The Effects of Motor Task Complexity on Sensorimotor Integration: Implications for Healthy and Subclinical Populations

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ABSTRACT

The central nervous system's (CNS) plastic ability allows for adaptation to the various physiological changes and experiences we encounter. This occurs through dynamic shifts within the connections and strengths of neural networks, altering the way in which the CNS integrates sensory information; a process termed sensorimotor integration (SMI). Plasticity is the mechanism for development and learning. However, it can also be a mechanism for maladaptive changes such as the organizational changes seen in people with overuse injuries and chronic pain. These maladaptive changes are associated with debilitating symptoms which include the deterioration of learning and retention of skills. The prevalence of repetitive strain and overuse injuries is steadily increasing given the rise of repetitive movement occupations and sedentary lifestyles. Typically, the neuroplastic changes associated with these disorders are identified with the use of neuroimaging techniques. While such techniques provide accurate imaging of the organizational changes that occur, they are expensive to provide, have long wait times and are generally only performed once symptoms have become debilitating. The investigation of repetitive movement and its effects on SMI can be combined with electrophysiological techniques such as somatosensory evoked potentials (SEPs) which directly measure the electrical activity of neural areas involved in learning. Understanding the processes of repetitive activity and the neuromodulatory changes which occur is fundamental in order to understand conditions which may lead to maladaptive changes that may initiate chronic pain and overuse disorders.

The studies in this thesis aimed to first investigate the changes which occur following a motor learning task in neural networks of a healthy population, with attention to the cortico-subcortical and cortico-cerebellar projections which play crucial roles in motor learning and SMI. This information was then applied to a low grade neck pain population, providing insight into the early maladaptive changes which occur before the condition becomes severely chronic. The studies indicated that following a complex motor training task, significant changes in activity occurred within those cortico-subortical and cortico-cerebellar projections, known to be critical for effective learning and reiterating the importance of these areas in learning and SMI. When applied and compared to participants with current and/or recurrent neck pain, marked differences in neural areas associated with learning and SMI were seen, which was corroborated by inferior performance on the motor task. This study provides evidence that SEPs can be used as a screening tool and potential marker of the early stages of maladaptivity and the need for preventative measures.

KEYWORDS: somatosensory evoked potentials (SEPs), cerebellum, sensorimotor integration (SMI), low grade neck pain (LGNP), motor training

STATEMENT OF ORIGINALITY

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

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LIST OF ABBREVIATIONS USED

ACC Accuracy

ANOVA Analysis of Variance

APB Abductor pollicis brevis

CNS Central nervous system

ECG Elecrocardiogram

EEG Electroencephalography

fMRI Functional magnetic resonance imaging

IFCN International Federation of Clinical Neurophysiologists

LGNP Low grade neck pain

M1 Primary motor cortex

OOI Occupational overuse injury

PET Positron emotion tomography

PMC Pre motor area

RSI Repetitive strain injury

RT Reaction time

SEP Somatosensory evoked potential

S1 Primary somatosensory cortex

SMI Sensorimotor integration

SMA Supplementary motor area

SNCP Subclinical neck pain

swLORETA Standardized weighted low resolution brain electromagnetic tomography

TMS Transcranial magnetic stimulation

VPL Ventro-posterior lateral

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INTRODUCTION TO THESIS

The peripheral and central nervous systems (CNS) are constantly relaying information to one another; this creates a fundamental feedback loop whereby sensory, or afferent input, is integrated by the CNS and used for assisting in the execution of the appropriate motor output. The ability of the CNS to perform this integration relies on its reorganization; plastic changes in the way that the CNS filters information in response to afferent input in a process termed sensorimotor integration (SMI). These CNS alterations have been shown to persist following the period of afferent input to induce organizational changes in synaptic connectivity and strength in both the primate and human cortices (Byl et al., 1997; Classen et al., 1998; Haavik Taylor and Murphy, 2007a, 2007b; Murphy et al., 2003). Input in the form of behavioural training has been shown to induce these organizational changes and the retention of such alterations reflects the reinforcement of sensorimotor skill acquisition or motor skill learning (Nelson et al., 2009). While these changes are desired for function and the learning of new skills, evidence also indicates impaired SMI and maladaptive plasticity in concordance with the development of movement disorders following prolonged periods of repetitive movements (Byl et al., 1997; Haavik Taylor and Murphy, 2007a, 2007b; Haavik Taylor and Murphy, 2010a, 2010b; Tinazzi et al., 1998; Tinazzi et al., 2000).

In various movement and neurological disorders, dedifferentiated anatomical changes are correlated with unfavourable behavioural changes and pain, thus lending strength to the hypothesis that pain interferes with the process of SMI (Byl et al., 1997; Elbert et al., 1998; Tinazzi et al., 1998). Typically, these disorders are diagnosed following the manifestation of debilitating symptomology and many studies investigating the changes which occur are done so with the use of positron emission tomography (PET) or functional magnetic resonance imaging

(fMRI) paradigms. While these techniques provide accurate information and images, they pose difficulty with wait times and are too expensive for routine use in research studies (Pelletier et al., 2007). While little is still known about the implications of repetitive muscular activity in humans, motor training tasks can be used in combination with electrophysiological techniques to investigate SMI. This has been demonstrated through studies which have shown changes in cortical somatosensory evoked potentials (SEPs) following the cessation of a repetitive typing task (Haavik Taylor and Murphy, 2007; Haavik Taylor and Murphy, 2007a; Murphy et al., 2003). These studies have focused on simple tasks which require little attention, resulting in automatic processing rather than learning. Additionally, many studies have focused on the occurrence of cortical changes but have not delved into the roles of subcortical structures and the cerebellum within the realm of SMI, both of which provide extensive understanding in to the processes of learning, retention and adaptation of skills.

One out of every 10 Canadian adults has had a repetitive strain injury (RSI) serious enough to limit their normal daily activities and an estimated 2.3 million people, aged 20 or older have reported having had an RSI at some point in the 12 months prior to their participation in the Canadian Community Health Survey in September of 2000. This is a marked increase in the prevalence of RSIs from the late 1990s and it is a condition that is continually rising (Tjepkema, 2003). Of these muscular disorders, neck pain has quickly emerged as common health problem, during any six month period, there is a 54% prevalence and 4.6% of those individuals are suffering from significant daily limitations because of it (Côté et al., 1998). Modern day society's lifestyle of increased technology use and poor work station set-up has exacerbated the occurrence of neck pain (Carroll et al., 2008; Hogg-Johnson et al., 2009). The technique of SEPs provides a cost-effective way to directly measure neural activity with high temporal resolution,

we can therefore use this to establish a timeline with regards to the changes seen in those suffering from neck pain.

One of the greatest challenges when utilizing SEPs is understanding the correlation of the changes seen in peak amplitudes with actual purpose and function. It is fundamental to first understand the changes that occur in a healthy population in order to establish a normative axis from which we can then compare to subclinical and furthermore, clinical populations. This research therefore aims to establish a better understanding of the neurophysiological and behavioural characteristics which underlie adaptive plasticity which in turn will provide an axis of normalcy to better understand and address those characteristics which accompany maladaptive plasticity. This research will utilize the technique of SEPs which consists of stimulation of a peripheral nerve of interest and recording the resulting central nervous system activity though surface and scalp electrodes. Measurement of peak amplitudes reflecting various neural structures along the pathway provides us with insight into the areas involved in SMI.

This issue is also of greater concern due to increased computer usage which is associated with neck pain in adolescents. As this is presenting more commonly, development of musculoskeletal disorders is no longer the problem of a middle aged person, the emergence of these symptoms 20 years earlier in the lifespan may lead to an even heavier burden on the healthcare system and to the workplace with increasing sick leaves (Hakala et al., 2006). A greater understanding of the mechanisms of changes that occur with regards to SMI and the role of various neural areas will aid in identifying the most effective motor training paradigms. Therefore, this research aims to gain a more in depth understanding of how sensorimotor processing is altered due to motor training tasks and variations of these tasks. Preventing the

development of chronic pain and enhancing function to decrease the risk of injury in occupational, recreational and domestic settings are outcome measures of this work. It is hoped that through further understanding of the effects of motor learning on SMI that opportunities for optimal methods of training and rehabilitation can be established and regulated.

HYPOTHESIS AND OBJECTIVES

Objectives of this Research

1. To improve and validate the use of two complex repetitive task modalities, one tracing and one typing task that can reflect the effects of long term motor learning in a healthy population.
2. To differentiate the neurological and behavioural characteristics following a motor learning task in a healthy population with a low grade neck pain population.

Hypotheses of this Research

1. A more complex motor training task will lead to greater changer in SEP peak amplitudes. Namely the N18, N24 and N30 SEP peaks.
2. Neural markers of excitability in those with low grade neck pain will differ from the healthy population, namely with elevated cortical SEP peaks, and smaller changes in subcortical peaks associated with long term learning.
3. Behavioural markers in those with low grade neck pain will differ from the healthy population in demonstrating unfavourable performance with decreased accuracy.

OVERVIEW

This thesis is divided into the following sections:

1. Literature review
2. Proposed Research
3. Manuscripts for each study, in the format specified for submission to Clinical Neurophysiology
4. Overall Summary
5. Appendices that include the questionnaires and consent forms

SECTION 1: LITERATURE REVIEW

Introduction to Literature Review

This section reviews current literature relevant to the proposed project of this thesis. An overview of sensorimotor integration, its functional neuroanatomy, the processes of motor skill learning/acquisition, an overview of the occurrence of neck pain, the impact of pain and repetitive motion on sensorimotor integration and the process of motor learning will be discussed. Additionally, the use of somatosensory evoked potentials (SEPs) with regards to the investigation of sensorimotor integration and motor learning will be presented.

Sensorimotor Integration

Sensorimotor integration (SMI) is the process whereby sensory input is integrated by the CNS and used for appropriate motor programme execution (Abbruzzese & Berardelli, 2003). The afferent information coming in from the environment is projected to cortical motor areas, resulting in the ability to appropriately utilize sensory information for assisting in the proper or desired motor program output in the musculature that is carrying out the task at hand. We live in an environment which is ever changing and we therefore need to be able to adapt to these changes; in order to effectively learn and perform a motor skill, the employment of appropriate SMI is required.

It is well known that the adult CNS retains its ability to reorganize itself in response to altered afferent input (Classen et al., 1998; Haavik Taylor & Murphy, 2007a, 2007b; Murphy et al., 2003; Tinazzi et al., 1998). Representations in a particular sensory or motor realm are said to expand, or contract, so that they occupy a larger or smaller "plot" of neural territory. These changes occur due to the plastic nature of the brain. Thus, relating this to sensory and motor

aspects which can either occupy larger or smaller areas; plasticity is an experience dependent enduring change in neuronal or network properties (Donoghue et al., 1996). The change is referred to as enduring as these plastic changes have been shown to alter CNS function which outlasts the period of the altered input itself (Tinazzi et al., 1998; Liepert et al., 2003; Murphy et al., 2003). These plastic changes can be correlated with changes in neuronal activity, that is, increases or decreases, as measured by SEPs. The formation of new synapses or the remodelling of existing synapses has been long believed to be involved in the cellular mechanisms of learning and memory (Rioult-Pedotti & Donoghue, 2000; Beinisman, 2000; Kandel, 1993). The study of SMI has increased in recent years due to the vast amount of evidence indicating that not only beneficial changes occur, but also that maladaptive plastic changes can occur. This can be observed in various movement and neurological disorders, such as overuse injuries (Byl et al., 1997; Topp and Byl, 1999), dystonia (Abbruzzese and Berardelli, 2003; Elbert et al., 1998), and carpal tunnel syndrome (Tinnazi et al., 1998). The study of SMI is crucial to the understanding of both normal physiological functioning and maladaptive plastic changes. Understanding the appropriate adaptive changes that occur in response to motor learning can facilitate identification of maladaptive responses or even potential precursors to maladaptive responses.

Functional Neuroanatomy of Sensorimotor Integration

When sensory input is used to instruct the generation of motor commands, it involves an overarching process of adaptation, use-dependent plasticity and optimization (Flanders, 2011; Krakaeur and Mazzoni, 2011). The integration of sensory input is performed by networks at multiple levels, taking place in the cortex, subcortical structures and in the spinal cord (Flanders, 2011; Liepert et al., 2003; Nyberg et al., 2006). Studies have in turn demonstrated the

spatiotemporal dynamics between the primary somatosensory (S1) and primary motor (M1) cortices with earliest activations being presented in the S1 and observations of inaccurate motor plans leading to degraded acquisition following impaired somatosensation (Vidoni et al., 2010; Ferezou et al., 2007).

The Somatosensory System

The brain is the site of integration and perception of all external and internal stimuli. In terms of organization, the brain is simplified into three levels: the neurons, clusters of neurons which form nuclei that connect to form functional systems, and specific regions of the cortex which perform sensory or motor functions through these complex connections of functional systems (Kandel et al., 2013). In order to function effectively, an individual needs to be able to obtain constant sensory feedback from the external environment. This allows for the transmission of information about conditions that directly impact one's body, maintenance of awareness of the body in space, and modulation of internal states and homeostatic mechanisms. These necessities are performed through multiple afferent or sensory feedback systems. The somatosensory system conducts information arising from muscles, joint capsules, skin and viscera. This information is conveyed by the dorsal root ganglion neurons, enters the spinal cord and is then processed by various cortical and subcortical regions (Classen et al., 2000; Ferrell et al., 1985). The dorsal root ganglion neurons are a type of bipolar cell in which the axon has two branches: the peripheral terminals of these neurons innervate the skin, muscle, joint capsules or viscera which contain receptors specialized for particular types of stimuli and the central branches terminate in the spinal cord or brainstem forming the first synapses with the somatosensory pathways. The somatosensory system subserves three main functions which

include proprioception, exteroreception and interoreception (Kandel et al., 2013). These three main functions encompass sensations such as touch, pressure, motion, vibration, and pain etc. In humans, the hand is the most important tactile organ for exploring the environment. Physiological, psychological and anatomical studies in humans and primates suggest that sensation from the glabrous skin of the hand is almost completely mediated by four different types of myelinated, rapidly conducting receptors (Kandel et al., 2013). Meissner's corpuscles and Merkel's disks are situated in the superficial skin layers while the Pacinian corpuscles and Ruffini endings are located in the subcutaneous tissue (Kandel et al., 2013). In order for the information which is collected by these receptors to be transmitted, they need to be transferred from the periphery to the CNS; this is performed by sensory fibres. Mechanoreceptors and proprioceptors are innervated by dorsal root ganglion neurons with large diameter, myelinated axons which conduct action potentials rapidly.

For the purposes of this review, the dorsal-column leminiscal system will be focused on as through ablation studies, it has been determined that somatosensory evoked potentials (SEPs) assess the integrity of this pathway in particular (Cruccu et al., 2008).

Dorsal-Column Leminiscal System

The dorsal-column leminiscal system specifically subserves mechanoreception and proprioception (Cruccu et al., 2008; Kandel et al., 2013). Central branches enter the ipsilateral dorsal column of the cord and on entry, form branches that either terminate within the spinal grey matter or ascend within the spinal cord to other nuclei in the brainstem. The local branches can activate local reflex circuits while the ascending branches carry information into the brain, where this information becomes raw material for the perception of touch, position sense, pain

etc. An orderly somatotopic distribution is maintained throughout the entire ascending somatosensory pathway. Sensory fibres from the lower body are located medially while fibres from the trunk, arm, shoulder and neck occupy progressively more lateral areas. At the cervical level, the axons which form the dorsal column are divided into 2 bundles: a medially situated gracile (slender) fascicle and a more laterally situated cuneate (wedge shaped) fascicle. Primary afferent fibres from the lower extremities and trunk pass in the medial, gracile fasciculus, and primary afferents from the upper extremities and associated trunk and neck travel in the lateral, cuneate fasciculus. The axons in the two bundles ascend to the medulla where they terminate in the gracile and cuneate nuclei respectively. These nuclei give rise to axons which decussate and ascend in the medial leminiscus, terminating in the thalamus (Kandel et al., 2013). The thalamus is an egg-shaped structure which allows for the projection of information between various cortical and subcortical structures. The cells in the ventro-posterior lateral (VPL) thalamus process somatosensory information and their axons project to the primary somatosensory cortex (S1). Other portions of the thalamus participate in motor functions, transmitting information from the cerebellum and basal ganglia to the motor regions of the frontal lobe (Kandel et al., 2013).

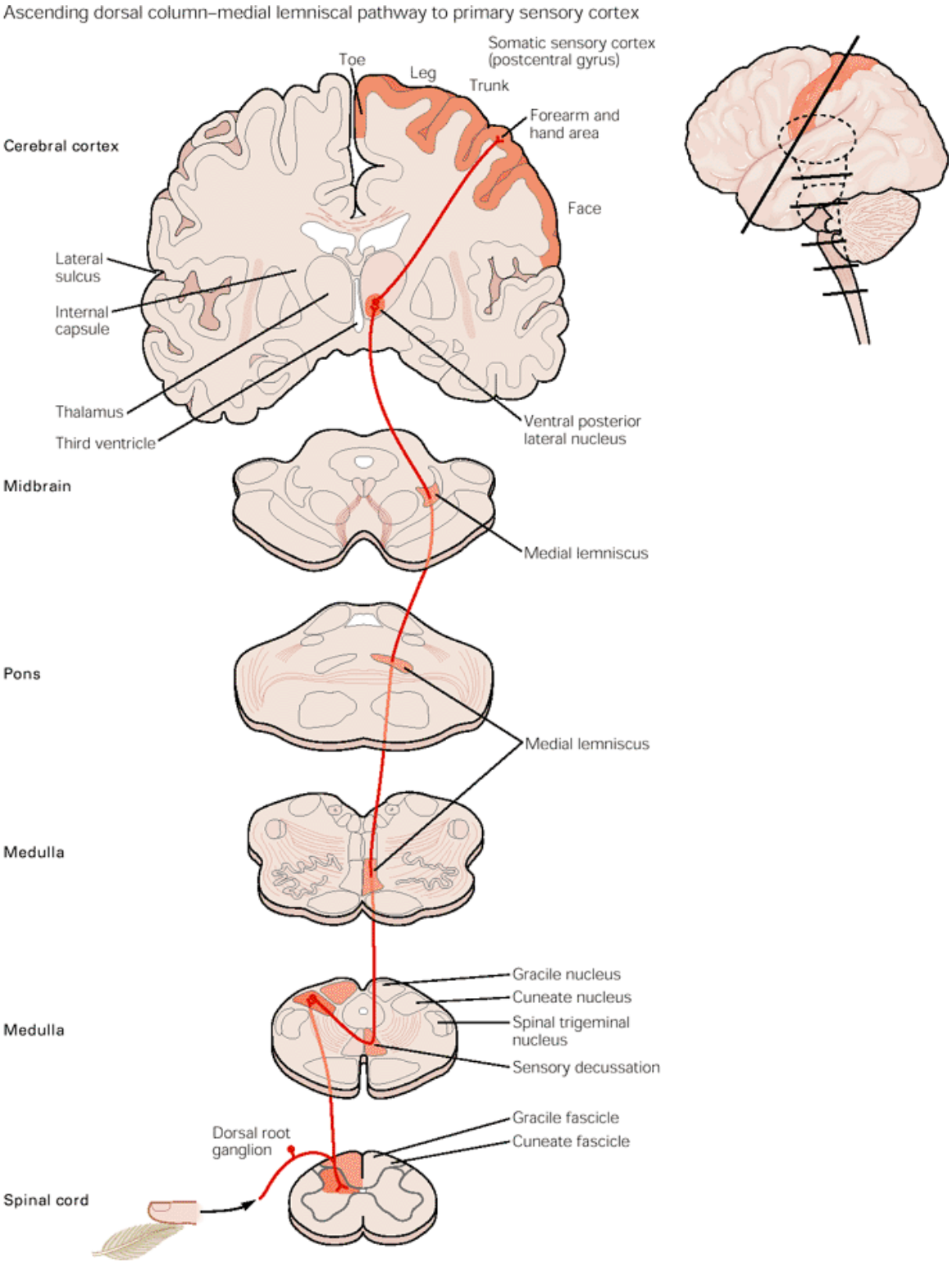

Figure 1: The Dorsal-Column Leminiscal System
A main ascending pathway of sensory information (Reproduced from Kandel et al., 2013, p.493). Tactile sensation and limb proprioception are transmitted to the thalamus.

