Measuring the effects of subclinical neck pain on sensorimotor integration using Electroencephalography event related potentials and Source Localization

by

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A Thesis Submitted in Partial Fulfillment of the Requirements of the Degree of

Masters of Health Sciences

in

The Faculty of Health Sciences Graduate Study Program

University of Ontario Institute of Technology

November 2017

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Abstract

Subclinical neck pain (SCNP) is recurrent neck pain that has not yet been treated. This thesis investigated whether acute pain affects motor learning acquisition in SCNP vs. healthy individuals. 10 healthy and 10 SCNP participants underwent stimulation of the right median nerve to generate evoked potentials before and after the application of capsaicin cream to elicit pain followed by motor learning acquisition of a tracing task. Both groups improved in accuracy following motor learning ($p<0.001$), with greater improvement in the healthy group during retention ($p<0.001$). Source localization revealed a medial dipole shift of the maximal brain source activity post motor learning in both groups, with greater medial shift in the SCNP group. This shift corresponds to the sensorimotor cortex, and lateral premotor cortex, with the SCNP group also showing potential contribution from the mesial premotor cortex, indicating altered neural responses to pain, and possible compensatory mechanisms to improve sensorimotor integration in an SCNP population.

Statement of Originality

I hereby declare that this thesis, to the best of my knowledge, is my own original work unless otherwise stated, and this material has not been previously submitted for a degree to this or any other institution.

Acknowledgements

I would like to give a special thanks to my supervisor Dr. Carolyn McGregor who has provided me with the utmost support in this thesis. This opportunity has allowed me to learn so much, and I am very grateful for this.

To Dr. Bernadette Murphy, Thank you for your guidance and support through the experimental procedure and ensuring that I followed the correct methodology. Your input has allowed me to appreciate the complexity of research design.

To Dr. Paul Yielder, your input and your feedback on the thesis, especially in methodology has helped me learn a lot and has provided with an insight into the amount of care needed when writing.

To Erin Dancey, Thank you for helping me with the analysis of the data in a timely manner when I needed help as well as providing feedback on it to ensure it was correct.

To Alexander Arteaga and William Cuthbert, Thank you for your quick response and meetings to help me understand concepts regarding EEG as well as providing feedback to ensure that I completely understood the EEG software.

To Bassim Farid, Thank you for believing in me and providing support when I needed it. You have been a great help since the beginning of our friendship.

To my family and friends, Thank you for providing me with support and encouragement to ensure that I completed my degree. It has been a long journey and the support has been gratifying.

Figures

Tables

Abbreviations

ACC: Anterior cingulate cortex

aMCC: Anterior mid-cingulate cortex

APB: Abductor pollicis brevis

CNS: Central nervous system

DCC: Dorsal column system

EEG: Electroencephalography

ERPs: Event related potentials

fMRI: functional Magnetic Resonance Imaging

LORETA: Low Resolution Brain Electromagnetic Tomography

LPMC: Lateral premotor cortex

MI: Primary motor cortex

MEG: Magnetoencephalography

MPMC: Mesial premotor cortex

PMC: Premotor cortex

PMd: Dorsal premotor cortex

PMv: Ventral premotor cortex

PNS: Peripheral nervous system

Pre-SMA: Pre-supplmementary motor area

SI: Primary somatosensory cortex

SII: Secondary somatosensory cortex

SCNP: Subclinical neck pain

SEPs: Somatosensory Evoked Potentials

sLORETA: standardized Low Resolution Brain Electromagnetic Tomography

SMA proper: Supplementary motor area proper

SMC: Sensorimotor cortex

SMI: Sensorimotor integration

STT: Spinothalamic tract

swLORETA: standardized weighted Low Resolution Brain Electromagnetic Tomography

VCA: Ventral anterior commissure

1. Introduction

The organization of the neocortex with its composition of billions of neurons helps determine the functional capabilities of the human body with respect to movement, proprioception and coordination. Specifically, cortical neuroplasticity defines change in the neurons that include their reorganization, connections and differential synaptical activity (Calford, 2002). Motor learning is the process of acquiring and performing movements without effort, which is associated with neuroplastic changes that alter its output based on repetition and these changes are also evident with acute and chronic pain (Flor et al., 1997; Kofler et al., 1998; Le Pera et al., 2001). Motor learning acquisition tends to improve cortical neuroplasticity which then leads to improved motor performance, whereas the presence of pain during motor acquisition may lead to a decrease (Boudreau et al., 2007) or an increase (Dancey et al., 2016) in motor performance.

Motor learning creates changes in motor control that primarily requires sensorimotor integration (SMI) and is defined as the processing of somatosensory information and its integration with the motor output from the primary motor cortex (MI) to improve motor task performance. Decreased motor learning can be caused by pain which may affect motor control which in turn can negatively impact the adaptive neuroplasticity associated with motor output leading to a potential decrease in motor skill acquisition (Flor et al., 2003; Schweinhardt, Lee, & Tracey, 2006). However, previous studies (Lamothe et al., 2014; Bouffard et al., 2014) have shown that acute pain can improve motor learning through the application of cutaneous pain that does not impact the movement being performed and may help to explain why no adverse effect on motor learning was observed. These contradictions in the literature require the need for

research that measures pain and its effect on motor control as the impact of pain whether remote or local, on motor learning may vary according to these factors.

Dancey et al. (2016) found that in the presence of acute pain, enhanced learning occurred when motor skill acquisition was tested after completing a complex motor task and its effects were also present 24-48 hours later when the same task was completed and the motor learning improved during a retention phase indicating that pain does not always have negative effects on motor learning. Performance improvements in the presence of acute cutaneous pain may have been caused by increased attention or arousal (Dancey et al., 2014). A limitation to this study was that acute pain was applied to individuals that had no history of pain or were otherwise healthy. Another limitation was that although the study used cephalic or scalp electrodes to measure the activity in order to assess whether SMI had improved based on a previous approach (Rossi et al., 2003) that only utilized two sites. Therefore, the origin of the areas of the brain contributing to changes in the amplitude of the SEP peaks, which would enable the determination of the areas of the brain contributed to changes in SMI as well as any shifts in the activity produced by the performance of a complex motor learning task could not be determined.

Electroencephalography (EEG) is an imaging tool that detects electrical activity in the neurons of the brain due to an electrochemical gradient that is created due to a stimulus. This modality has been used extensively in multiple fields in order to observe various changes that may be caused by certain physical or psychological conditions (Falconer et al., 2008). The use of EEG to acquire signals is more direct compared to other modalities such as fMRI because it provides real time information and it also provides critical information on parallel activation within the regions of the brain such as feedforward and feedback processes that occur simultaneously (Michel et al., 2004). It creates huge volume of data that requires extensive care

with processing of the data as well as the comprehension and interpretation of the data to be utilized in the future studies. To further localize the activity within the brain, source localization or dipole source localization is used to determine the origin of focal activity. This creates a dipole that represents active patches of neurons that synchronously fire in order estimate the location and orientation of the focal activity as it provides a mathematical description of EEG activity over a certain time interval using a single dipole model (Michel et al., 2004).

EEG has been comprehensively utilized in studying the patterns of the cortical and subcortical activity in chronic pain, where systematic reviews of numerous studies suggest that EEG could be considered a tool for the study of brain mechanisms involved in chronic pain. It could be used to identify differences in processing of information in those with chronic pain conditions, and may potentially be an applicable effective measure in the assessment of changes in therapeutic studies (Pinheiro et al., 2016). For instance, Montoya et al. (2006) investigated brain habituation to repetitive tactile stimuli that demonstrated that early (P50) and middle somatosensory potentials (160-360 milliseconds) were reduced in healthy control in comparison to fibromyalgia patients suggesting the existence of abnormal brain mechanism that inhibits unrelated somatosensory information in those with chronic pain.

Another study by Sitges et al. (2007) investigated the effects of negative mood on neural processing of pain-related descriptors, where visual potentials produced by both pain and pleasant words were recorded. This study found that the chronic pain patients reacted more slowly than healthy participants and pain elicited higher positive potential amplitudes than pleasant words, suggesting an altered contribution of attentional and motivational brain systems in fibromyalgia patients. These studies demonstrate the utilization of EEG in the assessment of associated brain changes in chronic pain population. There have also been studies that have

shown that pain improves motor learning acquisition and its retention even after 24-48 hours after the application of acute pain due to attention to the region of the body undergoing learning (Dancey et al., 2014, 2016). However, EEG has not been utilized to assess central changes, whether SMI or localizing the region of interest via source localization in individuals with neck pain, specifically subclinical neck pain (SCNP).

SCNP refers to recurring neck dysfunction such as neck pain, ache, and/or stiffness with or without a history of any previous neck injury (Haavik-Taylor & Murphy, 2007, 2011). Individuals with SCNP do not suffer from consistent symptoms and they may have sought treatment of their neck complaint. Since it is not consistently present, or the individual may not have another symptoms, it may not be considered as severe as a chronic condition. SCNP individuals that fall into this category may provide an opportunity to explore neurophysiologic dysfunction without the presence of pain. SCNP is known to alter sensory processing and motor control (Rossi et al., 2003). It would also aid in better understanding this group that may help improve subgrouping of neck pain patients as well as provide a marker of altered sensory processing and disordered SMI who need treatment to prevent the progression of neck pain into more long-term pain states (Paulus, & Brumagne, 2008).

Previous research by Haavik-Taylor & Murphy (2007) demonstrated that altered afferent input from SCNP leads to altered SMI that can result in improper motor or efferent response. SCNP can be treated which may improve somatosensory processing as well as proprioception such as elbow joint position sense (Haavik-Taylor & Murphy, 2011) as it can also cause decreased range of motion and endurance (Lee et al., 2004, 2005). Since SCNP negatively impacts SMI and proprioception, it would be critical to further understand central effects of SCNP on SMI and motor learning acquisition as well as with the application of acute pain to

understand if individuals with SCNP respond differently to acute pain in comparison to healthy individuals by utilizing EEG and localizing the source of activity.

1.1 Purpose and Hypothesis

The purpose of this thesis was to understand how acute pain affects motor learning acquisition by demonstrating changes in neural function extending the approach adopted by Dancey et al. (2016) and to determine the effects of pain on motor learning acquisition and SMI similar in SCNP individuals versus healthy individuals. A further goal of the thesis was to identify and source localize the maximal locus of neural activity through the use of EEG to extend our understanding of the potential source in both healthy and SCNP individuals. The induction of pain via application of capsaicin, provides a model to study the effects of acute experimental pain on movement induced plasticity. This thesis therefore extends the previous study by (Dancey et al., 2016) by analyzing the effects of acute pain in SCNP group and establishing a technique to localize the source of neural activity through the use of EEG. It is hypothesized that due to variable results found in the literature associated with pain, individuals with SCNP will have a variable SMI and altered motor learning acquisition in comparison to healthy individuals. The results will further our understanding of the impact of pain on motor learning acquisition sensorimotor processing in individuals with SCNP as well as potential central contributions.

This thesis includes an extensive literature review on foundation neuroanatomy and neurophysiology as well as a descriptive and developmental account of the modalities used relevant to the thesis and health informatics (Chapter 2) with commentary on the practical significance of the research as its applications to rehabilitation and injury prevention strategies (Chapter 3).

2. Literature Review

This literature review starts with background information on the somatosensory system, the premotor cortex, motor control, pain, motor control, capsaicin cream, SEPs, EEG and source localization as well as an overview of the neuroanatomy of neck pain.

2.1 The Somatosensory System

The somatosensory system allows the perception of sensory information such as temperature, pain, touch, pressure, and proprioception from the periphery that includes skin and the muscles through the transmission of information to the cortex (Riemann & Lephart, 2002). The transmission of information occurs via sensory transduction during which the external stimuli is converted into electrical signals, and transmitted through the central nervous system (CNS) (Hoshiyama & Sheean, 1998). The somatosensory system can be divided into two systems that include the dorsal column system (DCCs), and the spinothalamic system (STT) which carry ascending information to the contralateral cortex (Cruccu et al., 2008).

The purpose of the DCC is to transmit sensory information touch, pressure, vibration and proprioception whereas the STT transmits thermoreception (temperature), and nociception (pain) (Cruccu et al., 2008). Both pathways include specialized sensory receptors, afferent axons, and nerve cell bodies. This first neuron is located in the dorsal root ganglia that connects receptors of the limbs, trunk, neck, or posterior head with the spinal cord. For the DCC, the first neuron synapses with the second neuron at the medulla oblongata ascends to the thalamus after crossing the midline (decussation). The STT's first neuron synapses with the second neuron at the level of the spinal cord and decussates. The third neuron ascends from the thalamus into the somatosensory areas in both pathways. These areas include the primary somatosensory cortex

(SI; Figure 1), secondary somatosensory area (SII), posterior parietal cortex, posterior and mid-insula and the mid-cingulate cortex (Cruccu et al., 2008).

The SI is located the postcentral gyrus of the parietal lobe which is subdivided into different areas (Brodmann's area 1, 2, and 3). Brodmann's classification defines the cortical territories of the cerebral cortex based on the structure and organization of cells. Brodmann areas 1, 2, and 3 represent the SI, and area 4 represents the motor cortex (MI) (Cruccu et al., 2008; Zainos et al., 2002). The SI is involved in the processing of somatosensory input the include acuity, detection, and discrimination where specific areas of the SI receive sensory information from different parts of the body with each area containing a topographic representation of the contralateral body with the tongue represented laterally and the feet medially (Sessle et al., 2005). Certain areas of the body such as the hands and face occupy larger regions of the cortex due to their dense innervation (Sessle et al., 2005).

2.2 Motor Cortex

The corticospinal tract consists of two neurons where first neuron descends from the cerebral cortex that synapses with the second motor neuron in the spinal cord which innervates the muscle (Cruccu et al., 2008). The motor cortex (Figure 1) is situated in the precentral gyrus of the frontal lobe and is crucial in SMI, motor control, and motor learning (Sessle et al., 2005). Similar to the SI, the MI contains a topographic representation on the cerebral cortex of the contralateral body with the tongue represented laterally and the feet medially. The MI is composed of various layers with different structures that serve different functions (Kandel, Schwartz, & Jessell, 2000). These layers primarily composed of dendrites, pyramidal cells that allow for collecting motor signals to transmission of information between structures, respectively (Kandel et al., 2000). The human hand can perform diverse functions and research demonstrates

that humans have extensive cortical systems utilized for the control of hand muscles (Nowak et al., 2008; Lemon et al., 1986). The corticospinal tract initiates from the MI, premotor cortex (PMC), supplementary motor area (SMA) as well as cingulate motor areas that play a critical role in controlling movement (Dum & Strick, 2005).

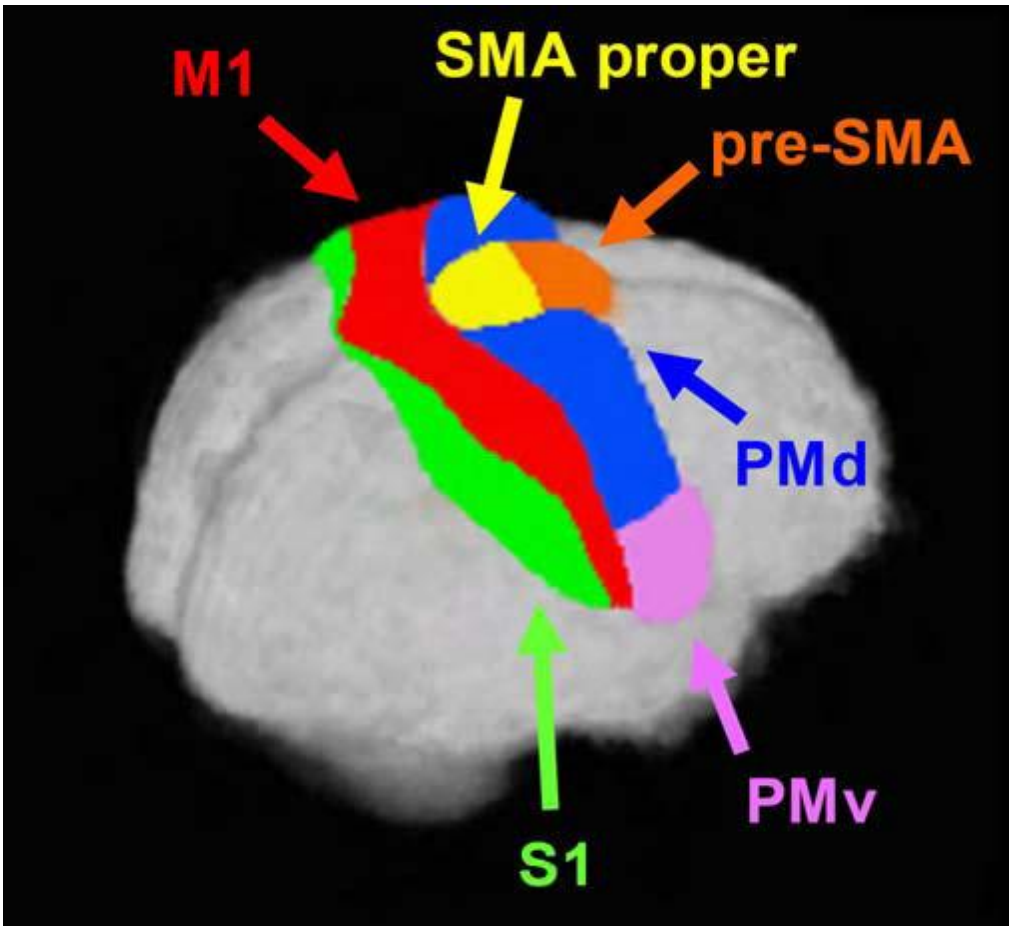


Figure 1. Human Motor Area Template based upon data generated from probability distributions. The regions shown are SMA proper (yellow), pre-SMA (orange), PMd (blue), PMv (magenta), MI (red) and SI (green). (Permission requested from Mayka et al., 2006).

2.3 Premotor Cortex

The cortical premotor cortex (PMC) performs different functions that underlie motor control. These areas can be divided into two main divisions that include the mesial premotor cortex (MPMC), and the lateral premotor cortex (LPMC) (Roland & Zilles, 1996; Rizzolatti,

1998; Luppino & Rizzolatti, 2000). The MPMC is primarily divided rostrally and caudally using the ventral anterior commissure (VCA) line into the pre-supplementary motor area (pre-SMA) and supplementary motor area proper (SMA proper), respectively (Rizzolatti et al., 1998; Picard & Strick, 2001). LPMC can be subdivided along the rostral and caudal plane (PMr and PMc) (Barbas & Pandya, 1987; Matelli et al., 1991), and also along the dorsal and ventral plane (PMd and PMv) (He et al., 1993; Fink et al., 1997). These regions can be seen in Figure 1.

The primary roles of the premotor areas is to provide inputs pertaining to cognitive, sensory or motivation for motor behavior, whereas the motor areas control more tangible aspects of movement (e.g. muscle patterns) (Picard & Strick, 2001). Pre-SMA has been shown to activate during tasks that required visuo-motor association and was highest in the conditional tasks with non-sequential responses with conclusive demonstration that the activation of the pre-SMA had minor effects on motor sequence learning as it contributed more towards establishing or retrieving visou-motor associations (Sakai et al., 1999). Pre-SMA processes and maintains sensory information rather than response selection or production. SMA proper is directly connected to the MI and to the spinal cord (Dum & Strick, 1991; Muakkassa & Strick, 1979) and its activation is due to motor execution.

In the LPMC, the PMd is similar in function to the SMA proper as both areas project into the MI and not greatly associated with the prefrontal cortex (Dum & Strick, 1991; Muakkassa & Strick, 1979). Since the LPMC is also divided into the rostral (anterior) and caudal (posterior) sections, rostral portion of the PMd contributes towards cognitive processing rather than motor processes. It has also been suggested the parietal cells that project into the rostral PMd convey eye movement signals, while parietal cell connections to the caudal PMd convey hand movement signals when studies were conducted on monkeys (Marconi et al., 2001; Battagila-Mayer et al.,

2001). In humans, a constant pattern is developed when MI is activated due to hand movement as there is also activations in the PMC relating to more cognitive types of movements when performance was tested indicating that the PMd is involved in movement preparation or generation, whereas rostral PMd is associated with cognitive processes (Picard & Strick, 2001).

PMv is also densely connected with the MI, however there is a lack of evidence as to the correspondence between the functional subdivisions as well as its exact function (Picard & Strick, 2001). Some studies suggest that the observation of recognizable faces, hand or foot actions result in somatotopically organized activation (Buccino et al., 2001), whereas other studies have shown activation during action observation and silent or covert speech (Grafton et al., 1997; Friedman et al., 1998).

2.4 Pain

Nociception (pain) can be a spinal reflex or a complex response when the cortex is involved due to the perception of pain that involves sensory, affective, motivational, and motor output-control (Tracey & Mantyh, 2007). The complexity of pain perception can also be accountable for variances in the individual's response to that pain based on memories, emotions, genetic, cognitive factors and are subjective that depend on the circumstances (Weich et al., 2008; Dubin & Patapoutian, 2010). Due to such differences and variability in the perception of pain as it is subjective and individual, it is difficult to define and treat clinically (Cruccu et al., 2008). The three types of pain include nociceptive, inflammatory, and neuropathic where nociceptive pain is the processing of brief nociceptive input, prolonged nociceptive input leads to inflammatory pain and neuropathic pain is the result of damage to the somatosensory nervous system. Neuropathic pain may include peripheral neuropathies and central sensitization (Tracey & Mantyh, 2007).

