Exploring Lateralized Sensorimotor Processing Using Somatosensory Evoked Potentials

by
Ryan Gilley

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Chairperson of the Supervisory Committee: Professor Paul Yielder

Faculty of Health Sciences

Abstract

Differences exist between the two upper limbs in the chosen motor control strategy when moving in dynamic environments. To date, a large body of literature has explored these differences but few studies have incorporated neurophysiological data to support their findings. By utilizing somatosensory evoked potentials (SEPs) we can gain insight into the underlying neurological processes at the levels of the spinal cord and the cortex in response to movement and motor learning. The research conducted showed greater accuracy in the non-dominant limb following a novel tracing task. This was complimented by differential SEP peak amplitudes in the pathways that reflect cerebellar activation and sensorimotor integration. Additionally, the research also showed that when motor task acquisition occurs in the presence of sensory perturbations, the non-dominant limb is more accurate than a control group and there are differential changes in peaks reflecting the primary somatosensory cortex and the cerebellum

Keywords: Somatosensory Evoked Potentials, Laterality, Sensorimotor integrations, Cerebellum, Motor Learning, Motor Control

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

APB	Abductor Policis Brevis
CNS	Central Nervous System
Dom	Dominant Hand
FDI	First Dorsal Interosseous
IFCN	International Federation of Clinical Neurophysiologists
M1	Primary Motor Cortex
NonDom	Non-dominant Hand
SEP	Somatosensory Evoked Potentials
S1	Primary Somatosensory Cortex
SMI	Sensorimotor Integration
TMS	Transcranial Magnetic Stimulation

Key Terms

Adaptation: A change or the process by which an organism becomes better suited to its environment

Feedback: The modifications or control of a process by its results or effects.

Feedforward: A command issued by the system preceding action.

Handedness: The tendency to use either the right or the left hand more naturally than the other.

Impedance Control: A method of control that specify the amount of force around a mechanism imposed by the environment.

Laterality: The dominance of one side of the brain in controlling particular activities or functions, or one of a pair of organs such as the hands.

Motor learning: The result of complex processes in the brain in response to practice or experience in a skill that cause synaptogenesis in the cortex.

Predictive Control: A method of control that plans all aspects of the control program prior to the activation of the program.

Sensorimotor Integration: The ability of the nervous system to integrate different types of sensory stimuli and transform them into motor actions.

Somatosensory Evoked Potentials: A non-invasive test to measure incoming sensory information at various levels of the CNS using peripherally evoked electrical stimulations.

Transcranial Magnetic Stimulation: A non-invasive test used to determine the excitability and functionality of the motor pathways in the CNS using magnetically generated electrical stimulations above the motor cortex.

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Introduction to Thesis

Motor control underlines how we interact with the world. Performance is often determined by how well we can adapt our motor system to the task or goal directed behavior. From studying how we interact and adapt to the world, asymmetries begin to arise with respect to our upper limbs, specifically in the control strategies they utilize. These strategies differ between the dominant and non-dominant arm. These finding have begun to explain the lateralized patterns of movement that characterize handedness (Mutha, Haaland, & Sainburg, 2013). Current research has explored the external observations associated with the asymmetries in motor control (de Oliveira, 2002; Mutha et al., 2013; R. Sainburg & Kalakanis, 2000; Schabowsky, Hidler, & Lum, 2007; V Yadav & Sainburg, 2011; Vivek Yadav & Sainburg, 2014). These various studies have shown that our dominant arm relies on pre-planned and predictive mechanisms, while the non-dominant arm optimizes movement based on impedance control and reactive mechanisms.

The need to further understand not just external motor control patterns, but to explore the internal connectivity of the central nervous system (CNS) is the subject of this research. In the literature SEPs has been shown to provide a direct measure of brain activity following motor learning (D Andrew, Haavik, Dancey, Yielder, & Murphy, 2015; Danielle Andrew, Yielder, & Murphy, 2015; E. Dancey, B. Murphy, D. Andrew, & P. Yielder, 2016a; Dancey, Murphy, Srbely, & Yielder, 2014; E. Dancey, B. A. Murphy, D. Andrew, & P. Yielder, 2016b; Hoshiyama & Kakigi, 1999). By using this technique, it provides the potential to add to the growing body of knowledge about the sensorimotor integration pathways the brain utilizes to complete everyday tasks. This technique has rarely been used in the literature on laterality. The following research is a pre-post experimental design that attempts to build on previously published work in the area of laterality and motor control by measuring neurophysiological and performance differences between the dominant and non-dominant limbs in response to novel motor skill acquisition. It further compares differences between the two limbs when the motor skill

acquisition takes place during a sensory perturbation in the form of pain induced by capsaicin cream. Motor skills are often learned or relearned during conditions of altered sensory input such as pain or vibration. If there are differences in the way the two limbs acquire these new skills due to differences in their underlying motor control strategies, it is important to know this. This research aims to further explore the neurophysiological differences in the sensorimotor systems that underlie differences in performance between the dominant and non-dominant upper limbs.

Objectives

1. Explore the differences (peak amplitude) in early (<50ms.) sensorimotor processing between the limbs following a novel motor tracing task.

2. Investigate the effects of sensory perturbations on the non-dominant limb with respect to learning and motor control.

Hypotheses of this Thesis

1. The non-dominant limb will be better at baseline motor performance and the novel motor tracing task will show differences in early somatosensory processing and sensorimotor integration differences between the hemispheres.

2. Based on past literature for the dominant limb, that the group performing the novel motor task in the presence of altered sensory input will be more accurate at motor training; and the N24 and N30 components of SEPs, which relate to cerebellar pathways and SMI, will show differential changes in excitability for the non-dominant limb, as compared to past work using the dominant limb.

Overview

Section 1: Literature Review

Section 2: Manuscripts for each study

Section 3: Appendix

Section 1: Literature Review

Introduction

We achieve most of our movement on a daily basis through dynamic interaction of our limbs. Whether that be reaching for an object, walking up a flight of stairs or driving a car. The interaction of our limbs and the environment they are surrounded with has an effect on how we perform. From studying these interactions, we can see some asymmetries begin to arise in respect to our upper limbs, specifically in the aspect of motor control. These control mechanisms differ between the dominant and non-dominant arm, which have also begun to explain the lateralized motor control that characterize what we call handedness (Mutha et al., 2013). Current research has explored the external observations associated with the asymmetries in motor control between limbs (de Oliveira, 2002; Mutha et al., 2013; R. Sainburg & Kalakanis, 2000; R. L. Sainburg, 2002; Schabowsky et al., 2007; V Yadav & Sainburg, 2011). These various studies have shown that our dominant arm relies on a predictive mechanism, movement that is based on previously generated internal models, while the non-dominant arm optimizes movement based on reflexive and voluntary corrections. Previous studies have found varying results with respect to neurophysiological differences between limbs (Aziz-Zadeh, Maeda, Zaidel, Mazziotta, & Iacoboni, 2002; Daligadu, Murphy, Brown, Rae, & Yielder, 2013; Hoshiyama & Kakigi, 1999). The following review explores differences in these observable, external mechanisms, and offers commentary on what is known about the neural pathways that the central nervous system (CNS) uses to conduct these strategies. This review also summarizes the growing body of knowledge about the sensorimotor integration pathways the brain utilizes to complete everyday tasks. These tasks often require a combination of sensory and motor information, and by using Somatosensory Evoked Potentials (SEPs) we can begin to explore these different sensorimotor pathways in the brain. A combination of the above techniques is a new territory of exploration for the literature base on laterality and handedness and provides the chance to further establish a link between hand dominance, lateralization and the sensorimotor systems in the CNS. In order to provide contextual background for interpreting asymmetry between the limbs, this literature review initially offers an overview on motor control theories and applications. It will then discuss known differences in control

between the dominant and non-dominant limbs, followed by a review of current studies investigating neurophysiological differences of movement and motor learning, and how these findings have been applied to the evaluation motor control differences between the dominant and non-dominant limbs.

Theory of Motor Control

The interaction between our limbs and their environment is a complex form of dynamic interactions, meaning that our limbs attempt to control the environment that involves movement (Hogan, 1985). Each limb is classified as its own system inclusive of unique relationships and patterns of movement involving the joints. This classification was initially presented by Bernstein in the 1930's in a contextual discussion on the degrees of freedom problem (N. Bernstein, 1966). This classical problem stems from the number of articulations in a multijoint system requiring constraint and control to produce any given movement and the chosen motor strategy best suited for it. Much of motor control theory as it is formulated today originated from the dynamic principles laid out by Bernstein (N. Bernstein, 1966). The aim of his approach being to identify the various principles of movement coordination, and then apply them to pattern formation in movement with different properties (Beek, Peper, & Stegeman, 1995).

Movement coordination involves multiple systems with many internal degrees of freedom, from neural synapses to the joints themselves, and coordinating these requires adaptable responses and subsequent control by the limbs. Coordination can therefore be applied beyond the perceived end point of an objective to encompass the systems responsible for creating the movement, whether that be movements of individual joints, muscle activation or neural input (Shenoy, Sahani, & Churchland, 2013).

Dynamic systems (Williams, Davids, & Williams, 1999), adapted from engineering principles, is one of the current post Bernstein theories used to explain movement. In dynamic systems, movements are described as being created from processes that self-organize based on the biological and physical system constraints of the task. Coordination has largely been described as a dynamic system (Beek et al., 1995; Bressler & Kelso, 2001; Kelso, 1997) where the

ability to coordinate both limbs to achieve one goal, or separate goals, is demonstrated to be a dynamic system of varying complexities. This indicates that there must be underlying neuronal structures and musculoskeletal interactions able to respond in a dynamical way to create complex, coordinated movement patterns. Contextually, the function and connectivity of some of these neural substrates are able to be measured through analysis of CNS activity.

Crucial to this review is the incorporation of a behavioural framework that includes a cognitive aspect, whereby movements are generated and modulated in the central nervous system. Schema theory is one of the predominant theories of control of movement (R. Schmidt & Lee, 2013; R. A. Schmidt, 2003). In Schema theory an action plan is selected based on the identification of a sensory input, allowing for a general motor program to be retrieved from long term memory (R. Schmidt & Lee, 2013). Each general motor program contains a set of invariant features, which are parts of an action that remain constant. These features make up movements each time they are performed. One feature that defines an action is the rhythm or relative timing of the movement (R. Schmidt & Lee, 2013). This feature is essential to the general motor program, as it contains a set of components that determine the timing of different movements that make up the action (R. Schmidt & Lee, 2013). The other components that are thought to be invariable are the relative force, which is the proportional force between muscles, and the order of events for each movement, which is the order of muscular contraction. Taken together these three invariant features create an output motor command that is stable, and forms the generalized motor program that defines an action (R. Schmidt & Lee, 2013). Crucial to the output of a motor program is the decision of how to execute the program, which is defined by the characteristics that are assigned to the motor program that do not influence the invariant features (termed the parameters) of the motor program (R. Schmidt & Lee, 2013). These parameters include the speed and amplitude of the movement (i.e., absolute timing and absolute force) as well as the selection of which limb to use. Once the GMP is selected the specific parameters are added before the commands are sent to the peripheral nervous system. The importance of this theory is it accounts for faster movements, where many previous theories postulated that interaction alone (i.e., sensory feedback) generated differences in movements. However, a purely sensory feedback approach to movement is very

slow, and unable to account for these faster actions like GMP theory does. One drawback of GMP theory is that it does not account for variability in movements, in that if movements are organized prior to completion, there is no clear basis for completing the same task multiple ways (R. A. Schmidt, 2003).

Other relevant theories to this thesis, are the forward and inverse models of motor control (Harris & Wolpert, 1998; Miall & Wolpert, 1996; Wolpert, Ghahramani, & Jordan, 1995). Forward models predict the next movement based on the previous or current movements, similar to that of the GMP theory mentioned above (R. A. Schmidt, 2003). Inverse models invert the system and match up current and desired position, and generate motor commands based on this (Wolpert & Kawato, 1998). Forward models specifically have been used to explain various aspects of movement such as the outcome of an action, anticipated actions and plan future actions based on the current or previous action (Wolpert et al., 1995). Systems that rely on real-time sensory feedback to complete movements often do not become more accurate, as sensory feedback is delayed and could require additional attentional resources, interfering with movement smoothness and accuracy rather than improving it (Shadmehr, Smith, & Krakauer, 2010). By building accurate forward models, the motor system can account for differences in the planned motor program and the movements that follow, as with many movements the body as well as the environment can change (Shadmehr et al., 2010). The benefit to forward models is that they can be used to produce calibrated movements, as well as help the body learn the dynamics of the body itself and the world surrounding it (Shadmehr et al., 2010). Forward models are similar to the theory of feedforward control discussed in later sections of this review, as well as Schema theory mentioned above. The similarities between all three theories is that they all hypothesize the existence of a pre-formed movement template, that is edited to fit the demands of the task at hand, prior to actually executing the movement. The similarities between these three major theories, indicates that a forward models are likely to be an important component of understanding how the CNS controls movement.

