wish to keep the data indefinitely, please ***briefly*** explain why.

Consent will be sought on the participant information form to use the data anonymously for future research as appropriate.

C5. Study Completion and Annual Report/Continuing Review Form: For the purposes of monitoring ongoing research,

the REB requires the completion of the "Study Completion Report/Form" form at the completion of the research and an "Annual Report/Continuing Review Form" at least annually.

a) Identify approximate dates when the REB should expect to receive reports on the progress or final report on the research.
b) Indicate whether any additional monitoring or review would be appropriate for this project. (Consider risks of research)

The REB will receive annual progress reports>

Section D: Signature pages

SIGNATURES : All investigators (Principal and Co-investigators) are required to sign the ethics application. (Fax signatures are acceptable for our records.) Student researchers are required to obtain approval and signature from his/her faculty supervisor.

Please indicate that you have read and fully understand all ethics obligations by checking the box beside each statement. Failure to submit the signatures may result in a delay in processing your request for ethics approval.

Name of Principal Investigator:	**(e.g., faculty, student, visiting professor, other affiliation)**	**Dept./Address**	**Phone No.**	**E-Mail**
Bernadette Murphy	Faculty	Faculty of Health Sciences	Ext 2778	Bernadette.murphy@uoit.ca

☒	I have read the University of Ontario Institute of Technology Research Ethics Policy and Procedures and agree to comply with the policies and procedures outlined therein.
☒	I will report any **Adverse/Unanticipated Events** (unanticipated negative consequences or results affecting participants) to REB Administration and the REB Chair, **as soon as possible** and in any event, no more than 3 days subsequent to their occurrence to the Research Ethics Board (REB).
☒	Any additions or changes in research procedures after approval has been granted will be submitted to the REB.
☒	I agree to complete an Annual Report/Continuing Review and a Change Request form for any project continuing beyond the expected date of completion or for more than one year.
☒	I will submit a final report to the Office of Research Services once the research has been completed.
☒	I take full responsibility in ensuring that all other investigators involved in this research follow the protocol as outlined in the application.

Signature _____ Date: _____

All co-investigators must be listed and signatures obtained.

Attach additional investigator information/signature **pages** to this application (found at Forms | Research)

Name of **Co-Investigator(s)**	(e.g., faculty, student, visiting professor, other affiliation)	Dept./Address	Phone No.	E-Mail
John Srebly	Visiting Professor	Department of Human Health and Nutritional Science, University of Guelph	416-760-7418	jsrbely@rogers.com

☐	I have read the University of Ontario Institute of Technology Research Ethics Policy and Procedures and agree to comply with the policies and procedures outlined therein.
☐	I will report any **Adverse/Unanticipated Events** (unanticipated negative consequences or results affecting participants) to REB Administration and the REB Chair, **as soon as possible** and in any event, no more than 3 days subsequent to their occurrence to the Research Ethics Board (REB).
☐	Any additions or changes in research procedures after approval has been granted will be submitted to the REB.
☐	I agree to complete an Annual Report/Continuing Review form or a Change Request form for any project continuing beyond the expected date of completion or for more than one year.

☐	I will submit a final report to the Office of Research Services once the research has been completed.
☐	I take full responsibility in ensuring that all other investigators involved in this research follow the protocol as outlined in the application.

Signature _____ Date: _____

Name of **Co-Investigator(s)**	(e.g., faculty, student, visiting professor, other affiliation)	Dept./Address	Phone No.	E-Mail
Mathew Weisbrod	Visiting Professor			

☐	I have read the University of Ontario Institute of Technology Research Ethics Policy and Procedures and agree to comply with the policies and procedures outlined therein.
☐	I will report any **Adverse/Unanticipated Events** (unanticipated negative consequences or results affecting participants) to REB Administration and the REB Chair, **as soon as possible** and in any event, no more than 3 days subsequent to their occurrence to the Research Ethics Board (REB).
☐	Any additions or changes in research procedures after approval has been granted will be submitted to the REB.
☐	I agree to complete an Annual Report/Continuing Review form or a Change Request form for any project continuing beyond the expected date of completion or for more than one year.
☐	I will submit a final report to the Office of Research Services once the research has been completed.
☐	I take full responsibility in ensuring that all other investigators involved in this research follow the protocol as outlined in the application.