2.4.1 Pain Pathways

The spinothalamic tract (STT) is an ascending pathway for nociception located in the dorsal horn that ascends contralaterally to the posterior thalamus reaching the SI, prefrontal cortex, insula, and the cingulate gyrus (Jones et al., 2003; Mense, 1983). When STT projects to the SI, it is responsible for mediating pain sensation based on ocation, texture, and intensity (Cruccu et al., 2008). Injury to the STT can cause severe pain termed central pain (Kandel et al., 2000). Other pathways such as the spinomesencephalic tract ascends to the amygdala that plays a role in the processing of emotion in the limbic system and affective processing of pain (Almedia, 2004). Tissue damage affects components of the peripheral nervous system (PNS) and the central nervous system (CNS) that lead to an increase in pain sensitivity also referred to as central sensitization (Ji et al., 2003). Central sensitization leads to hyperalgesia (exaggerated response to nociceptive input) that may result in persistent pain reducing threshold and amplifying subsequent input (Latremoliere & Woolf, 2009). This may become pathological as the perception of pain is maintained in the absence of nociception that can be present even after treatment is sought. This leads to chronic pain due to damage to the PNS or CNS and is commonly known as neuropathic pain (Latremoliere & Woolf, 2009). Acute pain is a response to peripheral input and is referred to as nociceptive pain.

Pain also leads to changes in excitability in the somatosensory system and patients with neuropathic pain display higher activity in the neurons of the thalamus, amygdala and the anterio cingulate cortex (ACC) (Neugebauer & Li, 2003; Wei & Zhuo, 2001). Injury tends to alter neural components at subcortical and cortical locations as they may cause rapid changes in peripheral, spinal, and brainstem components (Wall et al., 2002). Due to such alterations, individuals can recognize each sensation as being painful as this network receives multiple inputs from various

nociceptive pathways which is present in EEG, magnetoencephalography (MEG) recordings (Bushnell & Duncan, 1989).

2.4.2 Pain and somatosensory processing

Neuroplastic changes commonly occur in chronic and acute pain with subcortical and cortical changes in excitability in response to pain (Boroojerdi et al., 2001; Maihöfner et al., 2010). Chronic pain leads to cortical reorganization of the somatosensory area that represents the muscle as individuals with lower back pain have shown representational shift of the back muscles in the SI and reduced cortical spinal drive (Flor et al., 1997). Previous study by Tinazzi et al. (2004) on evoked potentials in chronic pain individuals found that amplitudes of certain peaks (N13, P14, N20, and N30 peaks) were significantly larger when stimulating their painful thumb. Meanwhile, other studies found no cortical and subcortical changes in peaks in response to altered input and modulation was observed in chronic pain (Haavik-Taylor & Murphy, 2008, 2010). On the other hand, acute pain has been shown to cause reorganization, specifically in the SI when pain was induced at the hand (Sörös et al., 2001). Dancey et al. (2014, 2016) also assessed acute pain in healthy individuals where significant changes were not seen the evoked potentials, however the N30 peak was significantly increased following motor learning acquisition.

These studies show that cortical organization occurs following acute pain with Dancey et al. (2014, 2016) demonstrating significant increase in evoked potentials, while Tinazzi et al. (2004) found significant differences in evoked potentials in chronic pain individuals, a gap in the literature exists in terms of measuring evoked potentials in individuals with SCNP as well as the source of the activity which this thesis will seek to address.

2.4.3 Pain and the motor system

It is well established that individuals have reorganization of the cortex for muscles affected by pain such as with lower back pain that have an altered representation of the back muscles in the SI and reduced cortical spinal drive (Strutton et al., 2005). Grönroos et al. (1993) determined the effect of cutaneous nociceptive reflex and found that pain led to a decreased threshold suggesting that pain facilitates the nociceptive flexion reflex. Pain usually inhibits movement, as individuals tend to limit movement in order to protect the painful region. Neuroplasticity leads to changes in excitability of the MI that has been reported with peripheral nerve lesions and in association with chronic and phantom limb pain (Hall et al., 1990; Cohen et al., 1991). Acute pain can lead to a reduced discharge and increased twitch amplitude of the motor units throughout muscular contractions (Sohn et al., 2000). The literature indicates that muscle pain tends to modulate motor control by altering the coordination of muscle groups leading to reorganization of the muscle activity (Madeleine et al., 1999, 2006). Lee et al. (2008) found that the effects of acute muscle pain varied with the task and this may lead to variability in the response to pain. Due to alterations in neuroplasticity caused by pain with motor learning, the modifications of the sensory and motor systems differ between muscles.

2.4.4 Research Gaps

The literature suggests that there are inconsistent findings from pain on motor control through excitability of the MI to the facilitation of the nociceptive reflex as well as alteration in the recruitment of the muscle groups. The variability in findings in the literature pertaining to how acute pain affects individuals with varying degree of neuroplastic changes requires the need for further research as it is difficult to predict how pain would affect SCNP individuals and whether this affects SMI.

2.5 Motor Learning

Motor learning has been described based on certain characteristics that include learning from experience or practice and is a process of acquiring the ability to produce skilled actions. Learning cannot be observed directly; therefore, it is based on changes in behavior, i.e. improved ability to produce a skilled action. Learning may also leads to permanent alterations in the ability to perform this skilled action (Schmidt & Lee, 2011). Motor learning acquisition is the process by which movements are performed effortlessly after practice and is measured by a reduction in response time and the error rates (Doyon & Ungerleider, 2002).

2.5.1 Motor learning and neuroplasticity

The literature has extensively studied the effects of motor learning on neuroplasticity (Doyon et al., 1996, 1999, 2002, 2003). Imaging studies have shown that the prefrontal cortex and the pre-SMA are activated during early stages of motor learning acquisition and the involvement of MI, the cerebellum, and the basal ganglia are also noted (Sakai et al., 1999). Changes in the MI has been shown to improve motor performance and motor control where long-term neuroplasticity is mediated by increased cortical synaptic connections and synaptogenesis (Rioult-Pedotti et al., 1998). There is also activation of the cerebellum with repetitive motor tasks and the basal ganglia that are active during early and later phases of learning suggesting that different components are responsible for different stages of learning (Jueptner & Weiller, 1998; Miyachi et al., 2002)

2.5.2 Motor learning: tracing

Learning tasks is an important tool that can be to measure cortical excitability using a pre-post design in conjunction with a measuring technique or a modality such as EEG. This can

provide insight into changes in excitability that occur following a motor learning acquisition task. There different type of tasks such as continuous and discrete that stimulate the SI, MI, premotor and parietal cortices (Spencer et al., 2007). Habas et al. (2008) demonstrated that recruitment of the MI and SI occurred with a continuous learning task and increased activation of the right prefrontal cortex. Smyth et al. (2010) used varying levels of performance feedback in two groups during a skilled movement task to see changes in cortical excitability and found an increase in performance with feedback, focus and attention being a possible variable. A drawback to most of the motor tasks is that they lack complexity. Therefore, a motor tracing that is more complex introduces a novel movement that is typically not used. Previous studies have demonstrated that using a novel task such as the tracing task that an individual has never seen or practiced, can improve motor learning as changes in the cerebellum have been shown that is vital for SMI (Andrew et al., 2015; Dancey et al., 2014, 2016).

2.5.3 Motor learning acquisition and pain

Pain has been known to impede motor learning with the findings of individuals who are undergoing rehabilitation as pain alters excitability at the level of the cortex and modulates the neuroplasticity associated with motor learning and impairs motor learning (Sörös et al., 2001; Tinazzi et al., 2000). However, Dancey et al. (2014, 2016) found improved performance in motor learning acquisition in the presence of acute pain and it was hypothesized that the mild acute cutaneous pain focused attention and increased motor learning acquisition. Improved motor learning during acute pain may have been caused through increased attention or arousal. Pain may have acted as a non-target stimulus and focused attention during skill acquisition. Since, acute pain was applied to healthy individuals, it may not necessarily yield similar results as the effects of pain on motor learning may depend on location of experimental pain. A few studies

have shown tested the impact of acute pain on retention of motor learning found that pain throughout the acquisition phase impacted retention despite not having an impact at baseline or motor learning acquisition (Bouffard et al., 2014). A full understanding of how pain affects the MI is not currently known, but could be due to cortico-thalamic connections, producing inhibition on the sensory pathway.

2.5.4 Research Gaps

There is currently a gap in the body of knowledge of how motor control is affected by pain, and how pain impacts motor control, motor learning acquisition, and retention in the SCNP population.

2.6 Capsaicin

Acute pain through the application of capsaicin cream as previously used by Dancey et al. (2014, 2016) that does not affect motor movements was selected for this thesis. Capsaicin can be applied topically that does not damage underlying tissue damage and provides nociceptive input with negligible contributions from other somatosensory modalities (Iadarola et al., 1998; Dancey et al., 2014, 2016). Capsaicin binds to the TRPV1 receptor (a protein channel on the membranes of nociceptive and thermoreceptive neurons) that results in acute pain and is often accompanied by heat (Caterina et al., 1997; Dancey et al., 2014).

Capsaicin leads to a sensitization of C-fiber nociceptors that release inflammatory mediators including vasoactive peptides (substance P) and inhibit the reuptake of substance P from C fibers (Sörös et al., 2001). Capsaicin induces sensitization produced by excitability changes of the nociceptors and central sensitization as they remain active. It also transiently induces sensory abnormalities that are associated with tissue inflammation including

hyperalgesia (increased pain sensation to painful stimulation) and allodynia (increased pain to non-painful stimulation) (Iadarola et al., 1998).

2.7 Electroencephalography

EEG is a noninvasive electrophysiological monitoring method that records electrical activity of the brain that usually utilizes multiple electrodes placed along the scalp (Niedermeyer & Lopes da Silva, 2005). EEG detects voltage fluctuations resulting from ionic currents within the neurons of the brain. This creates event related potentials (ERPs) as well as spectral waveforms that can be analyzed at the normal – abnormal axis and used for the purpose of diagnosis in conditions such as such as epilepsy, sleep disorders and other encephalopathies. EEG can also be used to detect and record evoked potentials (EPs) that are electrical potentials from the nervous system following a stimulus based on time-locked presentations of a stimulus for research purposes offering the possibility to measure temporal properties of the brain in sub milliseconds (Michel et al., 2004). EEG technique can also contribute data for processing to identify the source and the location of active neurons in the brain by application of an inverse source localization algorithm that tries to explain the scalp potentials by intracranial sources (Michel et al., 2004). This involves the introduction of a priori assumptions on the generation of the EEG data that may provide neurophysiological information about where the signal is generated (Michel et al., 2004).

The reliability of the EEG source imaging data requires careful manipulation with parallel consideration of the optimum number of receptive electrodes and their placement. For instance, Lantz et al. (2003) assessed 9 different electrode configurations demonstrating that that the precision of the data increased with the number of the electrodes from 25 to 100 electrodes which than reached a plateau. Data recorded using a reduced numbers of electrodes therefore

requires careful interpretation as the source localization precision decreases, hence the current accepted and recommended baseline requires at least 60 electrodes as their concentration over the scalp increases leading to an improvement in precision (Michel et al., 2004).

It should be noted application of the EEG technique requires a standardized system such as the 10-20 system to standardize application of the scalp electrodes. The use of a standardized system ensures reproducibility within and between subjects over time as it is based on the relationship between the electrode and the cerebral cortex. The “10” and the “20” refer to the actual distance between adjacent electrodes that should be 10%-20% of the front to back or left to right distance of the skull.

EEG data acquisition also requires the discriminated choice of an electrode based on type matched to the expected results of the experiment. It has been shown to influence waveform analysis such as evoked potentials where temporal resolution is of utmost importance. However, this discrimination is not necessary for the analysis of topographic maps and for source localization when it includes baseline reference (Michel et al., 2004). The choice of a reference electrode with assigned amplitude does not change biophysical information that is included in the potential distribution as well as the relationship between the source and the potential (Geselowitz, 1998). This was confirmed Michel et al. (2004) that demonstrated that the reference point only changed the zero line and the equipotential lines as well as the landscape remained the same when the location of the reference electrode was changed.

EEG has also been used extensively to localize sources in an anatomically defined brain structures so that comparisons can be made between methods adopted to demonstrate sources involving Brodmann topographic terminology and Talairach coordinate mapping approaches

(Michel et al., 2004). This allows one to draw potential contributions about the anatomical and functional structures.

Consequently, this thesis used whole head EEG to determine the differences in evoked potentials, as well as to localize the activity to determine the active areas in the brain. This enabled the comparison of differences in the strength and location of sources contributing to differences in neural activity between healthy and SCNP individuals during acute pain as previous studies (Dancey et al., 2014, 2016) did not utilize EEG to assess difference in potentials and localize the source while eliciting pain in both healthy and SCNP individuals. Andrew et al. (2017) also did not utilize EEG nor elicit acute pain in SCNP individuals to measure evoked potentials and localize the source. By doing so, it may provide us an insight into whether these populations differ through change in their evoked potentials as well as the source within the brain and the contributing regions.

2.8 Somatosensory evoked potentials (SEPs)

Evoked Potentials (EPs) are electrical responses of the nervous system to sensory stimulation that are evoked in differential neural pathways and can be elicited selectively from the visual pathway, auditory pathway, or peripheral nerves in the arms or legs in the form of SEPs (Cruccu et al., 2008). EPs are primarily produced by stimulating the peripheral nerve such as the median nerve (MN) and measuring the cortical response that provides a measure of conduction along the pathway with characteristic inherent signal data that enables recognition and discrimination of a peripheral and central component. SEPs are evoked by transcutaneous bipolar electrical stimulation applied over the selected nerve that produce an objective and direct method of assessing the integrity of the sensory pathways of the central and peripheral nervous

systems (Cruccu et al., 2008). As it propagates through the afferent pathway, it generates a wave-like post synaptic potential that can be recorded at the scalp (Mauguiere, 1999).

SEPs has the ability to bypass peripheral sensory receptors and directly stimulate nerves of interest. The most commonly stimulated nerves in the upper limb are the median, ulnar, and radial nerves. The stimulation intensity depolarizes large diameter myelinated afferents, but not the small myelinated A delta (Aδ) or unmyelinated C afferents that convey pain and temperature as long as the intensity is not high (Burke et al., 1981). SEPs are recorded at various locations along the pathway as it is a non-invasive technique that generates waveforms. Since the exact location of the neural generator cannot be visually determine in an individual, this may create some distance from the neural generators, which may attenuate the evoked potential (Mauguiere, 1999).

2.9 Neural Generators

The conduction pathway provides optimal sites for detection of potentials from different neural generators. SEP peaks measure the activity in the underlying neural structures that are referred to as neuronal generators (Figure 2). Waveform peaks are greater when recording electrodes are close to their neuronal generators and the amplitude of the peak reflects the degree of activity of each neural structure that the peaks represent (Mauguiere, 1999). Therefore, any alterations in the amplitude of the peaks that may be produced following an intervention are believed to be modifications in the amount of activity of the same neural structures. The latency of the SEP peak represents the transmission time between stimulation of the nerve at the site and the neural structures responsible for generating the peaks (Mauguiere, 1999). The International Federation of Clinical Neurophysiologists (IFC) (Nuwer et al., 1994) and the American Clinical Neurophysiology Society utilizes the convention of labeling upwards deflection as negative. The

recorded latency depends on the participant's height and age that can vary, For the purpose of this thesis, the peak-to-peak amplitude (μV) of the following SEP peaks were measured in the experiments: the far-field N18, the parietal N20 and P25, and the frontal N24 and N30 (Figure 3).

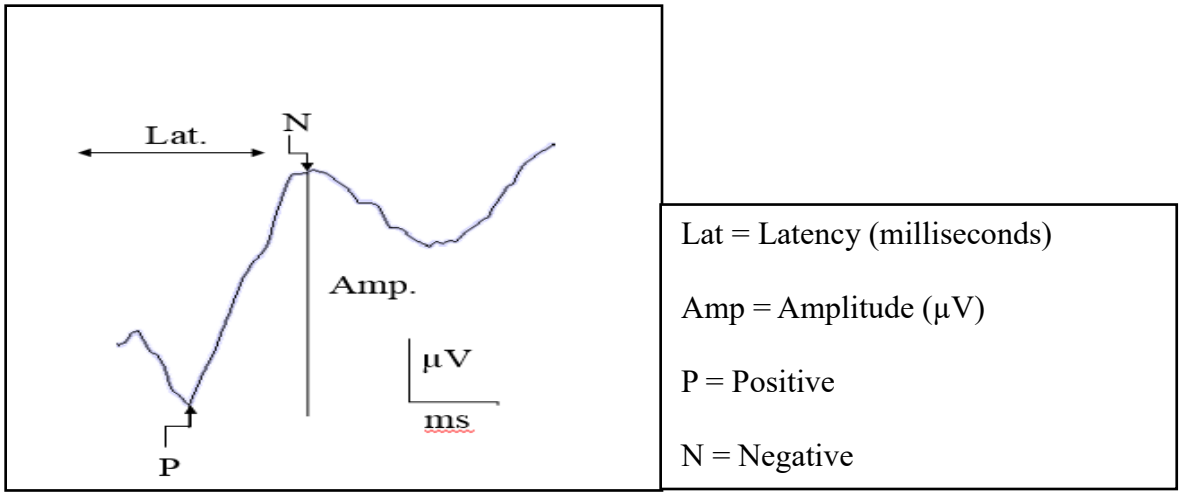


Figure 2. Example of a SEP peak.

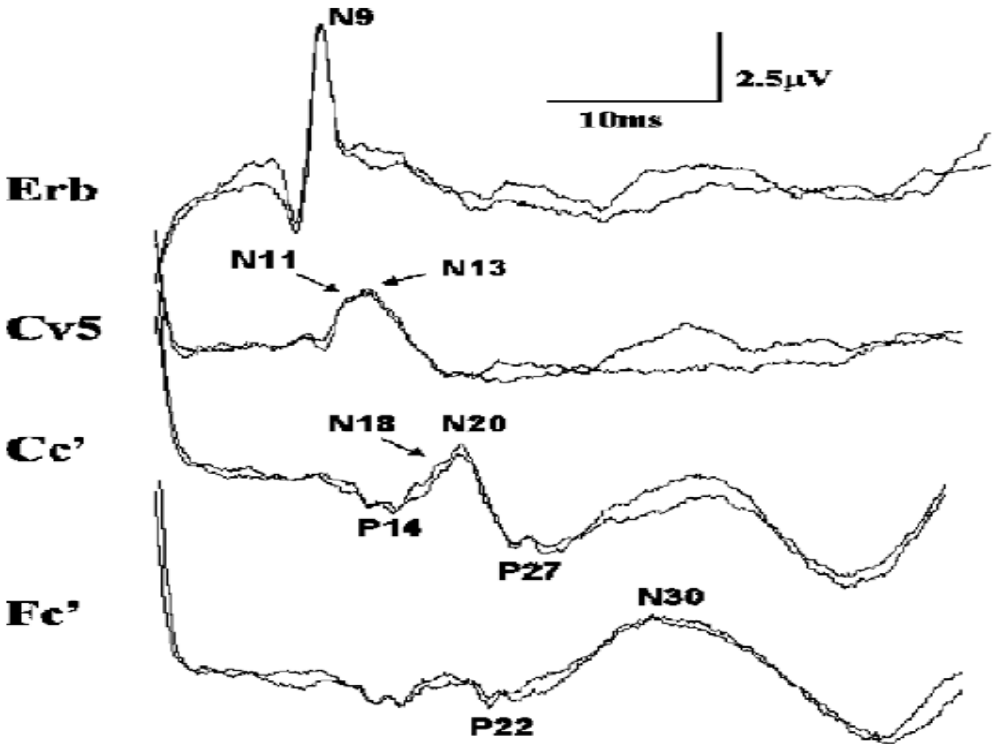


Figure 3. Examples of SEP peaks. Adapted from (Haavik-Taylor & Murphy, 2007).

N18

The N18 peak is the broadest elevation following the P14 peak (Figure 4). Noel, Ozaki and Desmedt (1996) demonstrated that the N18 peak was preserved in patients with lesions of the medial lemniscus which lead to the conclusion that the generator for the N18 SEP peak is the lower medulla. Therefore, N18 originates in the brain stem, between the lower medulla and midbrain-pontine region (the dorsal column and the inferior olives) that represents the activity in the olivo-cerebellar pathways. Thus the N18 peak thus originates above the spinal cord but below the cortex and can show alterations in cerebellar activity (Noel et al., 1996).

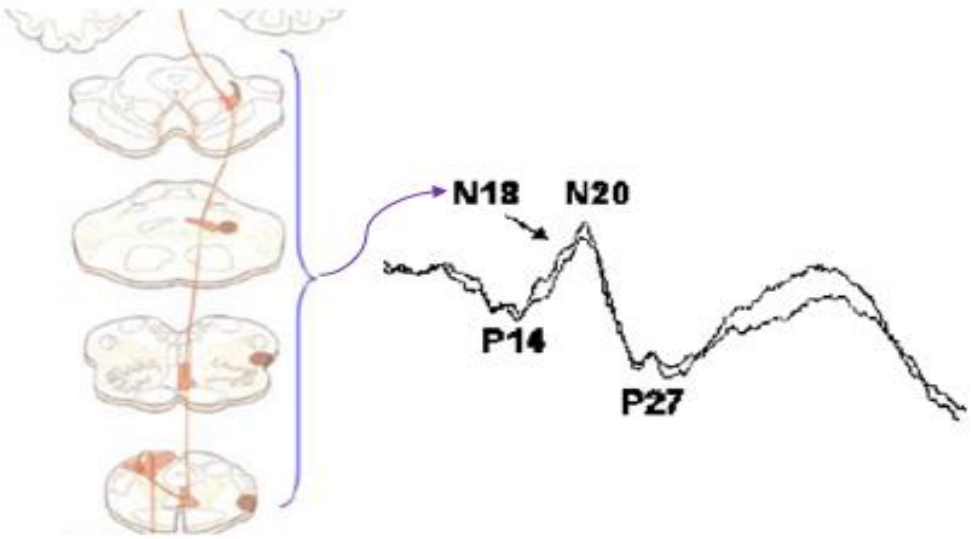


Figure 4. N18 SEP peak and its neural generator.