The motor control of bimanual movements, which are often more complex than unimanual movements, has generated theories of motor control which incorporate many systems of the body (de Oliveira, 2002). This interaction is taken one step further, in which the

introduction of a kinematic chain model was used to explain coordination of the limbs (Guiard, 1987). This model states that the limbs are represented by motors in a system. This model makes two assumptions; the first is that the two hands and their respective systems of motor control and regulation represent complimentary yet discrete systems that interact in nature in order to create motion. The second is that the two motors cooperate as if they were assembled in series (Guiard, 1987). This was proven in right-handers that were allowed to follow their preferences in movement. It was seen that the right hand articulated its movements with the left hand, suggesting an organization that these motors were assembled in series, being able to work together (Guiard, 1987). Complexity arises however when tasks that are deemed bimanual and asymmetric, dictate that the limbs work together to complete a task but achieve it differently. It is suggested that though the limbs appear to behave differently, it is possible that the control scheme is similar but the expression of movement and its application is different (Guiard, 1987). This claim is supported when looking at a bimanual asymmetric action, the movement performed by the non-dominant hand always seems to preclude the action by the dominant, in that we often initiate support or positioning of the object before we manipulate it. This suggests both the limbs utilize similar movement patterns, but the goal or application of them is different (Guiard, 1987). At present, the evidence for these speculations is based on physical observation and a theoretical framework with a mathematical basis. Understanding differences in the linkages between internal somatosensory structures through neurophysiological recordings would provide empirical data to increase our understanding of the neural mechanisms underlying the control differences.

Adaptations as a Form of Motor Control

The earliest understanding of human movement, specifically upper limb movement was developed by Bernstein as explained by Latash & Turvey (1996). They explained the process of learning and the early stages of adaptation from childhood. Around 3 months children begin to perform reaching movements. These movements are often “wobbly” and unorganized with a pattern that follows several acceleration and deceleration phases (N. A. Bernstein, Latash, & Turvey, 1996). This is similar to early learnings of a new task regardless of age. When we start

to see improvement in this pattern, we not only see an increase in accuracy but a change in the motor pattern as a whole. This suggests that there is a change in movement organization in the brain and that this reorganization results in the development of "dynamic postural control" (N. A. Bernstein et al., 1996). This enables the person to move their arm smoothly because of an increase in the ability to adapt and predict changes. Bernstein considered that movements must always contain a central impulse (a feedforward command) as well as a feedback component, this observation evolved into the a closed loop theory of movement control and regulation (N. Bernstein, 1966).

More recent work integrating biomechanics and kinematics to explore the same processes has contributed data to further understanding of movement control. Scheidt et al., (2000) conducted a study to investigate the interaction between the dominant arm and a dynamic environment produced by a robotic arm. They measured adaptation processes using dynamic and kinematic variables. When the participants were allowed to make kinematic errors they learned and developed an adaptation strategy much quicker. When they were not allowed to do this and the robot arm stopped them, the learning process was much slower. This infers that the kinematic errors associated with learning are crucial to the body's adaptation of motor control (Scheidt et al., 2000). Furthermore, Todorov & Jordan (2002) stated that this mechanisms discussed previously, is the result of an optimal feedback loop the arms use in the presence of variance. It was shown that the optimal strategy for adaptation was to allow for variability in the task (Todorov & Jordan, 2002). This is done by allowing the participants to make errors that are relevant and irrelevant to the task itself. These errors force the body to adapt using feedback mechanisms and forces it to correct only those deviations that interfere with the task goals (Todorov & Jordan, 2002). This not only shows the process of motor learning but it also shows early stages of specific adaptation strategies to motor control. In addition to this it can be seen in cerebellum research that the learning process is dependent on this feedback mechanism. Kitazawa et al., (2002) showed that during random walking, in which the steps were randomly determined based on the previous step, that the adjustments seen were not just in the mean error, but also served to reduce the variance in that error over the course of the learning process. This same thing was observed in the previous studies with respect to

the upper limb. The correction process that took place over the adaption period reduced not only the number of errors, but also the variability of the errors due to the over shoot or undershoot of the desired target (Kitazawa, 2002; Scheidt et al., 2000; Todorov & Jordan, 2002).

Optimization refers to the process of learning to do something, then learning to do it better and more efficiently. This is a key component of motor control. This was shown in the studies mentioned previously where the arms gradually get better at the reaching task with the robotic arm (Scheidt et al., 2000; Todorov & Jordan, 2002). Optimization occurs when the limbs begin to perform more efficiently than the previous attempts. Emken et al., (2007) showed that motor adaptation can be modelled using a general view of minimizing the energy cost of the activity. The authors postulate that the learning dynamics are a process achieved by an optimization of error and effort. This infers that the resulting adaptation the limbs undergo is a result of the CNS reducing the errors initially and then beginning to reduce the cost of the activity to make it the most efficient (Emken et al., 2007). By adapting the previous trial to the trial being performed currently, the limbs begin to gradually optimize the movement regardless of the environments interaction with it.

Motor control patterns observed in the early developmental and early expressive stage of the movement differ from those seen slightly later in the learning process and consequently adaptive processes of movement expression. The optimization process initially begins with a large number of errors. These errors gradually reduce and then the process migrates to a more efficient method and observable expression that eventually integrates the use of anticipatory mechanisms. This feedforward system has been shown in the dominant limb by Milner and Franklin (2005). The study consisted of a novel reaching task, and was done in sets of three trials in the presence of a velocity-dependent force field. When comparing the first, second and third trials there was two different adaptation patterns that emerged. The first was a feedback process by which the arm was corrected using a reflexive and voluntary mechanism (Milner & Franklin, 2005). This mechanisms is indicative of the previously mentioned patterns by which the initial way the CNS learns is by reducing the number of errors. The second pattern is more

of a feedforward mechanism, by which the limb begins to anticipate the effects of the force field by increasing muscle activation and changing the muscle activation patterns (Milner & Franklin, 2005). This shows that the CNS creates an internal model of the environment in which it uses to anticipate the effects of the force field and adapt the movement accordingly. The combinations of these two control mechanisms explains how the limb learns to react and adapt to a changing environment.

Lateralization

Seminal work in lateralization of neural function (Broca, 1861, 1863) initiated study of the topographical and functional regions of the cerebral cortices. From these early beginnings research began to explore the lateralized preferences that humans exhibit in motor control. Handedness as a theory has prevailed and is a classical formulation that has been under investigation since this time. One of the contemporary questionnaires developed as a measuring tool to identify the degree of "handedness", is the Edinburgh Handedness scale (Oldfield, 1971) and this questionnaire is routinely adopted in many current studies. However, present studies look to further expand the concept of hand dominance to understand the asymmetrical organization of human motor control systems (R. Sainburg & Kalakanis, 2000; R. L. Sainburg, 2002; R. L. Sainburg & Duff, 2006). Through handedness the development of lateralized motor control strategies emerges, in which the dominant hand is commonly used for more complicated tasks. In the early literature, these different motor control strategies were discussed in the context of observable performance differences between hands as the result of the task demands.

Most of the more skilled movements involving our upper limbs involve both the left and right hand (Guiard, 1987). Guiard (1987), as stated earlier, suggested that the arms themselves can be related to motors, or systems that work to control and produce movement. Additionally, they cooperate with one another as if they were assembled in series which allows for the formation of an internal kinematic chain (Guiard, 1987). This model was early in the theory of lateralization and there are some inconsistencies associated with it. The first is that the internal complexity of the upper limb systems (neural connections, muscle connections, ligaments etc.)

is ignored in the proposed model. The second is that there is no relation to the hemispheres or the cortex and the roles that they play, though this is early in the literature. Identifying and investigating these gaps could lead to a more thorough understanding of the mechanisms underlying lateralization of limb control.

The different hemispheres of the brain communicate via various pathways during unimanual tasks, and relay different dynamics of a given task to each other (size, weight etc.) (Gordon, Forssberg, & Iwasaki, 1994). However, in relation to motor control, we begin to see the asymmetries more clearly. For example, differences are seen when a right-hand dominant individual tries to write a sentence with their left hand. The motor pattern, though familiar, is much more complicated to execute. Gordon et al., (1994) demonstrated that during precision grip, the dominant hand stored relative information of the weight and force required to execute the movement, and the non-dominant hand adapted this information to a similar task, though not perfectly. This asymmetry is an example of lateralized motor control, where we see similar patterns executed but with different levels of coordination and accuracy. A similar principle is seen when comparing learning generalization between the limbs. Criscimagna-Hemminger et al., (2003) showed that generalization of motor patterns occurs more easily from dominant to non-dominant hand. This is indicative of the ability of the limbs to communicate. However, if the non-dominant arm is trained initially, then generalization does not transfer to the dominant arm. This means that the learned dynamics of the task are stored in the dominant hemisphere and is applicable to both sides, where as any information the non-dominant side retains is only relevant to that side (Criscimagna-Hemminger et al., 2003).

Lateralized Adaptation Strategies for Motor Control

Previous studies that involved adapting to a novel dynamic environment were only applied to the one limb. Where the asymmetries begin to arise is when we look at the non-dominant hand compared to the dominant hand. Multiple studies have shown that there is a noticeable difference between the limbs and the adaptation strategies they imply to achieve movement (Mutha et al., 2013; R. L. Sainburg, 2002; Schabowsky et al., 2007; V Yadav & Sainburg, 2011; Vivek Yadav & Sainburg, 2014). The difference arise from the implication of

different strategies that are similar to those proposed by Milner & Franklin (2005) (eg. predictive mechanisms and impedance control mechanisms). However, the difference is that the altered strategies are not just seen in the early and late stages of motor learning but between limbs. Schabowsky et al., (2007) found that when comparing limb adaptation to a novel dynamic environment produced by a robotic arm, the non-dominant arm relies on muscle impedance control more so than the dominant arm. This infers that in order to correctly compensate, the non-dominant arm reacts in a reflexive manor to keep the arm in a neutral position. This coincides with work done by Milner & Franklin (2005) in which the initial mechanism used by the limbs to adjust was a reactive and voluntary one. Additionally, the aftereffects, the distance the movement continues after the removal of the dynamic environment, suggested that the dominant arm relied more so on a reactive measure as these aftereffects were much larger in the dominant than the non-dominant (Schabowsky et al., 2007). The larger aftereffects are indicative of the use of anticipation because since the brain is predicting the force field to continue, when it is suddenly removed, the planned pattern it already has initiated is no longer valid, thus the large aftereffects. Contrary to this, it has been suggested that the dominant arm-hemisphere system was better at assimilating and processing in proprioceptive feedback and integrating it into an appropriate response (Roy, 1983). However, more recently this has been disproven in a study demonstrating that in right-handed dominant individuals the dominant arm relies on a predictive, feedforward system that assimilates internal models generated from previous tasks, while the non-dominant arm integrates muscle activation (impedance control) and aims for reflexive positional stability, functioning as complimentary feedback system (Mutha et al., 2013)

Another theory proposed by Yadav & Sainburg (2011) suggests that asymmetries may also be explained as a result of the relative time it takes to switch from a predictive system to a system that relies on impedance control or muscle activation. This infers that movements are initiated by predicting the environments effect and then switches to a control scheme that reacts to the feedback from the environment (V Yadav & Sainburg, 2011). This also coincides with an earlier study that suggests that interlimb differences are a product of the dynamic dominance hypothesis. It states that the factor that distinguishes the dominant and non-

dominant arm is the ability of the arm to integrate inertial dynamics (R. L. Sainburg, 2002). Combining these two studies we see a similar pattern to previously mentioned studies. The two hypotheses are similar in the sense that they contain different control schemes for the respective limbs, and that there is some level of feedback and feedforward response associated with movement. Further exploration into these concepts reveals possible therapeutic application of such a theoretical model. It has been shown in patients who have suffered from stroke, that the resulting lost motor pattern is different between limbs. Damage to the right-hemisphere tends to show positional accuracy deficits, while left-hemispheric damage leads to deficits in trajectory (R. L. Sainburg & Duff, 2006). Additionally, there is suggestion of differential neural control mechanisms that are distinct to each limb, however there is no specific method for determining which came first, the asymmetric use of the limbs, or the differential neural control strategies (R. Sainburg & Kalakanis, 2000).

Neurophysiological Differences in Laterality

The laterality trend is also evident in studies investigating corticospinal pathways. Transcranial magnetic stimulation (TMS) can be used to provide a measure of motor cortex excitability. Daligadu et al., (2013) used TMS to measure the excitability of the dominant and non-dominant motor hemispheres. The non-dominant hemisphere of both left and right handed individuals was found to be more excitable at rest as measured using TMS stimulus response curves of the first dorsal interosseous (FDI), an intrinsic hand muscle. This suggests that the resting excitability levels of the two hemispheres are different, and that the previously mentioned asymmetries seen in the reaching task may correspond to differences in internal representation and excitability of the area of the motor cortex innervating the muscles being studied (Daligadu, Murphy, et al., 2013). This also fills in the second gap of most models of lateralization as it incorporates the cortices, and what was at first a theoretical framework, becomes fleshed out with neurophysiological data.