When individuals are presented with a change in external dynamics, adaptation is gradually experienced. The fundamental feedback system of SMI develops an internal representation of the external world that it can use to generalize for novel movements. The introduction of these novel dynamics induces large errors and therefore large feedback responses which will in turn be gradually reduced; this is essentially the process of learning.

Motor Skill Learning and Acquisition

Functional participation in daily life involves motor activity; a learned sequence which together combines to form a smooth, efficient action and can be classified as either gross or fine. Gross motor skills involve the use of large muscle groups to perform tasks such as walking, balancing and crawling. Generally, the performance levels of gross motor skill remains unchanged after periods of non-use. Fine motor skills involve the use of smaller muscle groups to perform tasks which are precise in nature, this includes activities such as playing the piano, playing a video game or typing on a keyboard. There is a retention loss of fine motor skills over periods of non-use due their precise nature as compared to gross motor skills which are usually much more innate (Savion-Lemieux & Penhune, 2005).

The process by which movements are executed more quickly and accurately with practice can be defined as motor skill learning. Motor skills are typically learned slowly over multiple training sessions until performance reaches nearly asymptotic levels (Dayan and Cohen, 2011). Altered afferent input in the form of behavioural training has been shown to induce organizational changes in both the animal and human cortices (Byl et al., 1997; Classen et al., 1998; Kim et al., 2004). Specific patterns of afferent activation consisting of simultaneous inputs from peripheral areas are capable of producing reliable lasting changes within the monkey

sensory cortex. This use-dependent cortical reorganization facilitates the concept that the homuncular maps of the body in the SMI regions of the brain are ever changing. These changes of course, are reflecting the amount of use of various body parts in concurrence with various motor tasks and skills. The altered afferent input which induce these plastic changes in the CNS does not have to be of long duration, in fact, repetitive muscle contraction activities have shown that as little as 20 minutes of repetitive finger contractions can affect prefrontal and brainstem processing for up to 20 minutes following the cessation of the activity (Murphy et al., 2003). However, as mentioned, the mechanisms which underlie these use-dependent representations are not well understood and must be further investigated.

Motor learning itself consists of two distinct stages: an early, fast learning stage in which considerable improvements in performance occur within a single training session and a later, slow stage in which further gains occur across several sessions of practice (Doyon et al., 2002; Karni et al., 1998; Nudo et al., 1996). What can be defined as fast and slow learning is highly task-specific. The speed of skill acquisition will vary across different motor paradigms, for example: the fast stage of learning a simple three component key press sequence could last minutes whereas the fast stage of learning to play a complex musical piece may last months. Similarly, nearly asymptotic levels in end point measures of skill can be acquired very rapidly when learning a key press sequence but much slower when learning to play a complex musical piece. Experimental paradigms for motor learning fall into two categories: motor sequence learning and motor adaptation. Motor sequence learning refers to the incremental acquisition of movements into a well executed behaviour while motor adaptation refers to the capacity to compensate for environmental changes (Ungerleider et al., 2002; Karni et al., 1998). Through the use of these experimental paradigms, the differentiation between the fast and slow motor

learning processes can be better understood and identified. As previously mentioned, changes in neural activity will be measured through the use of SEPs, however behavioural data can also be looked at to establish the degree of learning. In both animals and humans, motor skill learning is measured by a reduction in reaction time (RT) and the number of errors, or accuracy (ACC). Additionally, the use of measurement of a change in movement synergy or kinematics can be utilized (Ungerleider et al., 2002; Doyon et al., 1996; Shadmehr & Holcomb, 1997). Having better learned a skill, a decrease in RT, ACC and movement variability will occur; ultimately making the performance of the skill efficient. Sequence learning tasks have been used extensively to study motor learning. A review article on cerebellar activity during learning found that sequence learning, used in conjunction with neuroimaging techniques not only demonstrated learning by a decreased reaction time from stimulus to onset of response but also decreases in superior cerebellar and deep nuclear region activation (Desmond & Fiez, 1998). Sequence learning involves rapid execution of a movement without much need for external guidance with movement patterns eventually requiring less external guidance because internal, mental representations indicate the order of the individual movements (Verway and Abrahamse, 2012). It has therefore been argued that sequence order can be learned implicitly because onset times are gradually reduced when subjects make sequential movements without explicit awareness (Krakaeur and Mazzoni, 2011). However, with predictable sequencing, this behaviour becomes automatic and no longer reflects true learning.

Neural Correlates of Motor Learning

Distinguishable brain activation networks are associated with short and long term motor skill learning. These networks have been highlighted through brain imaging studies which

typically require the performance of sequential movements (Floyer-Lea and Matthews, 2005; Doyon et al., 2003). Functional imaging studies have sought to show differentiation in those circuits involved in fast and slow motor learning respectively. With fast motor learning, increases in activation were present in the premotor cortex (PMC), supplementary motor area (SMA), parietal regions, and cerebellum with a decrease in the primary motor cortex (M1) (Dayan and Cohen, 2011; Floyer-Lea & Matthews, 2005; Sakai et al., 1998; Grafton et al., 2002, Honda et al., 1998). With slow motor learning, increases of the M1, primary somatosensory cortex (S1), and putamen were present along with a decrease in the activation of the cerebellum (Dayan and Cohen, 2011; Floyer-Lea & Matthews, 2005; Lehericy et al., 2005). The distinction is made between these two processes of motor learning in that an early, fast stage is seen with considerable improvements in a single training session; and a later, slow stage with further gains across several sessions (Dayan & Cohen, 2011). Through understanding the functions of the neural correlates of fast and slow motor learning, a consensus for their role in either stage is identified especially when considering cortical versus subcortical activations. The roles of the cerebellum with regards to motor learning have been long debated; however it is emerging as a main candidate for the role of integration and internal feedback in SMI. The thalamus which is known to have projections to the S1 also has connections which allow the cerebellum to play a role in voluntary movement (Aumann, 2002). SMI itself works to develop an internal representation of the external world that it can use to generalize for novel movements.

Supplementary Motor Area (SMA)

The SMA is involved in receiving sensory cues, information processing, motor behaviour and movement execution (Hoshi & Tanji, 2004). As such, it is involved in the integration of

sensory input and plays an important role in finger movements as seen with sequential and repetitive training (Shibasaki et al., 1993).

Primary Somatosensory Cortex (S1)

The S1 is located on the postcentral gyrus in the parietal lobe. It contains four distinctive areas: Brodmann's area 3a, 3b, 1, and 2. These four regions of the cortex differ functionally. Areas 3b and 1 receive information from receptors in the skin, whereas areas 3a and 2 receive proprioceptive information from receptors in muscles and joints; however, these regions are extensively interconnected (Romo et al., 2002). Observations of increased activity in the somatosensory and motor cortices is indicative of the notion that full motor task or action involves both areas. The S1 is anatomically connected to subcortical nuclei by the motor basal ganglia loop which projects between the motor and premotor cortices and the striatum (Floyer-Lea & Matthews, 2005). Increases in activation of both areas after long term motor training suggest that this motor loop becomes more active after extensive or more complex training.

Basal Ganglia

The basal ganglia consist of four main subcortical nuclei, the striatum, the pallidum, subthalamic nuclei and the substantia nigra. Of main interest is the striatum as it is related to the use of cognitive strategies and working memory (Lehericy et al., 2005). Lesions of the basal ganglia have demonstrated that these nuclei are essential for automatic movements that need sensory guidance (Hanajima & Ugawa, 2002), which suggests the basal ganglia are involved in sensorimotor integration for the control of automatic or highly trained movements (Kaji et al., 2005). The basal ganglia are therefore thought to play an important role in the filtering or gating of sensory input at various levels (Kaji et al., 2005; Tinazzi et al., 2000).

Cerebellum

In a population with cerebellar lesions, a lack of change-detection through the absence of a mismatch negativity potential was demonstrated with the use of an oddball paradigm (Restuccia et al., 2007). Cerebellar lesions impair the intracortical processing of somatosensory stimuli without affecting the arrival of the somatosensory volley to S1. Therefore, the cerebellum is identified as an ideal structure for detecting mismatch negativity which is generated by an automatic change-detection process in which discordance is found between input from the deviant event and the sensory memory representations of the regular aspects of the preceding stimulation. This is concordant with its increased activation in novel situations and further demonstrates the importance of the cerebellum to SMI and the constant feedback of the current state.

In order to effectively interpret target or sensory information into appropriate motor commands there are essentially problems that need to be solved. This is performed by the various cortical and subcortical loops. With movement, when subjects are presented with a change in external dynamics, the subjects will gradually adapt. The sensorimotor control system develops an internal representation of the external environment that it can use to generalize for novel movements. The introduction of novel dynamics induces large errors and therefore large feedback responses which will in turn be gradually reduced; this is essentially the process of learning itself. Learning evolves both spatially and temporally, this is where the correlation between physiological signal and behavioural or performance measures is imperative. Learning generated in any one movement is used to update a neural basis function that is used for control in a variety of similar movements. This allows the learning function to generalize control across the reachable state space so that movements that have never been performed can be appropriately

predicted and performed (Dayan & Cohen, 2011). With motor learning, we are observing a process whereby a movement is executed more quickly and accurately with practice. This process can be divided into short term and long term learning with the paradigms of motor sequence learning and motor adaptation respectively (Dayan & Cohen, 2011; Ungerleider et al., 2002). The importance of the cerebellum and basal ganglia needed for adaptation and optimization for competitive motor programs respectively can be seen.

Motor Training Paradigms

As mentioned, the processes which accompany motor learning are highly task specific; therefore, motor control processes can be tuned to specific tasks in order to improve overall performance. Motor behaviour is often initiated when an actor has a goal that something in the environment needs to be changed; this goal eventually results in overt movement (Willingham, 1998). There are essentially three processes upon which motor training tasks can be based. The processes are as follows: perceptual motor integration, strategic processes, and sequencing processes (Willingham, 1998). The perceptual motor integration process is based in the posterior parietal lobe and premotor cortex that selects targets for movements; the strategic process is based in the dorsolateral prefrontal cortex that identifies a goal; and the sequencing process is based in the supplementary motor area and subcortical areas which plan the sequencing of movements or skills (Willingham, 1998). These tasks can also become strategic when observational queues or explicit instructions indicate the identical repetitiveness of the sequences. Tasks used based on the sequencing process include pursuit tasks, serial reaction time tasks and explicit sequence learning tasks. Studies have aimed to investigate whether tracing (pursuit movement) or copying (explicit sequential movement) differentially improved learning,

it was concluded that the tracing group exhibited superior performance. However, there is no evidence of increased rates of learning as there is no interaction between the two tests (Gonzalez et al., 2011).

Sequential Tasks

Sequence learning tasks have been used extensively to study motor learning. These have been used to argue that sequence order can be learned implicitly because onset, or reaction times are gradually reduced when subjects make sequential movements without explicit awareness (Krakauer & Mazzoni, 2011). However, in terms of these sequential tasks being learned over a short period of time in relation to the concept of fast motor learning, it can be argued that explicit awareness of sequence order and declarative memory enhance the execution of these sequential elements (Krakauer & Mazzoni, 2011). In other words, in knowing what you have to perform, since it is explicitly stated at a global task level, improved precision will be observed which some may interpret as an implicit knowledge. Ghilardi et al. (2009) demonstrated that spatial accuracy was higher with an explicitly known, practiced target when the sequence itself was already known compared to when the order had yet to be learned. Crump and Logan (2010) found that even skilled typists showed a difference in sequence execution if they were given a word that they had recently seen before versus a new word. These results bring up an interesting point as it refutes a long standing idea that as tasks become well practiced, they automatically become free of explicit control and instead supports the idea of adaptation or automaticity versus actual long term skill learning.

These sequential tasks themselves involve the rapid execution of a movement series without much need for external guidance. These movement patterns eventually require less

external guidance because internal, mental representations indicate the order of the individual movements (Verway & Abrahamse, 2012; Lashley, 1951). The task itself is influenced by various factors such as the amount of practice, the nature of the stimuli and the length and difficulty of the movement sequence (Verway & Abrahamse, 2012).

Previous studies have demonstrated changes in sensorimotor integration following typing tasks involving repetitive voluntary movement. These studies focused on the effects of simple repetitive typing sequences which require little attention, resulting in automatic processing (Bossé et al., 2012; Haavik Taylor & Murphy, 2007a, 2007b; Murphy et al., 2003). The simple, repetitive motor task has resulted in minimal changes in sensorimotor processing. Murphy et al. (2003) examined the effects of a repetitive typing task and the subsequent changes seen in the somatosensory system. The typing task intervention involved the subject typing the numerical keys 7, 8, and 9 in ascending order with the three middle digits. While changes were seen in SEP amplitudes following the task, there were no follow up sessions to observe how long the effects lasted for and no measures of RT, ACC, or movement variability were taken into account. Bossé et al (2012) sought to examine the effects of a repetitive typing task with a slightly more complex sequence and with the use of RT and ACC measurements. The simple task as used by Murphy et al. (2003) was utilized and compared to the effects of a task which still utilized the numbers 7, 8, and 9 being pressed with the three middle digits. However, these three numbers were placed in randomly generated sequences of six digits (ie. 7, 8, 9, 8, 7, 9). Changes in SEP peaks for the complex typing task compared to the simple task suggest that exposure to a complex motor task results in changes in neural activation beyond what is necessary to perform the simple typing task alone (Bossé et al., 2012). In terms of RT and ACC, while the RT improved, the ACC remained unchanged or even decreased in some cases. This could be due to

participant fatigue, loss of concentration or predictability (Bossé et al., 2012). This is where the reasoning lies to utilize a task which can be more mentally engaging and more difficult to predict and perform.

Task Complexity

The mechanisms underlying the execution of simple and complex tasks have drawn the attention of many investigators. Studies have found greater increases in cerebral blood flow during self-paced complex finger movements than during the simple, simultaneous movements of all fingers; however, others have not disclosed any differences (Catalan et al., 1988, Roland et al., 1980; Colebatch et al., 1991, Remy et al., 1994). The heterogeneity in these results may be due in part from the nature of the motor tasks utilized in different studies.

Relating this back to the concept of motor chunking and spatial awareness or external guidance, having the ability to utilize the three middle digits on the three components which are located directly beside one another removes the need for any external guidance. Additionally, using these three numbers in a sequence of six allows for optimal ease of motor chunking which can lend to predictability even with a randomized sequence, the element of the initial first slow key press and rapid execution thereafter is utilized. Studies which present two sequences of finger movement reaction time tasks in which one task is predictable and the other is randomly generated, show a greater volume of activation associated with the unpredictable task, while repetition of motor behaviour leads to an overall decrease in activation (Dassonville et al., 1998). Changes in behaviour are associated with unpredictable tasks. For the unpredictable task subjects would be relying on the visual stimulus for information about both the spatial location and as a "go" signal. For the predictable task, the subject would not need to attend to spatial

location of the stimulus, therefore using the stimulus strictly as a "go" signal. Repetitive practice induces rapid and non-transferable motor skill improvements irrespective of the number of acquisition trials. Alternation between practice and testing sessions provides greater transfer capacities than does the mere repetition of practice sessions themselves (Boutin et al., 2012). Many studies focus on simple tasks where the roles of automaticity and motor chunking reinforce the simplicity of the tasks. Information enters the system, is processed, and a response is generated. Information is then stored for future use, the persistence of this stored information is termed memory. When a new environmental stimulus acts on the body, it is transferred into a neurological impulse, travels up towards the brain and eventually contacts memory, where an aspect of the stimulus has been memorized and stored for later retrieval (Schmidt & Lee, 2011). Relating back to the processes of fast and slow motor learning, the process of slow or long term motor learning is associated with a period of consolidation in which the retention of training is associated with alternation of training and follow up, it is additionally associated with motor training paradigms of increased difficulty (Adams, 1987).

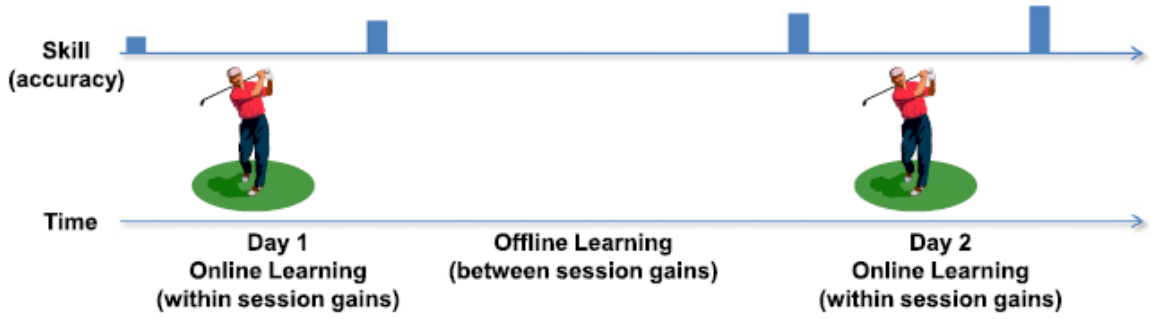

Figure 2: Temporal gains associated with learning
(Figure reproduced from Dayan and Cohen, 2011, p.444)

As mentioned, we are looking to increase the initial error rate so that the point at which RT and ACC asymptote are not so immediate, as has been the case in previous work, as well as increasing the attentional resources required in order to avoid automaticity. Few studies have shown the effects of increasing task complexity and comparing this to a simpler task. Increases in error with an increase in length of the sequence tasks have been demonstrated which argues that task complexity increases with length (Catalan et al., 1998; Pammi et al., 2012). Therefore elongating the sequence to a set of four letters randomly generated in sequences of eight will provide a task in which the boundaries of motor chunking are being challenged. Additionally, attentional resources can be increased by placing the keys further apart and having the subject only using their thumb to perform the task. This will ultimately increase spatial awareness and argue against automaticity of the task. In many instances, most gains in performance evolve in a latency or "offline" manner in between sessions. Optimal retention has been seen 5-6 days after an initial training session, but have also been seen a minimum of 6-8 hours after training (Karni et al., 1998). Therefore, a middle compromise in between these two time frames will be utilized with a time frame of 24-48 hours in between sessions to assess the changes which occur both behaviourally and neurally.