N20

The N20 SEP (Figure 5) peak is known to reflect the earliest cortical processing or activity in the SI, specifically in Brodmann's area 3b (Mauguiere, 1999). The parietal N20 SEP peak occurs contralateral to the site of stimulation and responds to contralateral tactile stimuli. Brodmann's area 3b (SI) is activated with response to cutaneous stimulation (Mauguiere, 1999).

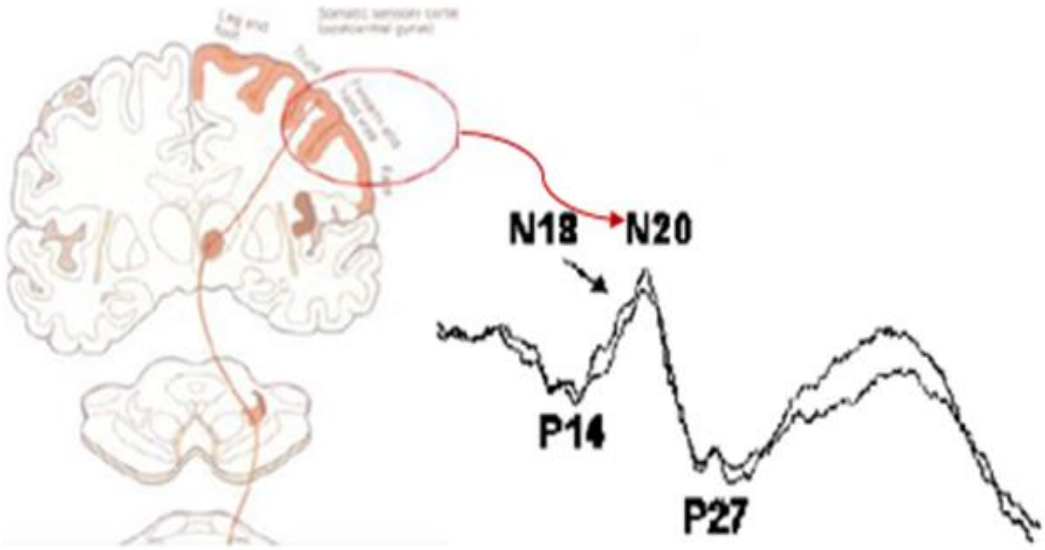


Figure 5. N20 SEP peak and its neural generator.

P25

The P25 (Figure 6) peak is recorded from the contralateral parietal region that originates in Brodmann's area 1 of the SI (Mauguiere, 1999).

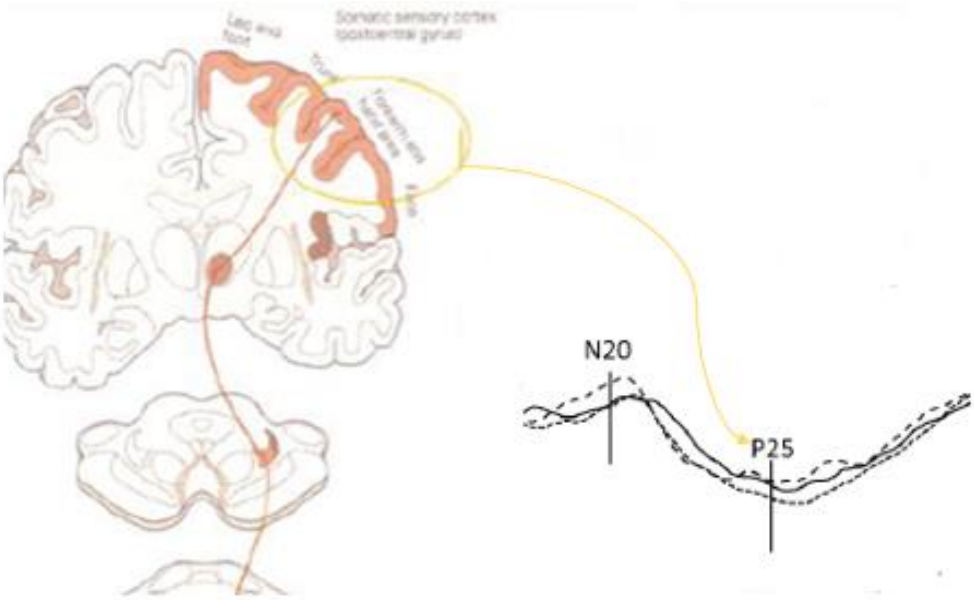


Figure 6. P25 SEP peak and its neural generator.

N24

The N24 SEP peak emerges on the ascending slope of the N30 SEP peak and is located close to the N20 SEP peak. The N24 SEP peak can be seen at higher stimulus rates (greater than 3 Hz) that decreases the N30 peak and is also referred to as the N23 or the N25 SEP peak due to some variability in the latency (Waberski et al., 1999). Source localization also identified the posterior wall of the central sulcus in area 3b of the SI as a neural generator of the N24 SEP peak (Waberski et al., 1999). The input to the SI travels through the cerebellum as demonstrated by Restuccia et al. (2001) that showed patients with lesions in the cerebellum had a reduced or absent N24 SEP peak. This shows that the N24 SEP peak is directly linked to the integrity of the cerebellum.

N30

The N30 SEP peak (Figure 7) reflects SMI that connects the thalamus, BG, premotor areas and the MI (Rossi et al., 2003). It has also been shown that the N30 SEP peak's neural generator was in the SMA due to N30 being absent in patients with lesion in the SMA, but Barba et al. (2001) demonstrated that no early SEP peak is generated in the pre-SMA or SMA. However, this does not rule out its contribution as regional cerebral blood flow is increased in the SMA during mental training of finger movements (Roland et al., 1980). Basal ganglia has also been shown as a neural generator for the N30 peak as Parkinson's disease (PD) demonstrate a decreased N30 peak as compared to healthy participants (Pierantozzi et al., 1999). MI also contributes to the N30 as Waberski et al. (1999) utilized source localization and determined that the MI is the N30 SEP peak generator. Cebolla et al. (2011) also utilized standardized weighted Low Resolution Brain Electromagnetic Tomography (swLORETA) to locate the N30 SEP peak is produced in the premotor, motor, and prefrontal areas as opposed to having a singular

generator. The N30 SEP peak has numerous inputs with separate thalamo-cortical pathways and is a marker of somatosensory processing.

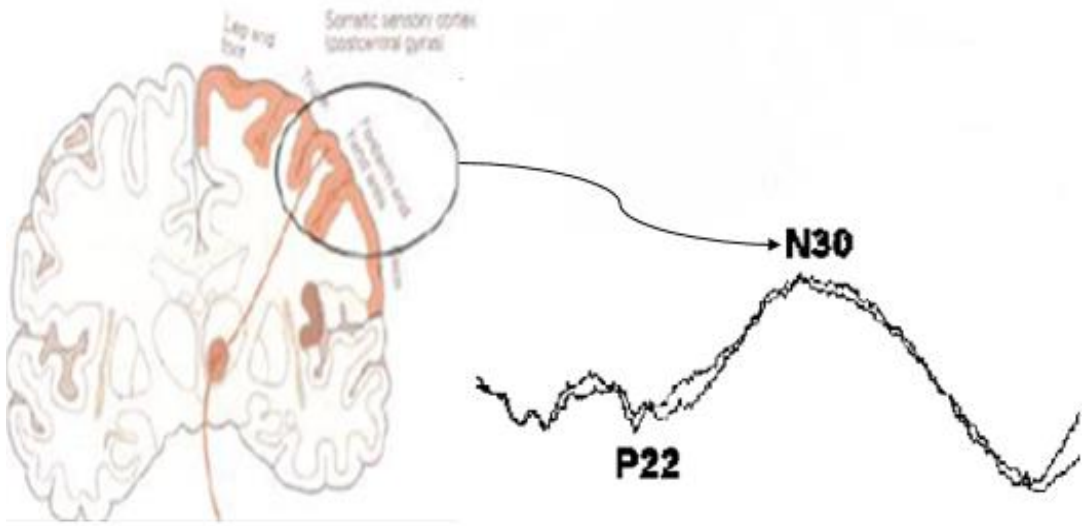


Figure 7. N30 SEP peak and its neural generator.

2.10 Source Localization

Source localization is a technique that optimally allows delineation and localization of scalp potentials related to underlying magnetic fields generated by intracranial sources (Michel et al., 2004). This is primarily achieved through the use of an inverse solution contained within interpretive algorithm that incorporates magnetic resonance image (MRI) data to visualize the activity. Localization modelling is however an inherently variable technique that has no single unique solution as there are an infinite number of current distributions that can be adopted to explain the electric potentials. In other words, a scalp potential can either be generated by current distribution or by neural generator that cannot be directly determined. To overcome these inherent variables a priori assumptions based on mathematical or anatomo-physiologic information about the brain have been introduced and adopted as standardized modelling sets for baseline application in modelling and localization studies. These standardized sets may then be

combined with different inverse modeling and dipole modelling approaches. Distributed models such as Low Resolution Brain Electromagnetic Tomography (LORETA), standardized LORETA, and standardized weighted LORETA (sLORETA, and swLORETA) have the capability to deal with data sources that cannot be considered point like as they assume a large number of dipoles with known fixed locations and orientations distributed over the whole brain volume. Thus, they avoid the intrinsic problem of having to estimate the exact number of dipole sources a-priori and are especially appropriate in cases where the number of sources is unknown. A current modelling approach adopted to explain the post-synaptic current potential involves the principle of mathematically assessing the current in dipole configuration with orientation along the dendrite in which the current flows as neurons are considered to be tiny current elements (Bailet et al., 2001).

Similarly, there is also the need to select a standardized head modelling method and systematic reproducible approach for accurate sampling purposes. Sampling involves the electromagnetic and geometrical properties of the volume as they are required for the calculation of the inverse solutions (Michel et al., 2004). Data elicited from these sites is normally designated as incident from the lead field matrix which is added to the estimated sources (current density vector) to produce the scalp potentials (Michel et al., 2004). This allows for the predictions of scalp potentials based on distance and actual measured potentials for finding and localizing the generators that requires a precise head model for the inverse.

The most common head model used is the spherical model that is uniform in terms of conductivity properties that allows for an easy calculation based on the solution of the forward problem (Michel et al., 2004). Another issue concerning source localization is the selection of the solution space which is referred to as fixed solution points. Spherical head models present the

whole volume within a sphere as the solution spaces which include the scalp and the brain. This means that white matter, ventricles and deep structures are included (Michel et al., 2004).

There are more realistic head models as in selected MRI modelling methodology that limit the solution space only to specific structures where EEG sources can generate (gray matter of the cortex and some well-defined deep structures) based on the segmentation of the MRI into gray and white matter (Michel et al., 2004).

However, in a generalized head model such as the Montreal Neurological Institute brain and the Collins 27 based on multiple brain scan data on group of individuals, variances in individual's source space are not considered. The use of a subject's actual MRI is eventually required due to the presence of lesions or deformations and only by using an individual's MRI can these areas be omitted from the solution space (Michel et al., 2004). Therefore, standardized head models and images should be interpreted with care as an illustration without great precision.

2.10.1 Dipole models

The basic assumption of the dipole model is that the EEG data is generated by a few, concentrated, point-like sources which are named dipoles. Pyramidal cell dendrites are arranged in a columnar fashion with an orientation locally normal (perpendicular) to the cortical surface and are deemed to be the probable generators of EEG activity. This arrangement allows the current fields generated by synchronous activation of a population of neurons within a small area of cortex. A well localized activity can be represented by a dipole located at the center of this area with moment normal to the cortical surface.

The location and the orientation of the dipole is estimated by application of a Minimum Squares method, however this method can be restrictive as the data sampled can become trapped and defined as a local minimum and disregard an appropriate solution based on the strength of the initial parameters such as amount and location of dipoles (Uutela et al., 1998). Directed search algorithms and the problem of establishment of the local minimum both increase with the number of dipoles as well as their complexity (Michel et al., 2004). To overcome such obstacles, a spatio-temporal model may be applied whereby the whole epoch is analyzed with an increasing number of sources, although it is difficult to estimate accurately the amount of active sources (Scherg et al., 1999).

2.10.2 LORETA

LORETA was first presented in 1994 by R. D. Pascual-Marqui (Pascual-Marqui et al., 1994) and is generally considered to be "smoothing" modelling algorithm. This method assumes that the brain works as a functional system. With assumptions that neighboring grid points (voxels) are likely to have similar orientation and activation strength than distant voxels (Pascual-Marqui et al., 1994). This produces a smooth solution where parameters changes only slightly from one voxel to the next one. Mathematically, this is achieved by introducing a discrete spatial Laplacian operator that serves as a high pass filter which enhances localized activity through electrode distribution whose inverse matrix implements a smoothing function to blur abrupt discontinuities in the solution (Pascual-Marqui et al., 1999).

The smoothest solution implies that additional brain configurations can be considered which leads to a smaller localization error. But this smoothest solution also implies that although the location of the maximal activity is preserved, the amount of dispersion around it increases. LORETA sacrifices spatial resolution in order to determine which unique configuration of

cerebral structures explains the data on the basis of a physiologically meaningful assumption and with a small localization error.

LORETA has received a wide acceptance by the scientific community but also some criticisms that it introduces physiological constraints. It is expected that neighboring neurons exhibit a comparable degree of activation. The mathematical smoothing procedure introduced by LORETA yields to a physiologically smooth image which should be considered cautiously (Hamalainen, 1995). The extent of the activated sources is another weak point of LORETA. The degree of dispersion of the current estimated by any inverse algorithm is influenced by the grid size, the distance between electrodes and the distorting effects of the noise (Hamalainen, 1995). The central point of LORETA is to be able to model but not to exactly reproduce the 3D distribution of the brain sources without a priori knowledge (Pascual-Marqui et al., 1994).

2.10.3 sLORETA

sLORETA was also introduced by Pascual-Marqui in 2002 (Pascual-Marqui, 2002). A novel approach aimed to integrate the information elicited by structural and functional MRI data with precise temporal in data (Dale et al., 2000). It was hypothesized that the noise present in the signal is the main source of uncertainties and errors and therefore, a standardized estimated signal to the noise sensitivity at each spatial location was used (Dale et al., 2000). This resulted in a statistical parametric map (SPM) which indicates the statistical reliability of the estimated signal at each location while preserving the fine temporal resolution (Dale et al., 2000).

sLORETA leads to a procedure which infers the generators of the scalp signal by standardizing the current density estimates as it does not calculate densities and provides a statistical map which uncovers brain locations that are significantly activated (Pascual-Marqui,

2002, Wagner et al., 2004). It presents zero localization error in noise-free measurements (Pascual-Marqui, 2002). In the presence of noise, the method can exhibit some degree of location bias and spatial spread which is nevertheless smaller than that of LORETA (Pascual-Marqui, 2002). Additionally, in particular the deep sources can be underestimated with sLORETA (Pascual-Marqui, 2002).

2.10.4 swLORETA

swLORETA has been recently presented by Palmero-Soler et al. (Palmero-Soler et al., 2005, 2006, 2007). This algorithm was motivated by the limitations of sLORETA such as its sensitivity to the presence of noise in the data and its tendency to underestimate deep sources. swLORETA normalizes the column of the lead field matrix which accounts for the dependency between the magnetic field measured over the scalp and the location of the generating source (Palmero-Soler et al., 2007). Deeper sources need a higher amount of activation to produce the same topography over the scalp compared to superficial sources. The normalization is performed by introducing a Singular Value Decomposition (SVD) on those columns of the lead field matrix which correspond to the location of the dipoles (Palmero-Soler et al., 2007). It introduces a statistical technique that reduces the number of values of the solution while containing a large fraction of the original variability. When compared to sLORETA, swLORETA exhibits a smaller localization error for deep sources and noisy signals (Palmero-Soler et al., 2005, 2007). In addition, swLORETA is able to focus the estimated activity around the true position of the dipole and thus produces less blurred images (Palmero-Soler et al., 2005, 2007).

2.11 Research Methodology

This thesis and research follows a quantitative research methodology. This is based on a systematic empirical investigation of observable occurrences through the use of statistical, mathematical or computational technique (Given, 2008). This method employs mathematical models and theories as well as hypotheses to achieve its objective. Measurement is central to quantitative research because it establishes a central link between empirical observation and mathematical expression of quantitative relationships. When speaking of quantitative data, it refers to any data that is in numerical form such as statistics, and percentages. (Given, 2008).

The premise of this method is to utilize statistics to yield an unbiased result that can be generalized if necessary. Quantitative research is primarily used in economics, sociology, marketing as well as sciences to prove an idea. Quantitative research follows a scientific method, which include:

Hypothesis

This research proposed that individuals with SCNP will have a variable SMI and altered motor learning acquisition in comparison to healthy individuals due to inconsistent response.

Instruments and methods for measurement

This quasi experimental design measured pre/post changes in SEP peak amplitudes and motor learning accuracy as the dependent measures. Whole head EEG was used to source localize the focal activity in the brain of healthy individuals as well as SCNP individuals to determine if there were baseline differences and changes in response to motor learning.

Experimental control and manipulation of variables

Experimental control utilized in this research were the collection of SEPs and EEG recording in both healthy and SCNP individuals prior to the application of capsaicin cream and motor learning acquisition. The manipulation component introduced two different intervention mentioned earlier to differentiate any findings.

Collection of data

The collection of data is completed through the EEG software that allowed for the extraction of SEP peaks as well as provided the ability to source localize the activity.

Modeling and analysis of data

The analysis of the data was completed through the use of IBM SPSS Statistics for Windows, Version 19.0 (Armonk, NY: IBM Corp). Shapiro-Wilk test for normality as well as Repeated Measures ANOVA was used to analyze the data in both groups before and after the interventions.

In regards to the modality used in this research to conduct the experiment, EEG is very cost effective as it is significantly lower than other techniques such as functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG). It can provide immediate care in high traffic areas such as hospitals where other technologies are limited. EEG is also mobile and can be transported anywhere versus other modalities such as fMRI. EEG has very high temporal resolution that is recorder in milliseconds and provide a greater image of the activity over time due to its very high sampling rate that can reach 20,000Hz (Michel et al., 2004). It is also tolerable by most individuals as it does not aggravate claustrophobia in individuals that are susceptible to it and is silent that can be beneficial is studies assessing sleep patterns as well as

auditory stimuli. It is also non-invasive as it does not require exposure to radioactive materials as it is the case in positron emission tomography (PET). Since it is a temporal, it can track changes in the brain over prolonged period of time to provide a better understanding.

EEG has disadvantages as it has a low spatial resolution. In other words, it cannot directly display active areas of the brain, hence requiring further processing and interpretation to hypothesize which areas are active during a response. EEG also has a poor resolution of subcortical neural activity, although the techniques used to source localize have advanced to create a much greater 3D map. It is also time consuming in terms of the setup as it requires the placement of multiple electrodes that need to be precisely calibrated to reduce noise and artifacts. It also leads to a poor signal to noise ratio due to multiple electrodes being active at once and any movement can create artifacts such as eye blinks or electromyography (EMG) activity that may interfere with the signal. However, the filtering techniques and artifact correction can reduce this poor resolution to create an adequate EEG trace that can be further processed.

3. Significance

Pain is one of the most common causes of disability that can be caused by extensive use or repetitive strain leading to a chronic condition that is debilitating and requires further interventions such as physical therapy or pharmaceuticals. Chronic pain has been known to create both peripheral and central changes leading to cortical reorganization which can be caused by repetitive movements (Byl et al., 1997). Altered SMI as well as the transmission of somatosensory input is attenuated due to repetitive activity that may lead to long term changes in the SMI. Prolonged peripheral input can also lead to pain and altered motor control as it creates central changes associated with chronic pain in different brain regions such as frontal, parietal, and occipital, or sensorimotor and somatosensory regions as shown in EEG activity. (Pinheiro et al., 2016).

Many individuals with pain undergoing rehabilitation also present with deficits in motor control. These motor deficits are the outcome of movement related pain and pain also impacts motor control and has the ability to negatively influence the neuroplasticity associated with motor output (Hodges & Tucker, 2011). EEG can be used in numerous populations with variable chronic pain chronic pain conditions to rationalize and identify the pathophysiology of pain and to provide a suitable treatment based on the functional brain data that may measure its efficacy. These effectiveness of interventions and their mechanism may be assessed by these imaging tools (Pinheiro et al., 2016).

By understanding the role of somatosensory processing in response to pain, future research might eventually lead to practical applications for the rehabilitation of diseases that occur without a peripheral cause. The results of this research may provide insight in to how acute experimental pain contributes to plasticity during motor learning acquisition in healthy and in

individuals with SCNP, and provides insight as to how well the motor skill has been reserved. Acquiring more knowledge regarding the influence of pain on motor learning is vital in providing effective rehabilitation programs.