Signature _____ Date: _____

Name of Faculty Supervisor(s) *(for student PIs only)*	(e.g., faculty, student, visiting professor, other affiliation)	Dept./Address	Phone No.	E-Mail

☐	I agree to provide the proper surveillance of this study to ensure that the rights and welfare of all human participants are protected.
☐	I will ensure an Annual Report/Continuing Review form or a Change request form for any project continuing beyond the expected date of completion or for more than one year is completed.
☐	I have read and approved the application and proposal.

Signature _____ Date: _____

13.2 Appendix 2: UOIT consent form – Central sensitization

Professor Bernadette Murphy

University of Ontario Institute of Technology

Faculty of Health Sciences

2000 Simcoe St. North

Oshawa, Ontario

CANADA L0B 1J0

Email: Bernadette.Murphy@uoit.ca

Phone: (905) 721-8668 Fax: (905) 721-3179

Effect of neck pain on evoked potentials

Purpose of the Study

The physiologic mechanisms of pain are poorly understood. Central sensitization in an important, if not fundamental, mechanism in expression of pain yet there is currently no objective measure of central sensitization. Central sensitization is defined as an 'increased excitability' of nerves in the central nervous system. The purpose of this study is to investigate the effect of central sensitization on the characteristics of nerve conduction in humans. Specifically, we are interested in finding out what, if any, changes occur to the properties of nerve impulses after sensitization and if there is a difference in this process between people with and without neck pain. This is important as it may provide insight into novel methods of quantifying sensitization. We are also interested in understanding if sensitization affects motor performance, that is, the way your muscles perform when learning a novel task. You are invited to participate in this study being conducted by Dr John Srbely (Department of Human Health and Nutritional Science, University of Guelph) and Dr Bernadette Murphy (Faculty of Health Sciences, University of Ontario Institute of Technology). It has received Ethical Approval from the University of Ontario Institute of Technology (REB# 11-067).

Procedure

Prior to the commencement of the study, you will be required complete a general heath questionnaire which gives us a profile of your current health status and how this may affect your results. You may fill this form out at home prior to arriving for the study. You will also be required to undergo a brief physical examination by one of the presiding clinicians to ensure that you are eligible to participate in this study. This exam will involve standard orthopaedic and neurologic testing to ensure that you do not have any conditions which may affect the way you process sensations on the skin. The study will require approximately two hours of your time.

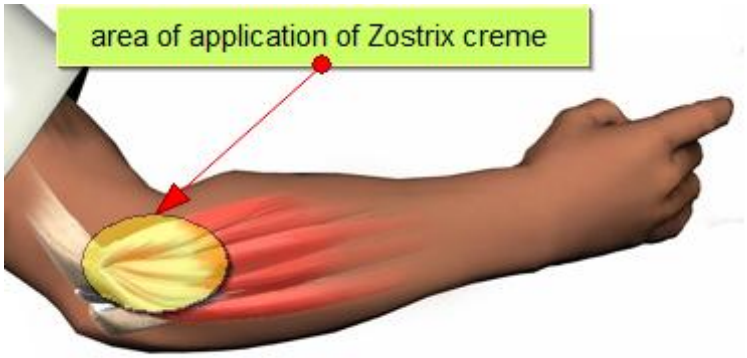
We will require access to your arm, shoulder, upper back and neck regions; please wear appropriate clothing that allows for exposure of these areas. In the event you do not have such clothing, you will be provided appropriate gowns for this study. In addition, you will have complete and sole privacy in the Human Neurophysiology lab for the duration of this study.

You will be seated in a comfortable reclining chair for the recording of the nerve impulses. There are three different types of nerve impulses which we wish to test. You may choose to participate in **one, two or three of the measurement types.**

They are: **1) Somatosensory evoked potentials, (SSEP)**. Surface electrodes will be placed on your skin at selected points along your arm, spine and scalp; these electrodes are sticky electrodes that affix directly to your skin. We will then apply a small electrical pulse to the electrode in the arm, and measure this pulse at the other electrodes along the arm, spine and scalp. The pulse will be very mild and may feel like a brief pin prick or irritation. These will be your 'baseline' readings. A typical SSEP experimental setup is illustrated above.