Central Nervous System Plasticity

Contrary to previous belief that the brain and central nervous system (CNS) was a physiologically static organ, increased research over the past decade have demonstrated that altered afferent input to the CNS leads to plastic changes in the way that the CNS processes information and responds to subsequent input (Brasil-Neto et al., 1993; Byl et al., 1997; Hallett et al., 1999; Pascual-Leone and Torres, 1993; Haavik Taylor and Murphy, 2006). Plasticity is

defined as any experience dependent and enduring change in neuronal or network properties which are either morphological or functional (Donoghue et al., 1996). These use-dependent changes rely on the CNS's continuous malleable capabilities through modifications in synaptic connections and the strength of these connections and they can take place following both increased (Byl et al., 1997; Pascual-Leone and Torres, 1993) or decreased (Brasil-Neto et al., 1993; Hallett et al., 1999; Ziemann et al., 1998) afferent input. This dynamic potential of the CNS is heavily involved in the processes of ontogeny, learning and damage (Duffau, 2006).

Effects of Repetitive Movement on Plasticity

Somatosensory information is crucial for motor control and the ability to acquire skills which is a consequence of behaviour alteration as a result of experience. In some instances, what is necessary for the retention of a skill may also lead to maladaptive plastic changes which are thought to be responsible to initiating and perpetuating certain movement, overuse disorders, and chronic pain syndromes (Byl et al., 1997; Topp and Byl, 1999; Tinazzi et al., 2003; Abbruzzese and Berardelli, 2003). In experimental and chronic pain, neuroplastic changes are often accompanied by behaviour deemed to be unfavourable, such as a decrease in performance. Sharply segregated and precisely differentiated cortical representations have been shown to dramatically deteriorate and dedifferentiate following repetitive use compared to those not suffering from pain or movement disorders (Byl et al., 1997; Boudreau et al., 2010; Elbert et al., 1998). Haavik Taylor and Murphy (2007) found a reduction in intrinsic inhibition processing at the cortical level following a repetitive movement task. This may reflect a normal part of motor learning, however, in some susceptible individuals the persistence of the release of inhibition appears to lead to maladaptive plasticity. Brain imaging studies have sought to demonstrate the

cortical and subcortical susbstrates which underlie pain. Rather than the identification of one singular pain center, networks of somatosensory and associative structures convey input to one another during pain (For full review, see Apkarian et al., 2005). Regions including S1, M1, the thalamus and basal ganglia are involved in pain perception; with these structures' prominent role in sensorimotor learning, further validation for the role that pain plays in the alteration of sensorimotor integration is seen.

Overuse Injury and Neck Pain

The prevalence of repetitive strain injuries (RSI) and occupational overuse injuries (OOI) have had a marked increase among Canadian adults since the late 1990s. According to the Canadian Community Health Survey, one out of every 10 Canadian adults suffers from an RSI or OOI serious enough to limit their normal daily activities (Tjepkema, 2003) Internationally, reported upper-extremity disorder rates in the United States tripled between 1986 and 1993 while large increases in these disorders have also been documented within the UK, Australia, Norway, Sweden and Japan (Yassi, 1997). Impaired SMI may help in explaining the occurrence of workplace injuries following high levels of repetitive activity.

Neck pain is a common health problem associated with significant disability in the general population (Côté et al., 1998; Manchikanti et al., 2009). During any 6-month period, 54% of adults suffer from neck pain and 4.6% experience significant limitations due to neck pain (Côté et al., 1998). Altered afferent input due to recurrent neck pain and associated neck joint dysfunction has been suggested by Haavik and Murphy (2012) to lead to altered afferent processing of incoming sensory information from the upper limb, leading to disordered sensorimotor integration, with the potential to interfere with motor sequence acquisition. Several

studies suggest that the treatment of neck joint dysfunction through spinal manipulation may improve afferent processing and motor control (Haavik-Taylor & Murphy, 2007; Haavik & Murphy, 2012; Haavik Taylor & Murphy, 2006; Haavik Taylor & Murphy, 2008; Haavik Taylor & Murphy, 2010a, 2010b).

The nature of these cortical changes can be investigated, quantified and correlated with functional behaviour in order yield a greater understanding of these changes and aid in the potential identification of when these changes can be long term beneficial or long term detrimental and the intervening mechanisms which can lead to beneficial functioning should these changes become maladaptive. Impaired SMI may help in explaining the occurrence of workplace injuries following high levels of repetitive activity. Understanding the processes of repetitive activity and their neuromodulatory effects can aid in enhancing the sensitivity of the brain to therapy techniques. Increases in cortical excitability have been correlated with motor learning and functional recovery (Chipchase & Schabrun, 2011). Investigation of the complex circuitry that is involved in SMI with a focus on not only cortical but subcortical and cerebellar projections will give a better understanding of underlying mechanisms which is needed before potential widespread clinical use of treatment and determination of who will benefit from such treatment.

Experimental Techniques

Evoked Potentials

Evoked potentials are time-locked responses of the nervous system to external stimuli. Signals travel along the nerves, though the spinal cord and to specific regions of the brain; they are then acquired, processed and displayed for interpretation (Rapuano, 2009). Studies measure electrical activity in the brain in response to stimulation of light, sound, or touch; these stimuli are delivered to the brain through any of these senses which evoke minute electrical signals.

Somatosensory Evoked Potentials

Somatosensory evoked potentials (SEPs) are a type of evoked potential which is generated by stimulation of afferent peripheral nerve fibres elicited through the use of electrical or tactile stimuli (Rapuano, 2009). These electrical potentials can be used to study the properties of both the peripheral and central nervous systems as they can be recorded at various sites along the pathway of the relevant peripheral nerve and at its central projections. It is a non-invasive technique which utilizes a controlled stimulation where potentials are recorded from the surface of the skin and over the scalp close to the location of the hypothesized neural generators (Mauguiere et al., 1999). The most commonly stimulated nerves in the upper limb are the median, ulnar and radial nerves. Through the use of an appropriate stimulation intensity, the large diameter myelinated (IA) afferents, but not the smaller myelinated Aδ or unmyelinated C afferents that convey pain and temperature sensation via the spinothalamic tracts are stimulated (Burke et al., 1981). Studies have demonstrated that muscle afferents most likely dominate the

cerebral potentials produced by stimulation of the mixed median nerve at the wrist (Gandevia & Burke, 1988; Gandevia et al., 1984). The magnitude of the signal recorded depends on the angle from which the potentials are recorded by the electrode; the SEP is a spatiotemporal average of postsynaptic potentials.

Clinical use of SEPs

The prognostic superiority of SEPs over electroencephalography (EEG) may be due to a number of reasons. EEG is strongly affected by factors which SEPs are not be affected by to the same extent if affected at all; this in turn makes EEG interpretation less objective than SEPs interpretation (Hutchinson et al., 1991; Judson et al., 1990). Short latency SEPs are responses which are recorded between 8 ms to 30 ms in latency post stimulus, while their amplitudes may not be as large as longer latency potentials, these potentials are stable in nature in that they are resistant to changes of consciousness making the waveforms observed reliable and reproducible (Leeman et al., 2007; Yamada et al., 1985). Longer latency potentials vary depending on cognitive functions such as vigilance, attention and distraction. This can be correlated with the fact that EEGs are recorded over a longer period of time in response to spontaneous cerebral electrical activity while SEPs are recorded over a shorter period of time in response to a controlled time-locked stimulus with a pretrigger. SEPs have a high temporal resolution which is in the order of milliseconds in comparison to other modalities such as magnetic resonance imaging (MRI), or functional magnetic resonance imaging (fMRI). Studies which sought to determine the use of EEG with regards to the optimal time to record post-head injury have not yet established one. Some have reported an increased yield of abnormalities within 30 minutes, while others have shown that significant changes may be delayed beyond 48 hours (Dow et al.,

1944; Dawson, 1947). By contrast, SEP recordings show less variability with time which allows for prognostic information to be determined at an earlier stage (Hutchinson et al., 1991; Judson et al, 1990). The use of SEPs also provides a cost-effective technique for measuring alterations in brain activity, in conjunction with its high temporal resolution it's use could be ideal for the identification of a timeline of neuroplastic changes leading to a potential pre-screening tool of maladaptive plasticity and concurrent disorders.

SEP Peak Nomenclature

The waveforms known as "early" waveforms, which are peaks occurring between 0-35 ms following stimulation, have so far been found to be clinically useful; these are the peaks and concordant neural generators which will be focused on (Mauguiere, 1999). As previously mentioned, the amplitude of a SEP peak represents the degree of activity of the neural structures which are responsible for generating that specific peak. Therefore, alterations observed in peak amplitudes represent alterations in the activity of the neural generator. The latency of the SEP peaks represent the transmission time between the point of stimulation and the activity of the neural generators (in milliseconds). Therefore, alterations in peak latency represent alteration in neural transmission. These alterations in activity and latency can be due to experimental conditions or potential pathologic mechanisms (Mauguiere, 1999). These SEP peaks are observed as waveform components whose nomenclature is based upon their deflection direction and title latency. The International Federation of Clinical Neurophysiologists (IFCN) (Nuwer et al., 1994), the American Clinical Neurophysiology Society (Epstein et al., 2006) and the authors of leading texts in this field (Mauguiere, 1999) utilize the convention of referring to upwards deflections as negative (N) and downwards deflections as positive (P). This convention shall

therefore be utilized throughout this research. The latency of a peak is essentially the time from the delivery of the stimulus to the appearance or activity or a response which is recorded from the specific neural generator in milliseconds. There may be slight variations due to various factors such as subject height and age (Sunwoo et al., 1990; Desmedt & Cheron, 1981; Nuwer et al., 1994). However, the overall title latency (ie. N20) is used to enable comparison between waveforms. This method is recommended by the IFCN and will also be used throughout this research (Nuwer et al., 1994). The main early SEP components that have been focused on in this research are N9, N11, N13, N18, N20, P22, N24, P25, and N30.

SEP Peak Neural Generators

The area of the brain or spinal cord generating these potentials is termed a neural generator, the ionic current flow across the cell membranes of active neural elements gives rise to potential differences, these changes in voltage are then measured. The investigation of cerebral regions generating electrical activity as recorded from the scalp surface continues to represent a challenge for neurophysiologists. Modern neuroimaging techniques such as PET and fMRI have increased knowledge through use of their high spatial resolution in showing the cerebral areas activated by afferent input. With these techniques the measurement of the brain's functional status is being based on variations of metabolic parameters and the temporal sequence can be larger (Valeriani et al., 2000). The difficulties in interpreting the EEG signal are due to the overlapping of activities coming from different neuronal sources and distortion of the current flows caused by the meninges, bone, and skin. The origin of EEG waves have been investigated assuming that the complex structure of a brain area can be reduced to an equivalent dipole, that is, to a linear source with two opposite poles (Valeriani et al., 2000). This simplification is valid

when a synchronous depolarization of closely grouped neurons occurs and since this is the most common situation in the generation of SEPs, this would make it the most beneficial technique to use when establishing neural activity and the generators of this activity (Valeriani et al., 2000). The following section will focus on the neural generators of various SEP peaks and the assurance of their location validity.

N9 Peak

The N9 peak is recorded at Erb's point, over the brachial plexus which is located on the shoulder above the proximal clavicle. The N9 component shows abnormalities for lesions from the peripheral median nerve to the brachial plexus (Nakanishi et al., 1983; Synek & Cowan, 1982). This is indicative that the neural generator of this potential is located in the peripheral pathways either close to or in the brachial plexus. The recording surface electrode at peripheral Erb's point should be placed within the angle formed by the posterior border of the clavicular head, the sternocleidomastoid muscle and the clavicle, with a reference electrode placed on either on the contralateral Erb's point, scalp electrode or an ipsilateral earlobe (Cruccu et al., 2008; Desmedt, 1988).

N11 Peak

The N11 peak can be recorded with a surface electrode place over the 5^{th} (Cv5), 6^{th} (Cv6), or 7^{th} (Cv7) cervical spinous process (Cruccu et al., 2008; Nuwer et al., 1994). The neural generator of the N11 peak is thought to reflect the peripheral nerve volley as it arrives at the spinal cord (Desmedt & Cheron, 1981). It is argued that the timing of the N11 component recorded from the lower cervical spine leaves little doubt about it being generated in the spinal cord rather than in the peripheral nerve (Desmedt & Cheron, 1981). Further evidence supports

this from patients with multiple nerve root avulsions demonstrating the absence of the cervical peaks although the Erb's point component, N9 is present (Synek & Cown, 1982). A non-cephalic reference electrode is recommended to eliminate the cancelation of the peak, therefore the references is typically placed on the anterior neck at the level of the glottis or the trachea (Cruccu et al., 2008; Haavik-Taylor & Murphy, 2007; Haavik-Taylor & Murphy, 2007a.; Nuwer et al., 1994). However, the validity of measuring and utilizing this peak is controversial as it is absent in approximately 20% of the normal population (Mauguiere, 1999; Nuwer et al., 1994).

N13 Peak

The N13 SEP peak presents as an inflection of the N11 peak. According to the IFCN, both of these peaks can be measured from the same channel, with the peak being recorded over the 5th, 6^{th}, or 7^{th} cervical spinous process (Nuwer et al., 1994). This peak reflects the activity of the interneurons within the dorsal horn and midcervical cord (Desmedt & Cheron, 1981; Sonoo et al., 1991). The peak is generated at or near the first relay of the spinothalamic tract (Cruccu et al., 2008; Tinazzi et al., 2000). The origin of this waveform has been debated; the dorsal horn of the cervical spinal cord, the dorsal column, spinal cord interneurons and the cuneate nucleus have all been proposed as the potential neural origin of the N13 component (Jones, 1977; Cracco, 1972; Buchner et al., 1992; Favale et al., 1982). However, the origin of the N13 component was clarified by Desmedt and Cheron (1981) through the use of esophageal recording electrodes. In this study, recording electrodes were inserted through the nostrils and further advanced through the esophagus down to the level of the sixth cervical vertebrae. It is at this point that an enhanced peak occurs where it was concluded that the N13 peak is a reflection of the postsynaptic potential of the dorsal horn interneurons (Desmedt & Cheron, 1981). This has also been supported through studying and comparing healthy subjects to patients with cervical

dorsal column lesions (Sonoo et al., 1990). However, they also suggested that the N13 peak responded differently when measured at the level of the 2nd cervical spinous process, at which point it was argued that the N13 peak originated in the cuneate nucleus when measured over this area (Sonoo et al., 1990). It is now widely accepted that N13 is generated in the dorsal horn interneurons. When recording the N13 peak it is necessary to utilize a non-cephalic reference electrode (Nuwer et al., 1994).

N18 Peak

This peak was initially recognized by Desmedt and Cheron (1981) and was thought to be generated by the thalamus. However, several groups have shown that the thalamus cannot be the generator of the N18 component, as this potential is preserved following thalamic lesions (Urasaki et al., 1992), and after retrograde degeneration of thalamocortical neurons following complete hemispherectomy (Mauguiere and Desmedt, 1989). Its origin must therefore be subthalamic. There have been suggestions that there are multiple generators of the scalp-recorded N18 potential (Mauguiere, 1999). There is clinical evidence indicating the N18 component is generated in the brain stem, up to the level of the midbrain-pontine region (Urasaki et al., 1992). Lesions at this level decrease the N18 amplitude significantly (Urasaki et al., 1992). It has also been suggested that the N18 has inputs from subthalamic generators such as the dorsal column medial leminiscus and the accessory inferior olives (Manzano et al., 1998; Noel et al., 1996; Sonoo et al., 1991). Therefore, the N18 peak may be indicative of cerebellar activity. Past work has demonstrated that the N18 component persisted in three patients with lesions involving the medial lemniscus at the level of the midbrain or upper medulla (Noel et al., 1996). Additional evidence for dorsal column nuclei playing an important role in the generation of the N18 peak comes from several cases of patients with pontine lesions, high cervical brain-stem, and thalamic

lesions who had profound disturbances of deep sensation (Sonoo et al., 1992; Sonoo et al., 1991). These researchers concluded that the cuneate nucleus was the most probable neural generator of the widespread N18 far field potential. Manzano et al. (1998) also found the dorsal column nuclei important for the generation for N18. They concluded that the N18 SEP component may be functionally related to inhibitory activity of the dorsal column nuclei as it was the only SEP component to not be affected by vibration (Manzano et al., 1998). N18 is recorded from a contralateral frontal cephalic site, it can also be confounded with the cortical N20 peak, recorded over the posterior parietal region (Rossi et al., 2003; Cruccu et al., 2008; Mauguiere, 1999). It is important to note that utilizing a cephalic reference might have a canceling effect or show only a small amplitude for far-field N18, compared to utilizing a non-cephalic reference (Urasaki et al., 1990).

N20 Peak

The contralateral parietal N20, recorded in normal subjects is known to reflect the earliest cortical processing or activity in the primary somatosensory cortex (S1). It reflects the activity of a dipolar generator in Brodmann's area 3b situated in the posterior bank of the rolandic fissure (Desmedt and Cheron, 1980; Mauguiere, 1999; Nuwer et al., 1994). This view is much less controversial and is consistent with the knowledge that the lemniscal somatosensory pathway terminates in areas 3b, 1 and 2 of the postcentral gyrus on the side contralateral to the stimulus. The N20 peak is recorded from a posterior parietal site with a reference electrode placed on the ipsilateral earlobe (Cruccu et al., 2008; Haavik Taylor and Murphy, 2007a).

P22 Peak

Evidence suggests that this peak is independent of the primary somatosensory N20 peak (Desmedt and Cheron, 1981; Garcia Larrera et al., 1992; Mauguire et al., 1983). Patients with parietal lesions had eliminated N20 peaks, while the P22 and N30 components remained. In patients with precentral lesions, the P22 was eliminated which indicates a separate precentral generator for the P22 (Mauguire et al., 1983). Following the clinical regression of motor deficits, the P22 component was once again present, suggesting that the P22 is generated in the primary motor cortex (M1) (Mauguire et al., 1983). The P22 peak is best recorded from the contralateral frontal cephalic site with a non-cephalic ipsilateral earlobe reference (Cruccu et al., 2008).

N24 Peak

At low stimulus rates the N24 can often be difficult to individualize since it appears in most cases as a notch on the N30's ascending slope. Increasing the stimulus rate selectively decreases the N30 component allowing a clear individualization of the early frontal negativity N24, which is not attenuated at high stimulus rates (Haavik Taylor and Murphy, 2007a; Fujii et al., 1994; Garcia Larrea et al., 1992). Using dipole source localization and current density reconstruction within individual realistically shaped head models Waberski et al. (1999) localized the source of the N24 SEP component near the posterior wall of the central sulcus (area 3b), close to the location of N20. The N24 has also been shown to be absent in those with cerebellar lesions which indicate that it reflects the pathway between the cerebellum and the primary somatosensory cortex (Restuccia et al., 2007).