4. Manuscript

Measuring the effects of subclinical neck pain on sensorimotor integration using somatosensory event related potentials

4.1 Introduction

Altered movement patterns may accompany chronic pain suggesting that pain negatively affects motor control and may lead to maladaptive neuroplasticity associated with altered motor output (Hodges & Tucker, 2011; Mercier & Leonard, 2011; Bank et al., 2013). In addition, the presence of acute pain during motor learning may interfere with skill acquisition (Flor, 2003; Schweinhardt et al., 2006; Boudreau et al., 2007).

Motor learning acquisition requires sensorimotor integration (SMI) which is the processing of somatosensory information received from the motor task and integrating this information with the motor command in order to fine tune and improve motor task performance. Effective SMI requires the integration of afferent information in the central nervous system (CNS) to formulate a motor response to the muscles which are essential to the changes in neuronal activity (Haavik-Taylor & Murphy, 2010). Cortical changes such as neuroplasticity lead to an increase in motor performance due to motor skill acquisition (Dancey et al., 2014). However, the presence of pain creates changes by decreasing performance and interference in skill acquisition that also influences the neural plastic changes that usually accompany motor learning (Flor, 2003; Schweinhardt et al., 2006; Boudreau et al., 2007). Neural plastic changes brought upon by ongoing neck pain may also create a reduced ability to maintain an upright posture (Falla et al., 2004) and decreased proprioceptive activity (Lee et al., 2008).

Previous research (Daligadu et al., 2013; Haavik-Taylor & Murphy, 2011; Dancey et al., 2014; Dancey et al., 2016; Rossi et al., 2003) has investigated the effects of altered sensory input and neck pain on SMI in subclinical neck pain (SCNP) individuals. SCNP refers to recurrent cervical spine pain or stiffness that may be mild to moderate and for which individuals have not yet sought treatment (Haavik-Taylor & Murphy, 2011; Lee et al., 2004, 2005, 2008). Its

recurrent nature means that individuals can be tested on pain free days. As such, it provides an interesting opportunity to study changes in neural processing that result from ongoing alterations in sensory input due to pain, without the confounding effect of pain on movement patterns.

Capsaicin is a widely used topical cream that induces pain which is applied to the skin topically, creating acute pain without major contributions from other somatosensory modalities such as electrical stimulation (Iadarola et al., 1998). Capsaicin works by inducing a strong nociceptive stimulus that affects central sensitization, and causes a temporary induction of a variety of sensory irregularities including hyperalgesia and allodynia (Iadarola et al. 1998). It leads to an altered cortical excitation (Knecht et al., 1998; Tinazzi et al., 2000, 2004; Sörös et al., 2001), impacts the type of neuroplastic changes associated with a motor training task and may also alter performance improvements that would occur normally (Boudreau et al., 2007).

Recent studies have found that motor skill acquisition actually improved in the presence of acute experimental pain (Dancey et al., 2014; Dancey et al., 2016). One of these studies (Dancey et al., 2016) used a novel tracing task rather than a typing task. Andrew et al. (2015) had recently demonstrated that a complex motor pursuit tracing task lead to greater learning than a typing task, even though the biomechanical demands of the task were similar. Holland et al. (2015) demonstrated that this pursuit tracing task lead to continued motor learning acquisition throughout the training period with a significant consolidation of motor performance at retention. Combining this complex pursuit task with electrophysiology measures has the potential to lead to more sensitive means of measuring the interactive effects of acute and chronic pain on SMI in response to motor learning.

Somatosensory evoked potentials (SEPs) are evoked in response to repetitive sensory stimuli, such as median nerve stimulation. Early SEPs (named for their approximate timing

relative to the time of stimulation, and occurring within 50 msec from the time of stimulation) represent early sensory processing that provides a tool for assessing changes in neural activity in areas related to SMI. For instance, the N18 SEP peak originates in the brainstem (Noel et al., 1996), N20 and P25 peak originates in the somatosensory cortex (Mauguiere, 1999), the N24 peak is linked to the processing between the cerebellum and primary somatosensory cortex (Waberski et al., 1999), and N30 peak reflects SMI from multiple frontal areas (Rossi et al., 2003).

Dancey et al. (2016) found that motor skill acquisition in the presence of capsaicin altered early SEPs where the N20 SEP peak significantly increased and the N24 SEP peak significantly decreased in response to motor training for the control group who learned without the presence of capsaicin, while the N18 SEP peak significantly decreased for the group who performed motor learning in the presence of capsaicin. The N30 SEP peak was significantly increased after motor learning acquisition for both capsaicin and control groups and the P25 SEP peak decreased significantly following the application of capsaicin cream (Dancey et al., 2016). In a just published study, (Andrew et al., 2017) investigated the effects of SCNP on neural plastic changes in SMI in response to motor learning. They found significant amplitude differences in N18 and N24 SEP peaks between healthy and SCNP groups. They found that accuracy increased for both groups in response to motor training, but only the control group improved further during retention, suggesting that the differences in SEP peaks may be related to changes in motor performance.

These studies primarily measured SEPs collected from a small number of recording electrodes placed over cephalic sites known as the Cc' (2 cm posterior to contralateral central C3/4) and a frontal site, Fc' (6cm anterior and 2cm contralateral to Cz) (Rossi et al., 2003).

Although these sites allow the investigation of SEP amplitudes and latencies, they do not allow the identification of changes in neural activity in different areas of the brain contributing to those changes. The use of whole head electroencephalography (EEG) to measure SEPs, involves numerous electrodes ranging from 25-180 (Michel et al., 2004) and is a technique which enables the use of software to identify changes in the strength of contribution from various brain sources to evoked activity recorded using SEPs.

For instance, recent work on source localization designed to identify loci of activation in response to median nerve stimulation, Lelic et al. (2016) identified that the N30 SEP peak had altered amplitudes in individuals with chronic pain and that the N30 amplitude decreased in response to spinal manipulation. Application of Source localization software utilizing Low Resolution Brain Electromagnetic Tomography (LORETA) identified a neural generator specifically in the pre-frontal cortex in association with multiple neural generators within the primary sensorimotor cortex, basal ganglia, promotor areas such as the lateral premotor cortex (LPMC) and the mesial premotor cortex (MPMC) (Mayka et al., 2006; Waberski et al., 1999).

However to date, EEG and source localization methodology has not been applied to elicit the source of altered early SEPs when motor learning occurs in the presence of acute pain in healthy individuals and those with SCNP. Since previous studies (Dancey et al., 2014; Dancey et al., 2016) did not explore early SEPs in individuals with SCNP in the presence of acute pain and Andrew et al. (2017) did not invoke any acute pain in the SCNP group, the goal of the current study was to determine the sources of differences of changes in early SEP peaks using source localization when motor skill acquisition occurs in the presence of capsaicin. We hypothesize that the altered afferent input from the neck muscles and joints in the SCNP group will lead to altered SMI in response to motor learning in the presence of acute pain, which will be

demonstrated by increased variability in SEP peak amplitudes relative to control participants, and differences in the brain regions contributing to the N30 SEP peak.

This study endeavoured to answer the following questions:

1. Is SCNP group different to a healthy group in their neurophysiological response (as measured by changes in SEP peak amplitudes) to capsaicin application?
2. Is SCNP group different to a healthy group in their neurophysiological response (as measured by changes in SEP peak amplitudes) to motor learning?
3. Is there a difference in motor learning in the presence of pain between the two groups?

4.2 Methods

1). Participants

In total, 20 participants with no known neurological conditions (10 males and 10 females; mean age 21.35; range 19-30) were recruited for the study. Informed and written consent was obtained for all the participants involved in the study and ethical approval was received from the Research Ethics Board of University of Ontario Institute of Technology in accord with the declaration of Helsinki.

Preliminary screening involved a confidential health history in order to identify any medical conditions that could impact normal somatosensation such as recent cervicothoracic injury, neurological conditions, and pain medication. Neck Disability Index (NDI) and Neck pain Mini-Questionnaire were completed to assess their history of pain and categorize the participants in healthy or SCNP group.

2). Subject groupings and experimental procedure

Ten SCNP participants (5 males, 5 females) and ten healthy participants (5 males, 5 females) were placed in a quiet room and sat in a comfortable chair to minimize any movement which could lead to contamination of the EEG trace with electromyography (EMG) artifacts. The room was well lit so it would not induce drowsiness or sleepiness.

Overall experimental design: (see Figure 8 for flow chart). Initially baseline EEG and SEPs were collected. Before performing the motor learning acquisition task, all the participants received a topical application of capsaicin (0.075% Zostrix) cream applied to a defined location on the upper forearm in an area approximately 5 cm x 10 cm area on the lateral aspect of the dominant elbow. The capsaicin was then massaged into the skin. The capsaicin generated pain

sensation in both groups. The Numeric Pain Rating Scale (NPRS) was administered at baseline, 20min post application, post motor learning and after the last EEG and SEPs collection. The SEP data was collected at baseline, at 20 min after application of the capsaicin cream, and also after the motor learning task (Figure 8).

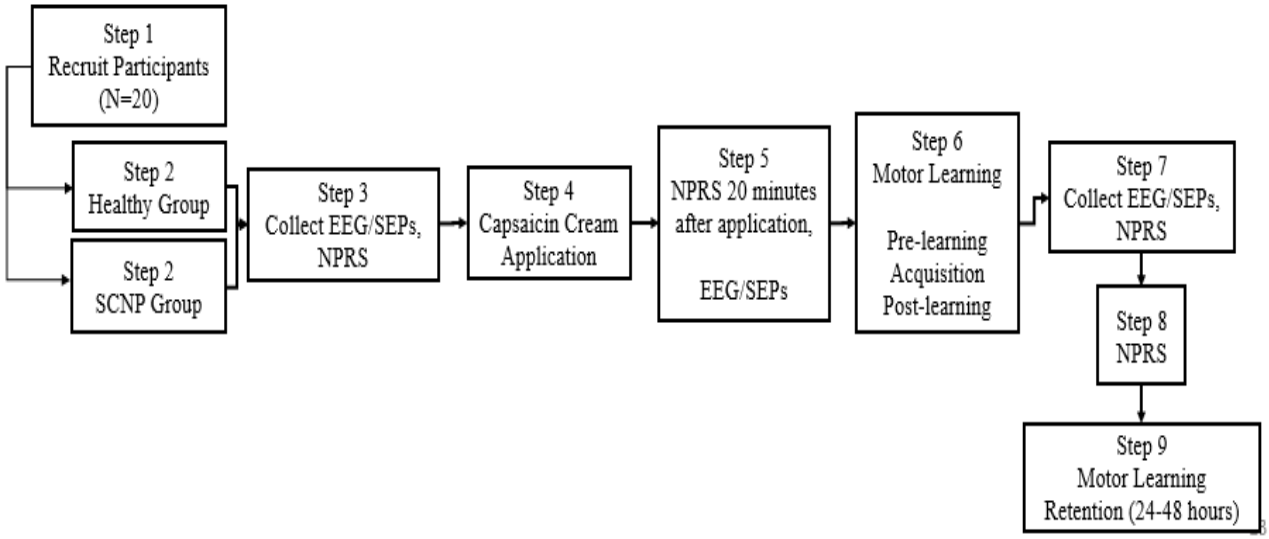


Figure 8. Experimental protocol (overview) for data collection during the study

3). EEG Setup

Continuous EEG was collected using Waveguard^{TM} 64 lead EEG cap and asaLab^{TM} software by ANT Neuro Imaging. The EEG amplifier used in this setup was REFA-8 amplifier with 64 EEG channels, 4 bipolar channels, and 4 auxiliary channels. The EEG cap (Figure 9) was placed on the scalp based on the international 10-20 system which provides the relationship between the location of the electrode and the underlying area of cerebral cortex and it signifies the actual distances between the adjacent electrodes to be 10 or 20 percent of the total front-back or right-left distance of the skull.

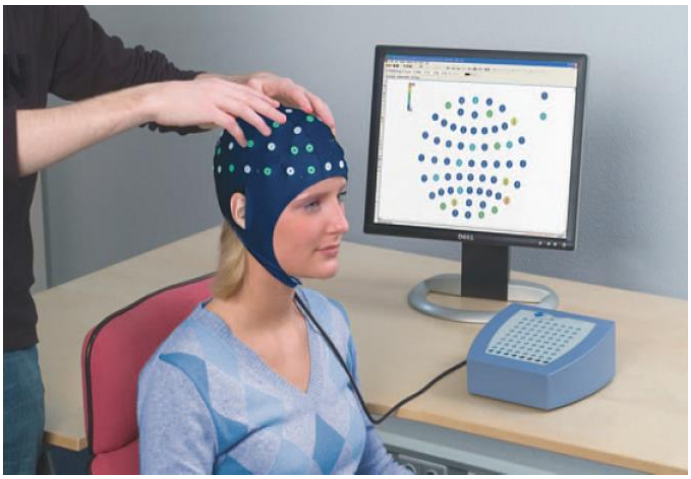


Figure 9. EEG/SEP data recording using Waveguard™ 64 lead EEG cap and asaLab™ software. Adapted from (Ant-neuro imaging, 2016).

This arrangement was achieved by measuring the circumference of the scalp from the nasion (intersection of the frontal bone and two nasal bones) to inion (projection of the occipital bone, posteroinferiorly) (Figure 9) and from the distance from one tragus (small eminence of the external ear) to the next tragus was then measured. The intersection of these two points was marked and the Cz channel was be placed as the central marker. To ensure that the cap covered the circumference of the head, additional measurements were conducted at the Fpz, Fp1, Fp2 electrodes located at the frontal cortex by calculating 10% of the circumference and utilizing it to place these electrodes. Fpz, Fp1, and Fp2 correspond to frontal channels located at the prefrontal cortex with numbers representing the left and right hemispheres. For instance, Fp1 represent the left prefrontal cortical channel, Fp2 represents the right prefrontal cortical channel, and Fpz represents the longitudinal cerebral fissure at the prefrontal cortex. The electrodes were then filled with conductive gel, ensuring the ground is filled first and the impedance is visually checked to be below 10 kΩ. The sampling rate was set to the highest applicable rate of 2048 Hz.

4). SEP Stimulation and Recording

SEPs were recorded at rest using a 64 channel EEG system where 1000 stimuli to the median nerve were delivered at 2.5 Hertz (Hz). This was followed by another 1000 pulses at 5 Hz to optimize visualization and measurement of the N24 SEP peak. The 5 Hz stimulation rate attenuates the N30 SEP peak, which allows for the identification and measurement of the N24 SEP peak (Haavik-Taylor & Murphy, 2007a, 2007b).

The pulses were repeated 20 min post application of capsaicin cream and after completing a motor tracing task using only the right thumb (described in the next section). The experiment utilized a ML856 PowerLab 26T by ADInstruments with Digital Output to send signals to the Digitimer stimulator model DS7A, which is used to generate electrical stimuli. LabChart™ 7 software with Event Manager v1.3.2. from ADInstruments was used to trigger the PowerLab. The manager was set with no initial delay with impulse time of 0.2 milliseconds (ms) and repetitions at every 400 ms to correspond to 2.5 Hz. The surface electrodes by Covidien™ constitute a conductive adhesive hydrogel for better conduction and increased surface area which will be placed proximal to the right wrist to stimulate the median nerve and it is measured by visible muscle contractions of the abductor pollicis brevis (APB) to ensure proper placement. Motor threshold was assessed in order to achieve optimal stimulus intensity for each individual participant with intensities that were strong enough to cause 1-2 cm thumb twitch (Nuwer, 1994). This setup can be seen in Figure 10.

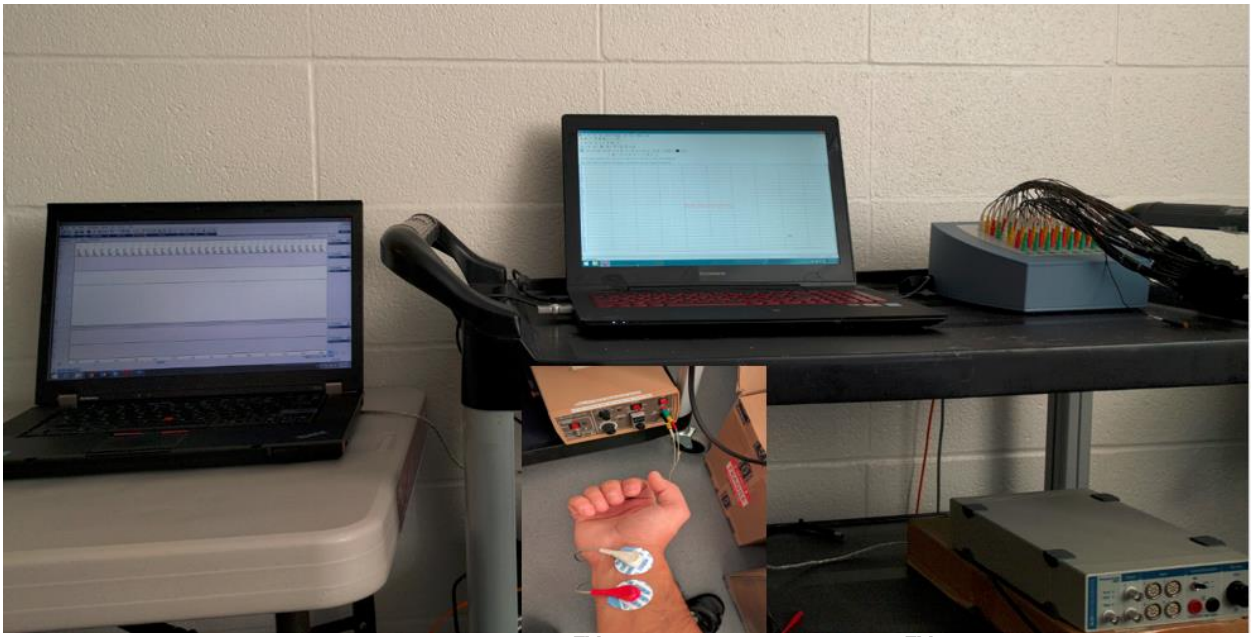


Figure 10. Experiment setup including LabChart™ 7 (left computer), asaLab™ (middle computer), REFA-8 EEG amplifier (top right), ML856 PowerLab 26T (bottom right), and DS7A Digitimer stimulator stimulating the median nerve (bottom middle).

5). Motor Training Task

The motor training task consisted of a tracing task that was represented in the form of sinusoidal wave on the computer monitor (Figure 11). This task was run through a custom Leap Motion software tool (Leap Motion, San Francisco, CA) which required participants to trace the waveform using only their thumb on an external wireless touchpad (Logitech, Fremont, CA). During the task, the participants were instructed to sit straight in the chair and to place their elbow on the arm rest in order to immobilize it while only using their right thumb to trace the waveform as accurately and as quickly as possible. Combined flexion and adduction thumb movements were performed, which required the participants to sweep their thumb from left to right, utilizing the APB muscle. The traces were formed by a series of dots, and each trial consisted of 500 dots. Each tracing task was comprised of four preselected sinusoidal patterns of varying amplitude and frequency, as determined by a previous study (Holland et al., 2015).

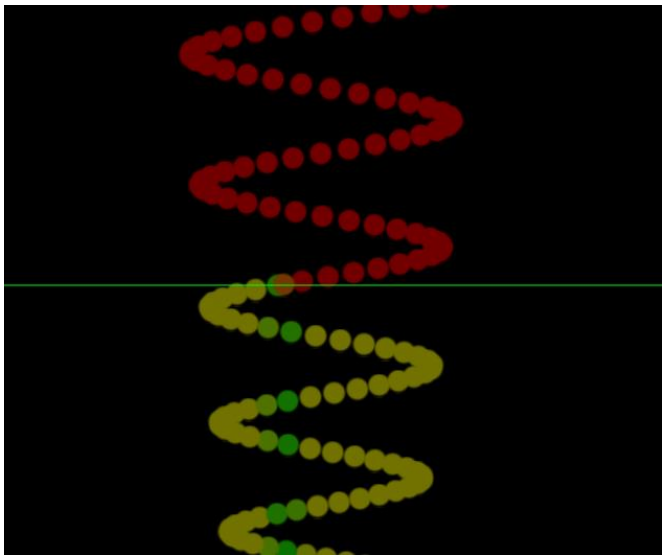


Figure 11. An example of the motor training task. The sinusoidal wave (red) moves vertically down the screen as the participant copies the trace using a horizontal cursor (orange) with only their thumb. The dots change color when following the trace correctly (green) and if missed (yellow).

The trace was randomized in 4 different versions of the sinusoidal waveform, with each waveform having a different frequency and amplitude with different degrees of difficulty to ensure that learning was able to occur for all participants, regardless of initial ability. Each participant was given 4 randomized version of the trials to measure baseline accuracy, prior to motor learning acquisition. Motor learning acquisition consisted of 12 randomized acquisition trials of the 4 sinusoidal waveforms presented in random order. Four additional randomized trials of the four waveforms were then completed to measure post-acquisition accuracy. All the participants completed 4 additional tracing tasks of the same versions 24-48 hours later in order to measure task retention.

Error was determined by the software as the average distance of the participant's attempted trace from the presented sinusoidal wave. The software captured the distance of the cursor from the actual trace and recorded the average distance of the cursor from the dots as it passed a horizontal line. The motor error was determined as a percentage from the actual trace.