2) **Transcranial Magnetic Stimulation (TMS)** During the evaluation session we will collect some information about the way your brain is processing information from your upper limb, and how it is controlling hand and forearm muscles. To do this it will be necessary to place some electrodes on your skin over these hand, and forearm, muscles to record the signals from your brain to these muscles. You may experience some mild discomfort as your skin is prepared for the electrodes by rubbing them with special abrasive tape and then wiping the area with alcohol. It is important to note that these are recording electrodes only and do not pierce the skin and do not run current through your body. The stimulation will only be over your scalp. Occasionally, some people experience mild, transient nausea or scalp discomfort, due to the activation of the scalp muscles by the stimulator. If you feel uncomfortable at any time during the experiment, please notify the experimenter. Each evaluation session will take approximately 2-3 hours and you will be given feedback about your results at each session.

3) **H-reflexes:** An H-reflex is similar to the tendon reflex except that it is elicited by electrically stimulating your nerve rather than tapping your tendons. The same electrical stimulator used for SSEP recordings will be used to stimulate the median nerve on the front of your elbow area in order to elicit a reflex in the flexor carpi radialis muscles which flexes your wrist. We will place recording electrodes over your flexor carpi radialis muscle which will record the muscle contraction evoked when we stimulate the nerve to this muscle at the front of your elbow. You may experience some mild discomfort as your skin is prepared for the stimulating and recording electrodes by rubbing them with special abrasive tape and then wiping the area with alcohol.



After recording the baseline readings for each type of experiments, you will randomly be assigned to have one of two types of topical cream to a specific area of your elbow. This cream will either be a moisturizing cream or Zostrix, an over-the-counter cream commonly used for reducing muscle and joint pain. The active component of this cream is a substance called capsaicin, which is derived naturally from chilli peppers and acts to mildly irritate the pain receptors in the skin. The irritation of pain receptors results in central sensitization and this process will not harm you in any way. SEP recordings will be taken again at 15 and 30 minutes after the application of the Zostrix cream.

The investigator applying the capsaicin cream will wear gloves at all times. After the application of the cream, please do not touch or scratch the treated area for 3 hours to avoid getting the capsaicin on your hands and potentially transferring it to other parts of your body. Capsaicin is mildly irritating to the skin, especially sensitive areas such as mucous membranes, mouth, eyes and groin. Please ensure you wash your hands vigorously with warm soapy water after the study is complete.

Typing task intervention

Some experiments will include a typing task which will take place after the cream has been applied. The intervention will consist of a repetitive typing task where you will be required to press keys on an external numeric keyboard with your middle three fingers for a period of 20 minutes. There will be sequences of three numbers arranged in random order e.g. 997878; 797889, etc that come up on a computer monitor

and you will be asked to reproduce them with the numeric key pad. We will be monitoring the typing rate and number of errors to determine the effects of capsaicin on the your ability to type these sequences.

Potential Risks and Discomforts

It is important to disclose any/all potential risks associated with this research study prior to participation. You may experience some local effects in the areas treated with the lotion. Specific symptoms may include a mild to moderate tingling and/or warmth sensation. The tingling will subside within 2 hours of application but may be mildly rekindled if warmed (eg. warm baths) within the first 24 hours after treatment at the site of treatment. You may also experience redness in the areas where the topical lotion was applied which corresponds to increased local blood flow. These symptoms can be effectively minimized or eliminated by icing the treated area(s) with a 10 min of icing (ON) followed by 10 min OFF pattern, as required symptomatically.

You may also feel some mild discomfort as your skin is being prepared for SSEP, TMS or H-reflex recordings. This will involve mild debridement (scraping) of the skin to remove debris and dead cells. The stimulating electrode on the arm will be used to stimulate some of the hand and arm muscles by passing a mild current through them. You will likely feel a mild tingling sensation on the skin over the nerve. While it is not painful or harmful, you may feel some of the hand and/or forearm muscles twitch mildly. This will not be painful nor is there any risk of harm or damage to the nerve and/or muscle, due to the very mild intensity of the stimulus.