Not only are the motor pathways lateralized, but the integration from the sensory system also impacts this lateralized model. Aziz-Zadeh et al., (2002) demonstrated that during action observation, the motor cortex is activated in contrast to the sensory information

displayed. During demonstration of a right handed movement, the left motor cortex was more excitable following TMS stimulation, and during left handed demonstration the right motor cortex was more excitable (Aziz-Zadeh et al., 2002; Aziz-Zadeh, Iacoboni, Zaidel, Wilson, & Mazziotta, 2004). This confirms that there are anatomical differences in the internal cortical representation between the two hemispheres which correspond to laterality of function.

The link between somatosensory and sensorimotor integration and adaptation strategies were explored in a comprehensive review authored by Desmurget and Grafton (2000). This review explored the likely basis of feedback and feedforward systems in the brain and explored the possible structures associated with them. Evidence of sensorimotor loops within the posterior parietal cortex (PPC), at the area of the intraparietal sulcus (IPS), and the cerebellum in the literature suggest the use of both feedforward and feedback control mechanisms associated with all of these structures (Desmurget & Grafton, 2000). These loops rely on a feedforward model that integrates the sensory inflow and motor outflow to understand and examine the consequence of the motor commands utilized by the limbs, and allows the command to unfold with the guidance of internal and external feedback (Desmurget & Grafton, 2000). This is known as a "hybrid model" as it incorporates both feedback and feedforward control paradigms. Interestingly, the suggestions of more current literature (discussed above) contradicts this by stating the independent use of feedback and feedforward in adaption to the left and right limbs respectively. By developing techniques that compares the limbs and integrates the cortex into the equation, we can develop a new framework that shows where the basis of laterality comes from and why the asymmetries are seen.

Overview of Somatosensory Evoked Potentials

The somatosensory system is an important integrated system to consider with respect to cortical asymmetry and motor control. Somatosensory Evoked Potentials (SEPs) have been used in the evaluation and observation of both the central and peripheral nervous systems (Cruccu et. Al, 2008). A somatosensory evoked potential is a measured response to a controlled peripheral stimulation (Cruccu et al., 2008). Measurement of the peak to peak amplitude of the SEP, at various latencies provides a way to measure changes in cortical excitability at the

corresponding neural generator of that peak. It is commonly used in the literature in response to an intervention such as a motor training task, as changes in early SEP peak amplitudes are seen when comparing pre-task and post-task measurements. (Andrew, Yielder & Murphy, 2015; Andrew et. Al, 2014; Dancey et. Al, 2014; Brown & Staines, 2015).

Two key characteristics of SEPs are latency and amplitude. From the various recording sites, peaks emerge either deflected upwards (denoted by a N) or downwards (denoted by a P) and are marked by a number following the letter to represent the latency (Cruccu et al., 2008). The amplitude correlates to the level of activity at that specific neural pathway and the latency indicates the time from the point of stimulation to activation of a given neural generator. The "nominal" latency reflects the approximate timing of given SEP peaks at specific points along the somatosensory pathway (Cruccu et al., 2008; Kimura & Yamada, 1980). Stimulations are given between 0.1-0.2ms square wave pulses over the peripheral nerve (Cruccu et al., 2008). Frequencies of the stimulations should be 2.47Hz, and 4.95Hz (Fujii et al., 1994; H Haavik & Murphy, 2013). Recording electrodes are placed peripherally, centrally (over the spinal cord) and cortically, keeping with IFCN recommendations (Cruccu et al., 2008). Peripheral information is recorded at the level of the brachial plexus of the stimulated arm, with the electrode placed posterior to the clavicle and as medial to the sternocleidomastoid as possible without placing directly over top of the muscle (Cruccu et al., 2008). Spinal information is recorded over C5 which was landmarked by starting from C7 and locating the ascending spinous processes. Cortical electrodes are measured from the vertex of each participant. The frontal electrode is measured 6cm forwards and 2cm contralateral to the stimulated hand, as this site has been found to be the optimal location to record the N30 SEP peak (Rossi et al., 2003). The parietal electrode is placed 20% of the subject's tragus to tragus measurement contralateral, and 2cm posterior. Each of the sites should be properly cleaned prior to electrode placement with abrasive gel and alcohol. For the purposes of this review only short latency SEPs are discussed as they are less susceptible to cognitive changes (Cruccu et al., 2008).

The peripheral site measures the N9 peak. This peak is used as a peripheral measure of the incoming sensory information into the central nervous system as it is thought to be the peripheral pathway close to the brachial plexus (Desmedt & Cheron, 1980). This peak is used as

a quality assurance peak whereby any deviation in this peak amplitude greater than ±10% is not included in the data (D Andrew et al., 2015; Danielle Andrew et al., 2015; Dancey et al., 2016a; Dancey et al., 2014). Following the peripheral peak we reach the central N11 peak and the N13 peak. These peaks represent the ascending sensory input arriving and entering the spinal cord (Desmedt & Cheron, 1980; Mauguiere et al., 1999). The N18 peak (recorded from the frontal cortical site (Rossi et al., 2003)) represents the activation in the brainstem, with generators in the dorsal column medial lemniscus and inferior olives (Manzano, Negrao, & Nóbrega, 1998; Sonoo, Sakuta, Shimpo, Genba, & Mannen, 1991). The N20 is the first cortical peak (measured from the parietal site) and represents activation of the primary somatosensory cortex (S1) (Mauguiere et al., 1999; Nuwer et al., 1994). This peak is often shown to have role in motor learning acquisition (Danielle Andrew et al., 2015; Dancey et al., 2016a). The N24 peak has been hypothesized to reflect the pathway between the cerebellum and the primary somatosensory cortex (S1) (Restuccia, Marca, Valeriani, Leggio, & Molinari, 2007; Waberski et al., 1999). The P25 peak represents an area of neurons in Brodmann's area 1 and area 3b (Mauguiere et al., 1999; Rossini, Gigli, Marciani, Zarola, & Caramia, 1987). The final peak of interest for short latency SEPs is the N30. The N30 has been localized in recent literature to prefrontal and frontal areas of the cortex (Lelic et al., 2016) but earlier studies have found sources in the basal ganglia and motor cortex (A.-M. Cebolla, Palmero-Soler, Dan, & Chéron, 2011; Kaňovský, Bareš, & Rektor, 2003). This peak is often labeled as the sensorimotor integration peak (Rossi et al., 2003) and a growing body of literature has demonstrated changes in this peak in response to altered SMI (Danielle Andrew et al., 2015; Dancey et al., 2016a; Dancey et al., 2014). In combination these peaks provide insight to multiple levels and areas of early sensorimotor process, and are an ideal tool for the evaluation of movement and motor learning.

Somatosensory Evoked Potentials as a Technique for Measuring Neurophysiological Data about Movement

Sensorimotor integration is a topic commonly associated with SEPs as there is a link between the two systems visible in SEP peak recordings (Dancey et al., 2014; Passmore, Murphy, & Lee, 2014). It has been shown following a motor learning task that SEP peaks show plasticity in the nervous system (D Andrew et al., 2015; Danielle Andrew et al., 2015; Dancey et

al., 2016a; Dancey et al., 2014; Passmore et al., 2014). This infers that after the learning process has occurred, there is a change in the wiring of the somatosensory system. If the control strategies utilized by the limbs are learned from environmental interaction, then there should be visible changes in SEP peaks as well. Similar learning is seen in the cerebellum following a pursuit task, which is a task known to be highly dependent on cerebellar function (Danielle Andrew et al., 2015). This is important because the adaptation tactics used by the limbs when adapting to a novel dynamic environment seem to stem from learned traits about the task. This is implied by the previous studies which looked at the control strategies not only early in the learning process but shown between limbs (Milner & Franklin, 2005; Mutha et al., 2013; R. Sainburg & Kalakanis, 2000; R. L. Sainburg, 2002; Schabowsky et al., 2007; V Yadav & Sainburg, 2011). By utilizing a motor learning task we can induce bottom up neuroplastic changes associated with learning of new skills (Dayan & Cohen, 2011; Doyon & Benali, 2005). Assuming these control patterns are learned through adaptation to the environment, whether it's the differential application of a similar pattern or different motor patterns all together, we will be able to see SEP peak differences within the cortex. By using SEPs, this is a non-invasive and accurate way to observe the effect of motor learning within the cortex, and analyze the findings (Passmore et al., 2014).

Movements performed by the dominant and non-dominant hand can be skilled or unskilled. The differences in these movements were observed by Hoshiyama and Kakigi (1999) using SEPs to examine the potential differences between unskilled and skilled movement of the dominant and non-dominant hand, in left- and right-handed individuals. By having their participants perform a writing task with both their left and right hand, they were able to compare any differences in SEP peaks during the movements. It was shown that though there was no differences in peak amplitude based on participant's handedness, there was a decrease in the dominant and non-dominant peak amplitude during writing (Hoshiyama & Kakigi, 1999). This indicates that as a result of the difference in skill level of the limbs at performing the task there is a difference in SEP peaks. This is important as it begins to show differences in somatosensory integration in the hemispheres during specific skill-level based tasks. The challenge with a writing task is that it favours the dominant limb. To understand inherent

difference in sensorimotor integration between the limbs, it is necessary to utilize tasks that are equally novel for both the dominant and non-dominant hand. In a TMS study, it was found that significant learning was observed in the dominant hand using a pursuit tracing task, and that the resulting change in the cortex was a decrease in cortical excitability (L. Holland, Murphy, Passmore, & Yielder, 2015).

Though SEPs have rarely been applied to analysis of upper limb SMI, using SEPs for work involving the upper limb is relatively straightforward. The brain is divided into hemispheres and there is constant communication between them. Cardoso de Oliveira (2002) suggested a crosstalk model associated with inter-hemisphere communication. It states that in order to initiate bimanual movements the limb-hemisphere systems must interact with each other to achieve the best outcome. This model is suggestive of a sensorimotor feedback loop, and is shown in practical use in an aforementioned study testing precision grip (Gordon et al., 1994). Since SEPs are known to be a measure of the somatosensory system, and the theories related to limb adaptation differences similarly converge on a sensory motor feedback/feedforward system, the potential for SEPs to reflect these asymmetries is high. Additionally, it has been shown that brain activity can directly show the influence of motor based errors, mostly in the cerebellum and frontal cortex (Nadig, Jäncke, Lüchinger, & Lutz, 2010). This is important as SEPs will be able to show differences in peaks as a result of the learning done by the limbs in adaptation to their environments.

Another application for SEPs is to observe the level of sensory processing. A study by Brown & Staines (2015b) used SEPs to observe changes in frontal lobe sensory processing. The results indicated that there was no reduction in SEP frontal peaks following an exercise that had participants use spatial attention, regardless of the sensory input. However, there was a significant reduction in peak amplitude in the task that had the participants typing following vibration and median nerve input. This indicates that there is a level of sensory processing or filtering that occurs in the CNS ahead of movement, and was reflected in the SEPs peak data (Brown & Staines, 2015a). The same type of process can be seen using an externally applied pain stimulus. It was shown by Rossi et al. (2003) that the sensory processing changes during muscle pain. This was determined using SEPs following an injection into the muscle belly of a

distal extremity muscle. Accompanying the significant differences in SEP peaks, the position sense of the finger was also distorted. This indicates that the sensory processing was affected by the sensation of pain (Rossi et al., 2003). This was also shown in a combination study that looked at painful stimuli, SEPs and motor learning (Dancey et al., 2016a; Dancey et al., 2014). The participants were asked to perform a motor learning task which was a tracing task, after having capsaicin cream placed on the elbow over their median nerve. The results showed that there was not only a difference in the learning of the participants, but there also was a significant difference found in the SEP peaks. This indicates that these peaks are a good indicator of the sensorimotor integration changes that accompany pain and motor learning (Dancey et al., 2016a; Dancey et al., 2014). This compliments with previously listed studies showing the effectiveness of SEPs to display electrical activity and allow the researchers to analyze it.

Most recent work uses whole head electroencephalogram (EEG) to analyze brain activity in motor control and learning studies. The benefit of combining SEPs and whole head EEG is the ability to get an idea of brain activity across the whole head at the specific time points necessary to evaluate the evoked potentials. It has been shown in a recent study by Lelic et al., (2016) which used whole head EEG to localize the effect of spinal manipulation on the sensorimotor integration of the CNS, that following spinal manipulation there was not only an increase in sensorimotor integration but a change in the sources contributing to the N30 peak (Lelic et al., 2016). A similar methodology has been used across a wide range of studies exploring separate techniques but ultimately they use SEP peaks to evaluate the plasticity of the brain as a result of a given intervention. The ability of SEP peaks to reflect these changes provides an excellent technique with which to explore the possible differences in sensorimotor integration as well as sensory processing present within the limbs and how they may differ as a result of handedness.