6). Assessment of Pain

Pain response was also measured in both groups at baseline, post-application of capsaicin cream, post-motor training and finally after the last round of stimulation by using a Numeric Pain Rating Scale (NPRS). NPRS allowed the participants to grade the intensity of their pain from 0 to 10 (Dolphin & Crue, 1989). Participants in both groups were asked to rate their pain at the start of the study at baseline, 20 minutes after the application of the capsaicin cream, after the motor learning acquisition and after the last round of SEP measurements to ensure that they were in acute pain for the duration of the experiment.

Data Analysis

The data was processed for each participant using Advanced Source Analysis (ASA™; version 4.10.1, *The Netherlands*) software by ANT Neuro Imaging. A step-by-step process can be observed in Figure 12.

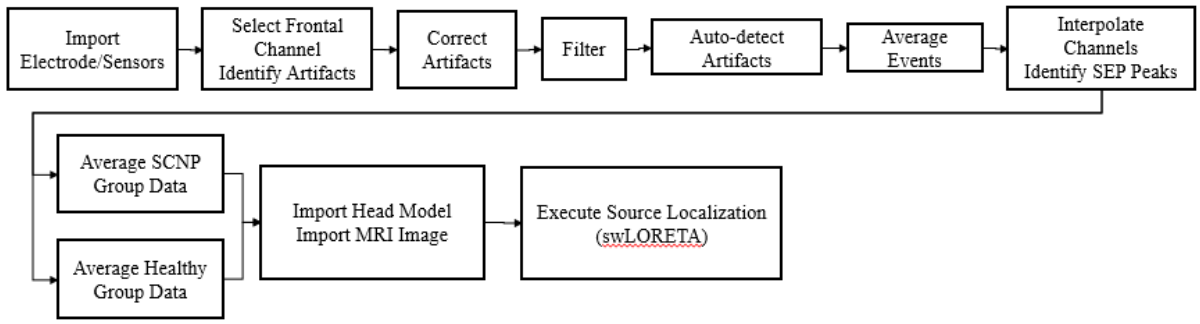


Figure 12. A step-by-step process of EEG data analysis as well as source localization.

Collins 27 Standard MRI electrode file from the Montreal Neurological Institute (MNI) consisting of 27 T1-weighted standardized scans with scanning data sourced from the same subject was initially imported representing a baseline in order to standardize the location of the electrodes between all participants.

Artifact Identification and Processing

To enable identification of artifacts such as eye blinks and eye movement that create high frequency artifacts (troughs) that can be easily observed (Figure 13), most of the EEG channels were t disabled except for the frontal channel, Fp1.

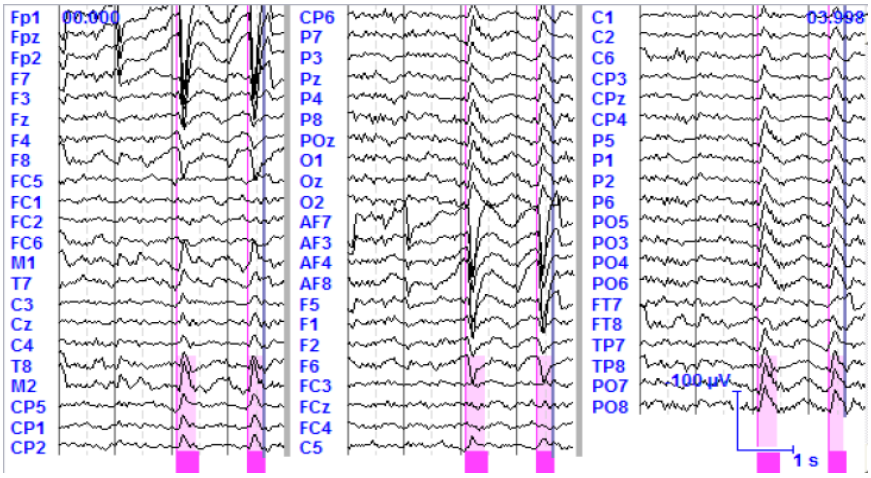


Figure 13. Artifact identification (pink) in the EEG channels based on high frequency artifacts created by eye blinks.

The manufacturer's recommendations (ANT Neuro Imaging) for artifact identification and correction were then applied. Firstly, three or more of artifacts were selected based on their similarity in appearance, this also ensured that other artifacts such as eye movement did not compound the artifact of interest, in order to maintain consistency of the selection process as well as testing the number of identified artifacts required to achieve an optimal artifact identification. This method separates brain signal from artifacts based on their topography which are then removed without distorting the underlying brain signals present in the EEG waveforms. Two principles were used to determine which part of the data was considered brain signal (subspace) and maintained and which part of the signal was artifact. Firstly, the highest amplitude of the brain signal allowed was selected at 100 microvolts (µV) and the second principle specified that the correlation between brain signal and artifact topography was ≤ 50%.

It was ensured that the first component of the first artifact subspace represented 95% or more of the total variance in the artifact such as eye blinks and movements. It was also ensured that these component fields represented 95% or more of the accumulated spectral power in order to ensure most of the artifacts including cardiac or muscle artifacts were corrected. If the first component or the accumulated spectral did not represent 95% or more artefact subspace, artefacts were reselected to ensure that this percentage was achieved in every participant and in every condition as per software manual. Once the artefacts selected met these criteria, they were then corrected for all channels.

Once a visual scan of the data revealed no remaining large repeating artifacts, the data set was then filtered with a band pass filter with a low cutoff frequency of 1 Hz and a high cutoff frequency of 1000 Hz. The filter steepness remained consistent at 24 decibels db/octave. Once filtering was complete, automatic artifact detection was executed to ensure that any remaining artifacts, especially in the event marker range that may have been initially missed by the artifact correction were identified. This was done by selecting amplitude threshold values at ± 100µV, where any amplitude greater than the threshold would be identified as an artifact and marked for a visual check. DC correction was applied to ensure that drift artifacts which is a low frequency activity that present as discontinuities.

The data was then carefully visually checked and any events that overlapped a region identified as an artifact were removed. The total number of remaining events were then equalized by comparing the number of events to determine if any recording had more events disabled due to artifacts. If this was the case, any recording that had less events disabled was further cleaned by disabling events in order to achieve the similar number of EEG sweeps for all participants and conditions to ensure that there was no inadvertent skewing of the data which could potentially

affect the SEP amplitude in a given group or condition (Lelic et al., 2016). A reference electrode at the parietal-temporal region contralateral to the right arm (TP7) was selected to increase the amplitude of SEP peaks at the frontal electrodes to make them easier to correctly measure (Lelic et al., 2016).

The events were then averaged to create a 100ms epoch for each of the N30 and the N24 peak during pre-application or baseline, post-application and post-motor condition in all the participants. Each of the averaged 64 channels were than assessed for any severe disturbances due to artifacts. If any channels were identified to be significantly noisy by visual inspection, these channels were interpolated by using 8 neighboring channels to ensure that the interpolated channel represented similar EEG activity, without being distorted by extraneous electrical noise.

Amplitude Analysis of SEP Peaks

Amplitude of the far-field N18 peak (P14-N18 complex), the frontal N24 peak (P22-N24 complex), and the frontal N30 peak (P22-N30 complex) was measured at the frontal electrode contralateral to the stimulated arm (F3).

This electrode was chosen based on visual inspection of both F3 and F1 in which N30 peak tended to be the highest at the F3 sight. This sight was also selected based on a previous study (Lelic et al. 2016) that demonstrated a similar finding as well as Rossi et al (2003) that highlights Fc' as a frontal cephalic site for measuring SEP peaks (6cm anterior and 2cm contralateral to Cz) that is in proximity to the F3. In order to obtain the parietal N20 peak (P14-N20 complex), and P25 peak (N20-P25 complex), CP3 electrode contralateral to the stimulated arm was selected based on the amplitude measurements of both C3 electrode and CP3 electrode in which CP3 showed a greater amplitude. This also approximately places the electrode similar

to Rossi et al's (2003) Cc' site (2 cm posterior to contralateral central C3/4) for measuring parietal SEP peaks. The amplitudes were measured as peak-to-peak for instance in the case of the N30, from the amplitude of the positivity preceding the N30 to the amplitude where N30 was the highest. Once all the SEP peak amplitudes were measured, the data was exported to Microsoft Excel™ (Microsoft, Washington, USA) for normalization.

Source Localization Technique

Advanced Source Analysis (ASA™; version 4.10.1, *The Netherlands*) software by ANT Neuro Imaging was used to source localize the location of these peaks at baseline, post-application and post motor condition in both healthy and SCNP groups.

Averages from each of the participants during each condition and group were separated and imported to create a grand average. Once the average was created, a temporal window via the epoch event from 15ms to 40ms was created in order to produce a source based on the N30 SEP activity. Collins 27 Standard MRI electrode file from the MNI was imported to standardize the location the electrodes. Collins 27 Standard MRI head model was then imported which also includes the brain source space. This represents a realistic head model (boundary element model) which included the three components such as the brain, scalp, and the skull.

The Collins 27 Standard MRI file with preset Talairach coordinates was then selected as the image file. The Talairach system is created by a piecewise linear transformation of the Anterior Commisure-Posterior Commisure (AC-PC) system that transforms the brain to a standardized size. The benefit of such coordinates system provides multiple reference points that can be used for the maximum extension of the cortex along the direction.

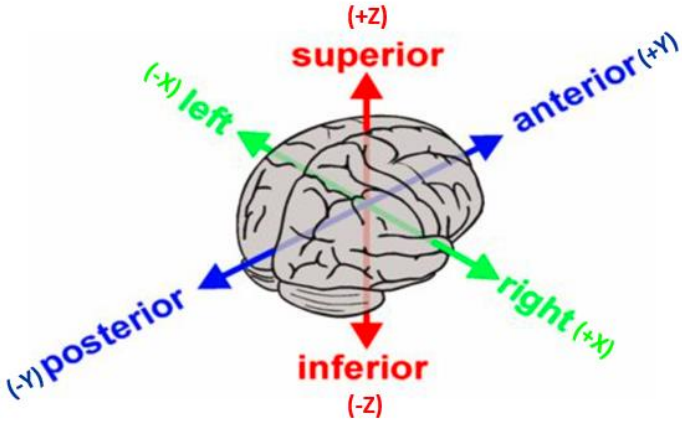


Figure 14. Radiological coordinates in the brain in x (green), y (blue), and z (red) using the Talairach system.

The coordinates (x, y, and z) of the system are based on radiological convention versus neurological system where the x represents the right to left axis (+/-), y represents the rostral to caudal (+/-) and z represents the dorsal to ventral (+/-) orientation when axially observing the brain (Figure 14). When the coordinates are represented in the Talairach coordinates, the center coordinate is represented as (0, 0, 0) which represents the intersection of the ventral anterior commissure (VCA) with the anterior/posterior commissural plane. Talairach coordinate system represents a 3-dimensional atlas of the human brain that is independent from individual differences in shape and size of the brain. This requires reorientation of the brain with six cortical outlines such as anterior, posterior, left, right, inferior, and superior to spatially warp an individual brain image to make inferences about tissue identity. Collins 27 Standard MRI with preset Talairach coordinates includes cortical outlines which can then be interpreted through the use of Brodmann areas or Talairach millimeters (mm).

Standardized weighted Low Resolution Electromagnetic Tomography (swLORETA) was then applied in order to map the neural generators of the N30 peak, using 3D grid of points that may represent the source of the signal. This method also generates a dipole to determine the

origin of focal activity as it mathematically describes a focal current source with an orientation. Groups of active neurons synchronously fire in a macroscopic sense which are represented by the single dipole model over a certain time interval. Source space was selected as 12mm as applying smaller source spacing did not show any significant changes to the coordinates of the dipole. The regularization value was automatically generated via generalized cross validation method as it provides stability to the solution in order to minimize the small variations in the data that may lead to large variations in source configuration (Michel et al., 2004).

Talairach coordinates for each of the dipole were extracted for all the conditions for both groups for comparison. SEP peak amplitudes were normalized to baseline values to account baseline variability as well as for the comparison of between participants. The coordinates were then compared to Mayka et al. (2006) probability maps that represent probability distribution describing the likelihood of activation of certain regions in the brain such as the premotor cortex, motor cortex and the somatosensory cortex. These probability maps were based on the Talairach space from 15 subjects that produced an averaged anatomical structure (Mayka et al., 2006). The probability maps were also presented using contour lines that represent the 95th, 75th, 50th, 25th, and 10th percent probability of an activation focus (dipole) will fall within the with each line thickness corresponding to a specific percentile (Mayka et al., 2006). The spatial overlap between the two regions produced a difference map with 0% difference (yellow regions), and with increasing probability difference shown as a gradient from yellow to red, and overlap of all three regions (purple) (Figure 22). This allowed the identification of the active areas of the brain as well as any overlap between different regions in both healthy and the SCNP group.

Statistical Analysis

SEP Peak Amplitudes: The Shapiro-Wilk's test for normality was first run on each SEP peak. The interactive effect of pain and motor learning acquisition on SEP peak amplitudes were then tested using a repeated measures ANOVA with factors TIME (baseline versus post application versus post motor learning acquisition) and GROUP (healthy versus SCNP).

Motor learning Accuracy: The Shapiro-Wilk test for normality was run on the accuracy data. To investigate the performance accuracy, a repeated measures ANOVA with factors TIME (pre-motor learning acquisition versus post-motor learning acquisition versus retention) and GROUP (healthy versus capsaicin) was then run on the accuracy data.

Pain ratings: Repeated measures ANOVA was also performed on the pain ratings with factors TIME (baseline versus 20 minute post application versus post motor learning acquisition versus post final sweep) and GROUP (healthy versus SCNP) with pairwise comparison.

All Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 19.0 (Armonk, NY: IBM Corp). Statistical significance was set at $p < 0.05$.

4.3 Results

Neurophysiological data: SEPs

The SCNP group following motor learning acquisition was not normally distributed in the N30 SEP peak. Since only one set out of four measurements in a repeated measures design was non-normally distributed, it is recommended to still run an ANOVA as is the ANOVA is robust against small departures from normality (Norman & Steiner, 2008). Type I and type II errors will not be inflated if the data are skewed and deviations in kurtosis will only affect power if the sample size is too low (Norman & Streiner, 2008). Note: data is expressed as the percent change from baseline where 1 represents 100 % with standard deviations (SD) in brackets.

A repeated measures ANOVA was run on all the SEP peak data. The N30 SEP peak approached significance ($p=0.070$) for the main effect of TIME. The interaction of TIME by GROUP was not significant ($p=0.714$). In the healthy group, the amplitude of the N30 peak following the application of the capsaicin cream decreased by 5 (± 17) % and it increased by 12 (± 17) % following motor learning acquisition. In the SCNP group, the amplitude of the N30 peak following the application of the capsaicin cream increased by 7 (± 56) % and it further increased by 26 (± 73) % following motor learning acquisition. The SEP peak changes can be seen in Figure 15, 20 minutes post-application of capsaicin in both groups. Figure 16 shows SEP peak changes following motor learning acquisition in both groups.

The other peaks (N18, N20, N24, and P25) did not show any significant differences.

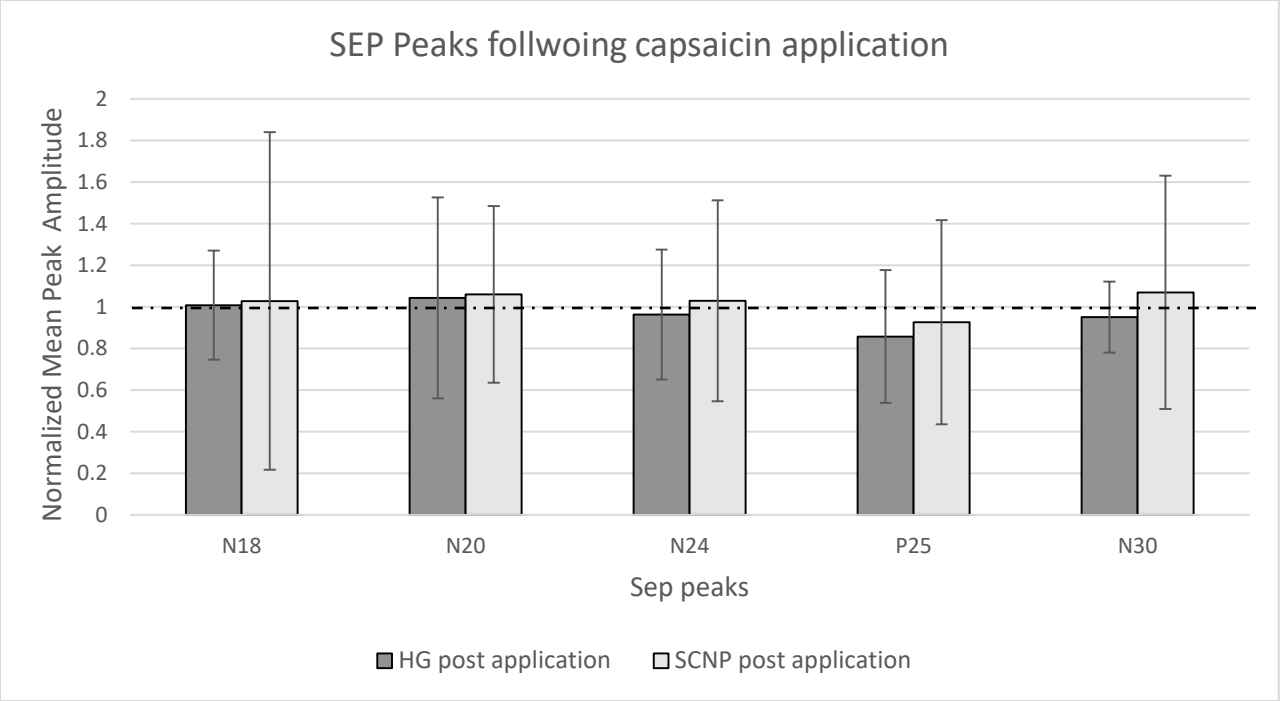


Figure 15. Averaged normalized SEP ratios showing healthy vs. SCNP groups after application. Dotted line represents baseline at 100%. Error bars represent SD.

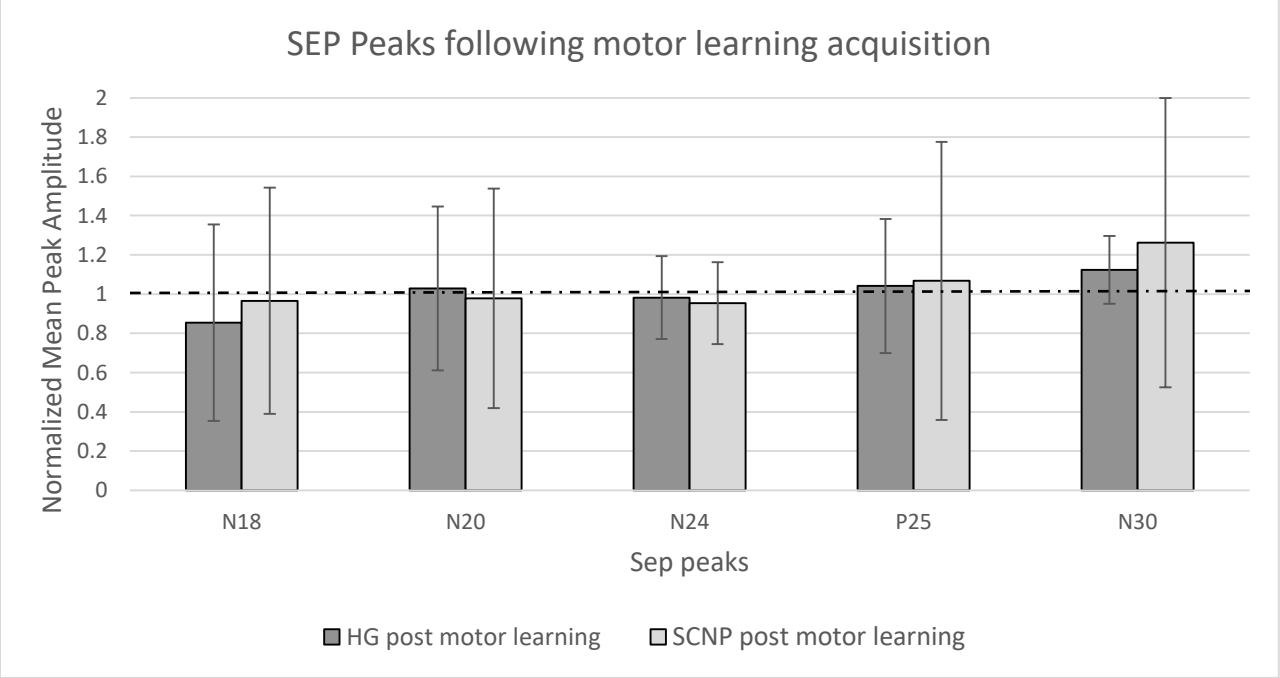


Figure 16. Averaged normalized SEP ratios showing healthy vs. SCNP groups after motor learning acquisition. Dotted line represents baseline at 100%. Error bars represent SD.