P25 Peak

The P25 peak represents neurons within Brodmann's area 1 of S1. The P25 peak is recorded at the contralateral posterior parietal site with a reference electrode placed on the ipsilateral earlobe (Cruccu et al., 2008; Haavik Taylor and Murphy, 2007a).

N30 Peak

Some authors suggest that N30 originates in the post-central cortical regions (Allison et al., 1989a; Allison et al., 1991), however most evidence suggests that this SEP component is related to a complex cortical and subcortical loop linking the basal ganglia, thalamus, pre-motor areas, and primary motor cortex (Kanovský et al., 2003; Mauguiere et al., 1983; Rossini et al., 1987; Waberski et al., 1999). The frontal N30 peak is therefore thought to reflect the overall process of sensorimotor integration (Rossi et al., 2003). The N30 is recorded from a contralateral frontal cephalic site; utilising a cephalic reference electrode may complicate results, due to interference from the frontal generators, it is therefore referenced to the ipsilateral earlobe (Restuccia et al., 2007; Rossi et al., 2003; Desmedt and Cheron, 1981). Some research has linked the basal ganglia with the N30 SEP component (Pierantozzi et al., 1999; Pierantozzi et al., 2000). The N30 peak amplitude is decreased in Parkinson's Disease patients (Pierantozzi et al., 1999; Pierantozzi et al., 2000), and deep brain stimulation of basal ganglia nuclei can produce a selective increase of the N30 amplitude, thought to be due to improved supplementary motor area (SMA) functional activity (Pierantozzi et al., 1999). Furthermore, blocking the neuromuscular junction in Parkinson's Disease patients also increases the N30 amplitude as well as decreases the rigidity of their muscles (Pierantozzi et al., 2000). A similar, although smaller, increase in N30 amplitude was observed in healthy subjects in response to neuromuscular

blockade (Pierantozzi et al., 2000). Further support for the connection between the basal ganglia and SMA comes from anatomical studies that have shown that the arm representation in the SMA receives projections from regions of the ventrolateral thalamus that are the site of termination of efferents from the basal ganglia (Schell and Strick, 1984; Wiesendanger and Wiesendanger, 1985). The basal ganglia may therefore be responsible for both altering SMA activity as well as the changes observed in N30 peak amplitude (previously attributed to changes in SMA activity). Other authors have provided evidence that the N30 peak is generated in primary motor cortex (Waberski et al., 1999). Waberski et al. (1999) applied dipole source localisation and current density reconstruction within individual realistically shaped head models, and demonstrated that the source of the N30 peak resided within the pre-central motor cortex. The N30 peak is also dramatically depressed by increases in stimulus rate (Garcia Larrea et al., 1992). This must be taken into account when valid N30 peak analysis is to be made. Garcia Larrea et al. (1992) demonstrated N30 attenuation at stimulus rates as low as 3.5 Hz and demonstrated that it was almost abolished at 10 Hz, separating it from the earlier N24 peak, as previously discussed. This rate attenuation suggests a saturation effect of the generator(s) of the N30.

Summary

With the increased prevalence of repetitive strain and musculoskeletal disorders, there is a large burden being placed on the healthcare system and within the workplace. Investigating the effects of impaired sensorimotor integration may aid in explaining the occurrence of workplace injuries following high levels of repetitive activity. Understanding the processes of repetitive activity and their neuromodulatory effects can aid in enhancing the sensitivity of the brain to

therapy techniques and to early, preventative intervention measures. We therefore must understand the necessary, adaptive changes in order to allude to the maladaptive changes that may occur. Using SEPs, we can measure the ionic current flow across cell membrane of active neural elements which gives rise to potential differences between different locations in the extracellular space. These changes in voltage can be measured to demonstrate activity in the brain, showing alterations following training which can then be quantified and correlated with behavioural measures.

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SECTION 2: PROPOSED RESEARCH

Proposed Research Framework

The proposed research framework will investigate two facets of human neurophysiology with the goal of running two separate but related studies. The first study aims to determine the effects that motor training task complexity has on sensorimotor integration in a healthy population. This utilizes two separate but validated motor training task modalities. The second experiment aims to draw upon the conclusions from the first study to determine the effects on sensorimotor integration in a population with low grade neck pain. The proposed framework has been built upon past work performed by Murphy et al. (2003), to form a comprehensive study which addresses multiple variables that span this working topic but which have not been successfully integrated into one study framework.

SECTION 3: MANUSCRIPT 1

Do pursuit movement tasks lead to differential changes in early somatosensory evoked potentials related to motor learning in comparison to tapping tasks?

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Abstract

Objective: The plastic nature of the central nervous system (CNS) is essential for development; however recent research has also demonstrated its role in pathology, particularly following overuse and repetition. Changes in sensorimotor integration (SMI) can be investigated using motor performance tasks. Previous studies have investigated these changes using relatively simple and automatic paradigms resulting in minimal changes in neural activity, as determined through the use of somatosensory evoked potentials (SEPs). This study therefore sought to utilize validated complex tasks and compare parallel but separate motor paradigms to determine which one best facilitates long-term learning, characteristic of more complex tasks.

Methods: Spinal, brainstem and cortical SEPs were recorded following median nerve stimulation at the wrist pre and post interventions. 18 participants performed the same paradigms, a control condition which consisted of 10 minute period of mental recitation, and two interventions, one consisting of 10 minutes of tracing and the other, 10 minutes of repetitive typing. A cross-over design was utilized with the two intervention conditions to ensure the elimination of effects due to order.

Results: For each of the SEP peak amplitudes, minimal changes were seen following the control condition. Significant increases in the N13, N20, P25 and N30 SEP peaks were seen for both interventions. A significant decrease in the N24 SEP peak was observed for both interventions. Significant improvements in accuracy were seen for both interventions post-acquisition but only for tracing during retention. Changes were consistently larger for the tracing intervention.

Conclusions: The changes seen following motor learning for both tasks are conducive with those associated with long-term learning, especially with regards to the cortico-subcortical and cortico-cerebellar neural networks. This long-term learning is also reflected by an effective consolidation period which was followed up by significant increases in accuracy during retention.

Significance: Further validation of the complex nature of the tasks utilized is provided, furthermore, tracing, or the pursuit movement paradigm was a more effective learning tool. The identification of a task which is sufficiently novel and complex, leading to robust changes in SEP peaks indicates a task which can be utilized in future work to study clinical populations and the effect of experimental interventions on SMI.

Keywords: Somatosensory evoked potentials (SEPs), motor learning, sensorimotor integration (SMI), cerebellum, retention

Introduction

The malleable nature of the central nervous system (CNS) enables it to change the way that it responds to subsequent sensory input following periods of altered afferent input (Byl et al., 1997; Classen et al., 1998; Haavik Taylor and Murphy, 2007a, 2007b; Murphy et al., 2003; Pascual-Leone et al., 2005; Tinazzi et al., 1998). These use-dependent changes seen following altered afferent input persist even after the input itself has ceased (Byl et al., 1997; Classen et al., 1998; Haavik Taylor and Murphy, 2007a, 2007b; Murphy et al., 2003). It is the persistence of these changes which are thought to be necessary for the learning and retention of skill, (Nelson et al., 2009) and as such, input in the form of behavioural training has been utilized to investigate these organizational changes. Many of these studies which investigate these organizational changes have utilized the technique of functional magnetic resonance imaging (fMRI) which measures the activity of neural structures in association to changes in blood oxygenation. This measure provides accurate spatial resolution however, it is measuring an indirect component of brain electrical activity; in addition to this, it poses difficulty with wait times and is too expensive for routine use in research studies (Pelletier et al., 2007). Plastic changes can also be investigated through electrophysiological techniques such as somatosensory evoked potentials (SEPs) which measure directly the electrical field potentials generated by various neural structures. SEPs provide a measure which offers the highest temporal resolution available in non-invasive investigation, on the order of milliseconds (Walsh and Cowey, 2000). Previously, electrophysiological techniques have presented more of a challenge in terms of spatial resolution with relatively large differences between electrodes and sources, the accuracy with which signal sources could be localized was limited, especially with regard to signals generated by deeper structures and complex cortical-subcortical loops (Cebolla et al., 2011). However, localizing techniques such as standardized weighted Low Resolution Brain Electromagnetic Tomography

(swLORETA) have resolved many limitations, such as sensitivity to noise and appropriate inclusion of deep sources allowing for increased confidence and accuracy in the generators of those signals which are measured through electrophysiological techniques (Cebolla et al., 2011). The use of SEPs under varying conditions provides a technique that enables the investigation of immediate changes following sensory processes (Angel et al., 1984). Therefore, this technique can be combined with behavioural input, such as motor learning paradigms in order to quantify the activation following training and correlate these with behavioural measures.

Studies have utilized repetitive voluntary movements in combination with SEPs to investigate repetitive muscular activity in humans and its implications on sensorimotor integration (SMI) and have demonstrated alterations in the processing of somatosensory information (Haavik Taylor and Murphy, 2007a; 2007b; Murphy et al., 2003; Bossé, 2012; Haavik and Murphy, 2013; Andrew et al., 2014). Following the cessation of simple, predictable repetitive typing tasks, changes in cortical SEPs were observed, however no subcortical changes were seen (Haavik Taylor and Murphy, 2007). The use of such a simple task which requires minimal attention results in automatic processing rather than learning. Further clarification of the roles that task characteristics play in learning is needed, therefore in a study by Bossé (2012); this same repetitive, predictable task was once again performed with the consideration of behavioural measures such as reaction time (RT) and accuracy (ACC). In terms of these behavioural measures, while reaction time decreased, accuracy was not seen to change as it was already so high to begin with (Bossé, 2012). To change the simple nature of the task, a randomly generated sequence was then used for the typing task and automaticity was removed through the use of unpredictable sequences (Andrew et al., 2014). Further changes were now seen in deeper structures and within cerebellar inputs, however, accuracy still did not show an increase. With

motor learning, we are observing a process whereby a movement is executed more quickly and accurately with practice; it occurs both spatially and temporally. This sequence only involved three numbers in close proximity to one another and a total of six numbers in each sequence, potentially leading to minimal need for external guidance and thus too simple of a paradigm.

Relating back to the point that learning occurs temporally, we see that there is an early fast stage in which improvements in performance occur within a training session and a later slower stage in which further gains occur following a period of consolidation (Doyon et al., 2002; Karni et al., 1998; Nudo et al., 1996). This is associated with retention of the skill, which can be observed in as little as 6-8 hours following practice and is associated with motor training paradigms of increased difficulty (Karni et al., 1998; Adams, 1987). The assessment of retention is therefore crucial in correlation to neurophysiological changes that may be observed.

When sensory input is used to instruct the generation of motor commands, it involves an overarching process of adaptation, use-dependent plasticity and optimization (Flanders, 2011; Krakaeur and Mazzoni, 2011). Structures involved in these processes in addition to the primary motor cortex and primary somatosensory cortex include the basal ganglia and cerebellum (Krakaeur and Mazzoni, 2011).The utilization of a more complex motor training paradigm in conjunction with electrophysiological and behavioural measures will enable the validation of the roles of not only cortical but also subcortical and cerebellar regions in relation to the processes of motor learning. Sequence learning tasks have been used extensively to study motor learning, within the realm of sequence learning the domains of explicit sequences to copy or pursuit movements to follow or trace are commonly utilized. It however, remains unclear as to whether tracing or copying provides the better training as there has been no interaction between the two tests (Gonzalez et al., 2011).

This study will therefore investigate the interaction between two complex sequence tasks, one tracing, and one copying; in order to determine which is the optimal learning paradigm. In a complex test, an environment is created where automaticity is virtually impossible to develop. By always presenting an unpredictable sequence, the participant is required to use more attentional resources whereby the movement response will no longer be automated. Often, the conclusions of studies posit that tasks utilized were in fact not as complex as first thought due to lack neurophysiological or behavioural changes. This work will utilize two motor tasks that have been previously used in transcranial magnetic stimulation (TMS) studies. If the use of SEPs can corroborate the findings of a parallel technique such as TMS, we can more stringent in our conclusions in terms of the effects of complexity on motor learning. Baarbé et al. (2014) performed rounds of cerebellar-M1 stimulations prior to and following motor learning of a typing task which consisted of randomized eight letter sequences of Z, D, F and P. When compared against a control group who did not perform this task, they found reduced cerebellar inhibition following the motor acquisition phase, additionally, significant increases in both reaction time and accuracy were observed, which has not been seen with simpler tasks. The overall purpose for this study is to determine which learning paradigm will induce measurable neurophysiological changes that reflect those changes observed in performance.

The goal of training should be pursued with projections to a real world setting. This idea promotes the importance of the level of performance in the long term through examining the effects of separate modalities and their effects on initial leaning but also on retention which has not yet been investigated.

Methods

Subjects/Participants

18 participants with no known neurological conditions, comprised of 9 males and 9 females (mean age 22.8; range 21-25) participated in this study. The study was a paired experimental design where participants were assigned to two different groups of motor training tasks, a typing task and a tracing task, with a minimum of 48 hours between sessions. Prior to the performance of either motor task, control data was collected on each of the participants. Informed consent was obtained and the study was approved by the ethics committee at the University of Ontario Institute of Technology.

Stimulation Parameters

The stimuli consisted of electrical pulses which were 1 ms in duration and delivered at rates of both 2.47Hz and 4.98 Hz through Ag/AgCl ECG conductive adhesive skin electrodes (MEDITRACE™ 130, Ludlow Technical Products Canada Ltd., Mansfield, MA) (impedance <5kΩ). These electrodes were placed over the median nerve on the skin, 2-3cm proximal to the distal crease of the wrist, between the tendons of flexor pollicis longus and palmaris longus with the anode proximal on the right arm. This was to allow for movement of the abductor pollicis brevis (APB) through stimulation of the median nerve which primarily innervates this muscle. SEPs were recorded at two different rates, to enable optimal conditions to record both the N24 and N30 SEP peak complexes. Using the slower rate of 2.47Hz does not lead to SEP peak attenuation while the faster rate, 4.98 Hz attenuates the N30 SEP peak, allowing for the N24 SEP peak to be accurately identified and measured (Haavik and Murphy, 2013; Fuji et al., 1994). Stimuli were delivered at motor threshold for each subject, which is defined as the lowest possible intensity at which a visible muscle contraction of the APB is elicited.

Recording Parameters

SEP recording electrodes were placed according to the International Federation of Clinical Neurophysiologists (IFCN) guidelines (Nuwer et al, 1994). Recording electrodes were placed on the ipsilateral Erb's point, over the C5 spinous process, as well as on two cephalic sites, the Cc'(2 cm posterior to contralateral central C3/4) and a frontal site (6cm anterior and 2cm contralateral to Cz) (Rossi et al., 2003). The two cephalic site electrodes were 2mm gold cup EEG electrodes (Grass Technologies, Astro-Med, Inc. Subsidiary, Rockland, MA) (impedance <5kΩ) as was the ground electrode which was placed in the mouth of participants. The C5 spinous process electrode was referenced to the anterior neck (tracheal cartilage) while all other electrodes were referenced to the ipsilateral earlobe. During data collection, the subjects were asked to sit with their eyes closed while remaining quiet and as still as possible; the lights in the room were turned off. To ensure participant comfort, the data was collected in a quiet room with the subjects seated in a comfortable but rigid office chair. The SEP signal was amplified (gain 10 000), filtered (0.2-1000 Hz) and saved on a laboratory computer for retrieval using a configuration written in Signal® software (Cambridge Electronic Design, Cambridge, UK). To ensure reproducibility and accuracy of the waveforms, it is recommended to average at least 500 stimuli presentations in order to differentiate noise and the desired signal to be measured (Cruccu et al, 2008).

Experimental Protocol

This study was a paired experimental design. All of the subjects were required to attend three sessions. In order to participate in the study, they were required to be neurologically normal, this was in order to ensure that no existing conditions would affect the SEP measurements. All participants performed the same intervention. Prior to performance of the

experimental intervention, control data was collected on each subject. During this time, double baseline measurements were performed for each subject though stimulation of the median nerve at the wrist for pre SEP measurements, followed by ten minutes of mental recitation of a series of six-digit numerical sequences which was automatically presented via Microsoft Powerpoint; a post SEPs measurement was then taken. Immediately following the control condition, participants were required to perform one of the two motor task interventions, either a typing task or a tracing task. In order to ensure that any changes seen were not due to the order of the tasks presented, the first 9 participants performed the tracing task first while the last 9 participants performed the typing task first. The tracing task was run through a custom Leap Motion software tool (Leap Motion, Inc., San Francisco, CA) and required participants to trace sequences of sinusoidal-pattern waves with varying frequency and amplitude using only their thumb on an external wireless touchpad (Logitech, Inc., Fremont, CA) during a pre test, an acquisition phase and a post test. No discernible lag time was present between the participant's movements on the external tracing pad and the movement observed on the monitor. The pre and post test were approximately three minutes in duration while the acquisition phase was approximately 10 minutes in duration. The tracing task comprised of four pre-selected sinusoidal patterns of varying amplitude and frequency, as determined by a previous study which utilized an anti-fatigue protocol (Holland, 2014). The trace itself is a sin(x) function, however for each of the four patterns, the frequency and amplitudes are varied by a certain factor through randomization to allow for unpredictability throughout the duration of the trace. The traces were formed by a series of dots, each trial consisted of 500 dots. For the pre and post tests, each of the versions, 1-4, were performed once; for the acquisition phase each version was performed three times for a total of 12 traces. Combined flexion and adduction thumb movements were

performed, which required the participants to sweep their thumb from left to right, utilizing the abductor pollicis brevis (APB) muscle. The APB muscle is innervated by the median nerve distal to the site of stimulation used throughout this experiment. The typing task was run through a custom E-Prime software tool (Psychology Software Tools, Inc., Pittsburgh, PA) and required participants to press letter keys on an external keyboard using only their thumb during a pre test, an acquisition phase and a post test. The pre and post test were approximately three minutes in duration while the acquisition phase was approximately 10 minutes in duration. The typing task was comprised of randomly generated sequences of the letters "Z, D, F, and P" in eight-digit sequences. There were a total of 15 eight-lettered sequences for the task. For the pre and post tests, each sequence was presented once; for the acquisition phase, each sequence was presented 4 times for a total of 60 sequences. The thumb movements were performed perpendicular to the palm, known as thumb abduction movements, thus involving contraction of APB. Immediately following the motor task intervention, post SEPs measurements were taken in an identical fashion to the pre measurements. The post SEPs measurements took 10.13 minutes at 2.47 Hz and 5.03 minutes at 4.98 Hz for a total post measurement time of 15.16 minutes. In addition to the SEP measurements, behavioural measurements of accuracy or error rate were also measured pre and post acquisition phase. After a minimum of 24-48 hours following the first session, participants came in for the second session in which they performed the next motor training task. Prior to performance of the new motor task, a retention test of the task performed 24-48 hours prior to the second session was done. The retention test consisted of simply one post test of either the typing or tracing task, depending on which one was performed in the first session. During this time, only accuracy was measured. The third and final session occurred 24-48 hours

following the second session and this was to administer a retention test of the motor task performed 24-48 hours prior.