Conclusion

Though the behavioral framework involving dominant and non-dominant differences in motor control is well studied, there is a need for a much deeper understanding of the

neurophysiological differences and mechanisms underpinning these motor control strategies. It has been shown that the dominant arm uses a predictive and anticipatory control scheme while the non-dominant arm uses a reflexive and voluntary pattern that uses impedance control to maintain equilibrium (Mutha et al., 2013). This has added to the body of literature by providing a new way to look at handedness building upon earlier observations done by Oldfield (1971). However, there are few studies investigating neurophysiological differences. Using tools such as SEPs provides the opportunity to explore the neural differences associated with limb adaptation strategies. Since most theories tend to show use of both feedback and feedforward approaches, sensorimotor integration as well as neuronal connections are likely to be seen. The potential for SEPs to reflect these changes is considerable based on with contribution to our understanding of the plasticity of the brain and the inherent sensitivity of SEPs to facilitate changes in it (D Andrew et al., 2015; Danielle Andrew et al., 2015; Dancey et al., 2016a; Dancey et al., 2014). The use of neurophysiological techniques not only contributes to the body literature but also opens up further opportunities to understand and apply knowledge of the CNS to various other situations.

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Section 2: Manuscript 1 – Increased accuracy and differential changes in early somatosensory evoked potentials in response to novel motor training for the non-dominant hand relative to the dominant hand.

Abstract

Background: The dominant and non-dominant hands have been shown to behave differently when training in a novel dynamic environment (Mutha et al., 2013), but little is known about the underlying complimentary neural mechanisms associated with the control mechanisms. It is postulated that the dominant limb adopts a feedforward mechanism that specializes in creating an internal model to compensate for external forces while the non-dominant limb adopts a feedback mechanism that is better at maintaining a consistent and more stable movement (Mutha et al., 2013). Previous research has shown a greater increase in the slope of a stimulus response curve for the non-dominant hand of both left and right handed individuals (Daligadu, Murphy, et al., 2013). This suggests that there may be inherent excitability differences between the dominant and non-dominant limbs. Early somatosensory evoked potentials (SEPs) (i.e. less than 50 msec post stimulation) provide a valid, non-invasive mechanism to explore possible differences in somatosensory processing and sensorimotor integration between the limbs. The aim of this study was to begin to explore possible differences in early sensorimotor processing between the right and left hand in healthy right handed participants.

Methods: Two groups of 12 participants (N=24 total) completed a novel motor training task which involved tracing a sinusoidal wave form varying in amplitude and frequency with different levels of complexity. SEPs were recorded in response to median nerve stimulation at baseline and post motor training. One group trained with the dominant hand and the other half trained with their non-dominant hand. Separate groups were used to avoid any transfer of skill acquisition between the limbs.

Results: The non-dominant limb showed greater accuracy at baseline, post training and at retention (24 to 48 hours later) also showing significant different SEP peak amplitudes in the P22-N24 complex and the P22-N30 complex. The Repeated Measures ANOVA showed a significant effect of group (Dominant vs Non-dominant) in the P22-N24 complex [$F_{1,22}$=16.3, p <0.001] and in the P22-N30 complex [$F_{1,22}$=18.7, p<0.0001]. Interestingly, these two peaks

showed opposite directional change in peak amplitude for the two hands, with dominant limb decreasing in the P22-N24 complex by 30% and, the non-dominant limb increasing 22% post training. The same was true for the P22-N30 complex, except the dominant limb amplitude increased by 23% while the non-dominant limb decreased by 25%.

Discussion: These results indicate that there are differences in the early sensorimotor integration between dominant and non-dominant limbs in response to novel motor training. These differences may reflect neural differences due to the preferred mechanisms utilized by each limb when performing movements.

Introduction

The limbs provide us with a dynamic way of interacting with our environment. This interaction is dependent upon the environment they are operating in and the efficiency with which the limbs adapt to change. Recent studies have begun to explore possible differences between the limbs as a result of different adaptation strategies, leading to what is termed "handedness" (Mutha et al., 2013). Current research has also explored differences displayed by the limbs adapting to a novel dynamic environment (Goble, Lewis, & Brown, 2006; Mutha, Haaland, & Sainburg, 2012; Mutha et al., 2013; Schabowsky et al., 2007; V Yadav & Sainburg, 2011; Vivek Yadav & Sainburg, 2014). These studies revealed that the limbs utilized different control schemes when adapting to the novel dynamic environment. It is well accepted that the dominant limbs utilizes more of a feedforward mechanism that specializes in creating an internal model to compensate for external forces while the non-dominant limb utilized more of a feedback mechanism that is better at maintaining consistent and more stable movements (Goble et al., 2006; Milner & Franklin, 2005; Mutha et al., 2012, 2013; Schabowsky et al., 2007). Literature also shows that when completing certain tasks the non-dominant limb is more accurate at performing the task (Mutha et al., 2013; R. Sainburg & Kalakanis, 2000; Schabowsky et al., 2007). This is thought to be because of the mechanism it tends to utilize. Impedance control is normally seen as an inefficient way to complete a task because of the higher cost of energy to the system, however it generally seen to be more accurate than predictive mechanisms applied by the dominant hemisphere, as these require accurate representations of

body and task dynamics (V Yadav & Sainburg, 2011). These mechanisms support potential differences between the dominant and non-dominant hemispheres (Broca, 1861, 1863).

It has been shown within the cortex that there are differences in baseline excitability between the two hemispheres (Daligadu, Murphy, et al., 2013). It was shown in right handers that their non-dominant limb had was more excitable and the effect was shown in left handers as well. This baseline excitability difference indicates potential motor pathway asymmetries that could manifest in the aforementioned strategies of adaptation. The same can be said of sensory information coming in as it has been shown that participants who observed a right handed task had activation of the left hemisphere, and activation of their right hemisphere when observing a left handed task (Aziz-Zadeh et al., 2002). Additionally, there is suggestion of differential neural control mechanisms that are distinct to each limb, however there is no way of determining which came first, the asymmetric use of the limbs, or the differential neural control strategies (R. Sainburg & Kalakanis, 2000). Though this is evidence of underlying mechanisms that lead to different motor control between the limbs, it has been shown that learning rates between the limbs are the same (L. Holland, Murphy, B., Passmore, S., Yielder, P. , In Press). This is important because if the learning process is the same for both the limbs, the differences in performance reported in the literature may relate to execution of the movement rather than the learning of it. Overall, this suggests potential wiring differences between the arm hemispheres systems that may result in observable adaptation strategies.

Somatosensory Evoked Potentials (SEPs) are a technique which has been used to investigate the integration of sensory and motor stimuli as well as the effects of motor learning within the cortex (D Andrew et al., 2015; Danielle Andrew et al., 2015; Dancey et al., 2016a; Dancey et al., 2014; Haavik-Taylor & Murphy, 2007; Hoshiyama & Kakigi, 1999; Passmore et al., 2014). Studies have found that changes in SEP peak amplitudes may reflect changes in processing in specific areas of the brain, which are the “neural generators” of specific short latency SEP peaks. Changes in various SEP peaks following a pre post measurement protocol reflect changes in the neural generators as a result of the intervention (D Andrew et al., 2015; Haavik-Taylor & Murphy, 2007). By utilizing this technique there may be a way to explore the change in the number or strength of differential synaptic pathways within the cortex following

motor learning. Changes in SEP peak amplitude have been observed following motor learning (D Andrew et al., 2015; Danielle Andrew et al., 2015; Dancey et al., 2016a; Dancey et al., 2014; Passmore et al., 2014), SEPs and EEG may provide a measure of the changes in synapse number or strength in these pathways as a result of the learning process (Mehrkanoon, Boonstra, Breakspear, Hinder, & Summers, 2016). Two of the peaks under close observation are the N30 and the N24. These peaks have been extensively studied in previous literature and have been hypothesized to reflect changes in sensorimotor integration pathways and the pathways from the cerebellum to S1 respectively (D Andrew et al., 2015; Danielle Andrew et al., 2015; Dancey et al., 2016a; Dancey et al., 2014; Hoshiyama & Kakigi, 1999; Restuccia et al., 2007; Rossi et al., 2003; Waberski et al., 1999). Any changes in these two peaks would provide insight into some of the major processes that may differ between the limbs that lead to different control strategies.

It is hypothesized in this study that the non-dominant limb will be better at baseline motor performance, consistent with literature mentioned above and that though the control strategies differ, the learning will be similar between the dominant and non-dominant limbs. It is also hypothesized that the novel motor tracing task will show differences in early somatosensory processing and sensorimotor integration between the hemispheres.

Methods

24 right hand dominant (mean age 20.3yrs ± 1.823yrs) individuals with no known neurological conditions were recruited to complete the learning paradigm. Each participant was required to fill out an informed consent form, outlining the details of the study. Following this, a safety checklist and a handedness questionnaire was used to ensure safe participation in the study. Ethical approval has been sought and approved from the UOIT ethics committee (REB# 07-072 & 07-073). Subjects were randomly assigned to a group that either had them use their dominant right hand (Dom) or their non-dominant left hand (NonDom). Groups only completed the task with one limb to avoid possible interlimb transfer of information.

Stimulation Parameters

The SEP stimulation protocol consisted of a 1ms duration pulse, delivered at the wrist over the median nerve. The stimuli were presented in two frequencies of 2.47 Hz and 4.98 Hz through adhesive skin electrodes. These different frequencies will be used to accurately differentiate between the N30 and the N24 peaks, as they often overlap each other and at faster rates the N30 diminishes and the N24 becomes more prominent and easy to measure (Haavik & Murphy, 2013). Stimulation was delivered at motor threshold, which causes a noticeable twitch in the abductor policis brevis (APB) muscle of the thumb. Recording of incoming information was done at the peripheral and cortical levels, as well as the spinal cord following the guidelines laid out by the International Federation of Clinical Neurophysiologists (IFCN) (Nuewer et al., 1994). Similar methodology to a previous study (Andrew et al. (2015), was used.

Stimulation electrodes were placed over the median nerve at the wrist on either the dominant or non-dominant hand. Peripheral information was recorded at the level of the brachial plexus of the given arm, with the electrode placed posterior to the clavicle and as medial to the sternocleidomastoid as possible without placing directly over top of the muscle. Spinal information was recorded over C5 which was landmarked by starting from C7 and locating the ascending spinous processes. Cortical electrodes were measured from the vertex of each participant. The frontal electrode was measured 6cm forwards and 2cm contralateral to the stimulated hand (Rossi et al., 2003). The parietal electrode was 20% of the subject's tragus to tragus measurement contralateral, and 2cm posterior. Each of the sites was properly cleaned prior to electrode placement with abrasive pads and alcohol swabs.