Accuracy Data

The Shapiro-Wilks test for normality demonstrated that both groups were normally distributed except SCNP group during the retention phase. Following motor learning acquisition there was a significant main effect of TIME [$F(2, 36) = 28.899$, $p<0.001$, $\eta 2=0.616$], while the interaction effect of TIME by GROUP was not significant ($p=0.661$). Post-hoc ANOVA testing demonstrated that there was a significant difference following motor learning acquisition [$F(1, 19) = 42.117$, $p<0.001$, $\eta 2=0.689$]. When comparing pre motor learning acquisition (20 minutes after the application of capsaicin cream) to retention (24-48 hours after initial motor learning acquisition), post-hoc ANOVA testing demonstrated that there was a significant difference at retention [$F(1, 19) = 38.159$, $p<0.001$, $\eta 2=0.668$] (Figure 17). The healthy group showed a decrease of 39% in motor error following motor learning acquisition that continued to decrease at retention (51%) from initial motor learning. The SCNP group showed a decrease in motor error of 41% following motor learning acquisition that did not change at retention when compared to initial motor learning acquisition.

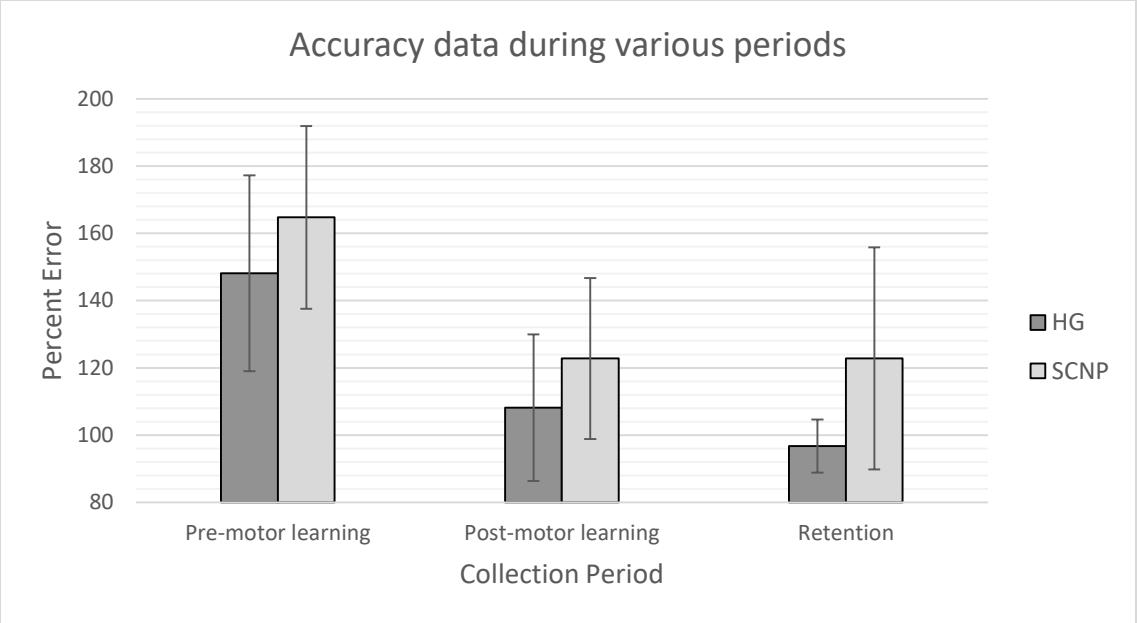


Figure 17. Percent error by group. Both groups improved in accuracy post motor learning. Healthy group continued to improve during retention. Error bars represent SD.

Pain Ratings

The Repeated measures ANOVA on the NPRS ratings demonstrated a significant TIME [$F(3, 54) = 47.094$, $p<0.001$, $\eta 2=0.723$], while the interaction effect of TIME by GROUP was not significant ($p=0.867$). Post hoc tests using the Bonferroni correction revealed that 20 minute post application of the capsaicin cream, post motor learning acquisition and after the final sweep differed significantly from the baseline ($p<0.001$). The average NPRS ratings are illustrated in Figure 18.

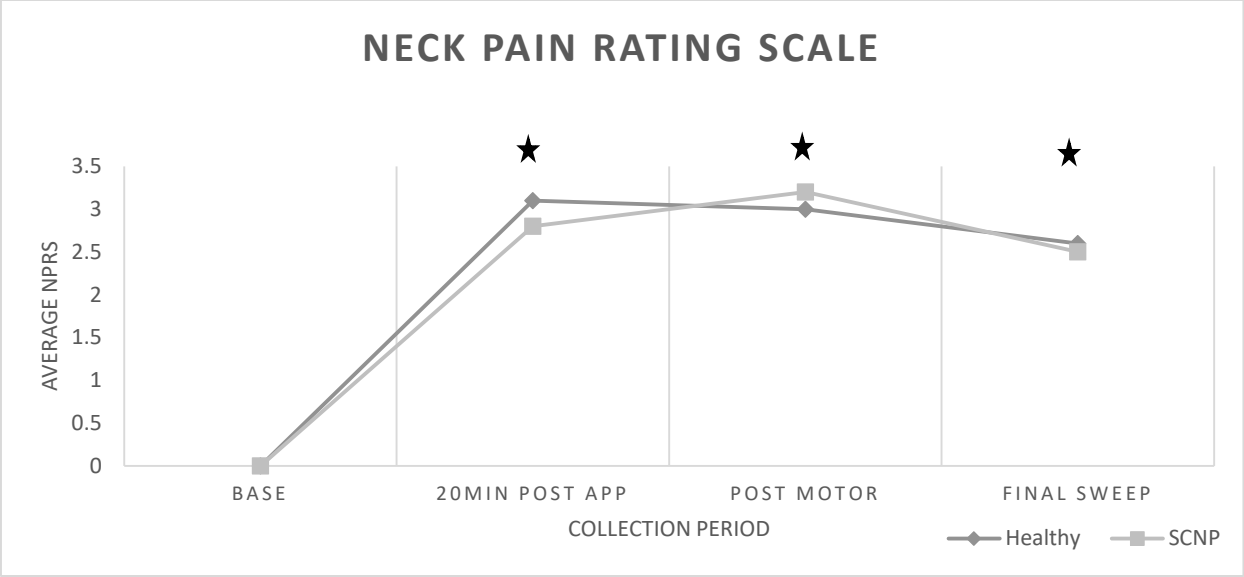


Figure 18. Averaged NPRS ratings of participants in the healthy and SCNP groups. Significant differences after application, post motor learning and after final sweep (Starred).

Brain Source Localization

Region of Interest

The source of activity as determined by ASA™ software was interpreted with respect to the regions of interest approach (ROI) based on Brodman's architectonic terminology. *Brodmann* areas are a *system* to divide the cerebral cortex according to cytoarchitectural organization, and are widely used as a standardised nomenclature which is superimposed on the somewhat variable gyral and sulcal anatomy of an individual's brain. The Brodmann areas encompassed by the regions calculated by the ASA™ software include the Lateral Premotor Cortex (LPMC) include the dorsal and ventral premotor cortex (PMd/PMv). The Mesial Premotor Cortex (MPMC) include areas such as pre-supplementary motor area (pre-SMA) and supplementary motor area proper (SMA proper) corresponding to Brodmann's area 6.

Regions of Interest	X coordinate range	Y coordinate range	Z coordinate range
Sensorimotor Cortex	-69 to 4	-45 to 6	18 to 78
Primary Motor Cortex	-70 to 4	-43 to 7	19 to 76
Primary Somatosensory Cortex	-70 to -20	-44 to -9	19 to 72
Lateral Premotor Cortex	-70 to -9	-21 to 20	-2 to 73
Dorsal Premotor Cortex	-55 to -8	-21 to 12	27 to 76
Ventral Premotor Cortex	-70 to -31	-8 to 8	-2 to 46
Mesial Premotor Cortex	-18 to 16	-32 to 27	33 to 73
Pre-supplementary Motor Area	-18 to 16	-7 to 27	33 to 72
Supplementary Motor Area Proper	-17 to 14	-30 to 7	42 to 76

Table 1. Regions of Interest (ROI) and the associated Talairach coordinate range.

The Sensorimotor cortex (SMC) consists of primary motor cortex (MI) which is generally located in the Brodmann's area 4 and the primary somatosensory cortex (SI) which corresponds to Brodmann's areas 1, 2, and 3. Brain source localization data was sampled from between the 15 and 40ms time interval from stimulus onset. The swLORETA solution performed on the average revealed a distinct solution that discriminated the different periods such as baseline, post application of capsaicin cream and post motor learning acquisition. The ranges for these regions of interest can be found in Table 1. (Mayka et al., 2006). The premotor cortex occupies Brodmann's area 6 that lies on the lateral surface of the cerebral hemisphere rostral to the SMC.

The location of the sources in the healthy group and the SCNP group during baseline can be seen in Figure 19. The location of the sources in the healthy group and the SCNP group 20 min post-application of capsaicin can be seen in Figure 20. The location of the sources in the

healthy group and the SCNP group post motor learning acquisition can be seen in Figure 21. The Talairach coordinates of both healthy and the SCNP group for all the conditions are listed in Table 2.

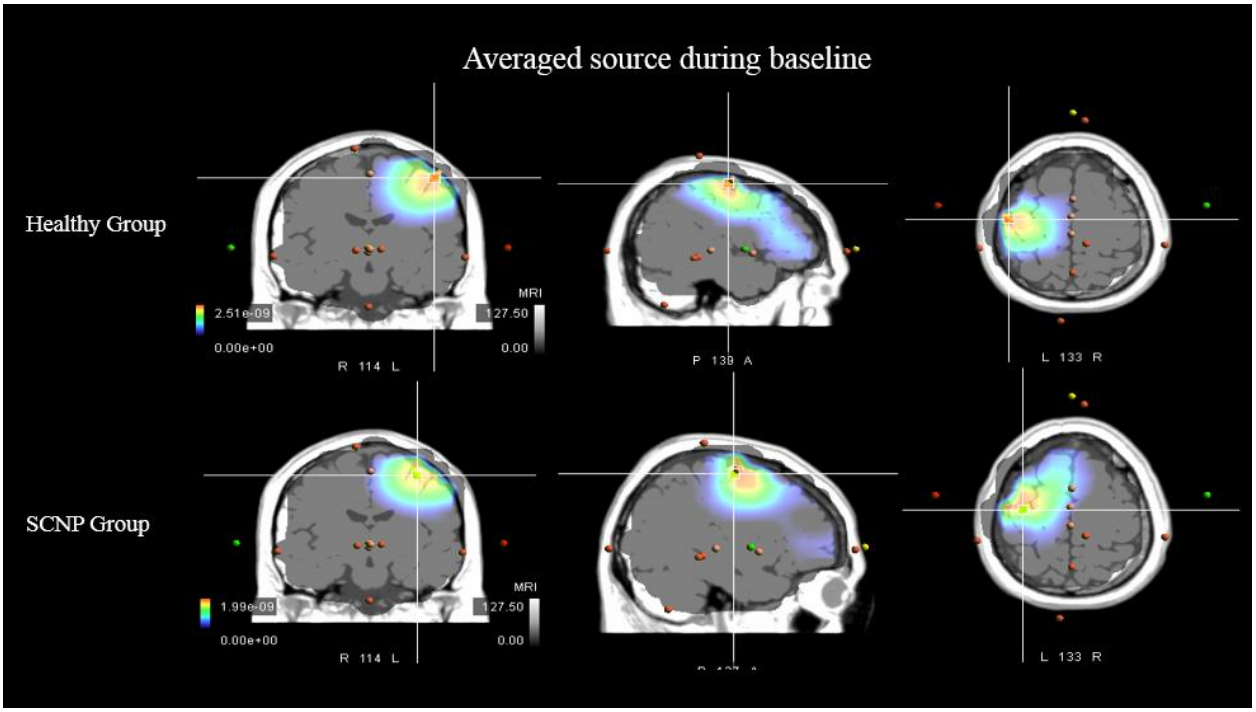


Figure 19. Average source localization (dipole) during baseline in both the healthy group (top row) and SCNP group (bottom row). Image (left) is in coronal plane, (middle) is in sagittal plane, and (right) is in the axial plane.

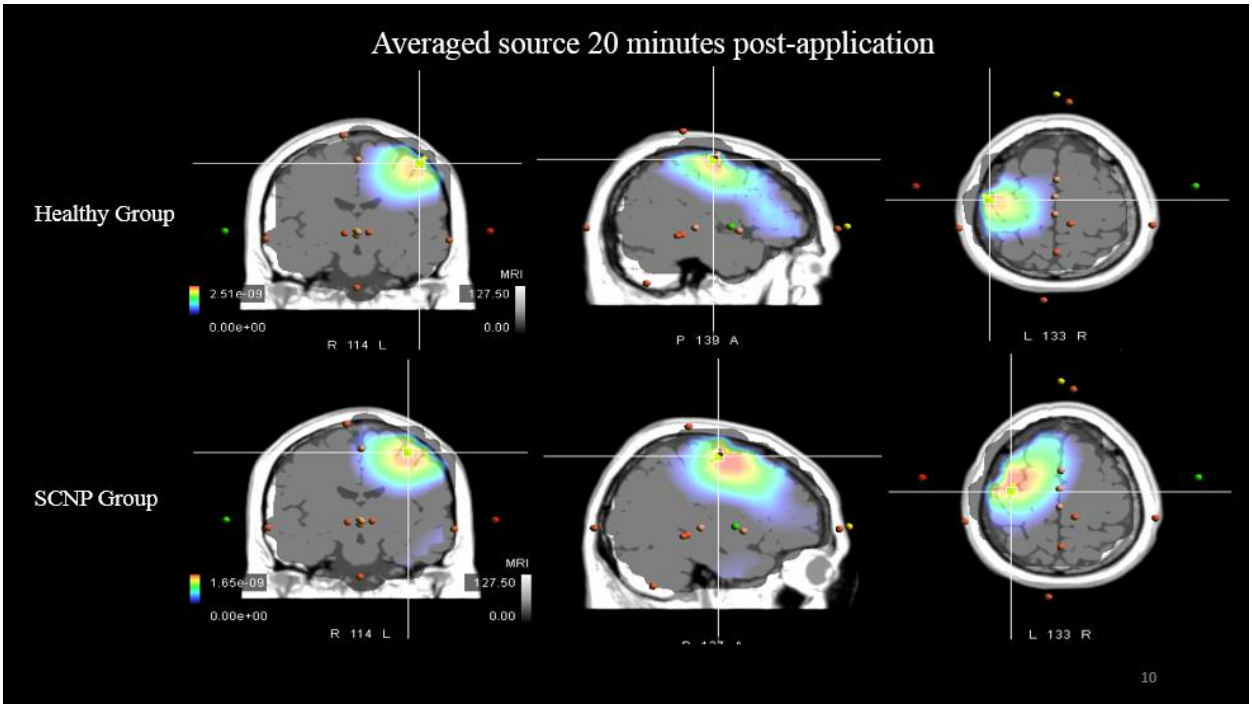


Figure 20. Average source localization (dipole) 20 min post-application of capsaicin in both the healthy group (top row) and SCNP group (bottom row). Image (left) is in coronal plane, (middle) is in sagittal plane, and (right) is in the axial plane.

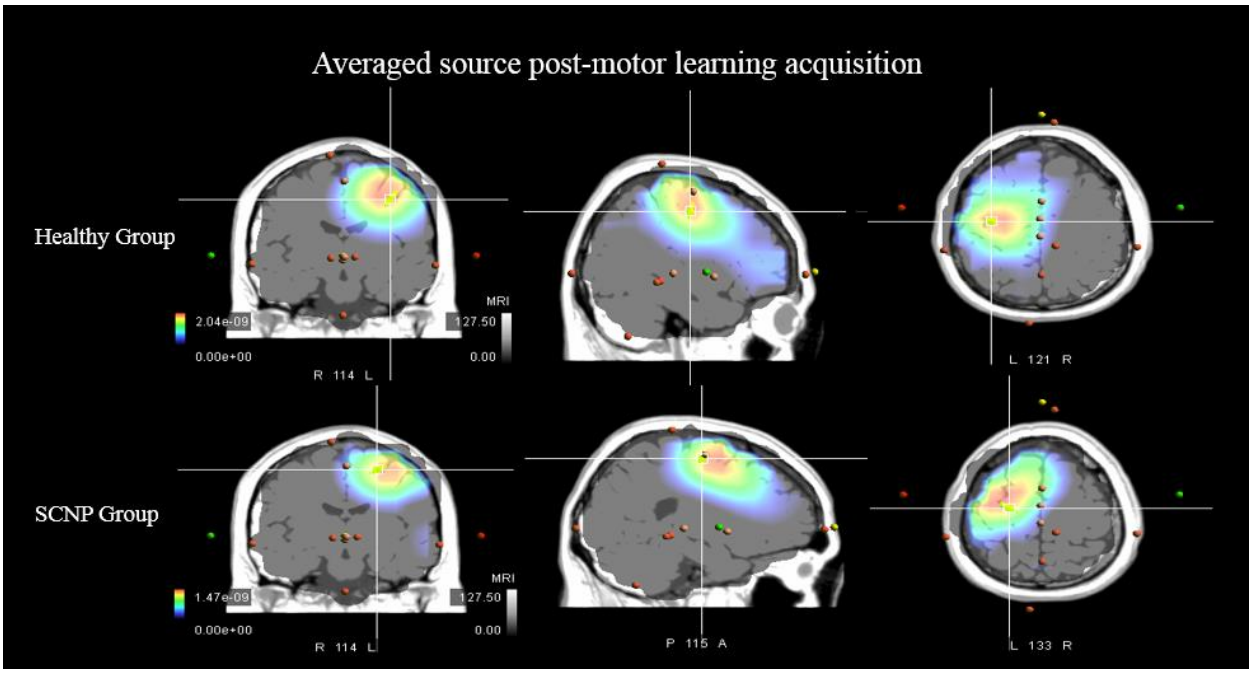


Figure 21. Average source localization (dipole) post-motor learning acquisition in both the healthy group (top row) and SCNP group (bottom row). Image (left) is in coronal plane, (middle) is in sagittal plane, and (right) is in the axial plane. Note the ventromedial shift in both groups.

	Healthy Group			SCNP Group		
Condition	Talairach (x)	Talairach (y)	Talairach (z)	Talairach (x)	Talairach (y)	Talairach (z)
Pre-application	-47.2	-18.9	54.8	-35.1	-18.6	54.8
Post-application	-47.2	-18.9	54.8	-35.1	-18.6	54.8
Post-motor learning	-35.2	-17.7	44.1	-23.1	-18.3	54.7

Table 2. Brain source coordinates in Talairach coordinates for the healthy and the SCNP group.

4.4 Discussion

The results in the healthy group follow similar trends to a previous study (Dancey et al., 2016) in the early cortical SEPs during which healthy control placebo group was compared to healthy capsaicin group following capsaicin cream application and motor learning acquisition. Although insignificant changes were seen in SEP peaks in the SCNP, the trend was similar to a recently published study (Andrew et al., 2017), especially in the N30 SEP peak with an upward trend following motor learning acquisition.

When motor learning was assessed, the healthy group increased significantly in accuracy following motor learning acquisition and during the retention test similar to previous studies (Dancey et al., 2016; Andrew et al., 2017)) where similar trend was observed. The SCNP group only demonstrated a significant increase in accuracy following motor learning acquisition, whereas the retention did not change in accuracy similar to Andrew et al (2017). If the period of consolidation required for learning is measured by the performance in retention, the lack of change in SCNP group during retention may suggest that the healthy group consolidated learning faster and to a greater extent than the SCNP group. Although not significant, the healthy groups had a lower baseline error (148%) error relative to the SCNP group (164%) error. The upper limb performance may potentially be compromised by altered afferent input in the SNCP group

prior to the measurement of acquisition (Haavik-Taylor & Murphy, 2011; Lee et al., 2004, 2005, 2008). Improvement in motor learning acquisition outcomes for the healthy group may be due to attention to the region undergoing learning where affective processing is modulated by attention and cognitive regulation (Ochsner & Gross, 2005) and stress leads to a narrowing of attention (Callaway & Dembo, 1958; Callaway, 1959).

The results of this study show that the SCNP group varied in their SEP peaks response to capsaicin during both post application (Figure 15) and post motor learning (Figure 16) when compared to healthy group that may be caused by the role of the underlying pathways related to motor control such as SI (N20), cerebellum (N18, N24, P25), and MI (N30). Since the N30 SEP peak almost reached significance with a greater increase post motor learning acquisition in both the healthy and the SCNP group, it reflects the activation of a neural network that links the thalamus, premotor areas, basal ganglia and MI (Kanovsky et al., 2003; Cebolla et al., 2011) and SMI (Rossi et al., 2003). A previous study by Cebolla et al. (2011) using swLORETA determined that the N30 peak is generated by network activity in the MI as well as the premotor and prefrontal cortex, however it is unclear whether the there is any change in activity in these areas when capsaicin was applied and when motor learning took place in both the healthy and the SCNP group. Nevertheless, since our findings showed a similar trend, where the N30 peak increased following motor learning for both groups, it may show that motor learning involves a neural network that integrates areas such as the MI, premotor and prefrontal cortex to fully process and comprehend changes induced by the activity.

Since it cannot be exactly determined whether the healthy group and SCNP group differed significantly in the N18, N20, N24 and P25 SEP peaks either during the application of the capsaicin or post motor learning acquisition due to the variability in the SEP peaks produced by

the SCNP group during acute pain, further work is needed to investigate these changes in order to determine the origin, severity and duration of pain in order to correlate them to the central changes in the brain. There is also the possibility that this variability in the SEP peaks in SCNP group during acute pain may represent maladaptive neuroplasticity where the recurrent pain may present with unpredictable central changes. Additionally, people with recurrent pain still have pain free days, and may be at different stages of altered neural processing which is reflected in the increased variability in this group.