Data Analysis

Changes in SEP peak amplitude and latency were measured both pre and post control and intervention. Additionally, to determine motor training effects, accuracy pre and post acquisition phase as well as accuracy during a retention test were measured. In order to ensure that participants were familiarized with the electrical stimulation, sufficient to elicit SEPs, motor thresholding to determine the stimulus intensity that caused movement of the thumb muscle, was performed in addition to a double baseline measurement. Following data collection, SEP peak amplitudes were measured from the averaged 1500 sweeps of the waveforms.

As two separate tasks were being compared to one another, in order to appropriately compare the differences pre and post the motor training tasks, data was normalized, being expressed as a proportion of the pre-intervention baseline so as to make the magnitude of individual measurements of SEP peak magnitude comparable between subjects and groups. A Mixed Measures Analysis of Variance (ANOVA) was performed in SPSS, comparing mean SEP amplitude changes with factors of TIME (pre and post) and INTERVENTION (control, tracing task and tying task). Statistical significance was set at $P=0.05$. Only trials which had a stable peripheral nerve volley (N9 SEP peak), were included for statistical analysis. For this criterion to be achieved, the N9 SEP peak was to differ by no more than ±10% pre and post intervention trials. This ensures that any potential changes observed in the SEP peaks known to have central generators were indeed due to the motor training intervention and not simply due to alterations in afferent input as a result of transient variables such as changes in posture. Following the

ANOVA, in order to discern which groups interactions were specifically between, post-hoc comparisons using Tukey's test were performed.

The amplitudes of the SEP peaks were measured from the peak of interest to the preceding or succeeding peak of opposite deflection in accordance with international recommendations (Nuwer et al., 1994) and previous studies which outline the optimal sites for recording (Cheron and Borenstein, 1987, 1991; Rossini et al., 1996; Sonoo et al., 1997; Rossi et al., 2003). The amplitudes and latencies of the following SEP components were identified and measured: the peripheral N9, the spinal N13, the far-field N18 (P14-N18 complex), the parietal N20 (P14-N20 complex) and P25 (N20-P25 complex), the frontal N24 (P22-N24 complex), and the frontal N30 (P22-N30 complex). The latencies were recorded from the time of stimulation onset to their maximal peak or trough for each of the SEP components.

The N24 SEP peak is often observed as a notch which resides of the upward slope of the N30 SEP peak (Garcia Larrea et al., 1992), this particular SEP peak's amplitude is only measured using the faster rate measurement trials of 4.98 Hz as the higher stimulation rate allows for attenuation of the N30 peak thus allowing for appropriate identification and measurement of the underlying N24 SEP peak (Haavik and Murphy, 2013; Fuji et al., 1994).

To investigate and compare the mean difference of accuracy both pre and post the acquisition phase and during retention of both motor tasks, paired t-tests were performed for both the tracing task and typing task comparing both pre and post-acquisition and post-acquisition with retention phase. For the tracing task, accuracy was measured by averaging the distance from each dot the participant's cursor was for each trial. For the typing task, accuracy was measured

based on whether the letter key in the sequence was pressed correctly (1) or incorrectly (0) and this was averaged for each of the trials. Statistical significance was set at P=0.05.

Results

All 18 participants who took part in this study were included in the analysis of SEP peaks and in the analysis of behavioural data. No significant changes in latency were seen.

N13 SEP Peak

The Mixed Measures ANOVA showed that the mean peak amplitude change for the spinal N13 was significant post motor learning, [$F(1,51)=25.05$, $p<0.001$]; with a significant interaction between factors of INTERVENTIONS and TIME, [$F(2,51)=7.98$, $p=0.001$]. Post-hoc analysis showed that for the N13 peak, the interaction exists between the control and tracing groups ($p=0.001$). There was a 1% ± 1.8 decrease following the control vs a 20.6% ± 5.6 increase following tracing and a 11.6% ± 3.7 increase following typing.

The N20 SEP Peak

The mean peak amplitude change for the parietal N20 was significant post motor learning [$F(1,51)=43.03$, $p<0.001$] with significant interactions between factors of INTERVENTIONS and TIME, [$F(2,51)=11.22$, $p<0.001$]. Post-hoc analysis showed that this interaction was present between the control and tracing groups ($p<0.001$) and between the control and typing groups ($p=0.003$). There was a 0.7% ± 2.2 increase following the control vs a 42.6% ± 9.9 increase following tracing and a 32.3% ± 4.9 increase following typing.

The P25 SEP Peak

The mean peak amplitude change for the parietal P25 was significant post motor learning [$F(1,51)=13.5$, $p=0.001$], with a significant interaction between factors of INTERVENTIONS and TIME, [$F(2,51)=3.98$, $p=0.025$]. Post-hoc comparison showed that this interaction exists between the control and tracing groups ($p=0.018$). There was a 0.8% ± 3 increase following the control vs a 26.1% ± 9.1 increase following tracing and a 13.4% ± 5.3 increase following typing.

The N24 SEP Peak

For the frontal N24, the mean peak amplitude change was significant post motor learning, [$F(1,51)=78.46$, $p<0.001$] with significant interactions between factors of INTERVENTION and TIME [$F(2,51)=21.95$, $p<0.001$]. Post-hoc comparisons determined that this interaction was observed specifically between the control and tracing groups ($p<0.001$) and between the tracing and typing groups ($p=0.049$). There was a 1% ± 1.6 increase following the control vs a 29.8% ± 4.6 decrease following tracing and a 16.5% ± 3.1decrease following typing.

The N30 SEP Peak

For the frontal N30 SEP peak, the mean peak amplitude change was significant post motor learning, [$F(1,51)=91.04$, $p<0.001$] with significant interactions between factors of INTERVENTIONS and TIME, [$F(2,51)=24.08$, $p<0.001$]. Post-hoc analysis showed that this interaction exists between the control and tracing groups ($p<0.001$) and between the control and typing groups ($p<0.001$). There was a 1% ± 0.9 increase following the control vs a 25.5% ± 4 increase following tracing and a 20% ± 2.3 increase following typing. These changes are demonstrated in the group percent mean changes as seen in Figure 3 and in the individual traces for a representative participant in Figure 4.

As previously mentioned, only those trials in which the N9 SEP peak differed by no more than ±10% between pre and post trials were included for analysis. In fact, the peripheral N9 SEP peak showed no significant changes following either the control or both of the interventions.

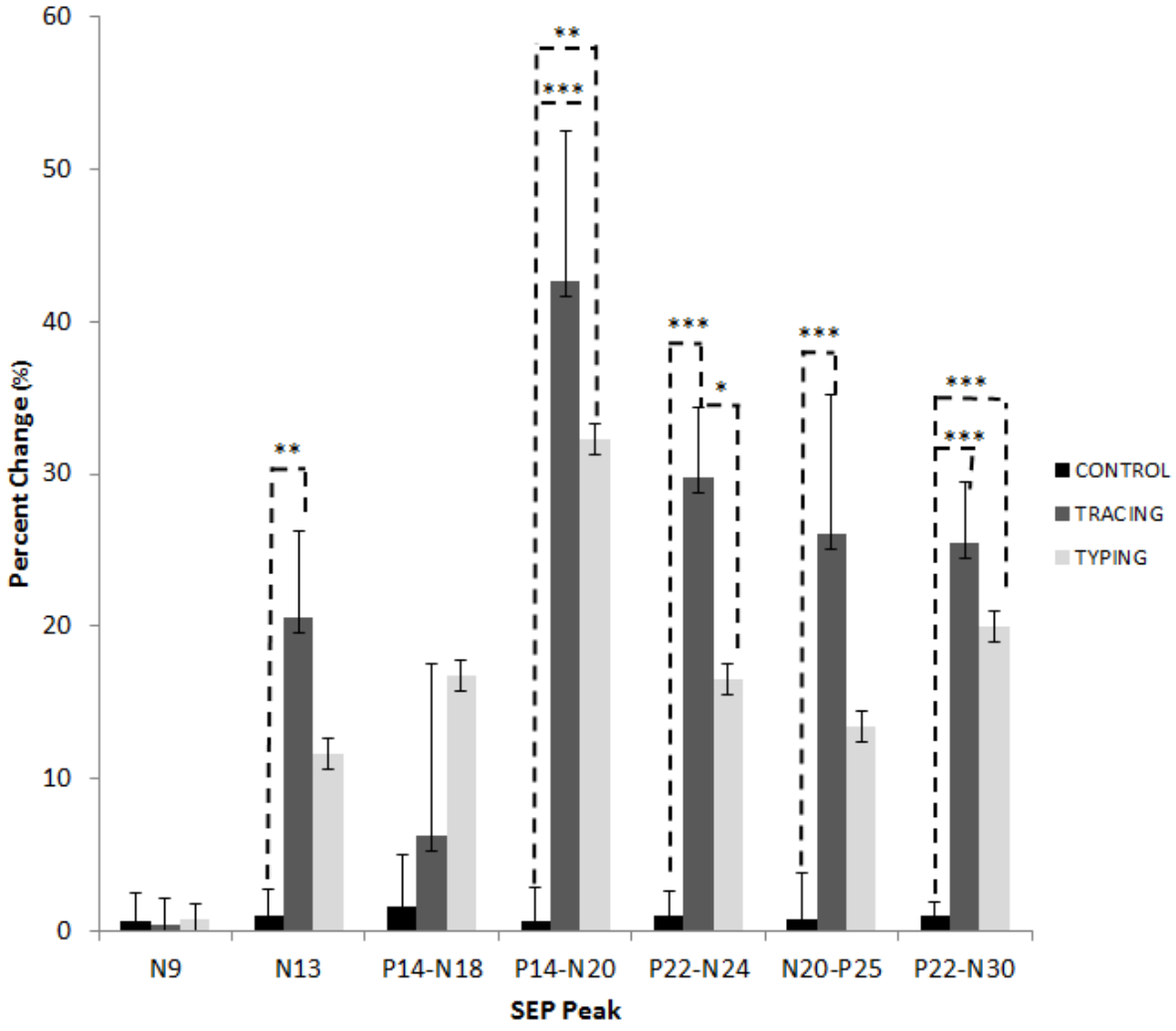


Figure 3: Mean percent amplitude change following control, tracing and typing tasks + SD
Note the significant main effect of interventions for the N13, N20, N24, P25 and N30 peaks.

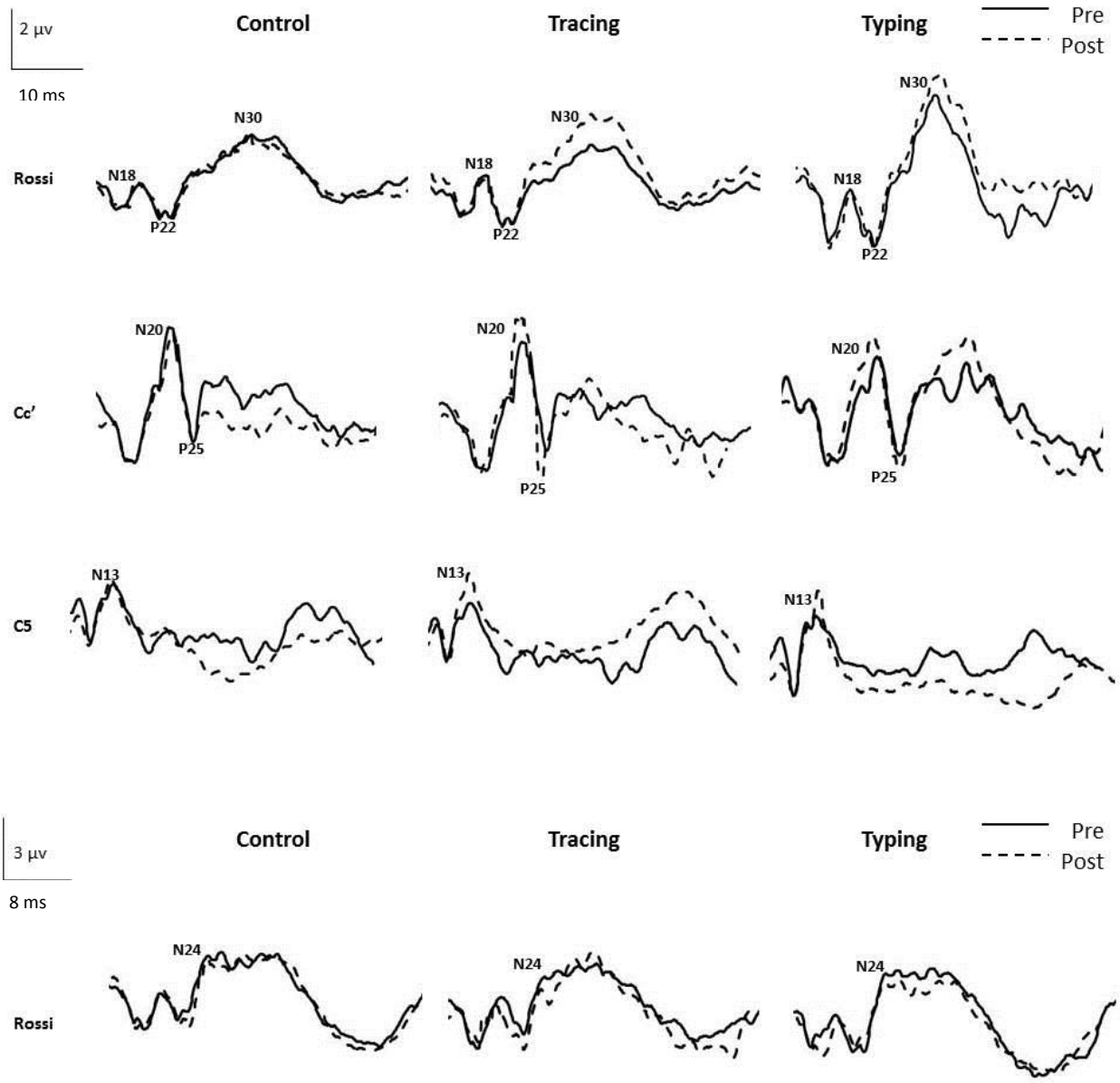
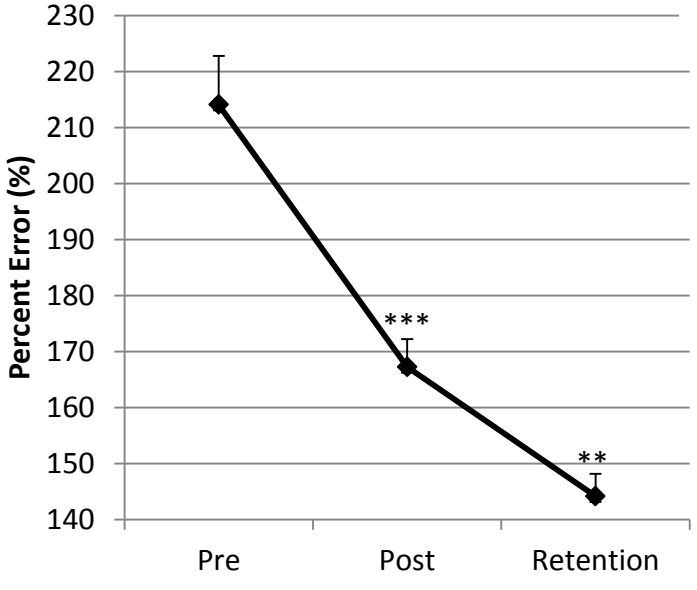


Figure 4: SEP peak changes for one representative participant following each condition

When looking at behavioural data from both the tracing task and the typing task, the paired t-test for the tracing task showed a significant increase in accuracy, $p<0.001$ post-acquisition phase and a significant increase in accuracy, $p=0.001$ during the retention test (See Figure 5A). For the typing task, the paired t-test showed a significant increase in accuracy,

p<0.001 post-acquisition phase and but no significant change in accuracy during retention (See Figure 5B).

A



B

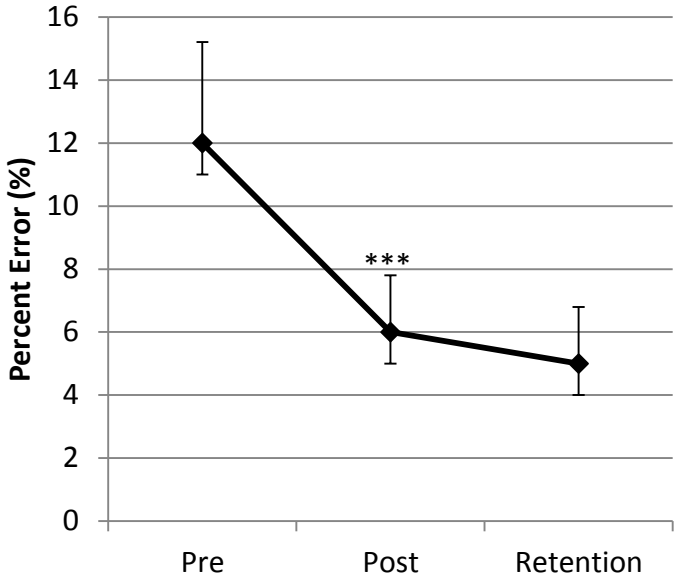


Figure 5: A) Percent error for tracing + SD B) Percent error for typing + SD

Discussion

This study has demonstrated that both of the tasks utilized are of increased complexity as seen through both neurophysiological and behavioural characteristics. This work has expanded upon previous work investigating sensorimotor integration following a repetitive typing task which did not exhibit the same complex characteristics (Haavik Taylor and Murphy, 2007; Bossé, 2012; Haavik and Murphy, 2013; Andrew et al., 2014). This work sought to evolve the characteristics of the motor task used so as to reflect the way that learning occurs, both temporally and spatially. The use of a control group to this study is crucial, seeing that there was a lack of change following no motor training ensures that those changes seen following motor

training are in fact a result of a change in central nervous system processing due to the repetitive movement. Previous work, which focused on the effects of simple repetitive movements (Haavik and Murphy, 2013; Haavik Taylor and Murphy, 2007a, 2007b, Murphy et al., 2003) resulted in minimal changes in sensorimotor processing, although increases in cortical and cerebellar-cortical complexes and changes in intracortical inhibitory processing were observed. However, further research was needed to clarify the role that task characteristics play in determining how well the task is learned, emphasizing the importance of behavioural relevance of the task. Building upon this, in a study by Andrew et al. (2014), in order to change the simple nature of the task, a randomly generated sequence was used, therefore automaticity was removed through the unpredictable sequences. The motor task sequence showed a significant increase in the N24 peak which represents neurons within the pathway between the cerebellum and the primary somatosensory cortex (Restuccia et al., 2007). This corroborates findings seen by Haavik and Murphy (2013), suggesting that the cerebellum plays a key role in integrating and learning complex motor tasks, far beyond its role in simple motor tasks. A change in the N30 peak which represents a complex loop between sensorimotor regions was also seen, once again suggesting the importance of the unpredictable nature of the task utilized (Andrew et al., 2014). Additionally, behavioural indices of reaction time and accuracy were used. While a decrease in reaction time was seen, accuracy did not change indicating this task was still too simple.