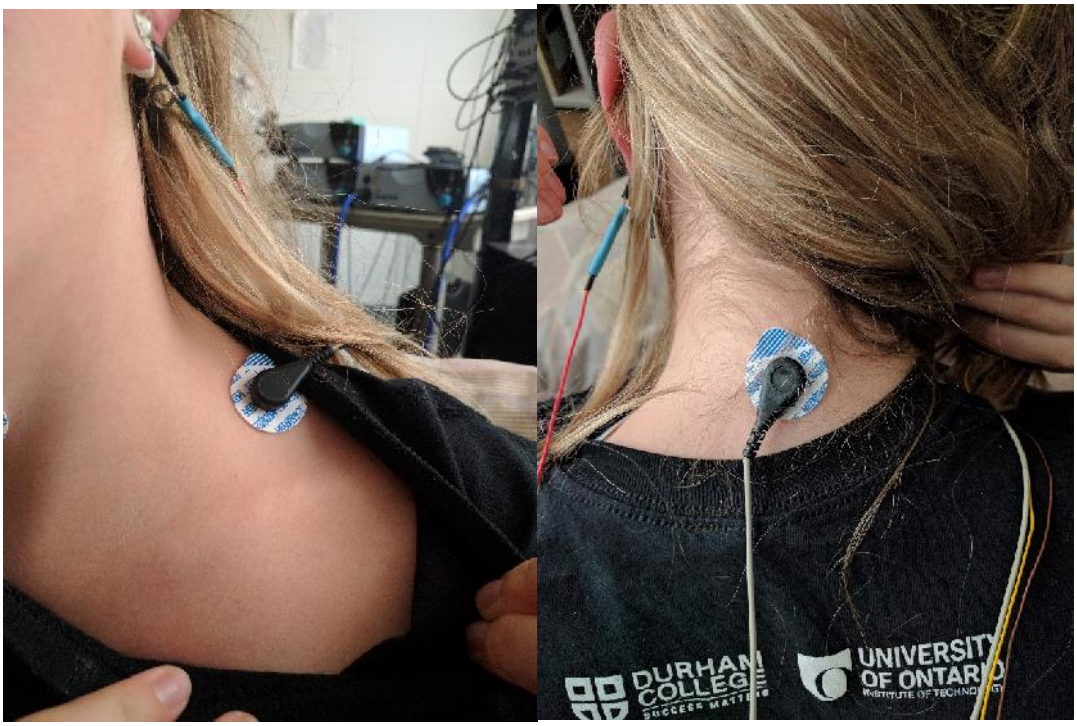

FIGURE 1: PERIPHERAL AND SPINAL ELECTRODE PLACEMENT

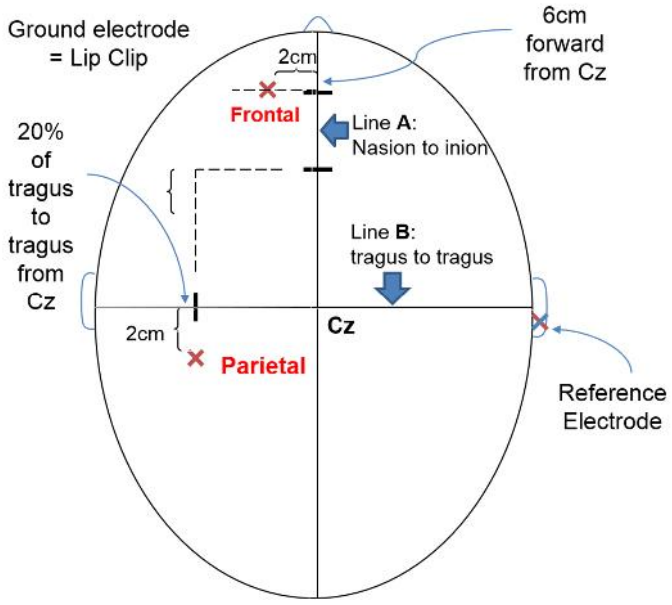

FIGURE 2: CORTICAL ELECTRODE DIAGRAM

Task Parameters

The tracing task (motor learning) protocol was run through a custom Leap Motion software tool (Leap Motion, San Francisco, CA). The task consisted of 4 different sinusoidal waveforms that are randomly varied in amplitude and frequency, with varying degrees of difficulty to allow for continuing improvement over time. The easiest trace can be performed easily by all participants and the most difficult is challenging to all participants with the other two traces of medium difficulty as described in previous work (D Andrew et al., 2015; Danielle Andrew et al., 2015; L. Holland et al., 2015; L. Holland, Murphy, B., Passmore, S., Yielder, P. , In Press). The first block contains four traces and acts as the "pre-test". The last block also contains 4 traces and acts as the "post-test" portion. The middle block, the "acquisition" phase, is the learning portion of the protocol which contains 12 traces. Each trace is made up of dots, with 500 dots equaling one trace. Participants were asked to replicate each trace as accurately as possible using the thumb on an external track pad. The traces can only be followed in the left-right direction, eliminating up and down error. The participants were instructed to use little to no wrist or elbow action to replicate the trace, utilizing only the abductor pollicis brevis (APB) muscle.

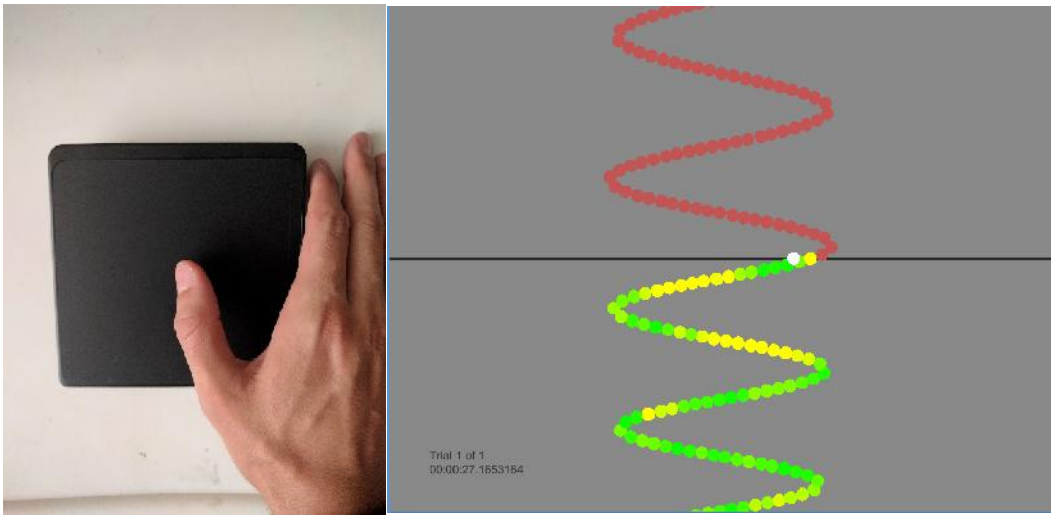

FIGURE 3: TRACING TASK

Data Analysis

SEP peak amplitude and the motor learning performance were analyzed separately. The tracing task software produced data that could be downloaded to Excel™ spread sheets, and listed percent error and delta values for each trials for each participant. The percent error represents distance from the dot on the trace, where 100% equals one dot width in distance away from the template. The delta value represents the direction of error where a negative number represents favouring the left side, and a positive number represents favouring the right side. These were averaged per trial for each participant in the pre, post and retention tests and compared to determine the degree of learning. SEP peak to peak amplitudes were measured pre and post learning and latency was also checked to determine if there were any changes in processing time or speed following the motor learning protocol. The peak to peak amplitudes were normalized relative to the baseline trial to facilitate comparison between groups. Once normalized, group averages were calculated to measure the proportional changes in pre and post motor learning SEP peak amplitudes.

Statistical Analysis

All data was tested for homogeneity of variance and skewness to ensure parametric statistics could be run. In order to investigate the statistical significance of the SEP peak results a repeated measures ANOVA was used with statistical significance set to 0.05 for repeated measures and $p<.05$ for interaction effects. Factors of peak amplitude (pre and post) and of hand (Dom vs NonDom) were used. It was important that trials included in this study had a peripheral N9 amplitude change of no greater than ±10%. A change greater than this would indicate changes in the incoming volley, perhaps due to changes in posture, and a stable afferent volley is essential when attributing changes in centrally generated SEP peak amplitude to learning induced plasticity. For the tracing data a repeated measures ANOVA was also used with statistical significance set to 0.05. For this analysis we compared factors of time (pre, post and retention) and factors of group (Dom vs. NonDom**).**

Results

All of the recruited subjects (N=24) completed the study and were included in the SEP peak analysis. Upon analysis of latency for each peak, no significant differences in latency were seen. Statistical analysis of each peak was run using a repeated measures analysis of variance.

Neurophysiological Data

The N11 peak showed a mean increase of 16% (±6%) for the non-dominant hand and a mean increase of 15% (±5%) for the dominant hand with no significant difference between the hands. The N13 peak increased by 4% (±13%) for the non-dominant and 18% (±5%) for the dominant with no difference between hands. The N18 peak increased 1% (±8%) for the non-dominant, while the dominant hand showed a mean increase of 6% (±9%). The N20 peak showed a significant increase for both groups (NonDom increase of 13% (±9%), and Dom increase of 42% (±14%)) [$F(1,22)=12.75, p<0.01$) with a significant interactive effect [$F(1,22)$ 3.93,$p=0.06$). The P25 peak increased significantly for both groups (NonDom increase of 3% (±11%), Dom increase of 26% (±13%)) [$F(1,22)=5.19, p<0.05$), with a significant interaction [$F(1,22)=3.40, p=0.07$).

For the P22-N24 complex, the repeated measures ANOVA showed a significant interactive effect of group [$F(1,22)=16.35$, $p<0.001$]. The non-dominant hand peak increased by22% (±6%), while the dominant hand showed a mean decreased by 30% (±4%)For the P22-N30 complex, the repeated measures ANOVA showed a significant effect of group [$F(1,22) = 16.89$, $p<0.0001$] with a mean decrease of 26% (±9%) for the non-dominant hand, and a 25% (±5%) increase for the dominant.

TABLE 1: SUMMARY OF SEP PEAK AMPLITUDE CHANGES FOR DOMINANT AND NON-DOMINANT GROUPS ± SEM

Group	N9	N11	N13	N18	N20	P25	N24	N30
Dom	↑0.003% (±1%)	↑15% (±5%)	↑18% (±5%)	↑1% (±8%)	↑42% (±14%)	↑26% (±13%	↓30% (±4%)	↑25% (±5%)
NonDom	↑0.006% (±1%)	↑16% (±6%)	↑4% (±13%)	↑6% (±9%)	↑13% (±9%)	↑3% (±11%)	↑22% (±6%)	↓26% (±9%)

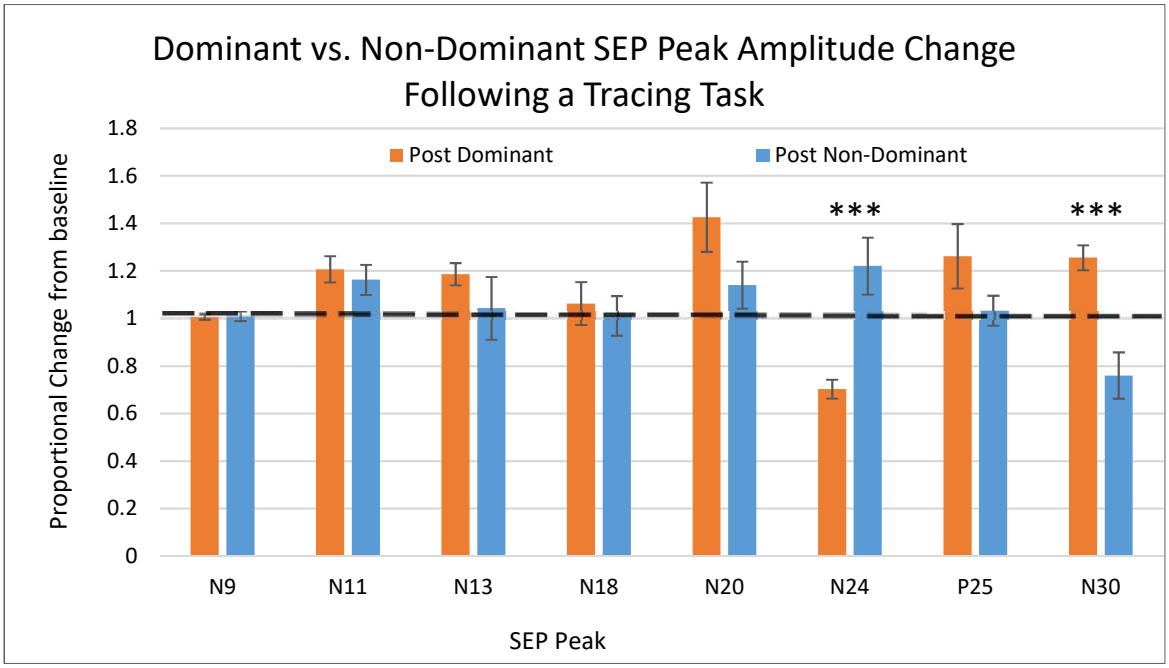

FIGURE 4: DOMINANT VS. NON-DOMINANT SEP PEAK AMPLITUDE CHANGE RELATIVE TO BASELINE (DOTTED LINE) FOLLOWING A NOVEL TRACING TASK. (ERROR BARS REPRESENT SEM. ASTERISKS DENOTE SIGNIFICANT INTERACTIONS (***=P<.001))

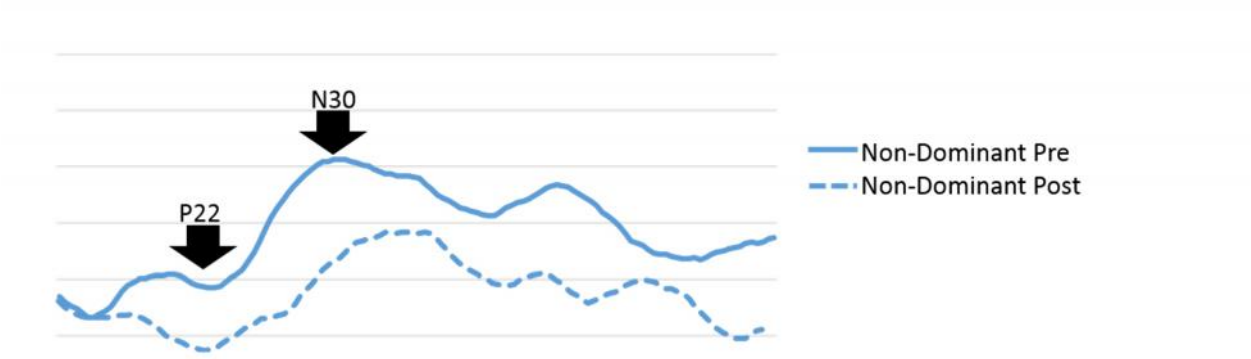

FIGURE 5: PRE MOTOR LEARNING AND POST MOTOR LEARNING SEP TRACE FOR NON-DOMINANT HAND OF ONE PARTICIPANT.

Tracing Data

The non-dominant limb was more accurate at pre, post and retention testing points. At initial testing the non-dominant limb showed an average error of 163.4% (±7.9%) while the dominant hand group showed an average error of 216.8% (±6.2%). After learning, a post test measurement showed the non-dominant group to average 135.8% (±7.8%) error, and the dominant hand group averaged 160.9% (±4.7%). At retention (24-48 hours after) the non-dominant hand group showed an average error of 117.5% (±4.9%) and the dominant hand group showed an average error of 142.2% (±3.8%).