Pain has been associated with altered brain functioning that affects intellectual processes such as attention due to significant changes in the ERP amplitudes that correspond to somatosensory and visual pain-related information (Sitges et al., 2007). Early SEP components can be linked to distribution of attentional resources that process sensory information located on primary and secondary sensory areas. This distribution or resources is usually altered in people with chronic pain conditions, such as those with fibromyalgia who may have impaired short term adjustment to repetitive tactile stimuli due to deficits in the cognitive assessment of the somatosensory information caused by delayed cognitive processes (Montoya et al., 2006). There is also research that indicates representation of muscles affected by pain are altered in the sensorimotor system and that the level of ongoing pain and associated neuroplastic changes can be reversed by motor learning acquisition (Pleger et al., 2005). There are conflicting findings that associate pain with interference in learning-induced motor plasticity (Boudreau et al., 2007) and also with improved motor performance and learning acquisition (Dancey et al., 2014, 2016). Enhanced SEPs amplitudes have also been observed in the presence of noxious stimuli during visual SEPs due to pain in patients with musculoskeletal pain, which indicate an important change in neural processing caused by emotional stimuli in individuals that suffer from chronic

pain (Sitges et al., 2007). In individuals with SCNP, the pain is not yet chronic, and this group may experience variable changes where some individuals experience improved motor performance compared to others where pain may interfere with such learning as it modulates both cortical responses to external stimuli and internal events that process painful events, cognitive, and emotional processes (Pinheiro et al., 2016).

Source Localization

Healthy Group

The premotor cortex has multiple functions that range from guiding of movement to participation in learning. Pre application and post application (Figure 22) coordinates show that the primary focal activity lies in the SMC, whereas the post motor acquisition coordinates demonstrate the activation of the PMC as well as the SMC with an increasing degree of probability between the two areas that may demonstrate an unequal contribution of these two regions. The post motor acquisition coordinates reside at the border of the SMC and the LPMC approximately and may represent overlap with an increasing difference in the probability in the axial plane which may explain that SMC has a greater contribution to the focal activity. It may also indicate that both of these areas are involved in the processing of the stimulus. When looking at the y coordinates of the three conditions, it can be seen that the value decreases between pre-application and post motor acquisition (Table 2) which may indicate a greater activation of the PMd, rostrally that is involved in the association of sensory stimuli with specific movements (Mayka et al., 2006).

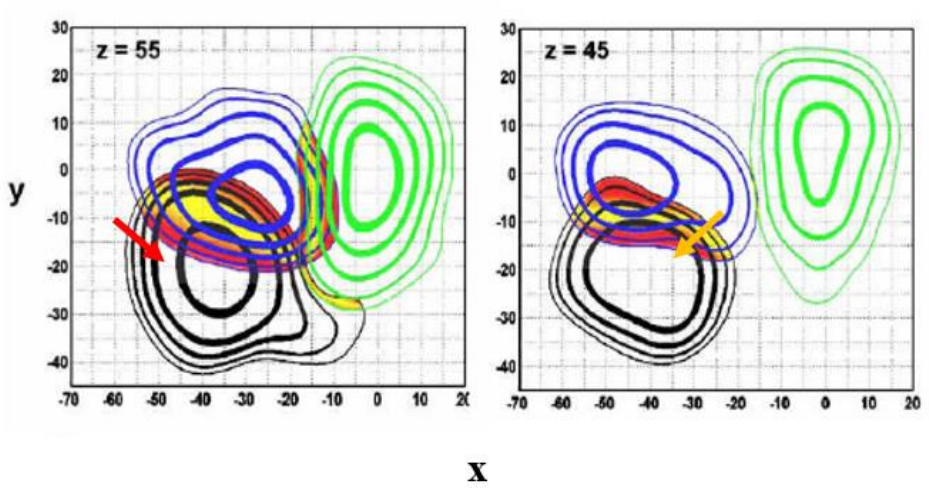


Figure 22. The probability map above shows MPMC (green), LPMC (blue) and SMC (black) that represent the percent probability. Red arrow indicates the location of the source during baseline and post application in healthy group. Orange arrow indicates the location of the source post motor learning acquisition (adapted from Mayka et al., 2006).

The rostral PMd has also been suggested to evoke a complex movement of the shoulder, arm, and hand that resembles reaching with the hand opened in preparation to grasp and is often studied with respect to its role in guiding reaching (Churchland et al., 2006). The LPMC plays a role in preparing movements to be executed through the MI which have modulatory roles on early somatosensory processing in premotor areas as well as association with cognitive processes (Brown & Staines, 2016; Picard & Strick, 2001). Since the participants are involved in the motor training task prior to this condition, it may help explain the relative shift to the rostral PMd. The frontal N30 appears to generate from neuronal populations within non-primary motor areas such as PMC and SMA with enhancement of the frontal N30 SEPs that are revealed during execution

of repetitive hand movements contralateral to the limb receiving median nerve (MN) stimulation (Brown & Staines, 2015).

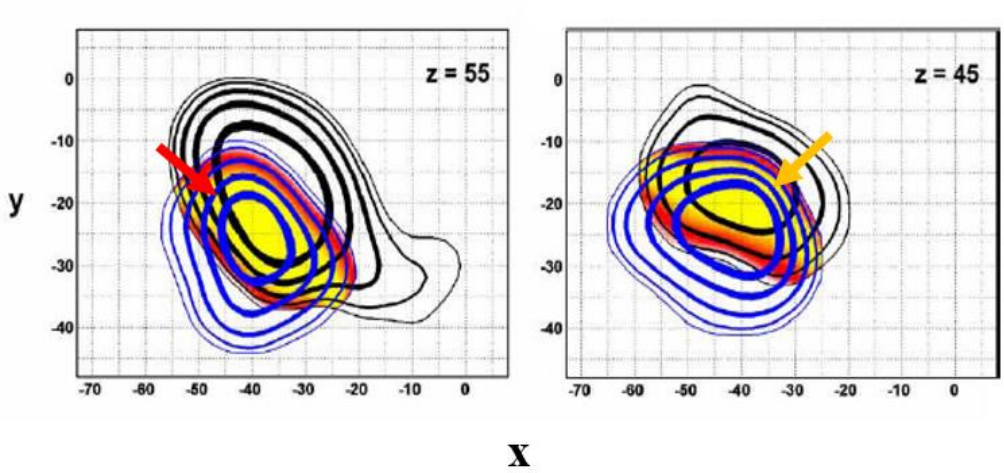


Figure 23. Contour lines and spatial probability maps between the regions designated as MI (black) and SI (blue). Pre application, post application and post motor coordinates indicate the activation of both MI and SI with equal probability in the axial plane. Red arrow indicates the location of the source during baseline and post application in healthy group. Orange arrow indicates the location of the source post motor learning acquisition (adapted from Mayka et al., 2006).

The activation of the SMC (Figure 23) is equally observable in all of the conditions where both the primary motor cortex and the primary somatosensory cortex are involved with the same probability which demonstrates an equal contribution of the regions. The difference in the z coordinates show that pre application and post application contributions were more dorsal versus the post motor acquisition condition. This may be due to the increased contribution of the premotor cortex leading to a rostral shift.

SCNP Group

In the SCNP group, the coordinates in the z axis and the y axis stayed relatively similar when compared to the x axis (Table 2) during which there is a medial shift towards the intrahemispheric fissure. Based on the coordinates, activity in all the conditions maps onto an overlapped region of the SMC and the LPMC that represents an increasing difference in the

probability in the axial plane favoring LPMC (Figure 24). The pre application and post application conditions show that the focal activity may reside at the border of the SMC and LPMC. The post motor acquisition condition shows that the focal activity is more medial and has a greater contribution of the LPMC as well as the SMC. Due to the medial shift in the x coordinates, the MPMC may also be contributing to the focal maximum during post motor acquisition condition.

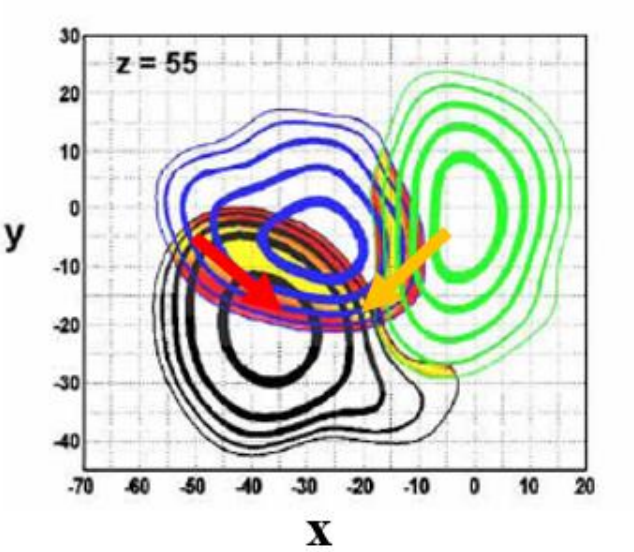


Figure 24. The probability map above shows MPMC (green), LPMC (blue) and SMC (black) that represent the percent probability. Red arrow indicates the location of the source during baseline and post application in SCNP group. Orange arrow indicates the location of the source post motor learning acquisition (adapted from Mayka et al., 2006).

The role of the MPMC was substantiated by Cunnington et al. (2002) showing that SMA proper and pre-SMA are active prior to volitional movement or action, as well as the cingulate motor area (CMA) and anterior mid-cingulate cortex (aMCC). SMA proper is directly connected to MI and to the spinal cord where its activation is due to motor execution (Dum & Strick, 1991). Pre-SMA has been shown to activate during matched tasks that required visuo-motor association (Sakai et al., 1999). A possible explanation to the potential activation of the MPMC post motor learning acquisition may arise from the findings of Sakai et al. (1999) that demonstrated that the

activation of the Pre-SMA in association with visuo-motor learning occurred when participants responded to visual cues. Since the tracing task used in the current study also incorporated color change from yellow if the wave was missed, to green if the cursor was on the wave, it may have provided a visual feedback to the SCNP group leading to an associated motor response through adjustment of the cursor to improve accuracy. In other words, the SCNP group may have relied to a greater extent on the visual cues of the tracing task to execute and correct the motor response leading to a possible activation of the MPMC. Previous studies have indicated that those with SNCP have worse proprioception (Haavik-Taylor & Murphy, 2007a, 2010, 2011) and slower mental rotation response times which would suggest that they would need to rely more on visual feedback during visuo-motor pursuit tasks.

It has also been shown by integrating simultaneously acquired EEG and fMRI that SMA and aMCC have strong reciprocal connections that act to sustain each other's activity, and that this interaction is mediated during movement preparation. The cingulate cortex has multiple functions which are divided by regions. For example, the anterior region is involved in executive function, while the dorsal region is involved in cognitive processes, the ventral region is involved in emotional regulation, and the posterior region is involved in evaluative processes (Rainville et al., 1997). The anterior cingulate gyrus (ACC) is integrally involved in pain processing and emotions which has anatomical connections between ACC, IC, SI, and SII that suggests that these regions do not function independently but are highly interactive. Possible local interconnections might allow the output of the ACC pain area to command immediate behavioral reactions such as escape from noxious stimuli as it serves as the conduit between the cognitive functions of the prefrontal cortex and the emotional experiences of medial temporal limbic systems (Rainville et al., 1997). It has also been demonstrated that ACC is involved in the

processing of pain-related affect, but not in the sensory processing of noxious stimuli (Fuchs et al., 2014). The medial shift towards the MPMC and its associated connections to the ACC may help explain that individuals with SCNP may have a hypersensitive processing of pain in the presence of noxious stimuli leading to an increased avoidance from pain (Fuchs et al., 2014). Since acute pain was elicited in the form of application of the capsaicin cream, it may explain increased affective processing of pain by the ACC leading to its avoidance due to hypersensitivity in the SCNP population.

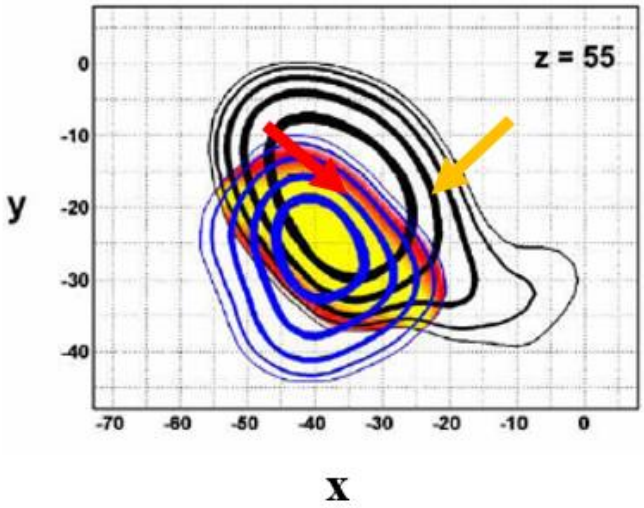


Figure 25. Contour lines and spatial probability maps between the regions designated as MI (black) and SI (blue). Pre application, post application coordinates indicate the activation of both MI and SI in the axial plane. Red arrow indicates the location of the source during baseline and post application in SCNP group. Orange arrow indicates the location of the source post motor learning acquisition (adapted from Mayka et al., 2006).

When considering the activation and the contribution of the SMC (Figure 25), both pre-application and post application conditions show an equal contribution of the MI and SI towards the focal maximum. During post motor acquisition, the focal maximum lies primarily in the MI bordering the SI which may reflect the transition that occurs with retention.

A previous study (Brown & Staines, 2015) suggested that the enhancement of N30 peaks during non-dominant limb movement may be caused by increased activity in SMA, MI and/or

basal ganglia, however this may also occur during dominant limb movement (Brown & Staines, 2015). Previous studies state that this cannot fully explain the facilitation of N30 peaks with dominant rather than non-dominant limb movements. Direct intra-cerebral recordings have found evidence that the frontal N30 is generated from neuronal populations in the dorsolateral PMC and SMA (Kaˇnovsk´y et al., 2003). This may supports the idea that enhancement of somatosensory processing, as indicated by the increased N30 amplitude during movement preparation and/or execution, occurs through intra-hemispheric connections between PMC and MI to PMC and/or SMA (Brown & Staines, 2015). Studies that have used EEG (Rossini et al., 1999; Waberski et al., 1999) have suggested through dipole modeling that the frontal N30 may be generated by summated somatosensory input into SI and MI as well as premotor areas. If this were the case, then increased frontal N30 peaks could reflect disinhibition or increased excitation in a more widespread network that includes PMC, SMA, MI and/or SI (Brown & Staines, 2015).

The SCNP population showed an upward trend in the N30 amplitude, even though it was more variable than the healthy group, suggesting similar involvement of the SMC and PMC leading to a more connected network which can also be observed in the healthy population. The changes observed in the SCNP population in which there is a more medial dipole shift may be due to the greater contribution of the MI and the MPMC, as well as CMA, potentially due to the recurrent pain experienced by the SCNP group.

The probability maps which were used to interpret the Brodmann areas related to the focal maxima found by the source localization software (Mayka et al. 2006) were based on a meta-analysis of 126 studies which included the premotor cortex and the sensorimotor cortex. The purpose of the Mayka et al. (2006) article was to define the three-dimensional boundaries as well as any overlap in these regions when specific tasks were tested. These models (Mayka et al.,

2006) represent regions of interest that are based on a probabilistic models characterizing the location of the activated voxel, with the variability used to generate the probability map. The use of the probabilistic model enables the visualization and ability to interpret the regions of interest that may have contributed in producing the focal maximum in this current study.

Mayka et al. (2006) also used the Talairach coordinate system as well as Brodmann areas, enabling us to interpret the anatomical location of the focal maxima found in this study as well as any overlap within the regions of interest.

Talairach coordinates, also known as Talairach space, is a 3-dimensional stereotaxic space created by Jean Talairach and Gabor Szikla in their work on the *Talairach Atlas* in 1967 which created a standardized grid of the human brain (Talairach & Szikla, 1980). This system uses Brodmann areas to classify brain regions by marking two anchors at the anterior and posterior commissure as horizontal plane and identifying anterior commissure as the origin point. The use of this system allows one to define standard anatomical landmarks that can be identified on different subjects using images obtained through MRI and positron emission Tomography (PET). A benefit to using Talairach coordinate system is that the normalization it provides establishes a common framework that can allow the comparison of results from different facilities (Mayka et al., 2006).

Limitations

As more variability in the data processing is introduced during steps such as post-processing, filtering, motion correction, and normalization, the results may also reflect this variability. Variability is unavoidable with this sort of data and data processing. Several studies have shown that the cytoarchitecture, the form and the shape of the brain is variable between

subjects that has probabilistic nature leading to the approximation of activation rather than an exact location (Mayka et al., 2006). The use of a probabilistic model template in imaging studies is not a gold standard, but it serves as an initial direction or a lead that may allow future neuroimaging studies to accurately quantify and describe the data in Talairach space.

This study also used a standardized Collins head model. The use of individual head models based on actual MRI images may have improved accuracy due to its segmentation of the MRI into dissimilar head compartments, which include the skull that may not be as prevalent with standard T1 weighted MRI. However, the standardized spherical head model used in this study is the most commonly used model due used to describe the lead field that represents the electromagnetic (conductivities) and geometrical (shape) properties of the volume (Michel et al., 2004). The use of the Talairach system also has disadvantages as it is an approximate method based on gross visual inspection rather that histology that was created from a single post-mortem brain that was smaller than average cranium (Talairach & Szikla, 1980).

There is also the possibility of Type II error due to small sample size which may not have demonstrated all changes in the SEP peaks following capsaicin application and motor learning acquisition in the SCNP group. The variability in the SEP peaks of the SCNP group may have contributed to the lack of significance. Increasing the number of participants in future work may help determine whether the variability is consistent, as well decreasing the probability of a Type II error.

5. Thesis Summary

The study in this thesis showed that the N30 SEP peak almost reached significance where both the healthy and the SCNP group had an increased SEP peak amplitude post motor learning acquisition when compared to baseline. Their accuracy at performing the tracing task also improved during acute pain, however, only the healthy showed a greater improvement in accuracy during retention which may explain that this group had an improved learning experience compared to the SCNP group which did not show any improvement during retention. The healthy group also showed a similar trend in SEP peak changes to a previous study by Dancey et al. (2016) when these changes were observed after the application of the capsaicin cream as well as post motor learning acquisition that showcases the similarity in obtaining evoked potentials regardless of the modality. It also demonstrates that the neural generators associated with the SEP peaks represent improved sensorimotor integration in the presence of acute pain.

The variability in the generated SEP peaks in the SCNP group may also indicate variable sensorimotor integration in these individuals during acute pain. This may be explained by maladaptive neuroplastic changes in some of the individuals in the SCNP group where the introduction of pain may have led to unpredictable outcomes. Although SCNP may not be considered chronic, previous studies assessing chronic pain demonstrated impaired short term habituation to stimuli due to impaired cognitive evaluation of the somatosensory information (Montoya et al., 2006) and abnormal brain functioning in association with cognitive processes (Sitges et al., 2007). It is a possibility that the SCNP group may have similar impairments as individuals with chronic pain as well as a similar reaction to a healthy population in the presence

of acute pain leading to the introduction of variability in the SEP peaks and sensorimotor integration.

The utilization of EEG and swLORETA to source localize the brain activity contributing to the SEP peaks at baseline, post application of cream, and post motor learning acquisition allowed the focal maxima to be visualized as well as the extraction of coordinates to determine the cerebral regions contributing the generation of the peak. This made it possible to compare the results to previous literature relating Talaraich coordinates to different brain regions (Mayka et al., 2006). The software determined the probability distribution, which enabled the determination of the likelihood that at least one activation focus lies in a given voxel. It also allowed us to determine whether there was any overlap within the neighboring regions such as the SMC and the PMC in the established motor area template. The use of such technology demonstrated that sensorimotor integration following motor learning requires the contribution from the SMC as well as PMC that is divided into LPMC and MPMC. The evoked potentials primarily involved activity in the SMC as a potential neural generator for the N30 peak. Post motor learning acquisition revealed that the LPMC also contributed to the SEP peak in the healthy individuals. The LPMC is involved in movement execution through the MI as it has a modulatory role, and the enhancement of the N30 peak in the PMC is seen with repetitive hand movement such as in the tracing task used in the current study.

The study also demonstrated that SCNP group had a contribution from the SMC and the PMC during baseline and post application of capsaicin cream. However, post motor learning acquisition, the focal maximum had a greater medial shift towards the intrahemispheric fissure that may also include the contribution of the MPMC to generate the N30 peak. Previous research (Cunnington et al., 2002) demonstrated that the MPMC that includes the pre-SMA and SMA

proper are active during volitional movement and has connections to the CMA that processes pain and elicits behavioral reactions leading to avoidance of pain. This may lead to hypersensitivity to pain through increased affective processing and avoidance (Fuchs et al., 2014). Another explanation of the dipole medial shift toward the MPMC and its contribution might be the pre-SMA's visuo-motor associations in which the visual cues from the tracing task may have provided feedback to the SCNP group allowing them to adjust their response (Sakai et al., 1999). Individuals with SCNP are known to have worse proprioception (Lee et al., 2004, 2005; Haavik-Taylor & Murphy, 2011), therefore they may need to rely more on visual feedback to improve their performance and increase SMI.