Potential Benefits to Participants and/or to Society

While there are no direct benefit to subjects, this study will provide us with valuable information on the effects of sensitization in the nervous system. You will be provided with a summary of findings at the end of the study, if you so desire. Please advise us of your preferable format for communication (check one and provide details in the space provided):

☐ email_____

☐ fax_____

☐ written _____

Compensation for Participation

You will be offered your choice of $10 gasoline voucher or a Tim card to thank you for your participation in this experiment.

Confidentiality

Every effort will be made to ensure confidentiality of personal information that is obtained in connection with this study. Confidentiality will be secured by the use of participant ID Codes on all correspondence. Data will be kept indefinitely on a password-protected computer in the researcher's laboratory and all written material secured in a locked cabinet on site for a period of seven years, after which it will be shredded.

Participation and Withdrawal

You may choose whether to be involved with this study or not. If you volunteer, you may withdraw at any time without consequence. You may exercise the option of removing your data from the study up to and including the point where it is anonymously coded and can no longer be identified. You may also refuse to answer any questions you don't want to answer and still remain in the study. The investigator may withdraw you from this research if circumstances arise that warrant doing so.

Rights of Research Participants

You may withdraw your consent at any time and discontinue participation without penalty. This study has been reviewed and received ethics clearance through the University of Ontario Institute of Technology Research Ethics Board REB 11-067.

Any questions regarding your rights as a participant, complaints or adverse events may be addressed to Research Ethics Board through the Compliance Officer compliance@uoit.ca (905 721 8668 ext 3693).

Thank you very much for your time and help in making this study possible. If you have any queries, concerns about side effects or you wish to know more please contact Dr Bernadette Murphy, an Associate Professor at the University of Ontario Institute of Technology, Faculty of Health Sciences, 2000 Simcoe St North, Oshawa, Ontario, L1H 7K4 Phone (905) 721-8668 ext 2778 or email : Bernadette.Murphy@uoit.ca or Dr John Srbely (at 416-760-7418).

Please read the following before signing the consent form and remember to keep a copy for your own records.

- I understand that taking part in this study is voluntary (my choice) and that I am free to withdraw from the study at any time without giving a reason. If I am a student, I understand that this will in no way affect my academic progress, irrespective of whether or not payment is involved.
- I have read and I understand the consent form for volunteers taking part in the study designed to investigate central sensitization. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.
- I will be attending **at least one session** where measurements will be taken of the electrical activity in my nervous system before and after the application of cream, which may be either capsaicin or control cream.
- I understand that by signing this consent form I am not waiving any legal rights.
- I have completed an eligibility checklist to ensure I am eligible to participant in this research.
- I understand that I can withdraw any data I supply up to and including the completion of my last measurement session.
- I understand that my participation in this study is confidential to the researchers and that no material which could identify me will be used in any reports on this study.
- I have had time to consider whether to take part.
- I know who to contact if I have any side effects to the study.
- I know who to contact if I have any questions about the study.

I give consent for the data from this study to be used in future research as long as there is no way that I can be identified in this research. ☐ YES ☐ NO

(tick one)

I would like to receive a short report about the outcomes of this study (tick one) ☐ YES ☐ NO

_____ __ _____

(Name of Participant) (Date)

_____ _____

(Signature of Participant)/ (Signature of Researcher)

13.3 Appendix 3: Confidential health history form

UOIT
CHALLENGE INNOVATE CONNECT

UNIVERSITY of GUELPH
COLLEGE OF BIOLOGICAL SCIENCE
Department of Human Health and Nutritional Sciences

RESEARCH STUDY CONFIDENTIAL HEALTH HISTORY

Subject CODE: _____

How old are you?

You are: Male □ Female □

Do you suffer from any joint or muscle pain? Yes □ no □

How long have you had the above pain?