The non-dominant group was significantly more accurate at baseline ($p<.005$) but both groups significantly increased in accuracy [$F(2,44)=25.5$, $p<0.0001$] with no significant interaction. Pre-planned contrasts showed improvements both baseline to post training ($p<0.0001$) and baseline to retention ($p<0.0001$) overall.

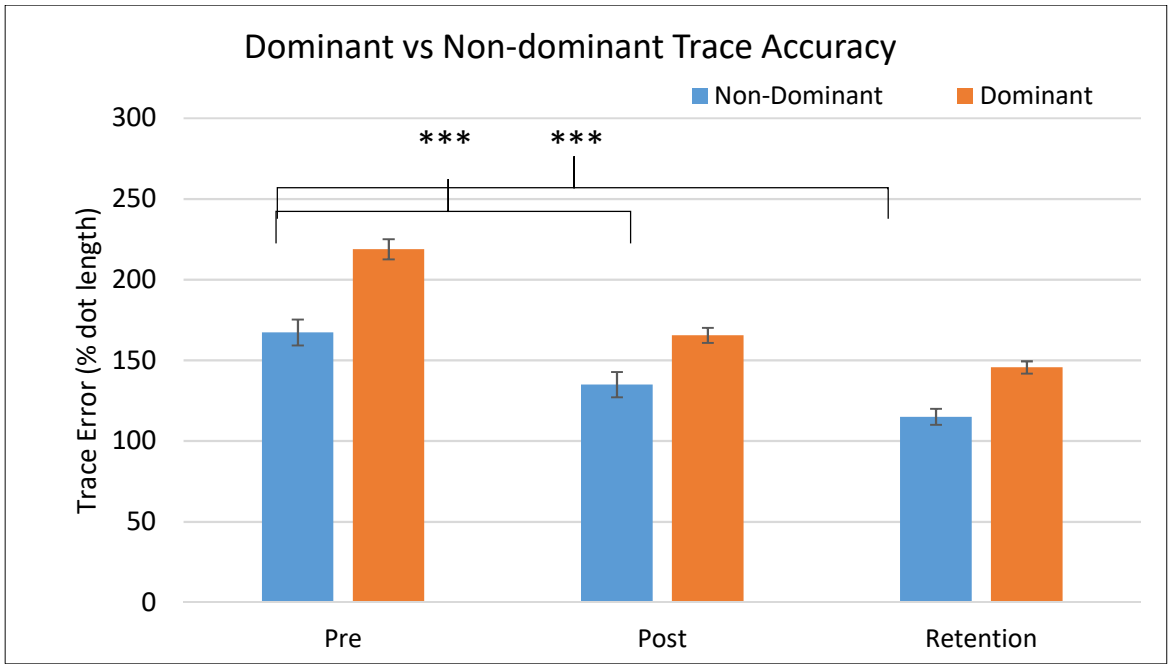

FIGURE 6: DOMINANT VS. NON-DOMINANT TRACE ACCURACY AT PRE, POST AND RETENTION. ERROR BARS REPRESENT SEM. ASTERISKS DENOTE SIGNIFICANT INTERACTIONS (***=P<.001)

Discussion

The results of this study show differences in the early sensorimotor processing between the limbs. The non-dominant limb showed directionally different SEP peak amplitude when compared to the dominant hand. Additionally, the non-dominant limb was more accurate at each of the three testing time points (pre, post and retention).

The directional differences in peal amplitude changes between the limbs may be the result of different neural pathways that reflect a selective way to produce movement. Previous research has shown that following a reaching task the non-dominant limb seemed to follow a movement pattern specialized for stability and utilized feedback information more efficiently, while the dominant limb followed a movement pattern generated from an internal model and utilized feedforward information more efficiently (Mutha et al., 2013; R. Sainburg & Kalakanis, 2000; R. L. Sainburg, 2002; Schabowsky et al., 2007). The neurological data collected in this study may support a similar idea.

The N30 peak has been demonstrated to represent activation in the premotor, motor and prefrontal areas of the cortex (A.-M. Cebolla et al., 2011) and previous literature has source

localized some of these areas (Lelic et al., 2016). The combination of these areas may suggest a role in movement planning and sensorimotor integration (Danielle Andrew et al., 2015; Brown & Staines, 2015b; A.-M. Cebolla et al., 2011). The decrease in the N30 peak for the non-dominant limb may suggest that the areas associated with sensorimotor integration and motor planning were less active in the early processing phase when compared to the dominant hand. It may also represent an increase in inhibition within the pathway as learning occurred. This would mean that in order to produce corresponding movements, information was inhibited online, indicative of the use of a mechanism based around impedance control and feedback. However, the dominant limb showed an increase in peak amplitude following the task. This may be the result of a decrease in inhibition or an increase in sensorimotor integration and motor planning areas. Both of these findings are consistent with literature which suggests differences in control strategies utilized in the limbs (Milner & Franklin, 2005; Mutha et al., 2013; Schabowsky et al., 2007).

The N24 peak has been hypothesized to reflect activation changes in the neural pathways between the cerebellum and S1 (Restuccia et al., 2007; Waberski et al., 1999). Based on this finding, many studies have shown the cerebellum to play an active role in motor learning (D Andrew et al., 2015; Danielle Andrew et al., 2015; Baarbé et al., 2014; Daligadu, Haavik, Yielder, Baarbe, & Murphy, 2013; Dancey et al., 2016a; Dancey et al., 2014; Doyon & Benali, 2005). The results of this study support these findings in that following the motor learning task, both groups showed changes in the activity of this suggested pathway. The directional differences were seen in the N24 peak as well. Following the task, the non-dominant group showed an increase in peak amplitude. This might suggest an increase in cerebellar inhibition as the cerebellum uses inhibition to learn the motor program demonstrated in the task. The decrease seen in the dominant hand may reflect a decrease in cerebellar inhibition as a result of the learning. This finding is supported by previous work showing a decrease in cerebellar inhibition following motor learning (Baarbé et al., 2014).

It has also been suggested that even though these specializations are present in the control of each limb, each hemisphere can draw on the others preferred strategy to efficiently complete movements (Mutha et al., 2013). This is also reflected in the neurological data

collected in this study. Some of the peaks show similar directional and amplitude changes, suggesting that the underlying structures that create these peaks are either similar or are working at similar levels in both hemispheres. Most interestingly, the spinal N11 and N13 peaks are nearly identical in their amplitude and directional change, meaning that any differences in structures would be limited to the cortex itself and any information entering would be utilized the same as these peak represent the peripheral information arriving and entering the spinal cord.

In regard to the behavioural data, the non-dominant limb was significantly more accurate at baseline, and showed significant improvement along with the dominant limb following learning and at retention. These results support findings where the non-dominant limb was more accurate at performing a task (Mutha et al., 2013; R. Sainburg & Kalakanis, 2000; Schabowsky et al., 2007; Vivek Yadav & Sainburg, 2014). Though similar results are seen, there is one contrast between the findings of this study and others that have found similar changes. The task itself differs from the more gross motor control scheme required by reaching tasks used in previous work (Mutha et al., 2013; R. Sainburg & Kalakanis, 2000; Schabowsky et al., 2007; Vivek Yadav & Sainburg, 2014) to the fine motor control required for the tracing task. Nevertheless the tasks are different and the results being similar suggests a globally adaptable control scheme (feedforward for the dominant limb, and feedback for the non-dominant limb) that can be applied to both gross motor movements and fine motor movements. In contrast, it has been shown that the non-dominant limb was less accurate when completed a similar fine motor learning task, however this previous study used the first dorsal interosseous muscle (FDI) as opposed to APB (L. Holland, Murphy, B., Passmore, S., Yielder, P. , In Press). With technology the way it is in the present day, utilizing a muscle such as APB that is more widely used for handheld electronics may provide a more “level playing field” for comparing differences in performance between the limbs.

The greater accuracy seen in the non-dominant hand has a couple of possible explanations. As previously stated, the non-dominant limb is thought to use a control strategy that centers around impedance control which generally is an inefficient way to achieve a goal, however the accuracy of this type of a system is much higher than one that uses more of a

predictive approach like the dominant limb has been shown to use (V Yadav & Sainburg, 2011). There is also evidence to suggest the use of both types of control strategies in both of the limbs. V Yadav & Sainburg (2011) showed that it may not just be the differences in strategies but the time it takes to switch from one to the other that causes differences in accuracy. Results showed that both the dominant and non-dominant limb utilized predictive mechanisms at the onset of movement, however the non-dominant limb switched to the feedback mechanism earlier than the dominant limb (V Yadav & Sainburg, 2011). Based on these findings, it is intuitive that the non-dominant limb was more accurate at the task. Whether a mechanism based on impedance control or feedback is solely utilized, or the delay to switch to it is shorter, the result is an increase in accuracy for the non-dominant limb.

The other possible explanation for the increase in accuracy seen in the non-dominant hand has to do with attention and complexity. Challenge point framework states that the level of functional difficulty of the task leads to difficulty learning (Guadagnoli & Lee, 2004), which would lead to participants being closer to their optimal challenge point, thus leading to enhanced learning. Participants may have thought that the non-dominant hand would be harder or actually found it harder, thus leading to an increase in concentration and attention. In most cases this increase in attention leads to a greater ability to learn and retain information required by the task (Wulf, 2007). This would explain the increase in accuracy during the initial stages of learning. During the later stages in learning the increase in accuracy is still seen, meaning either the increase attention to or complexity of the task continued throughout each stage, or once the initial learning was done in this sensitive state, the brain continued to learn from that initial point as it normally would.

Strengths

Strengths of this study are found in the results showing differential peak amplitudes and motor performance between the non-dominant and dominant limb. This is one of the few studies to compare novel learning between the limbs using neurological measures. The results themselves suggest underlying mechanisms of motor control brought on by differences in early processing within the brain.

Limitations

An issue that arose in the planning of this study is how to best compare the differences. Most studies use the participants as their own control to best account for inter-subject differences. However, in the literature there is much evidence to support the idea of inter-limb transfer of information following learning. There is also no concrete evidence as to when this effect expires, meaning using subjects that have used a different limb, regardless of which limb performed the task first, might lead to an increase in performance before the task has even been done. This means that true pretest measurements are harder to show, and in order to avoid this separate groups were used. However, by using separate groups we cannot use subjects as their own controls. Future considerations could include prolonged absence from learning using the other limb at various time points to see how the effects of inter-limb transfer expire, and then repeating this study when this is known.

Conclusions

The results of this study suggest there may be underlying neurological differences responsible for performance differences within the limbs. A future direction would be to observe the non-dominant limb is an environment that has been shown to challenge motor control and see whether these differences hold true or if it distorts the learning process completely.

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Manuscript 1 Summary and Reasoning for Manuscript 2

Study one found that that the dominant and non-dominant hand show differential SEP peak changes following a motor learning task. This was accompanied by an increase in performance accuracy for the non-dominant hand. This suggests that there are differences in the neural mechanisms that underlie motor control of the different hemispheres that goes beyond the utilization of similar motor control mechanisms. One explanation for these findings is that the neural generators associated with the N30 and the N24 peaks are active at different levels during motor control. Evidence discussed in study one indicates that the N30 reflects activity in the pathways within the prefrontal and frontal areas of the cortex that represent sensorimotor integration. The increased peak amplitude for the dominant hand suggests an increase in sensorimotor integration during motor control. This would support literature that suggests the use of a predicative (feedforward) mechanism in the dominant upper limb as there would need to be constant correcting and integration of different stimuli to complete a motor command accurately. The decrease in the non-dominant hemisphere might suggest a decrease in the activation of this pathway, or alternately an increase in inhibition throughout the motor control process. This would also support literature that speculates the use of a reactive (feedback) mechanism during motor control in the non-dominant hand as there would be a greater amount of inhibition needed online to correct as well as learn the motor program.

Evidence suggests that N24 represents activity in the pathway from the cerebellum to the primary somatosensory cortex. The increased N24 amplitude in the non-dominant hemisphere might suggest an increase in cerebellar inhibition during motor control, as it attempts to learn the new motor program needed to complete the task in this study, and the cerebellum to S1 pathway is inhibitory. The decreased amplitude in the dominant hemisphere might suggest that there was a decrease in cerebellar inhibition during learning which supports other studies that have used the dominant hand during motor control. Taken together the neurological data suggests that there is underlying somatosensory processing differences during motor control of the dominant and non-dominant arm. This finding provides new

neurophysiological evidence to understand the mechanisms underlying laterality differences in motor control.

The rationale for manuscript 2 stems from the findings of manuscript 1 in that the differential SEP peak amplitudes have suggested neurological differences in motor control between the limbs. However, does this process change when the limbs are forced to adapt to altered sensory inputs? This has been done in much of the literature as many of the tasks have been reaching tasks using a robotic manipulandum to explore differences in the limbs. These tasks often introduce mechanical perturbations to disrupt the movements of the limbs and examine adaptation. Since manuscript 1 sought to explore somatosensory processing differences between the limbs during motor control, the use of a sensory perturbation, during a similar task might disrupt the findings from above. The chosen method for introducing altered sensory input is noxious painful stimuli, as this has been shown in the literature to affect motor learning with the dominant hand. Given that the effects on the dominant hand are known, manuscript 2 will focus only on motor learning in the presence of pain for the non-dominant hand, as compared a non-dominant control group which performs the learning task without the sensory perturbation. Study Two will reveal if there are differences in neural mechanisms associated with adaptation that are observable in SEP peak amplitudes for the non-dominant hand as compared to previous reports for the dominant hand. The results of this study will provide additional insight into differences in motor control underlying hand preference and lateralized somatosensory processing.