There are numerous motor task paradigms to use when studying the effects of motor learning, of the most common are the sequential tasks, which include explicit sequences and pursuit movement sequences. Studies have aimed to investigate whether tracing or copying differentially improved learning, it was concluded that the tracing group exhibited superior performance. However, there was no evidence of increased rates of learning as there was no interaction between the two tests (Gonzalez et al., 2011). The current study sought to investigate this through the use of two complex

tasks; previous work has often indicated the need to increase the complexity of the tasks whether it is from a lack of change in neurophysiological measures or from lack of improvement in behavioural measures.

N13 SEP Peak

The N13 SEP peak is reflective of the activity of the interneurons within the dorsal horn and midcervical cord (Desmedt and Cheron, 1981; Sonoo et al., 1991). While there were increases in amplitude for both tracing and typing post-acquisition, the change was larger for the tracing group and the interaction was only seen between control and tracing. This finding corroborates other studies which posit that SMI may occur directly at the spinal level (Garcia et al., 1979). The larger increase seen following the tracing task may indicate that it is a more complex task.

N20 SEP Peak

The N20 SEP peak reflects the earliest activity in S1 and is situated in Broadmann's area 3b (Desmedt and Cheron, 1980; Mauguiere et al. 1999; Nuwer et al., 1994). Therefore the similar amplitude increases and interaction with the control group demonstrates the role of S1 in motor learning.

P25 SEP Peak

The P25 SEP peak reflects neurons which reside within Brodmann's area 1 of S1 (Maguiere et al., 1999). The similar increase observed in both tasks following training is once again indicative of the role which the S1 plays in motor learning and sensorimotor integration. Observing that the interaction effect was only seen between the control and tracing and not the control and typing group could be reflective of the fact that the tracing task was more complex in nature.

N24 SEP Peak

The N24 SEP peak origination has been localized to near the posterior wall of the central sulcus (Waberski et al., 1999). However, selective N24 SEP peak amplitudes abnormalities in patients with unilateral cerebellar lesions with continued dipole source analysis at the primary somatosensory cortex (S1) has been observed (Restuccia et al., 2007). It is therefore suggested that the N24 reflects the activation of neurons in the pathway between the cerebellum and S1 (Restuccia et al., 2007). The interesting finding with this SEP peak is that there is not only a significant interaction effect between the control and tracing groups but also that there is a significant interaction between the tracing a typing groups. The N24 for both of the tasks decreased, although this decrease was larger for the tracing group. The decrease following learning seen in the peaks for both tasks could be reflective of the role that cerebellar input plays in this cortical peak and in line with previous studies which have proposed a decrease in cerebellar inhibition following true learning (Baarbe et al., 2014). The cerebellum is involved in coordination, with slow learning patterns, the need for this is decreased and therefore decreases in cerebellar activity have been demonstrated (Miall et al., 2001; Doyon et al., 2003). This is indicative of the learning pattern associated with more complex tasks, the larger decrease seen in the tracing task suggests this type of task, which provides more of a visuo-spatial stimulus is in fact superior to an explicit sequence. Previous work has shown that during initial performance of a coordinated eye-hand tracking task, the cerebellum was significantly activated in comparison to the performance of isolated hand movements (Miall et al., 2001). This activity was decreased following the learning of the tracking task more so than following learning of the discrete isolated movement task. With visuo-spatial stimuli, there are larger amounts of initial feedback due to the larger number of errors made allowing for continuing gradual improvement. The constrained nature of the typing task does not provide a large gradation of spatial feedback lending to a more automatic performance versus the learned improvement seen in the tracing task due to that feedback.

N30 SEP Peak

Evidence suggests that the N30 SEP peak is relayed by a complex cortical-subcortical loop which links the basal ganglia, thalamus, pre-motor areas, and the primary motor cortex (Mauguiere et al., 1983; Rossini et al., 1989, Rossini et al., 1987; Waberski et al., 1999). It is therefore suggested that this peak reflects the over-arching process of sensorimotor integration (Rossi et al., 2003). The similar increase in amplitude following both motor training tasks suggests that there is an increase in neural activity conducive to those regions involved in SMI. The increase in amplitude seen here compared to the minor increase in amplitude seen by Andrew et al. (2014) with the six-numbered sequences and to those studies which observed no change in the N30 with a predictable sequence (Haavik and Murphy, 2013) once again validates the role of the N30 SEP complex in SMI and the nature of complexity, specifically in terms of the motor preparation involved for both tasks.

Motor Performance

In using behavioural input to induce these CNS changes in sensory processing, it is crucial that behavioural performance be measured; this was done through observation of accuracy. For both the tracing and typing tasks, there was a significant increase in accuracy following the acquisition phase. However, following a 24-48 period of consolidation, during the retention test, only a significant increase in accuracy was observed for the tracing task. In previous work which used the technique of SEPs to investigate the effect of a repetitive typing task on SMI, retention had not been measured; this study has provided further insight into the learning aspect of the task through measurement of performance 24-48 hours later. This provides further evidence for the nature of complexity of both tasks utilized in comparison to those automatic and predictable tasks that have been observed in previous studies.

In previous work, changes conducive to rapid, or short-term learning were observed both neurophysiologically and behaviourally (Andrew et al., 2014). It was suggested that the development and use of a motor training task with an increased amount of numbers or letters would elicit greater changes reflective of long term learning which is what this study has shown.

In comparing two modalities of motor task, this work built upon previous studies which have investigated whether tracing or copying was a better medium with which to elicit learning (Gonzalez et al., 2011), and was able to have an interaction between the tasks to truly compare the two against one another in the same subjects. It was posited that tracing provides large amounts of continuous feedback which may be beneficiary to learning but that copying explicitly would allow for greater memory in the long term as it forces memorization (Gonzalez et al., 2011). They found that the tracing group exhibited superior performance to the copying group but no real differences in retention following one week. This statement is corroborated by the current study as greater performance was exhibited by the tracing group, and taking both neurophysiological and behavioural measures into account, the tracing task can be seen as the more complex of the two. While copying an explicit sequence, although randomized, relative to the tracing task the spatial and discrete nature of the task is much more constrained, ultimately making it easier than and not as novel as the varying frequency and amplitudes presented in the tracing task. This work further demonstrates the potential for the use of SEPs as a tool to investigate the effects of repetitive movement on sensory processing. Further work in which retention tests are performed at multiple time points past 24-48 hours along with repeated SEPs measurements would strengthen the implications of a more complex task and its relation to long term learning. One benefit of the tracing task is that it is sufficiently novel so as not to be too easy for experienced typists and musicians, in comparison to the typing task. Taking this and applying it to a clinical population or following an intervention thought to interfere with motor learning, would be beneficial in better understanding the way that these factors may interfere with learning and sensory processing, with the hopes of potential early identification and prevention.

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SECTION 4: MANUSCRIPT 2

The effects of low grade neck pain on sensorimotor integration following a complex motor pursuit task

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Abstract:

Objective: Cortical sensorimotor representations are reorganized as a result of experience. However, changes are also seen following highly demanding and automated tasks resulting in repetitive strain and overuse injuries (Byl et al., 1997). These disorders are characterized by pain, degraded cortical representations and unfavourable behavioural limitations. These changes are often investigated and identified through the use of neuroimaging techniques following the onset of chronicity. Somatosensory evoked potentials (SEPs) provide a tool for measuring electrical neural activity with high temporal resolution, on the order of milliseconds. The use of such a measure would enable the early identification of potential problems presenting acutely before they transition to a chronic issue. Neck pain is now very commonplace and it provides an ideal population to study the effects of transient pain on sensorimotor integration (SMI) as it does not involve the constant input of pain and can therefore provide a gradation scale of the temporal nature of any plastic changes that may occur. This study therefore sought to study the effects of a complex motor training task on the SMI of those with low grade neck pain compared to a healthy population with the goal of identification of neural markers of maladaptive plasticity through the use of an electrophysiological technique.

Methods: Spinal, brainstem and cortical SEPs were recorded following median nerve stimulation at the wrist pre and post intervention. 24 participants performed the same paradigm, a motor training intervention which consisted of a 10 minute tracing task.

Results: Significant interactions between the factors of GROUP and TIME were observed for the far-field N18 SEP peak, and the frontal N24 peak. Significant mean peak amplitude changes post motor training were regarded for the spinal N13, parietal N20, and the frontal N30

SEP peaks. Accuracy increased significantly for both groups post-acquisition, however, during retention a further significant increase in accuracy was only observed for the healthy control group.

Conclusions: The changes observed in this study reflect that when compared to a healthy group, a low grade neck pain group demonstrates deteriorated learning and therefore deteriorated retention of a skill due to altered afferent input. The changes observed, particularly in the peaks known to reflect cerebellar activity, demonstrate the importance of the role of the cerebellum in processes pertaining to both short and long term motor learning.

Significance: The observance of marked differences in neurophysiological and behavioural measures in a neck pain population with similar grades of recurring neck pain provides a starting point for the early identification of maladaptive changes. When compared to normative data, SEPs could be implemented as a potential early screening tool for repetitive strain and overuse injuries so that the appropriate rehabilitative measures can be provided to avoid transition into a severe chronic disorder.

Keywords: Somatosensory evoked potentials (SEPs), motor training, sensorimotor integration (SMI), low grade neck pain (LGNP), retention

Introduction

The central nervous system (CNS) is ever-evolving; with specific electrophysiological and structural changes occurring in neurons and neuronal networks in response to experiences (Pascual-Leone and Torres, 1993). These plastic changes are essential to the processes of recovery of function after injury, learning and memory (Marshall, 1984; Lederhendler and Alkon, 1986; Kass, 1991; Pascual-Leone and Torres., 1993). However, there is a growing body of evidence which suggests that these changes which are necessary for learning and adaptation can also occur following dysfunctional input, thus causing maladaptive changes associated with unfavourable performance and learning outcomes. Cortical and sensorimotor representations are substantially reorganized following peripheral nerve transection, dorsal root damage, amputation, spinal dysfunction and various musculoskeletal and pain syndromes (Sanes et al., 1988; Merzenich et al., 1984; Byl et al., 1997; Classen et al., 1998; Haavik Taylor and Murphy, 2011; Tinazzi et al., 1997, 1998; Falla, 2004), as a result of altered afferent input.

For individuals with spinal dysfunction, musculoskeletal disorders and pain syndromes, these disorders are typically diagnosed after the pain and debilitating symptoms concurrent with these plastic changes have manifested. Disorders of the musculoskeletal system are a major health problem affecting substantial proportions of the general population in their work, daily living and social lives. The incidence of these disorders is rising in Canada, the United States and Europe due to age and lifestyle factors and they account for the vast majority of long-term disability costs in Canada (Curwin et al., 2013). Due to the fact that these disorders are generally non-life threatening, the effect that they have on quality of life and their economic costs are often overlooked (Curwin et al., 2013). Of these disorders, neck pain has emerged as one of the most common and most persistent musculoskeletal pain symptoms with significant disability in the

general population; during any six-month period, 54% of adults suffer from it and 4.6% of those individuals experience significant activity limitations from it (Hakala et al., 2006; Côté et al., 1998, Côté et al., 2004). A specific category of neck pain is subclinical neck pain (SNCP) which refers to a lower grade neck dysfunction where individuals do not have constant symptoms and have not yet sought regular treatment of their neck complaint. Haavik Taylor and Murphy (2007) investigated the changes in baseline somatosensory evoked potentials (SEPs) in participants with SCNP compared to those without any neck pain and found that SNCP does lead to alterations in cortical somatosensory processing and early sensorimotor integration of input from the upper limb. It is known that altered afferent input in the form of repetition and overuse can induce organizational CNS changes in the way that sensory information is processed (Byl et al., 1997; Classen et al., 1998; Haavik Taylor and Murphy, 2007a, 2007b; Murphy et al., 2003). Therefore, investigating a population with low grade neck pain provides an insightful medium for exploring neurophysiologic dysfunction without the consistent interaction of pain. Using such a population to investigate the effects of a transient, low grade dysfunction on sensorimotor integration and motor learning could potentially provide a marker of altered sensory processing, thus aiding as an early identifier of disordered sensorimotor integration where measures can then be taken to prevent further exacerbation to a stage of severe chronicity (Haavik and Murphy, 2011). Daligadu et al. (2013) utilized transcranial magnetic stimulation (TMS) and found that a group with SNCP had altered cerebellar outputs following a motor sequence learning task. This corroborates with multiple studies demonstrating the role that the cerebellum plays in motor learning and sensorimotor integration of afferent input from the joints of the neck and spine (Doyon et al., 2003; Doyon et al., 2002; Molinari et al., 2007; Manzoni et al., 2005; Manzoni et al., 2007). In this particular study however, accuracy remained unchanged, suggesting that

perhaps a more novel and complex motor task is required to further understand the role that neck pain plays within SMI and motor learning.

This study used the non-invasive neurophysiological method of SEPs to compare the effects of a complex, novel motor tracing task on SMI in a population with recurring, low grade neck pain (LGNP) to a healthy control population without neck pain. The tracing task utilized in this experiment is the same that was utilized in Project 1 which demonstrated the superiority of the tracing task through not only the neurophysiological changes it induced but also through the increases seen in accuracy and retention (Andrew, 2014). By using a complex task, which is associated with longer term learning, we can understand how LGNP affects an individual's ability to learn. This study also looks to measure retention which is a crucial aspect to long term learning, which has yet to be investigated in individuals with LGNP. By understanding how healthy individuals respond to the motor tracing task and comparing this to individuals with neck pain, we can identify potential differences and investigate those further. This will enable potential early identification of disorders through not only neuromarkers but also through behavioural measures whereby SEPs can be used as a preventative screening tool for the onset of chronic pain and disorders.

Methods

Subjects/Participants

24 participants with no known neurological conditions comprised of 10 males and 14 females (mean age 22.3; range 21-27) participated in this study. This was a between group experimental design where 12 participants (3 males, 9 females), suffering from low grade chronic neck pain, formulated the neck pain group and another 12 participants (7 males, 5

females), not suffering from neck pain, formulated the healthy group. Participants in both groups were assessed using the chronic pain grade scale (Von Korff et al., 1992; see appendix 3), to ensure that those participants who made up the healthy control group were in fact healthy, and that those in the neck pain group shared a similar low grade of neck pain, since chronic pain may differentially modulate areas of the brain which are not affected by acute pain states (Dancey et al., 2014). Therefore, attention to ensure similarity of pain grade would enable the groups to be appropriately compared to one another, with changes being conducive to early plastic changes. Those in the neck pain group ranged from a grade of I-II and those in the healthy control had a grade of zero. Participants in both groups performed the same intervention. Informed consent was obtained and the study was approved by the ethics committee at the University of Ontario Institute of Technology. This study was a pseudo-randomized experimental design.

Stimulation Parameters

The stimuli consisted of electrical pulses which were 1 ms in duration and delivered at rates of both 2.47Hz and 4.98 Hz through Ag/AgCl ECG conductive adhesive skin electrodes (MEDITRACE™ 130, Ludlow Technical Products Canada Ltd., Mansfield, MA) (impedance <5kΩ). These electrodes were placed over the median nerve on the skin 2-3cm proximal to the distal crease of the wrist, between the tendons of flexor pollicis longus and palmaris longus with the anode proximal. SEPs were recorded at two different rates, to enable optimal conditions to record both the N24 and N30 SEP peak complexes. Using the slower rate of 2.47Hz does not lead to SEP peak attenuation while the faster rate, 4.98 Hz attenuates the N30 SEP peak, allowing for the N24 SEP peak to be accurately identified and measured (Haavik and Murphy, 2013; Fuji et al., 1994). Stimuli were given at motor threshold for each subject, defined as the lowest possible intensity at which a visible muscle contraction of the APB was elicited.

Recording Parameters

SEP recording electrodes were placed according to the International Federation of Clinical Neurophysiologists (IFCN) guidelines (Nuwer et al, 1994). Recording electrodes were placed on the ipsilateral Erb's point, over the C5 spinous process, as well as on two cephalic sites, the Cc'(2 cm posterior to contralateral central C3/4) and a frontal site (6cm anterior and 2cm contralateral to Cz) (Rossi et al., 2003). The two cephalic site electrodes were 2mm gold cup EEG electrodes (Grass Technologies, Astro-Med, Inc. Subsidiary, Rockland, MA) (impedance <5kΩ) as was the ground electrode which was placed in the mouth of participants. The C5 spinous process electrode was referenced to the anterior neck (tracheal cartilage) while all other electrodes were referenced to the ipsilateral earlobe. During data collection, the subjects were asked to sit with their eyes closed while remaining quiet and as still as possible; the lights in the room were turned off. To ensure participant comfort, the data was collected in a quiet room with the subjects seated in a comfortable but rigid office chair. To ensure isolation of the muscles of the thenar eminence during task performance, the wrist was splinted to prevent ulnar or radial deviation and was positioned on an armrest to prevent shoulder fatigue. The SEP signal was amplified (gain 10 000), filtered (0.2-1000 Hz) and saved on a laboratory computer for retrieval using a configuration written in Signal® software (Cambridge Electronic Design, Cambridge, UK).

Experimental Protocol

This study was a between group experimental design, comparing the effects of the intervention on a group with low grade neck pain to a healthy group, without neck pain. All subjects were required to attend two sessions. In order to participate in the study, they were required to be neurologically normal, this was in order to ensure that no existing conditions

would affect the SEP measurements, which were performed at rest throughout this experiment. All participants performed the same intervention. Double baseline measurements were performed for pre SEP measurements through stimulation of the median nerve. Immediately following baseline SEP measures, participants were required to perform a repetitive, pursuit movement sequence tracing task, as was utilized in the first experiment. The tracing task was run through a custom Leap Motion software tool (Leap Motion, Inc., San Francisco, CA) and required participants to trace sequences of sinusoidal-pattern waves with varying frequency and amplitude using only their thumb on an external wireless touchpad (Logitech, Inc., Fremont, CA) during a pre test, an acquisition phase and a post test. The trace itself was a sin(x) function, however for each of the four patterns, the frequency and amplitudes were varied by a certain factor through randomization which allowed for unpredictability throughout the duration of the trace. The traces were formed by a series of dots, each trial consisted of 500 dots. No discernible lag time was present between the participant's movements on the external tracing pad and the movement observed on the monitor. The pre and post test were approximately three minutes in duration while the acquisition phase was approximately 10 minutes in duration. The tracing task comprised of four pre-selected sinusoidal patterns of varying amplitude and frequency. For the pre and post tests, each version, 1-4, was performed once; for the acquisition phase each version was performed three times for a total of 12 traces. Combined flexion/adduction movements of the thumb were performed, consisting of a sweeping from left to right of the thumb utilizing the abductor pollicis brevis (APB) muscle. The APB muscle is innervated by the median nerve distal to the site of stimulation used throughout this experiment. Immediately following the motor task intervention, post SEPs measurements were taken in an identical fashion to the pre measurements. The post SEPs measurements took 10.13 minutes at 2.47 Hz and 5.03 minutes at

4.98 Hz for a total post measurement time of 15.16 minutes. In addition to the SEP measurements, behavioural measurements of accuracy or error rate were also measured pre and post acquisition phase. After a minimum of 24-48 hours following the first session, participants came in for the second and final session in which they performed a retention task of the tracing task which consisted of tracing versions 1-4 one time each. During this time, only accuracy was measured.