Is your pain getting: better □ worse □

Was this pain a result of an accident, fall or injury? Yes □ no □

Does the pain wake you at night? Yes □ no □

Do you experience pain/discomfort in morning? Yes □ no □

What does the pain feel like? Burning □ numb/tingling □ deep/achy □ sharp/stabbing □

What seems to help your pain? Physiotherapy □ chiropractic □ massage □ acupuncture □ medication □ rest □ exercise □ Other:_____

Do you have any allergies to topical ointments? Yes □ no □

Are you allergic to deep heat crèmes? Yes □ no □

Are you allergic to capsaicin (active ingredient in some deep heat crèmes and chili peppers)?

Yes □ no □

Do you have a history of:

-Use of anticoagulant medication or therapy yes □ no □

-Stroke or transient ischemic attacks yes □ no □

-Serious cervical spine trauma/fracture/dislocation yes □ no □

-Whiplash within the last year yes □ no □

-Cervical spine surgery yes □ no □

-Clinically important hypertension yes □ no □

-Connective tissue disorders yes □ no □

-Focal neurological symptoms such as:

Dizziness/vertigo yes □ no □

Tinnitus (rining in ears) yes □ no □

Blurred vision yes □ no □

Sensory/motor disturbance yes □ no □

13.4 Appendix 4 –Tables

	Intervention: Placebo					Intervention: Intervention			
Subject	**INITIALS**	**AGE**	**GENDER**	**HANDEDNESS**	**Subject**	**INITIALS**	**AGE**	**GENDER**	**HANDEDNESS**
3*	SS	23	F	R	1*	JP	25	M	R
4*	KP	26	F	R	4*	EW	23	M	R
8*	PM	20	M	R	5*	NN	21	M	R
11*	CS	34	F	R	6*	* NS	22	M	R
14*	DM	21	F	R	7*	*MM	22	M	R
15*	EJ	19	F	R	8*	*HB	21	M	R
17*	JW	34	F	R	9*	*PB	20	M	R
18*	VL	18	F	R	13*	*BL	20	F	R
19*	MO	18	M	R	15*	*MB	41	M	R
21*	LC	32	F	R	16*	*NU	19	M	R
Average:		24.5			Average		23.4		

Table 9-1: Study participant age, gender, and handedness details.

Participant #	VAS Pre Intervention	VAS Post Intervention	VAS Post Intervention/Post Motor Learning	VAS Post Intervention/Post Motor Learning (45 mins)
1*	0	5	7.5	6
4*	0	4	3	0
5*	0	4	3	1
6*	0	4	4	0
7*	0	6	8	3
8*	0	5	6	3
9*	0	7	2	1
13*	0	8	3	3
15*	0	4	4	0
16*	0	4	1	1
Average:	**0**	**5.10**	**4.15**	**1.80**

Table 9-2: VAS ratings of subjects in the experimental condition. The average VAS rating pre-intervention was 0, post-intervention was 5.10, post-motor learning was 4.15, and post-motor learning (45 minute mark) was 1.8.

Participant #	Allodynia Pre Intervention (cm)		Allodynia Post Intervention(cm)		Allodynia Post Intervention/Post Motor Learning(cm)		Allodynia Post Intervention/Post Motor Learning (cm)(45 mins)	
	Upper	Lower	Upper	Lower	Upper	Lower	Upper	Lower

1*	0	0	4	3.4	4	3.6	4	3.2
4*	0	0	4.2	3.8	3.1	3.3	0	0
5*	0	0	2	1.8	1	1.2	0	0
6*	0	0	1.9	1.6	1.2	1.3	0	0
7*	0	0	1.9	1.8	7.1	6.9	4.2	3.2
8*	0	0	4.1	3.2	3.1	4.2	3.1	4.2
9*	0	0	4.6	2.1	1.9	1.6	0	0
13*	0	0	2.1	1.1	3.1	1.8	5.2	1.8
15*	0	0	1.2	1.3	2.1	1.7	0.8	1.7
16*	0	0	1.1	1.3	0.9	1.2	0.6	1
Average:	0.0	0.0	2.7	2.1	2.8	2.7	1.8	1.5
Total Average:	**0**		**4.8**		**4.9**		**3.3**	

Table 9-3: Allodynia results for subjects in the intervention condition. Pre-intervention the total average allodynia was 0 cm. Post-intervention, the total average allodynia was 4.8 cm. Post-intervention/post-motor learning the total average allodynia was 4.9 cm. At the 45 minute mark, the total average allodynia was 3.3 cm.