Section 2: Manuscript 2 – Impact of a sensory perturbation on somatosensory evoked potentials and motor learning for the non-dominant hand.

Abstract

Background: When limb movements are perturbed, the system adapts and corrects for these changes in the task dynamics. The dominant limb tends to favour feedforward control mechanisms whereas the non-dominant limb favours feedback control in response to motor perturbations. However, possible asymmetry in response to sensory perturbations have are not well studied. Early somatosensory evoked potentials (SEPs) (less than 50msec post stimulation) can be used to investigate the neurophysiological impact of sensory perturbations.

Methods: 19 participants of dominant right handed volunteers were split into two groups. The intervention group (N=9) which received altered sensation during motor learning in the presence of cutaneous pain induced by application of capsaicin cream on the lateral aspect of the left elbow and a control group (N=10) received innocuous control cream. Both groups completed a novel training task which consisted of a sinusoidal wave, varying in amplitude and frequency with different complexity levels. Prior to cream application, in the presence of pain, and after motor training, SEPs were elicited by stimulation of the left median nerve at the wrist. Each group completed the protocol with their non-dominant (left) hand.

Results: The repeated measures ANOVA showed no significant interactive effects for any of the SEP peak components. There was a significant increase in N24 amplitude following motor training for both groups [$F(2,34)=5.25$, $p<0.01$]. The behavioural data showed the intervention group was significantly better at baseline motor training ($p<0.01$) compared to the control group. Both groups also significantly increased in accuracy over the course of learning [$F(2,34)=41.04$,$p<0.0001$] with pre planned contrasts showing significant improvements from pretest to post test ($p<0.0001$)

Discussion: These results indicate that though learning was increased as a result of the sensory perturbation, these findings did not reflect in the neurological data entirely. There may be

some evidence to suggest the change in preferred motor control strategy, evident by the change in N24 following motor training in the intervention group.

Introduction

Movement is our primary tool we use to achieve goal directed behaviours. Often these movements go uninterrupted and we complete the goal oriented movement. However when our movements are perturbed, we have to adapt and correct for these changes in the task dynamics. The ability to maintain control of the upper limb in response to various perturbations is critical to maintain the speed and accuracy of tasks such as reaching, grasping and fine finger movements. Several theories have been developed as to how the upper limbs adapt to achieve correct movements in the face of various perturbations (Criscimagna-Hemminger et al., 2003; Desmurget & Grafton, 2000; Milner & Franklin, 2005; Mutha et al., 2013; R. Sainburg & Kalakanis, 2000; R. L. Sainburg, 2002; R. L. Sainburg & Duff, 2006; Schabowsky et al., 2007). These studies often use mechanical perturbations and measure adaptation in force and trajectory of upper limb movement. There is evidence to suggest altered patterns of motor control between the dominant and non-dominant upper limb in relation to these adaptation processes (Milner & Franklin, 2005; Mutha et al., 2013; R. Sainburg & Kalakanis, 2000; Schabowsky et al., 2007).

Earlier work largely studied the response to motor system perturbation during reaching movements with the use of velocity dependent force fields (Milner & Franklin, 2005; R. Sainburg & Kalakanis, 2000; Schabowsky et al., 2007). These studies measure the change in task performance in response to a mechanical perturbation in a motor learning paradigm, these perturbations become learned and are continue to be anticipated for even after they are removed (Schabowsky et al., 2007). Other literature has studied the use of sensory perturbations that didn't directly interact with the musculature of the upper limb, but rather change the goal of the task by altering sensory input. This can be done by covertly shifting the starting position of the hand cursor on a screen, when the subject has no view of their limb (Mutha et al., 2013). When this is done, the limb has to adapt to the change in cursor position without any feedback directly on the movement. This visuomotor transformation generates the

use of internal feedback that stems from the altered sensory input. This altered sensory input can cause a partial proprioceptive recalibration, accompanied by sensorimotor transformations to accurately adapt (Cressman & Henriques, 2009). This adaptation is suspected to be driven by the cerebellum, as the mismatch in information needs to be edited online (Tseng, Diedrichsen, Krakauer, Shadmehr, & Bastian, 2007).

Fine motor control tasks such as typing tasks and pursuit tracing tasks have more recently been used to explore motor control as well (D Andrew et al., 2015; Danielle Andrew et al., 2015; Dancey et al., 2016a; Dancey et al., 2014; Dancey et al., 2016b). This work also explored responses in the cortex by measuring changes in the amplitude of early somatosensory evoked potentials (SEPs). SEPs in combination with EEG may show changes in the number or strength of various synapses in the cortex directly related to motor control and learning (Mehrkanoon et al., 2016). This technique provides a way to explore sensorimotor integration, a crucial component of movement and adaptation. The N24 and the N30 peak components of SEPs are hypothesized to reflect the pathway from the cerebellum to S1 and the activation of sensorimotor integration (SMI) pathways respectively (Lelic et al., 2016; Restuccia et al., 2007; Rossi et al., 2003; Waberski et al., 1999). Evaluation of these peaks following movement learning paradigms has been able to provide insight into cortical motor control (D Andrew et al., 2015; Danielle Andrew et al., 2015; Dancey et al., 2014; Passmore et al., 2014). These studies specifically use a learning paradigm, however this is crucial as the adaptation process could be considered a learning phase, as the limbs readjust to a new environment. Having a technique which provides insight into pathways from the cerebellum to sensorimotor cortex is important due to the role played by the cerebellum in the adaptation process (Tseng et al., 2007).

Any incoming information that is altered can be considered a perturbation to the sensory system. This input may be an abrupt, one time stimulus as seen in visuomotor rotations, or a continuous stimulus. An example of a continuous type or stimulus is input from acute pain. It has been shown that subjects who experience subclinical neck pain, that is neck pain that the subject has not sought treatment for, have altered performance of joint position sense of the elbow (Heidi Haavik & Murphy, 2011). The subjects who experienced recurrent

pain were worse at accurately replicated joint angles compared to a healthy control. This same effect was seen in participants whose neck was fatigued prior to testing of joint position sense (Zabihhosseinian, Holmes, & Murphy, 2015). This shows the impact of mild to moderate levels of painful or obstructive stimuli to the movement process. Additionally, these findings have been expanded into movements such as throwing, where the individuals who had recurrent neck pain showed different throwing kinematics in a dart throwing task as compared to a healthy controls (Baarbé, 2016). This highlights the importance of the adaptation process mentioned above in that the painful stimuli has caused a change in the throwing mechanics.

Literature has also combined the use of SEPs with acute experimental pain (Dancey et al., 2016a; Dancey et al., 2014; Dancey et al., 2016b; Poortvliet, Tucker, & Hodges, 2015). These studies utilized capsaicin cream to generate a noxious sensory stimuli. This incoming information may obstruct sensory information traveling towards the CNS during the learning process and may be treated as a sensory perturbation. Interestingly, these studies showed the group perturbed by the noxious pain stimuli to be more accurate at the learning task. This might suggest a heightened adaptation process in the presence of a sensory perturbation. However, these studies have only explored this effect in the dominant hand, and as previously mentioned the adaptation processes are different between the limbs with the non-dominant limb relying more on feedback vs feedforward control. By Measurement of SEP peaks known to reflect changes in SMI in response to motor learning allows investigation of potential cortical differences for the non-dominant upper limb between when skills are acquired in the presence of noxious cutaneous pain.

It is hypothesized based on past literature for the dominant limb that the group receiving altered sensory input (a noxious pain stimuli) will be more accurate at motor training. However it is hypothesized the N24 and N30 components of SEPs will show differential changes in excitability in SEP peaks related to cerebellar pathways and SMI as compared to past work using the dominant limb. These peak amplitudes are expected to increase to a lesser degree than for previous work in involving the dominant limb due to the increased reliance of the non-dominant limb on feedback control (Mutha et al., 2013; R. Sainburg & Kalakanis, 2000).

Methods

Similar methodology to a previous study done by Dancey et al., (2016a) in the dominant limb was utilized. 19 right hand dominant (21.1 ± 1.3 years, average handedness score = 66 (Oldfield, 1971)) individuals with no known neurological conditions were recruited to complete the learning paradigm. Each participant was required to fill out an informed consent form, outlining the details of the study. Following this, a safety checklist and a handedness questionnaire was used to ensure safe participation in the study. Ethical approval has been sought and approved from the UOIT ethics committee (REB# 11-067). Subjects were randomly assigned to a control group which received a skin cream, and an experimental group which received a capsaicin based therapy cream. All Subjects completed the learning protocol with their non-dominant hand.

Somatosensory Evoked Potentials (SEPs) were collected at three different time points to observe the processing differences before application of whichever cream the subjects were given, and following the motor training task. Recording electrodes were placed over the brachial plexus (erb's point), the C5 spinous process and on the frontal and parietal cortices. Cortical sites were measured from the vertex of each participants head, with the frontal electrode being 6cm anterior, and 2 cm contralateral (right) to the stimulated hand (Rossi et al., 2003) and the parietal electrode being placed at 20% of tragus to tragus measurement contralateral, and 2cm posterior. Each site received electrode preparation by applying an abrasive paste to the site which was then wiped with alcohol.

The experimental group had capsaicin cream (0.075% Zostrix) applied to the lateral aspect of the left elbow. The cream was massaged into the elbow for a 5 minute duration, or until all of the cream had been absorbed. Participants in the control group had a similar protocol expect they were given LifeBrand™ lotion instead. Application was followed by a 15 minute absorption time before post-application SEPs were measured.

Stimulation Parameters

Pulse parameters were set to 1ms in duration, delivered at 2 different frequencies (2.47Hz and 4.98Hz). These different frequencies enable differentiation between the N30 and

the N24 peaks, as past work has shown that the faster rate enables the N24 peak be visualized at the N30 diminished in size at faster stimulation rates (H Haavik & Murphy, 2013). The stimulations were delivered over the median nerve at the wrist with the anode proximal. Intensity of the stimulation was determined by motor threshold, which elicited a slight twitch of the thumb APB muscle. Information was recorded peripherally and centrally using electrodes placed over the brachial plexus, C5 spinous process as well as a frontal (6cm anterior of Cz, 2 cm contralateral) and parietal electrode (20% of tragus to tragus measurement contralateral from Cz and 2 cm posterior) on the scalp. Locations used matched guidelines laid by the International Federation of Clinical Neurophysiologists (IFCN) and that of studies which were following similar protocols (D Andrew et al., 2015; Danielle Andrew et al., 2015; Dancey et al., 2014).

Task Parameters

Subjects completed a pursuit tracing task run through a custom Leap Motion software tool (Leap Motion, San Francisco, CA). Each testing day consisted of 3 separate blocks of training. A pretest which consisted of 4 traces, an acquisition phase in which the participants learned the parameters of the task consisting of 12 traces, and a post-test consisting of 4 traces. Any given trace was 1 of 4 pre-sets that were randomized so that no trace was expected. The traces consisted of 500 dots and varied in frequency and amplitude. Participants were required to pursue the trace on an external track pad using their thumb. To avoid any confusion, participants were locked on the screen to a horizontal plane of movement so even if their thumb drifted vertically it would not register on the screen. Participants were also required to avoid the use of any wrist, elbow or shoulder movement. Following the combined 20 traces participants were then brought back 24-48 hours following to do a retention day that consisted of 4 randomized traces. Both groups completed this day in the absence of their learning conditions (capsaicin cream or skin cream).

Pain Rating Score

Subjects were asked to identify the intensity of painful sensation prior to cream application, following cream application (following the 15 minutes to allow the cream to set in) and following the motor training task. This was done using a Numeric Pain Rating scale (NPRS)

participants were asked to identify their pain rating on a 0-10 scale. The NPRs was shown to be reliable in the measurement of different types of pain, making it an appropriate tool for this study (Chapman et al., 2011; Mintken, Glynn, & Cleland, 2009). Use of it will give evidence of the impact of the sensory perturbation given to the intervention group.

Data Analysis

Analysis of the data included SEP peak amplitude and the motor learning data. The tracing task was measured as averaged percent error per dot, whereby 100% was equal to one dot length in either direction from the target location. These were averaged for each participant in the pre and post motor acquisition and post retention and compared to determine the degree of learning. For the SEP results, peak to peak amplitude were used to measure change in activity following cream application and following motor acquisition. SEP peak latencies were also measured to determine if any of the interventions changed the timing of early sensory processing. The peak to peak amplitudes were normalized to pre-intervention amplitude for each peak for each participant.