Data Analysis

Changes in SEP peak amplitude and latency were measured both pre and post intervention for both healthy and neck pain groups. Additionally, to determine motor training effects, accuracy pre and post acquisition phase as well as accuracy during a retention test were measured. Accuracy was measured by averaging the distance from each dot that the participant's cursor was for each trial. In order to ensure that participants were familiarized with the electrical stimulation sufficient to elicit SEPs, motor thresholding was performed in addition to a double baseline measurement. Following data collection, SEP peak amplitudes were measured from the averaged 1500 sweeps of the waveforms.

As two separate groups were being compared to one another, in order to appropriately compare the differences pre and post the motor tracing task, data were expressed as a proportion of the pre-intervention baseline so as to make the magnitude of individual measurements of SEP peak magnitude comparable between subjects and groups. A Repeated Measures Analysis of Variance (ANOVA) was performed in SPSS, comparing mean SEP amplitude changes with factors of TIME (pre and post) and GROUP (healthy control and neck pain). Statistical significance was set at P=0.05. Only trials which has a stable peripheral nerve volley (N9 SEP peak), were included for statistical analysis. For this criterion to be achieved, the N9 SEP peak

was to differ by no more than ±10% pre and post intervention trials. This ensures that any potential changes observed in the SEP peaks known to have central generators were indeed due to the motor training intervention and not simply due to alterations in afferent input as a result of transient variables such as changes in posture.

The amplitudes of the SEP peaks were measured from the peak of interest to the preceding or succeeding peak of opposite deflection in accordance with international recommendations (Nuwer et al., 1994) and previous studies which outline the optimal sites for recording (Cheron and Borenstein, 1987, 1991; Rossini et al., 1996; Sonoo et al., 1997; Rossi et al., 2003). The amplitudes and latencies of the following SEP components were identified and measured: the peripheral N9, the spinal N13, the far-field N18 (P14-N18 complex), the parietal N20 (P14-N20 complex) and P25 (N20-P25 complex), the frontal N24 (P22-N24 complex), and the frontal N30 (P22-N30 complex). The latencies were recorded from the time of stimulation onset to their maximal peak or trough for each of the SEP components.

The N24 SEP peak is often observed as a notch which resides of the upward slope of the N30 SEP peak (Garcia Larrea et al., 1992), this particular SEP peak's amplitude is only measured using the faster rate measurement trials of 4.98 Hz as the higher stimulation rate allows for attenuation of the N30 peak this allowing for appropriate identification and measurement of the underlying N24 SEP peak (Haavik and Murphy, 2013; Fuji et al., 1994).

To investigate and compare the mean difference of accuracy both pre and post the acquisition phase and during retention of both motor tasks, a repeated measures ANOVA was performed comparing both pre and post acquisition and post acquisition with retention phase. Statistical significance was set at P=0.05.

Results

All 24 participants who took part in this study were included in the analysis of SEP peaks and in the analysis of behavioural data. No significant changes in latency were seen.

The Repeated Measures ANOVA revealed a significant mean peak amplitude changes for the spinal N13 post motor learning [$F(1,22)=10.50$, $p=0.004$], with a mean percent change of 9.6% for the healthy control vs 9.2% for the neck pain group. Similarly for the parietal N20, a significant mean peak amplitude change post motor learning was observed [$F(1,22)=23.52$, $p<0.001$], with a mean percent change of 53.8% for the healthy control and a 27.7% change for the neck pain group. For the far-field N18 peak, a significant main effect for the factors of TIME and GROUP [$F(1,22)=4.23$, $p=0.042$] was observed. The healthy control group had a mean percent change of 8.3% vs a mean percent change of 20% in the neck pain group. The frontal N24 peak showed a significant main effect for the factors of TIME and GROUP [$F(1,22)=7.09$, $p=0.014$]. The healthy control had a mean percent change of 29.7% while the neck pain group only differed by 7.5% following the tracing task. Lastly, for the frontal N30 peak, a significant mean amplitude change post motor learning [$F(1,22)=30.175$, $p=<0.001$] was observed. The healthy control group had a mean percent change of 30.1% while those in the neck pain group had a mean percent change of 23.2%. These mean group changes can be seen in Figure 6 as well in Figure 7 as demonstrated through representative participants in both groups. There were no significant changes in latency data for any SEP peak in either the healthy control or neck pain groups.

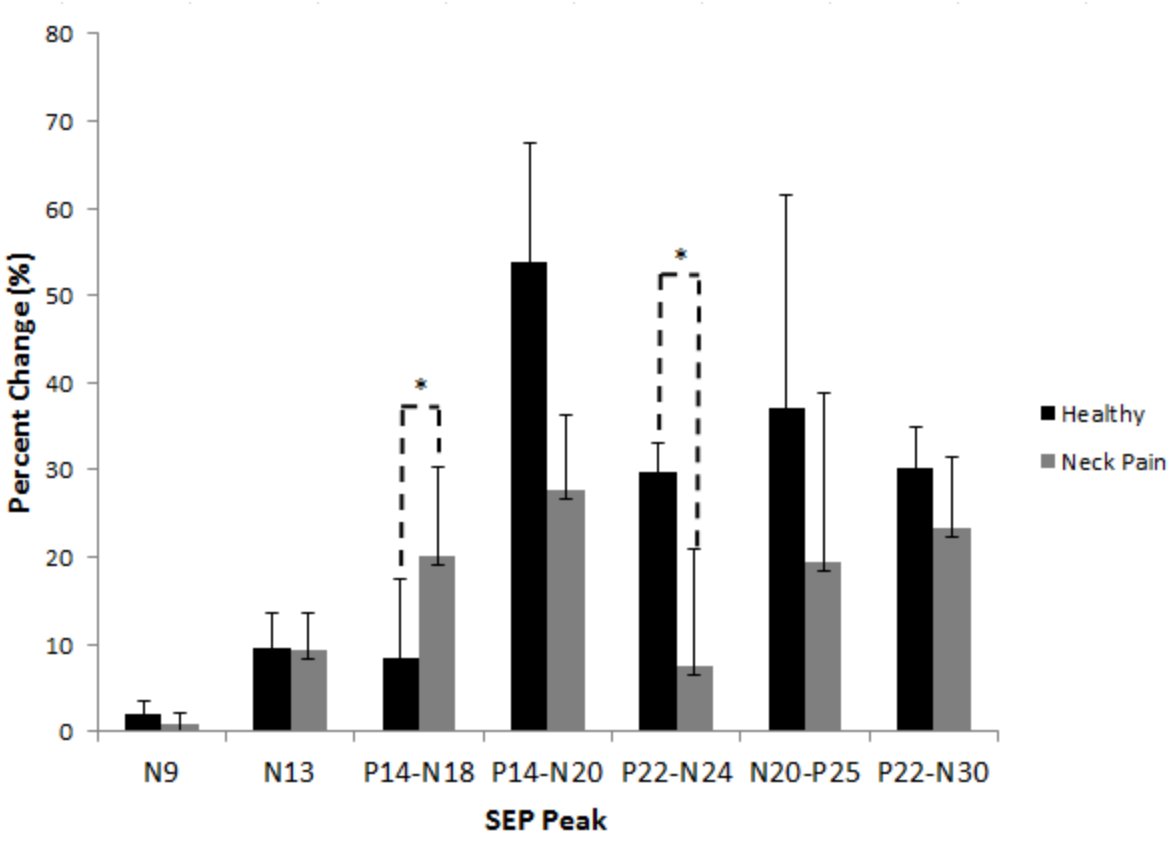

Figure 6: Mean percent amplitude change following motor training + SD
Note the significant main effects between groups for N18 and N24.

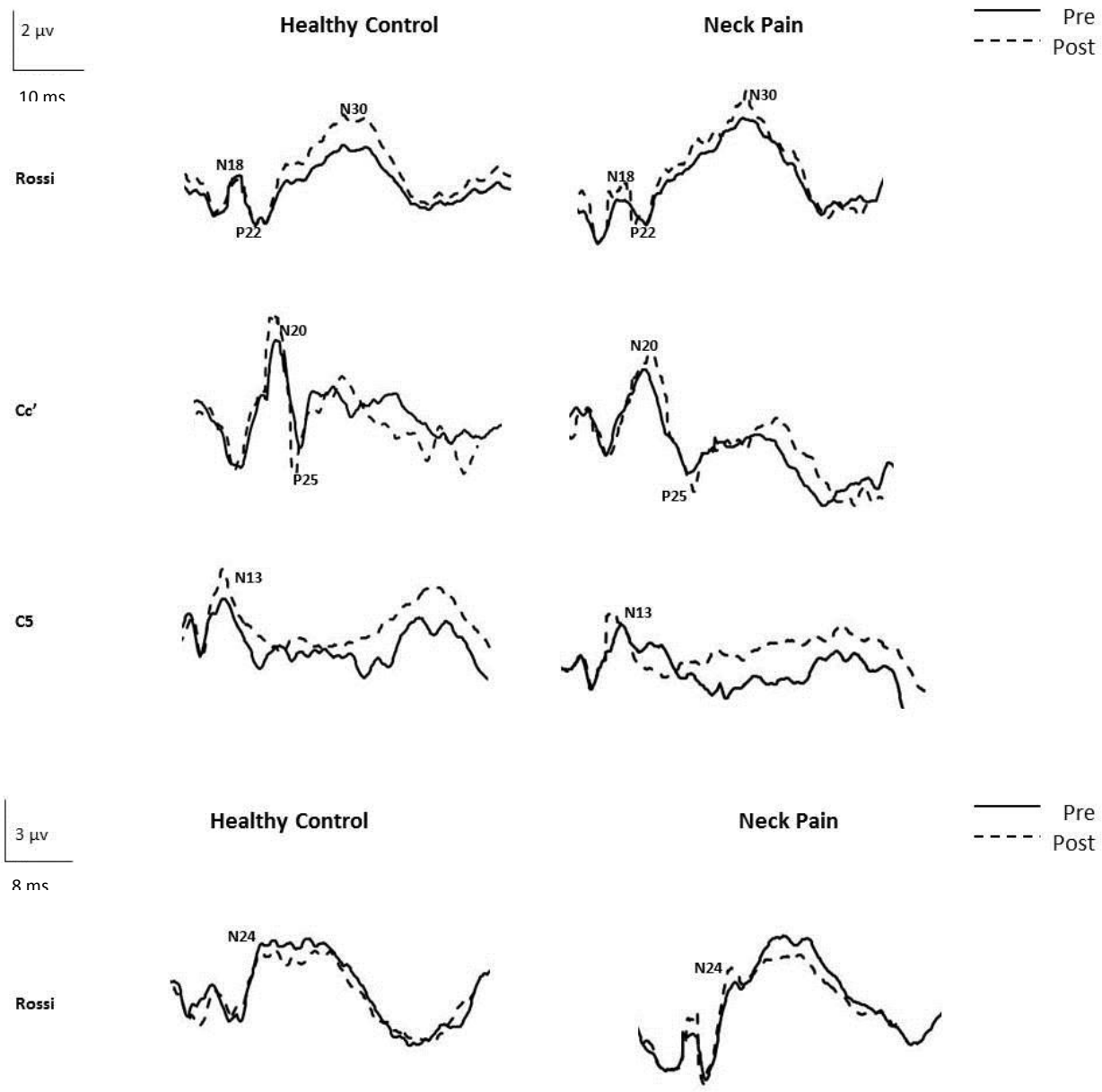

Figure 7: SEP peak changes for two representative participants from both groups

When looking at behavioural data, comparing accuracy of the tracing task for both the healthy control and the neck pain group, the repeated measures ANOVA showed a significant increase in accuracy post-acquisition for both healthy control and neck pain

groups,[F(1,22)=83.63, p=<0.001]. The mean percent error for the healthy control group decreased by 46.81% while for the neck pain group, it decreased by 41.9%.

For the retention test, the ANOVA once again showed a significant increase in accuracy, [F(1,22)=15.63, p=0.001] with a significant interaction of TIME*GROUP, [F(1,22)=9.64, p=0.005]. The mean percent error for the healthy population decreased by 23.08% during retention while for the neck pain group, it increased by 5.12% , these changes are demonstrated in Figure 8.

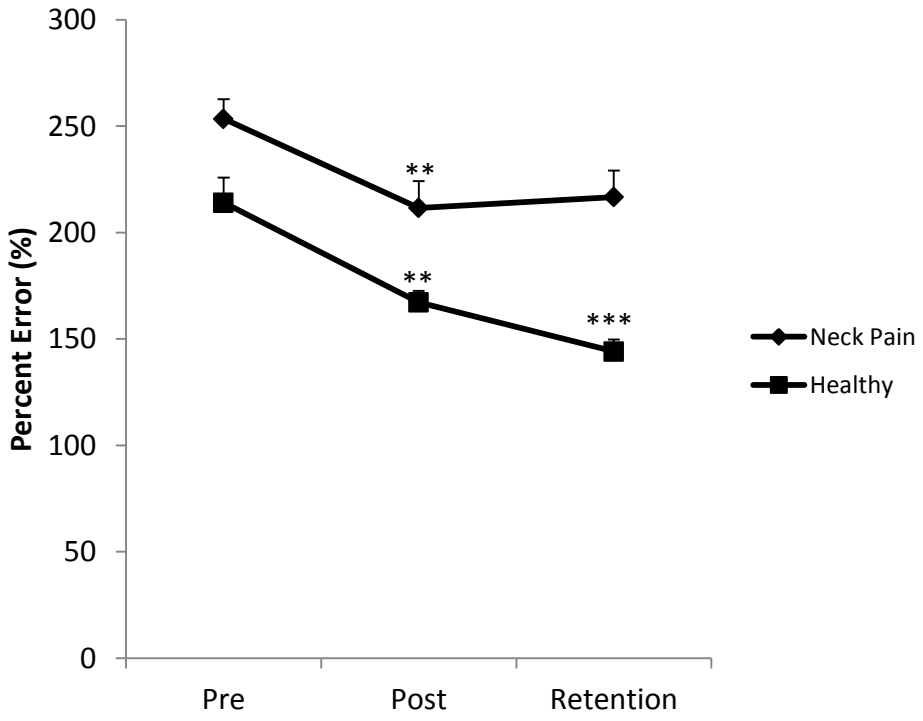

Figure 8: Mean percent error changes post-acquisition and during retention task for both groups

Discussion

This study sought to examine the effects of a complex motor tracing task on individuals with low grade chronic neck pain (LGCNP) and to differentiate those changes observed with that of a healthy population performing the same experimental procedure. The changes demonstrated throughout this study are in agreement with previous work that shows neck pain and related musculoskeletal disorders have a direct impact on the way the CNS processes and integrates incoming information (Daligadu et al., 2013; Haavik Taylor and Murphy, 2011; Haavik Taylor and Murphy, 2007; Byl et al., 1997; Tinazzi et al., 1998; Elbert et al., 1998).

The N13 SEP Peak

This particular SEP peak originates at the spinal level, reflecting the interneurons in the dorsal horn of the midcervical cord, generated at or near the first relay of the spinothalamic tract, which is the most prominent nociceptive pathway (Desmedt and Cheron, 1981; Sonoo et al., 1991; Cruccu et al., 2008; Tinazzi et al., 2000; Valeriani et al., 1998). There is a similarity in change seen for both groups, indicating that the changes due to the presence of low grade neck pain do not occur at level of the incoming spinal volley.

The N18 SEP Peak

The N18 SEP peak reflects the activity of the brainstem, in between the lower medulla and midbrain-pontine regions (Manzano et al., 1998; Noel et al., 1996). It has also been suggested that there are inputs from subthalamic generators such as the dorsal column medial leminiscus and the accessory inferior olives (Manzano et al., 1998; Noel et al., 1996; Sonoo et al., 1991). Therefore, the N18 peak may be indicative of cerebellar activity. The interaction effect observed between the neck pain and healthy groups may be reflective of the ability of the

N18 to show cerebellar activity. A key function of the cerebellum is to modify extracerebellar output through inhibition, which is seen through its increased activity during the early stages of learning (Baarbé et al., 2014; Daligadu et al. 2013, Doyon et al., 2002). Following the performance of a complex motor typing task, reduced inhibition in cerebellar outputs have been observed (Baarbé et al., 2014). Observing a smaller N18 amplitude in the healthy control group following motor training may reflect a decrease in cerebellar inhibition, thus lending to a greater learning effect as compared to the larger N18 amplitude observed in the neck pain group following motor training.

The N20 SEP Peak

The N20 SEP peak reflects neurons within Brodmann's area 3b in the primary somatosensory cortex (S1) (Mauguiere et al., 1999; Nuwer et al., 1994; Tinazzi et al., 2000). Both groups had increases in the N20 peak amplitude following motor learning, however those in the healthy group had a larger change, suggesting that chronic low level neck pain has the capacity to affect the earliest stages of somatosensory processing. Within S1, Brodmann's area 3b specifically processes cutaneous and tactile sensory information. The larger amplitude seen for both groups could reflect the novelty of the thumb movement needed to accurately trace varying frequencies and amplitudes of sine waves.

The N24 SEP Peak

The N24 SEP peak origination has been localized to near the posterior wall of the central sulcus (Waberski et al., 1999). However, selective N24 SEP peak amplitudes abnormalities in patients with unilateral cerebellar lesions with continued dipole source analysis at the primary somatosensory cortex (S1) has been observed (Restuccia et al., 2007). It is therefore suggested

that the N24 reflects the activation of neurons in the pathway between the cerebellum and S1 (Restuccia et al., 2007). The significant interaction observed for this peak between the healthy and neck pain groups is complementary to the changes seen with the N18 peak. The healthy group had a larger decrease in amplitude following motor training than the neck pain group which could be indicative of less inhibitory input from the cerebellum subsequent to learning. Contrary to this finding, previous studies have demonstrated selective increases in N24 peak amplitude following motor training, these studies however have focused on rather simple and automatic repetitive movements which could be considered a motor performance task as opposed to a more complex motor learning task, which was used in the current study (Haavik and Murphy, 2013; Dancey et al., 2014; Andrew et al., 2014). The decrease in N24 amplitude seen in the healthy population may reflect the decrease of cerebellar nuclei activity which is associated with the later stages of learning and the greater reliance on well-formed internal schema formulated through skill acquisition (Doyon et al., 2002). In comparison, the neck pain group appeared to have increased cerebellar input demonstrated by the increase in N24 peak amplitude suggesting that those in this group had not reached the later stage of consolidated learning in the same way as the healthy controls.