	Accuracy						MEAN ACCURACY	Reaction Time						MEAN REACTION TIME
Trial	1	2	3	4	5	6		1	2	3	4	5	6	
1	1	1	1	1	1	1		1229	163	140	399	126	169	
2	1	1	1	1	1	1		665	189	166	231	445	227	
3	1	1	1	1	1	1		761	179	171	188	252	153	
4	1	1	1	1	1	1		706	221	156	173	150	151	
5	0	1	1	1	1	1		704	1579	268	425	151	81	
6	1	1	1	1	1	1		661	186	170	219	177	186	
7	1	1	1	1	1	1		189	357	190	673	222	197	
8	1	1	1	1	1	1		493	185	393	201	145	139	
9	1	1	1	1	1	1		820	147	181	165	126	105	
10	1	1	1	1	1	1		779	212	211	331	189	125	
11	1	1	1	1	1	1		655	165	109	241	87	59	
12	1	1	1	1	1	0		792	184	176	217	399	135	
13	1	1	1	1	1	1		680	157	166	167	135	121	
14	1	1	1	1	1	1		612	435	209	320	171	140	
15	1	1	1	1	1	1		685	177	162	187	179	156	
MEAN	0.933	1	1	1	1	0.933	**0.978**	695.4	302.4	191.2	275.8	196.9	142.9	**300.778**
STDV	0.258	0	0	0	0	0.258		212	361.9	66.15	137.8	100.2	43.15	

Table 9-4: A single subject's data depicting how the mean accuracy and mean reaction time post-motor learning was obtained. For this subject, the average accuracy post-motor learning was 0.978, and the average reaction time post-motor learning was 300.78 ms.

	Accuracy	
Subject	Pre	Post
SS	1.000	0.944
KP	1.000	1.000
PM	0.911	0.978
CS	1.000	0.978
DM	0.989	0.944
EJ	0.989	0.978
JW	0.978	0.944
VL	0.933	1.000
LC	1.000	0.933
SF	1.000	0.944
VF	0.989	1.000
RM	0.978	0.989
GW	1.000	0.978
JB	0.989	0.922
CD	1.000	1.000
Mean	0.984	0.969

Table 9-5: Average subject accuracy data for individuals in the placebo group. The average accuracy declines post-motor learning.

	Reaction Time	
Subject	Pre	Post
SS	476.71	361.77
KP	710.18	531.54
PM	431.76	487.83
CS	391.42	352.82
DM	569.58	413.04
EJ	522.46	413.17
JW	687.71	541.22
VL	487.21	451.00
LC	605.73	611.54
SF	531.76	447.34
VF	642.68	454.34
RM	567.97	573.04

GW	474.73	404.94
JB	469.57	328.12
CD	633.97	407.92
Mean	546.89	451.98

Table 9-6: Average subject reaction time data for individuals in the placebo condition. The average reaction time declines post-motor learning.

	Accuracy	
Subject	Pre	Post
JP	0.958	0.978
EW	0.911	1.000
NS	0.978	0.989
MM	1.000	1.000
HB	1.000	1.000
PB	0.878	0.978
BL	0.900	0.956
MB	1.000	1.000
NU	1.000	0.956
NE	1.000	1.000
MF	1.000	1.000
DH	1.000	0.989
DM	0.967	0.989
PS	0.989	0.900
RG	0.956	0.989
Mean	0.969	0.981

Table 9-7: Average subject accuracy data for individuals in the intervention group. The average accuracy increases post motor learning.

	Reaction Time	
Subject	Pre	Post
JP	349.21	300.78
EW	571.77	415.49
NS	292.64	275.92
MM	449.10	292.44
HB	424.80	310.17
PB	737.06	527.19
BL	656.78	487.00
MB	549.73	433.79
NU	488.81	354.60
NE	484.03	385.98

MF	446.43	367.69
DH	427.13	362.38
DM	436.48	356.14
PS	604.00	363.57
RG	617.37	466.57
Mean	502.36	379.98

Table 9-8: Average subject reaction time data for individuals in the intervention group. The average reaction time decreases post motor learning.