The study offers an interesting insight into the neural generators of the SEP peaks as well as localizes the focal maxima in order to determine the underlying regions that contribute to the SEP peak. It allows us to visualize the areas of interest and whether other neighboring areas also contribute through the presence of overlap between these regions. This provides us an opportunity to interpret the findings based on previous research in order to help explain the results so clinical work as future research work can build upon such findings. By determining that individuals with SCNP may also use visual feedback to correct or enhance their movement, it may allow us to establish rehabilitation programs where both visual and tactile feedbacks are provided in order to improve SMI. Since individuals with SCNP may also have hypersensitivity to pain, the reduction of noxious stimuli that may increase pain may help reduce its avoidance leading to improved attention to a task. Further research would also be needed that specifically targets these areas such as the PMC and ACC through the use of source localization to determine whether different tasks improve SMI as well as different types of noxious stimuli elicit a different responses in the SCNP population.

5.1 Implications of this research for Health Informatics

Informatics incorporates a set of methodologies that are applicable for managing data, information, and knowledge across the healthcare fields and research to clinical care that include bioinformatics, imaging informatics, clinical informatics, and public health informatics (Sarkar, 2010). This gathered information and research findings provide support for the transfer and integration of knowledge. Imaging informatics allow for the development and analysis of visualization approaches for understanding pathogenesis and identification of treatments (Sarkar, 2010). EEG has been used to assess and address central changes related to pathophysiological and biopsychosocial factors which has continued to evolve over the past few decades where it has been heavily utilized in sleep, epileptic, as well as pain studies. The incorporation of EEG to assess sensorimotor integration in neck pain individuals may provide explanation to the source of the activity and whether it is altered in comparison to a healthy group.

The implications of using this modality in a larger population and in bigger facilities such as hospitals may allow it to grow exponentially in the future. Although EEG source imaging has evolved tremendously where it can provide statistical interpretations of scalp recordings (Michel et al., 2004), it can also be time consuming as the setup requires utmost care. Therefore, its translation to the bedside requires further streamlining where the process of application of the EEG cap for recording and analyzing the data is efficient and automated, respectively. Currently, EEG requires an appropriate selection of the electrode montage (channels) and their location measurement on the scalp which is inefficient. It also requires extensive noise reduction through the cap application as well as through the collection process that may interfere with the signal leading to erroneous results. In order to achieve greater optimization and streamlining of the procedure, these steps need to be automated where a clinician such as a physician, a psychiatrist,

or a nurse can simply apply the EEG cap to collect and analyze data at the same time without introducing noise that could weaken the results.

There is also an increased chance of introducing artifacts with EEG data acquisition due to an increase in the number of recording channels. For instance, artifact contamination due to poor scalp contact or amplifier malfunction can affect source localization if the data are averaged over conditions or over a cohort of individuals (Michel et al., 2004). There is also the possibility of the inability to recognize artifacts in the early stages of data collection that may only appear once the data is processed and averaged that could potentially affect the final results as well as the interpretation of the data. In order to overcome this limitation, artifact identification and correction needs to be more rigorous or automated where it does not alter the final outcome such as source localization of the EEG activity as well as it can be easily recognized and automatically implemented by the software. This would make EEG as an effective alternative to an MRI in a clinical setting where the user can simply implement it without considering or worrying about artifact contamination and effecting the final outcome. For example, if any artifacts such as eye blinks or muscle movement are detected by the software, they are automatically detected, marked and omitted from the signal in order to ensure that the user recognizes their omission and obtains a clean signal.

Current research allows one to understand that even though EEG has evolved over the past few decades, it still requires a great amount of attention to detail to ensure the data is clean and authentic where its application may not be as efficient as MRI.

The spatial resolution of EEG is considered its biggest limitation, but through careful processing, modern inverse solutions such as swLORETA and using realistic head models based on the individual's MRI can lead to it as a true neuroimaging tool (Michel et al., 2004). The EEG

method used to achieve results in this thesis may allow for the development of a framework and identification of the streamlined techniques that could be used to measure EEG waveforms and identification of areas of interest within the brain using these imaging techniques. It may lead to the advent of new techniques and algorithms that may not require numerous electrodes to accurately capture brain wave data; or better source localization algorithms that can be easily utilized and interpreted in the field. The development of advanced design in EEG data collection, and better algorithms for data processing and analysis, built upon this framework, will advance the ability of EEG to be used as a sensitive diagnostic measure. It may potentially enable clinicians to identify neurological issues in patients without long wait times as well as reduced cost to the system. Future EEG standards would be an essential component towards the goal of integrating relevant data across the translational barriers where it would be considered as a more viable alternative to the current imaging techniques in multiple disciplines. These standards can facilitate the access and integration of information associated with a particular individual in light of available biological and clinical data to create a personalized care plan.

5.2 Conclusion

In conclusion, the observed results of this thesis show that the trends in early SEP peaks follow previous studies (Dancey et al., 2016; Andrew et al., 2017). The healthy group experienced a consistent neurophysiological response after the application of the capsaicin cream and motor learning acquisition as compared to the SCNP group which demonstrated a more variable neurophysiological response. The motor performance in the healthy continued to improve in the healthy group, same as previous study, but the SCNP group failed to improve during retention. Source localization also established a different neurological contribution to the

SEP peak in the healthy group as compared to the SCNP group where the latter showed a greater medial dipole shift.

5.3 Future Research

Future research work should include placebo or a SCNP group that is exposed only to placebo cream that does not elicit pain. This would enable direct comparison of the two groups through source localization via whole head EEG, which assesses the underlying cortical areas such as the SMC and PMC in order to determine whether there are any similarities or differences in SMI as well as active areas. With respect to health informatics, future research should also examine and assess the effectiveness of EEG as a diagnostic tool, similar to MRI where the application of the modality is simplified to a degree that can be easily utilized by any clinician in any setting, as it is more compact and versatile, with on-line analysis algorithms possible. Future research should assess the efficiency of EEG and source localization as compared to other modalities such as functional magnetic resonance imaging (fMRI).In addition to better temporal resolution, EEG has the capacity to investigate changes in neural processing and could become routinely used to assess neural changes in the rehabilitation field following stroke and in individuals with chronic pain. Mobile EEG systems are becoming increasingly affordable, which means that EEG will be able to be used in brain computer interfaces to improve movement ability following strokes and spinal cord injuries. Informatics approaches to streamline signal processing and analysis will enhance the diagnostic and therapeutic potential of this modality.

6. Appendix

Confidential Health History

RESEARCH STUDY CONFIDENTIAL HEALTH HISTORY

Subject CODE: _____

How old are you?

You are: Male □ Female □

Are you: Left Handed □ Right Handed □

Do you play a musical instrument Yes □ No □

If yes, how many times a week?

Do you play competitive sports? Yes □ No □

If yes, please indicate what sport and how often?

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 (ringing in ears) yes □ no □

Blurred vision yes □ no □

Sensory/motor disturbance yes □ no □

The Neck Disability Index

This questionnaire has been designed to give your therapist information as to how your neck pain has affected your ability to manage in everyday life. Please answer every question by placing a mark in the **ONE** box which applies to you. We realize that 2 of the statements may describe your condition, but please mark only the **ONE** box that most closely describes your current condition.

Neck Pain Intensity

- ○ I have no pain at the moment.
- ○ The pain is very mild at the moment.
- ○ The pain is moderate at the moment.
- ○ The pain is fairly severe at the moment.
- ○ The pan is very severe at the moment.
- ○ The pain is the worst imaginable at the moment.

Concentration

- ○ I can concentrate fully when I want to with no difficulty.
- ○ I can concentrate fully when I want with slight difficulty.
- ○ I have a fair degree of difficulty in concentrating when I want to.
- ○ I have a lot of difficulty in concentrating when I want to.
- ○ I have a great, great deal of difficulty in concentrating when I want to.
- ○ I cannot concentrate at all.

Personal Care (eg washing, dressing)

- ○ I can look after myself normally without causing extra pain.
- ○ I can look after myself normally but it causes extra pain.
- ○ It is painful to look after myself, and I am slow and careful
- ○ I need some help, but manage most of my personal care.
- ○ I need help every day in most aspects of self care.
- ○ I do not get dressed, I wash with difficulty, and stay in bed

Work

- ○ I can do as much work as I want too.
- ○ I can only do my usual work, but no more.
- ○ I can do most of my usual work, but no more.
- ○ I cannot do my usual work.
- ○ I can hardly do any work at all.
- ○ I cannot do any work at all.

Lifting

- ○ I can lift heavy weights without extra neck pain
- ○ I can lift heavy weights, but it gives extra neck pain
- ○ Neck pain prevents me from lifting heavy weights off the floor, but I can manage if they are conveniently positioned, for example on a table
- ○ Neck pain prevents me from lifting heavy weights, but I can manage light to medium weights if they are conveniently positioned
- ○ I can lift only very light weights
- ○ I cannot lift or carry anything

Driving

- ○ I can drive my car without any neck pain at all.
- ○ I can drive my car as long as I want, with slight pain in my neck.
- ○ I can drive my car as long as I want, with moderate pain in my neck.
- ○ I cannot drive my car as long as I want, because of moderate pain in my neck.
- ○ I can hardly drive at all because of severe pain in my neck.
- ○ I cannot drive my car at all because of the pain in my neck.

Reading

- ○ I can read as much as I want, with no pain in my neck.
- ○ I can read as much as I want, with slight pain in my neck.
- ○ I can read as much as I want, with moderate pain in my neck.
- ○ I cannot read as much as I want, because of moderate pain in my neck.
- ○ I can hardly read at all because of severe pain in my neck.
- ○ I cannot read at all because of pain in my neck.

Sleeping

- ○ I have no trouble sleeping.
- ○ My sleep is barely disturbed (les than 1 hr, sleepless).
- ○ My sleep is mildly disturbed (1-2 hrs, sleepless).
- ○ My sleep is moderately disturbed (2-3 hrs, sleepless).
- ○ My sleep is greatly disturded (3-5 hrs, sleepless).
- ○ My sleep is completely disturbed (5-7 hrs, sleepless).

Headaches

Recreation

○ I have no headaches at all. ○ I have slight headaches which come infrequently. ○ I have moderate headaches which come infrequently. ○ I have moderate headaches which come frequently. ○ I have severe headaches which come frequently. ○ I have headaches almost all the time.	○ I am able to engage in all my recreational activities, with no neck pain at all. ○ I am able to engage in all my recreational activities, with some pain in my neck. ○ I am able to engage in most, but not all of my usual recreational activities, because of pain in my neck. ○ I am able to engage in few of my usual recreational activities, because of pain in my neck. ○ I can hardly engage in any recreational activities because of pain in my neck. ○ I cannot engage in any recreational activities at all because of pain in my neck.

Vernon, H. and S. Mior, *The Neck Disability Index: A Study of Reliability and Validity.* Journal of Manipulative and Physiological Therapeutics, 1991. **14**(7): p. 409-415**.**

Neck Pain Mini-Questionnaire

Indicate which statement best describes your neck pain.

I have neck pain all the time.

I have neck pain most of the time.

My neck pain comes and goes. Sometimes I have neck pain and sometimes I don't.

I have neck pain on the rare occasion.

I never have neck pain.

In your own words, please describe the location, onset, and type of pain you experience:

Approximately how long have you had this problem? _____

Have you had previous care for this condition? Yes No

If yes, please check one: chiropractic physiotherapist Other:

_____

Approximately when did you have these treatments:_____

Have these treatments helped? Please explain._____

Can you think of an accident or other event that caused your pain or stiffness? Check one:

Yes No Unsure

If yes, please explain: _____

Have you had previous trauma? Yes No

Explain:_____

Have you had previous surgery? Yes No If applicable,

explain:_____

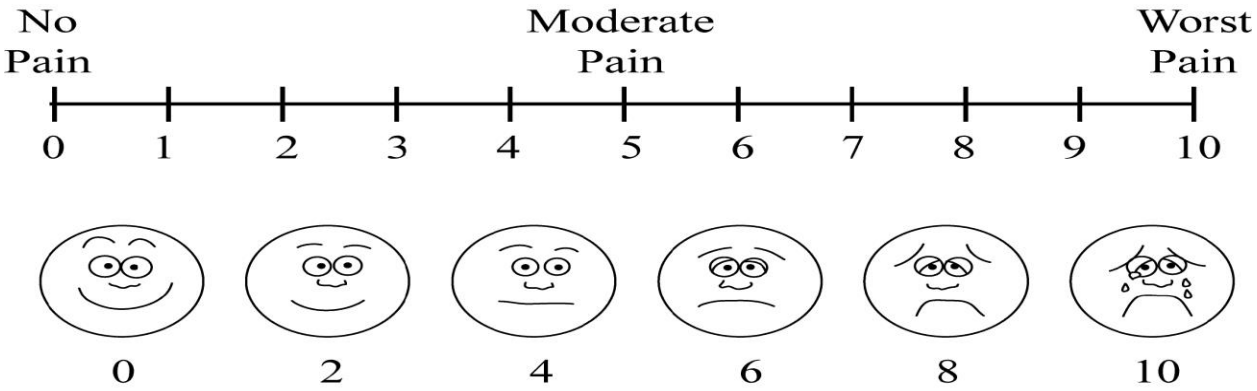
_____

On a scale of 1 to 10 how severe is your neck pain or stiffness? 1 indicates little or no pain. 5 indicates uncomfortable, but manageable. 10 indicates unbearable – seek help now!

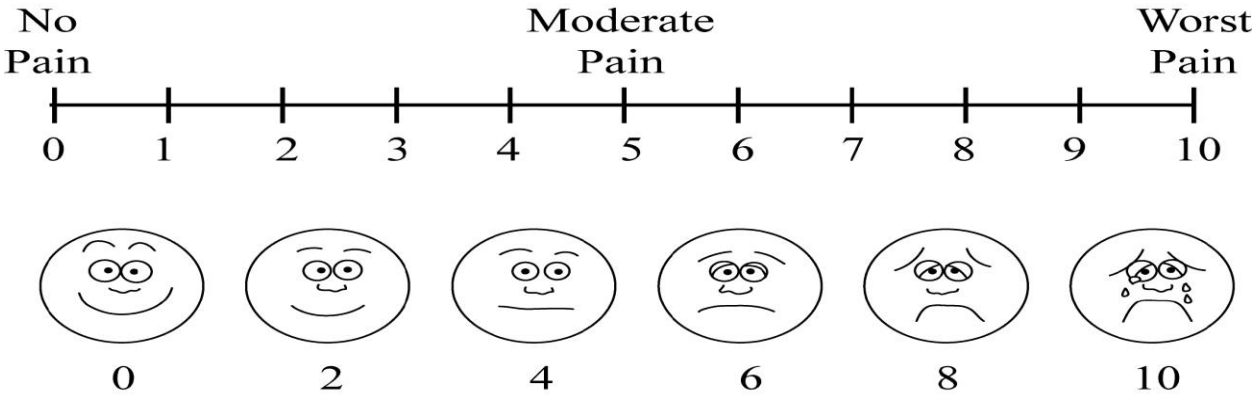
How often does your neck pain or stiffness occur (ex. Every two weeks) _____

When is your birthdate? _____

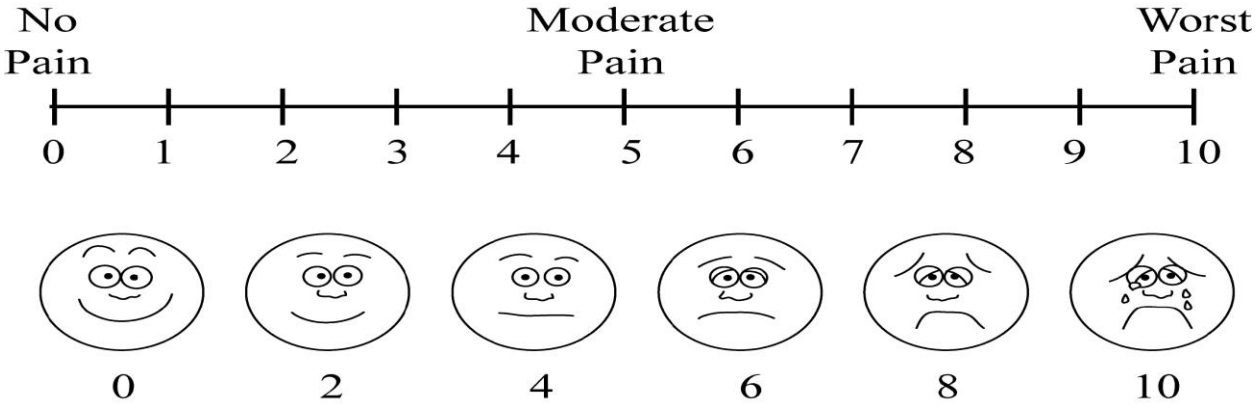
Numeric Pain Ratings Scale



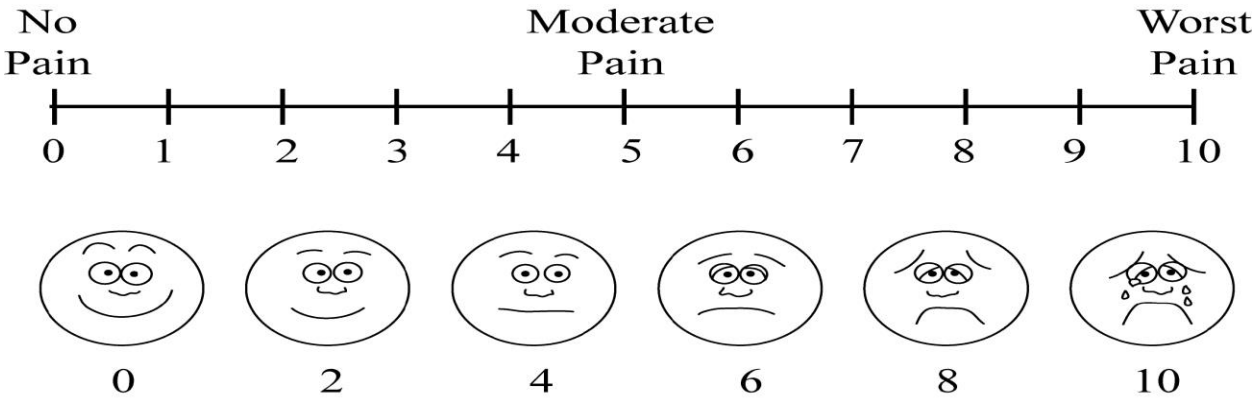
Baseline



20min Post Application



Post Motor



Following Last Sweep

Consent Form

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Central sensitization evokes changes in the properties of nerve conduction

Purpose of the Study

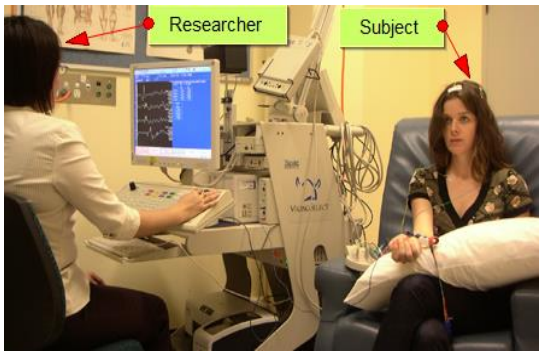
The physiologic mechanisms of pain are poorly understood. Central sensitization in an important, if not fundamental, mechanism in expression of pain yet there is currently no objective measure of central sensitization. Central sensitization is defined as an 'increased excitability' of nerves in the central 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 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 Bernadette Murphy, Dr. Paul Yielder and Hasan Shafiq

(Masters student) all from the Faculty of Health Sciences at UOIT; and Erin Dancey and Joanne Gourgouvelis, PhD students from the Faculty of Science at UOIT. (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.



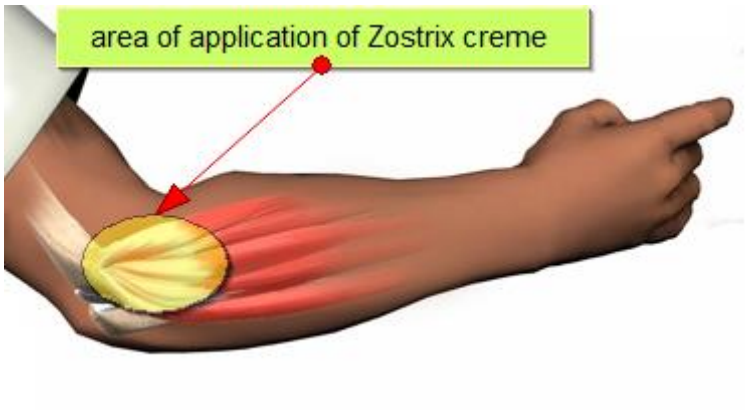
You will be seated in a comfortable reclining chair for the recording of the nerve impulses. There are three different types of nerve impulses which we wish to test. You may choose to participate in **one, two or three of the measurement types.**

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 thumb for a period of 20 minutes. There will be sequences of four letters arranged in random order 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 your ability to type these sequences.

Tracing task intervention

Some experiments will include a tracing task which will take place after the cream has been applied. You will be required to trace sequences of sinusoidal-pattern waves with varying frequency and amplitude using only you thumb on an external wireless touchpad for a period of 20 minutes. We will be monitoring accuracy in order to determine the effects of capsaicin on your ability to trace these sequences.

Cortisol

Cortisol is a steroid hormone released during stressful episodes such as acute pain. Cortisol elevation is a normal part of the physiological response to stress. Elevations in cortisol production is linked with changes in the way the brain functions which can affect task performance. The researchers will use swabs under your tongue to collect your saliva three times throughout the experiment. These samples of your

saliva (spit) will then be put in the freezer and will be later tested at a laboratory for the stress hormone cortisol.

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 Research

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