The N30 SEP Peak

The N30 SEP peak is relayed by a complex cortical-subcortical loop which links the basal ganglia, thalamus, pre-motor areas, and the primary motor cortex (Mauguiere et al., 1983; Rossini et al., 1989, Rossini et al., 1987; Waberski et al., 1999). It is therefore suggested that this peak reflects the over-arching process of sensorimotor integration (Rossi et al., 2003). No significant interaction was observed between the two groups, however, the larger increase in the

N30 seen in the neck pain group may be related to the role which the basal ganglia play in pain perception (Arsalidou et al., 2013).

Motor Performance

Measurement of accuracy following acquisition and during a retention test was performed on both groups. In doing so, this provides clarification of the neurophysiological changes seen following the motor training. For the healthy group, significant increases in accuracy were observed following the acquisition phase and 24-48 hours later during a retention test. In the neck pain group, a significant increase in accuracy was seen following the acquisition phase, however there was no significant change seen during the retention test. As long term learning is related to a period of consolidation and thus retention, this finding validates that the healthy group did in fact, learn to a greater extent than those in the neck pain group.

It is known that pain plays a role in the determination of reorganization of the CNS and sensorimotor processing, however, many studies have come to these conclusions under the constraints of the coexistence of acute pain or in those with a diagnosed disorder of deafferentiation. This study however, is able to provide an insight into preventative screening and early identification of the potential for a maladaptive response to motor training by using a low grade neck pain population whose pain is recurring and therefore not acute and potentially confounding to the results at the time of data collection simply due to the presence of pain. When learning, initial exposure to the task involves the detection of sensory information, this is the gateway to information processing, which then integrated to generate the appropriate response (Sternberg, 1969). The response is predicted to be impeded if the quality of the stimuli is somehow degraded during this initial detection stage (Sternberg, 1969). The results from this

study indicate that with the presence of low grade neck pain, there is impaired stimulus detection, or somatosensation leading to the development of an inaccurate internal model created by the fundamental SMI loop. This would lead to a degraded acquisition of the task which is confirmed through decreased task retention and the observed differences in the neurophysiological changes when compared to the healthy control group. In observing that there are in fact differences, both neurophysiologically and behaviourally, between individuals with and without neck pain, we see a potential for utilizing SEPs as a potential pre-diagnostic tool for markers of pain even while symptomology is not necessarily apparent. Combining SEPs with varying motor learning paradigms known to be associated with specific cortical and subcortical regions, for example, differential activation of areas involved in cognitive versus motor learning tasks may provide further insight into those main areas affected with pain in conjunction with potential observations of motor dysfunction (Ghilardi et al., 2000). Future work in which more severe grades of neck pain are investigated could aid in establishing whether there is a gradient of the effects of neck pain on motor learning from lower grade subclinical all the way up to clinical diagnosis.

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SECTION 4: THESIS SUMMARY

Overall Summary

Cortical neuroplastic changes are associated with altered motor function or behaviour. In novel motor skill acquisition, cortical neuroplastic changes are often accompanied by behaviour deemed to be advantageous; conversely, in experimental or chronic pain, neuroplastic changes are often accompanied by changes deemed to be unfavourable (Boudreau et al., 2010; Karni et al., 1998; Classen et al., 1998; Kleim et al., 2004). With this information, this thesis sought to use the assessment and evaluation of motor skill learning to assess and identify potential or existing problems in motor learning in a population with low grade chronic or recurrent neck pain. Past work has focused on relatively simple paradigms, often recommending the development and use of a more complex task to assess potential alterations in SMI. More complex tasks are associated with long-term learning; an important component of long-term learning is consolidation, in which further skill gains are made through offline learning. Therefore, the importance of not only measuring performance immediately following the task but also following a 24-48 hour period of consolidation is crucial to provide a more comprehensive study.

The first study demonstrated that the use of an unpredictable motor task paradigm induces greater changes in neural structures associated with SMI which is conducive to long-term motor learning, as has not been seen in previous work. The increases in accuracy following motor learning and during retention are in alignment with this. This study also validated the complexity of a novel pursuit movement tracing task which, when compared to an explicit sequence repetitive typing task, proved to be slightly more complex in nature as well as being more novel to more potential participants (as it does not rely on keyboard skill) and is therefore a better task to use in studying changes to SMI following repetitive movement. In investigating the

effects of a complex task on a healthy population, these results can now be applied and compared to a population with neck pain in order to understand the effects of transient pain on SMI. Pain itself affects sensory processing as evidenced by elevated SEP peaks and functional reorganization (Tinazzi et al., 2000), however, the constant presence of pain can confound SEP measurements independent of learning effects and this study sought to identify early markers of maladaptive plasticity. Therefore, the use of a low grade chronic neck pain population provides an ideal group to investigate potential early markers of change. The second study therefore aimed to compare the neurophysiological and behavioural changes in a healthy control and a neck pain group following the same complex tracing task utilized in the first study. The results from this study demonstrated marked differences in the amount of neural activity in areas involved in SMI between the two groups. Most notable are those peaks associated with cerebellar input. Various imaging studies have demonstrated the activation of the cerebellum during motor sequence tasks (Doyon et al., 2003; Miall et al., 2001; Floyer-Lea and Matthews, 2005; Lehericy et al., 2005). Current evidence suggests that the cerebellum aids in learning through the formation of an internal model of experiences and through network connections which dictate the needed movements for executing a task, which is essentially coordination (Doyon et al., 2003; Dalidagu et al., 2013). As such, the increased activity of cerebellar nuclei is seen in the early stages of learning while decreases are seen in later stages (Doyon et al., 2002; Floyer-Lea and Matthews, 2005; Lehericy et al., 2005). Therefore, the ability of the cerebellum to effectively establish these internal models needed for successful learning is impaired due to the effects of altered afferent input resulting in the increased activity of the cerebellum even following a training paradigm. The insignificant change regarded during retention also corroborates this, indicating that the input from pain affects the fundamental SMI loop, and

creates a faulty internal representation of the task, so that when it is recalled, it is not as well learned as compared to the healthy population.

This study sets the foundation to use SEPs to explore the influence of different types and intensities of pain on motor learning. Using a direct electrophysiological measure combined with behavioural input, SEPs may be utilized as an early screening tool for the presence of maladaptive plasticity. With the increase in the prevalence of musculoskeletal, repetitive strain and overuse disorders, it is critical to identify these problems before they become long-term and to intervene with the appropriate preventative measures.

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SECTION 5: APPENDICES

APPENDIX 1: Participant Consent Form Study 1

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Research Information for participants
Title: ***The effects of motor task complexity on cerebellar function and sensorimotor integration- SEPs Nov, 2013.*** **This study has received ethical approval from the UOIT ethics committee (REB# 07-072 & 07-073)**

This is a research study being conducted by Danielle Andrew under the supervision of Dr. Bernadette Murphy and Dr. Paul Yielder from the Faculty of Health Sciences at the University of Ontario Institute of Technology (UOIT), in Oshawa, Ontario, Canada. We are investigating how different repetitive motor tasks alter neurophysiological function in the central nervous system particularly related to cerebellar function. In order to do this we will need to collect some information about the way your brain processes signals from your hand and forearm muscles before and after a period of repetitive thumb movement. We will also get you to complete some questionnaires, which will provide information regarding your current functional capacity, level of neck pain (if any), and general well being.

You are invited to participate in our research and we would appreciate any assistance you can offer us. Your participation in this study is entirely voluntary and you are free to decline taking part in this study, as well withdraw from the study at any time without giving a reason. This will in no way affect your future chiropractic care and/or academic progress, irrespective of whether or not payment is involved. We are seeking people who have had a history of chronic neck pain for at least three months and are aged between 18 and 50. To participate in this study you must complete an eligibility checklist in conjunction with one of the researchers, to ensure you are eligible to participant in this research.

Measurement sessions

Should you agree to participate, we will need you to attend up to three different evaluation sessions. The motor training task will consist of either a repetitive typing task where you will be required to press keys on an external numeric keyboard with only the thumb for 10 minutes or a repetitive thumb tracing task for 10 minutes. In one session you will be required to complete the typing motor task which will consist of pressing four keys in a randomized sequences of eight of the letters Z, P, D, and F e.g. Z, P, D, F, F, P, D, Z etc. In the second session you will be required to complete the thumb tracing task using a tracking pad in which you will have to trace a wave pattern of dots appearing on the screen in front of you. These sessions may not necessarily be in the order as stated above but you will be completing both tasks. The first two sessions will take approximately 2 hours and you will be given feedback about your results at each session. In order to monitor and analyze motor training effects, all subjects will be required to perform the motor tasks for two minutes both pre and post the 10 minute training phase. Typing and tracing rates and number of errors will be analyzed to determine motor training. The third session will consist of performance of both of the tasks once more; this will take just 10-15 minutes. Typing and tracing rates and number of errors will be analyzed once again to determine retention.

During each evaluation session we will collect some information about how your brain processes electrical signals from your hand and arm muscles. To do this it will be necessary to place some electrodes on your skin over your nerves at the wrist, and over your neck, ear and scalp. 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. The electrodes over your neck, ear and scalp are only recording electrodes and do not pierce the skin and do not run current through your body. Only the electrodes on your arm will be stimulating electrodes. These stimulating electrodes will be used to stimulate some of your hand muscles by passing mild electrical current through them. This creates a mild tingling sensation on the skin over the nerve. This is not painful but may feel quite strange to you. It will also make some of your hand and/or forearm muscles twitch which is not painful either, but can also feel strange.

Risks and benefits

The benefits of participating in this study that you will learn more about how your brain "learns" new tasks and how this might relate to neck pain. You will also be aiding our understanding of these costly and disabling conditions. Only safe conventional equipment will be used for the electrical stimulation, which is not painful but you will experience a light twitch of the muscles in your hand as the nerves at the wrist send signals to make these muscles contract. The surface electromyography (EMG) techniques have low risks such as the person getting a skin irritation from the alcohol swab or electrode gel, but these again are uncommon and not serious.

If the information you provide is reported or published it is done in a way that does not identify you as its source. All data will be kept confidential to the investigators and will be stored in a locked filing cabinet at UOIT for 7 years from the completion of the study after which it will be destroyed. You are free to withdraw from the data collection at any time up until the completion of your last data gathering session. Taking part in this study is voluntary and your decision to take part in this study (or not) will in no way influence your relationship with your professor, etc. The surface EMG techniques have low risks such as the person getting a skin irritation from the alcohol swab or electrode gel, but these again are uncommon and not serious. The electrical stimulation is not painful but you will experience a light twitch of the muscles in your hand as the nerves at the wrist send electrical signals to make these muscles contract. We recommend that students having any reactions, irritations, discomfort, pain, headaches, migraines etc. go to campus health services and to contact the Researcher.

Thank you very much for your time and help in making this study possible. If you have any queries or wish to know more please contact Danielle Andrew, graduate student at the University of Ontario Institute of Technology, Faculty of Health Sciences, 2000 Simcoe St North, Oshawa, Ontario, L1H 7K4 Phone (905) 706-0723 email : danielle.andrew@uoit.ca, Dr. Bernadette Murphy Phone: (905) 721-8668 ext 2778 email: bernadette.murphy@uoit or Dr. Paul Yielder Phone (905) 721-8668 ext 2768 email: paul.yielder@uoit.ca

For any queries regarding this study, please contact the UOIT Research and Ethics Committee Compliance officer (compliance@uoit.ca and 905-721-8668 ext 3693). The data from this research will be submitted to scientific conferences and peer reviewed journals. At the completion of the study, you will be sent a summary of the research findings and any place where the data has been published. All published data will be coded so that your data is not identifiable.

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 and that this will in no way affect my future chiropractic care and/or academic progress, irrespective of whether or not payment is involved.
- I have read and I understand the information sheet dated November 2013 for volunteers taking part in the study designed to investigate the effects of motor task complexity on cerebellar function and sensorimotor integration. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.
- I will be attending up to two sessions where measurements will be taken of the electrical activity in my brain following electrical stimulation of the nerves in my wrist.
- 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 the completion of my last measurement session.
- I understand that my participation in this study is confidential 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. (tick one) YES ☐ ☐

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

Signed …… Date ……..

Contact numbers of main researchers:
Danielle Andrew, Phone: + 905 706 0723
Dr. Bernadette Murphy, Phone: + 905 721-8668 ext 2778
Dr. Paul Yielder, Phone +905 721-8668 ext 2768

RESEARCHER TO COMPLETE

Project explained by: _____

Project role: _____

Signature: _____ Date: _____

Appendix 2: Participant Consent Form Study 2

University of Ontario Institute of Technology
Faculty of Health Sciences
2000 Simcoe St. North
Oshawa, Ontario
CANADA L1H7K4

Research Information for participants

Title: ***The effects of motor task complexity on cerebellar function and sensorimotor integration- SEPs Nov, 2013.*** **This study has received ethical approval from the UOIT ethics committee (REB# 07-072 & 07-073)**

This is a research study being conducted by Danielle Andrew under the supervision of Dr. Bernadette Murphy and Dr. Paul Yielder from the Faculty of Health Sciences at the University of Ontario Institute of Technology (UOIT), in Oshawa, Ontario, Canada. We are investigating how different repetitive motor tasks alter neurophysiological function in the central nervous system particularly related to cerebellar function. In order to do this we will need to collect some information about the way your brain processes signals from your hand and forearm muscles before and after a period of repetitive thumb movement. We will also get you to complete some questionnaires, which will provide information regarding your current functional capacity, level of neck pain (if any), and general well being.

You are invited to participate in our research and we would appreciate any assistance you can offer us. Your participation in this study is entirely voluntary and you are free to decline taking part in this study, as well withdraw from the study at any time without giving a reason. This will in no way affect your future chiropractic care and/or academic progress, irrespective of whether or not payment is involved. We are seeking with no known neurological conditions and are aged between 18 and 50. To participate in this study you must complete an eligibility checklist in conjunction with one of the researchers, to ensure you are eligible to participant in this research.

Measurement sessions

Should you agree to participate, we will need you to attend up to two different evaluation sessions. The motor training task will consist of a 10 minute thumb tracing task using a tracking pad in which you will have to trace a wave pattern of dots appearing on the screen in front of you. The first session will take approximately 2 hours and you will be given feedback about your results at each session. In order to monitor and analyze motor training effects, all subjects will be required to perform the motor task for two minutes both pre and post the 10 minute training phase. Tracing rates and number of errors will be analyzed to determine motor training. The second session will consist of performance of the tasks once more; this will take just 10-15 minutes. Tracing rates and number of errors will be analyzed once again to determine retention.

During each evaluation session we will collect some information about how your brain processes electrical signals from your hand and arm muscles. To do this it will be necessary to place some electrodes on your skin over your nerves at the wrist, and over your neck, ear and scalp. 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. The electrodes over your neck, ear and scalp are only recording electrodes and do not pierce the skin and do not run current through your body. Only the electrodes on your arm will be stimulating electrodes. These stimulating electrodes will be used to stimulate some of your hand muscles by passing mild electrical current through them. This

creates a mild tingling sensation on the skin over the nerve. This is not painful but may feel quite strange to you. It will also make some of your hand and/or forearm muscles twitch which is not painful either, but can also feel strange.

Risks and benefits

The benefits of participating in this study that you will learn more about how your brain "learns" new tasks and how this might relate to neck pain. You will also be aiding our understanding of these costly and disabling conditions. Only safe conventional equipment will be used for the electrical stimulation, which is not painful but you will experience a light twitch of the muscles in your hand as the nerves at the wrist send signals to make these muscles contract. The surface electromyography (EMG) techniques have low risks such as the person getting a skin irritation from the alcohol swab or electrode gel, but these again are uncommon and not serious.

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Thank you very much for your time and help in making this study possible. If you have any queries or wish to know more please contact Danielle Andrew, graduate student at the University of Ontario Institute of Technology, Faculty of Health Sciences, 2000 Simcoe St North, Oshawa, Ontario, L1H 7K4 Phone (905) 706-0723 email : danielle.andrew@uoit.ca, Dr. Bernadette Murphy Phone: (905) 721-8668 ext 2778 email: bernadette.murphy@uoit or Dr. Paul Yielder Phone (905) 721-8668 ext 2768 email: paul.yielder@uoit.ca

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- I understand that my participation in this study is confidential 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. (tick one) YES ☐ NO ☐

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

Signed …… Date ……..

Contact numbers of main researchers:
Danielle Andrew, Phone: + 905 706 0723
Dr Bernadette Murphy, Phone: + 905 721-8668 ext 2778
Dr. Paul Yielder, Phone +905 721-8668 ext 2768

RESEARCHER TO COMPLETE

Project explained by: _____
Project role: _____
Signature: _____ Date: _____

Appendix 3: Von Korff Chronic Pain Grade Scale

Pain intensity items

1. How would you rate your neck pain on a 0-10 scale at the present time, that is right now, where 0 is 'no pain' and 10 is 'pain as bad as could be'?

									Pain as bad	
No pain									as could be	
0	1	2	3	4	5	6	7	8	9	10

2. In the past 6 months, how intense was your worse pain rated on a 0-10 scale where 0 is 'no pain' and 10 is 'pain as bad as could be'?

									Pain as bad	
No pain									as could be	
0	1	2	3	4	5	6	7	8	9	10

3. In the past 6 months, on the average, how intense was your pain rated on a 0-10 scale where 0 is 'no pain' and 10 is 'pain a bad as could be'? (That is, your usual pain at times you were experiencing pain.)

									Pain as bad	
No pain									as could be	
0	1	2	3	4	5	6	7	8	9	10

Disability items

4. About how many days in the last 6 months have you been kept from your usual activities (work, school or housework) because of neck pain? (# of days) _____

5. In the past 6 months, how much has neck pain interfered with your daily activities rated on a 0-10 scale where 0 is 'no interference' and 10 is 'unable to carry on any activities'?

										Unable to carry on
No interference									on any activities	
0	1	2	3	4	5	6	7	8	9	10

6. In the past 6 months, how much has neck pain changed your ability to take part in recreational, social and family activities where 0 is 'no change' and 10 is 'extreme change'?

No change									Extreme change	
0	1	2	3	4	5	6	7	8	9	10

7. In the past 6 months, how much has neck pain changed your ability to work (including schoolwork and housework) where 0 is 'no change' and 10 is 'extreme change'?

No change Extreme change

0 1 2 3 4 5 6 7 8 9 10

Scoring guide

characteristic pain intensity = (((response question 1) + (response question 2) + (response question 3)) / 3) * 10

disability score = (((response question 5) + (response question 6) + (response question 7)) / 3) * 10

disability points = (points for disability days) + (points for disability score)

Disability points			
Disability days (0-180)		**Disability score (0-100)**	
0-6 Days	0 Points	**0-29**	0 Points
7-14 Days	1 Point	**30-49**	1 Point
15-30 Days	2 Points	**50-69**	2 Points
31 + Days	3 Points	**70 +**	3 Points

Classification

Grade 0 Pain free	No pain problem (prior 6 months)
Grade I Low disability-low intensity	Characteristic Pain Intensity Less than 50, and less than 3 disability points
Grade II Low disability-high intensity	Characteristic Pain Intensity of 50 or greater and less than 3 disability points
Grade III High disability-moderately limiting	3-4 disability points, regardless of Characteristic Pain Intensity
Grade IV High disability-severely limiting	5-6 disability points, regardless of Characteristic Pain Intensity