Statistical Analysis

All data was tested for homogeneity of variance and skewness to ensure parametric statistics could be run. A repeated measures ANOVA with group (Intervention vs control cream) and time (pre-application, post-application and post-training) as factors was used to measure changes in in response to motor acquisition. Pre-planned contrasts to baseline were used to determine which intervention(s) lead to significant changes in SEP peak amplitude. Trials were only included where the peripheral N9 amplitude was within ±10% of baseline, as a change greater than this could indicate changes in the incoming sensory volley, which would impair the ability to attribute changes in later SEP peaks to central changes. For the tracing data a repeated measures ANOVA with group (intervention vs control) and time (pre, post and retention) as factors was used. Statistical significance set to 0.05 for all tests.

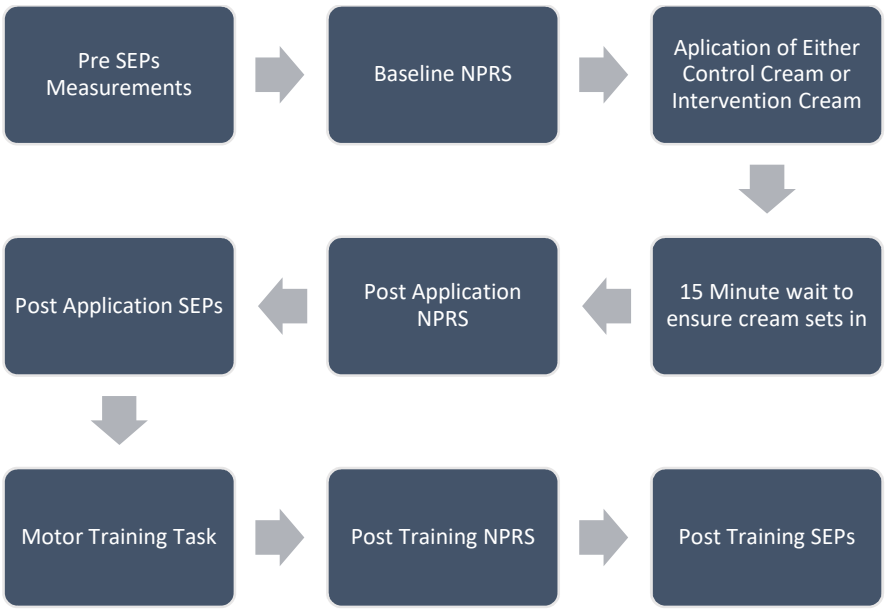

FIGURE 7: STUDY 2 METHODOLOGY FLOW CHART

Results

Neurophysiological Data

Peak to peak amplitude was measured before motor training, following application as well as following motor training. SEP measurement following application allowed for measurement of the possible impact of pain itself. 19 of the 22 subjects completed the study and were included in the analysis of neurological and accuracy data. One subject was excluded due to N9 variance greater than 10%, the other two were excluded due to unaccountable noise. Latencies of each of the peaks were measured and no significant differences were found.

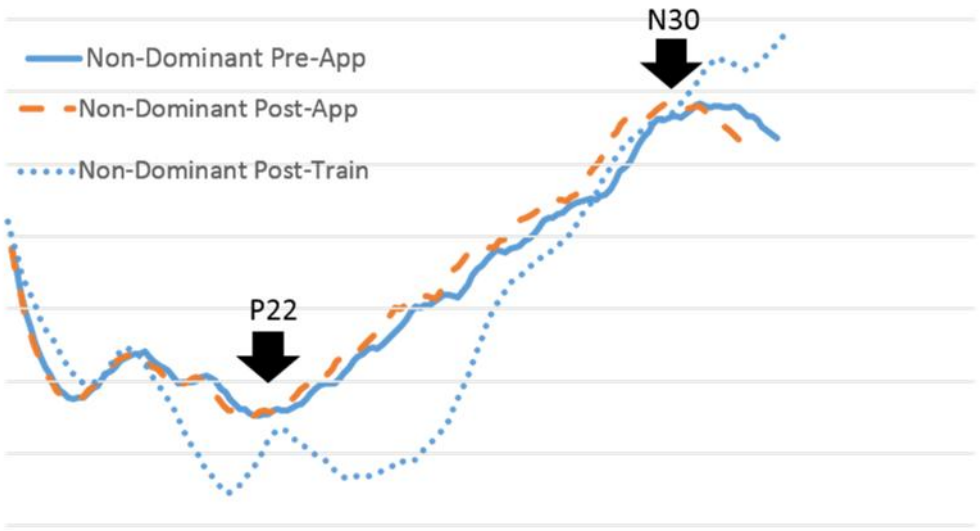

FIGURE 8: NON-DOMINANT SEP TRACE FOR INTERVENTION GROUP

The control group showed an increase of 15% (±21%) following application and an increase of 8% (±19%) following training for the N11 peak. A decrease of 19% (±11%) following application and a decrease of 7% (±11%) following training for the N13 peak. A decrease of 3% (±6%) following application and an increase of 21% (±15%) following training for the N18 peak. An increase of 2% (±7%) following application and an increase or 3% (±13%) following training for the N20 peak. A decrease of 9% (±6%) following application and an increase of 2% (±7%) following training for the P25 peak. An increase of 14% (±10%) following application and an increase of 44% (17%) following training for the N24 peak. As well as an increase of 9% (±3%) following application and an increase of 5% (±8%) following training for the N30 peak.

The intervention group showed an increase of 10% (±10%) following application and an increase of 13% (±6%) following training for the N11 peak. An increase of 12% (±41%) following application and a decrease of 10% (±14%) following training for the N13 peak. An increase of 4% (±6%) following application and an increase of 11% (±17%) following training for the N18 peak. An increase of 12% (±10%) following application and an increase or 40% (±19%) following training for the N20 peak. An increase of 16% (±16%) following application and an increase of 16% (±18%) following training for the P25 peak. A decrease of 3% (±6%) following application

and an increase of 10% (13%) following training for the N24 peak. As well as a decrease of 1% (±8%) following application and an increase of 7% (±15%) following training for the N30 peak.

TABLE 2: SUMMARY OF SEP PEAK AMPLITUDES FOR INTERVENTION AND CONTROL GROUPS ± SEM (**=P<0.01)

	Intervention		Control	
N9	Post Application	Post Training	Post Application	Post Training
	↓5% ± 5%	↓2% ± 2%	↑4% ± 2%	↑5% ± 3%
N11	Post Application	Post Training	Post Application	Post Training
	↑10% ± 10%	↑13% ± 6%	↑15% ± 21%	↑8% ± 19%
N13	Post Application	Post Training	Post Application	Post Training
	↑12% ± 41%	↓10% ± 14%	↓19% ± 11%	↓7% ± 11%
N18	Post Application	Post Training	Post Application	Post Training
	↑4% ± 6%	↑11% ± 17%	↓3% ± 6%	↑21% ± 15%
N20	Post Application	Post Training	Post Application	Post Training
	↑12% ± 10%	↑40% ± 19%	↑2% ± 7%	↑3% ± 13%
P25	Post Application	Post Training	Post Application	Post Training
	↑16% ± 16%	↑16% ± 18%	↓9% ± 6%	↑2% ± 7%
N24 **	Post Application	Post Training	Post Application	Post Training
	↓3% ±6%	↑10%± 13%	↑14% ± 10%	↑44% ± 17%
N30	Post Application	Post Training	Post Application	Post Training
	↓1% ± 8%	↑7% ± 15%	↑9% ± 3%	↑5% ± 8%

There was significant increases in peak amplitude for the N24 peak [$F(2,34)=5.25$, $p<0.01$]. Preplanned contrasts showed significant increases in amplitude from pre training to post training for both groups ($p<0.05$). The N20 peak showed an increase in amplitude approaching significance [$F(1,32)=2.67$,$p=0.08$) with pre planned contrasts approaching significance from pre training to post training ($p=0.07$). No significant interactive effects were seen between the groups for any of the SEP peak measures.

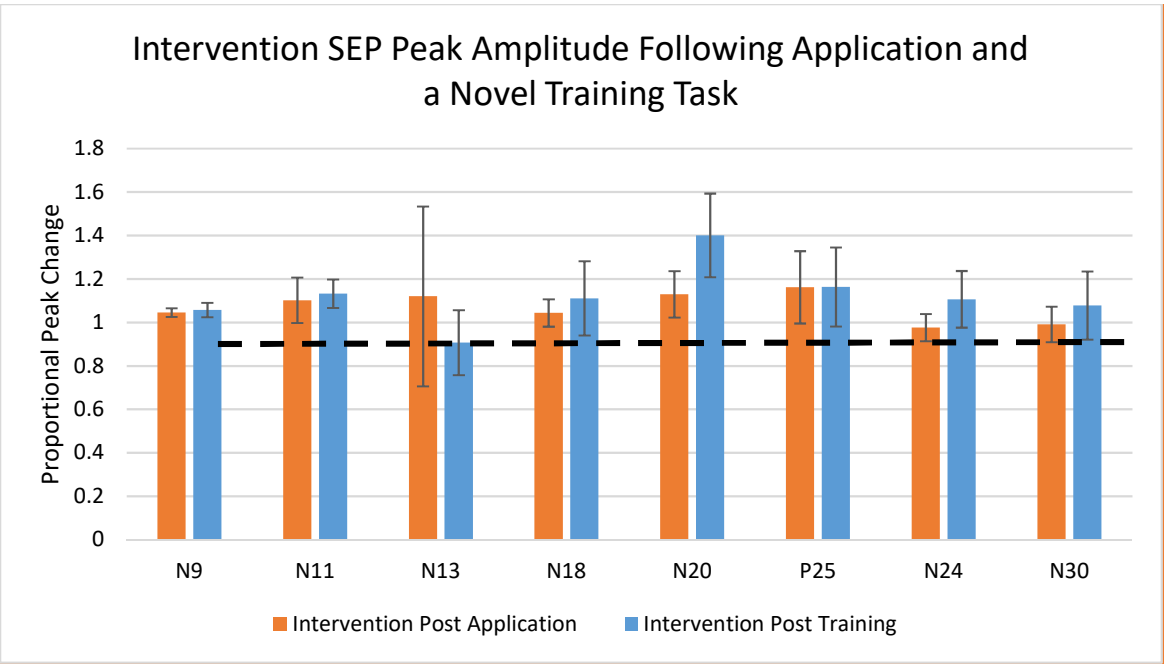

FIGURE 9: INTERVENTION GROUP'S PEAK AMPLITUDE FOLLOWING A NOVEL TRAINING TASK RELATIVE TO BASELINE (DOTTED LINE) (ERROR BARS REPRESENT SEM.)

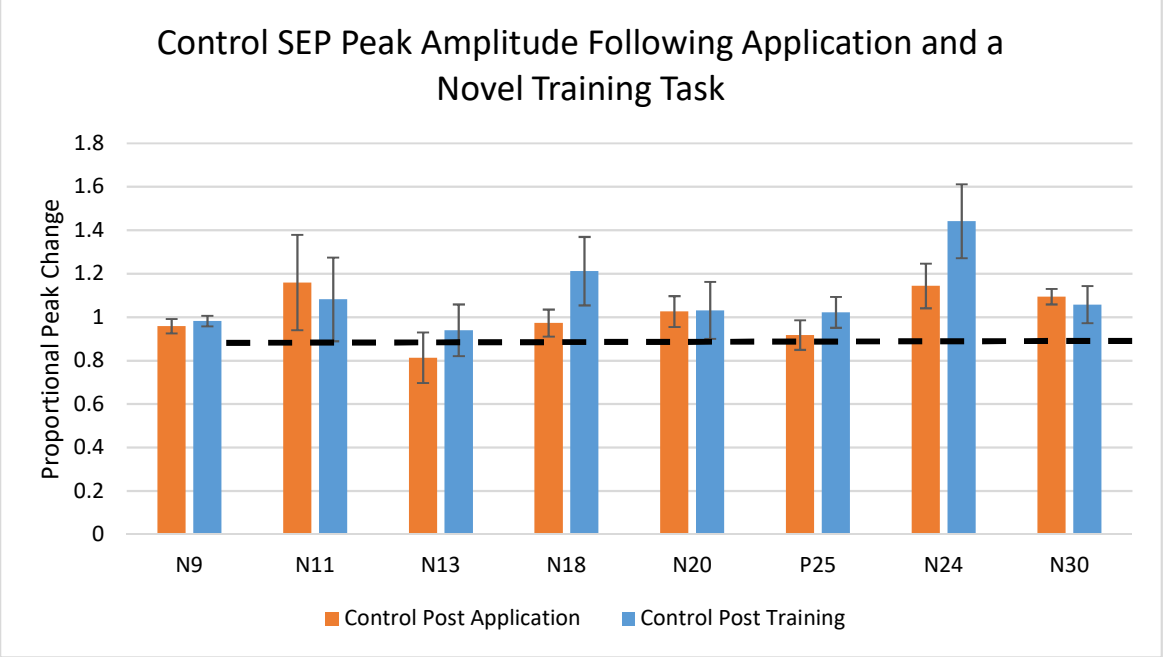

FIGURE 10: CONTROL GROUP'S PEAK AMPLITUDE FOLLOWING A NOVEL TRAINING TASK RELATIVE TO BASELINE (DOTTED LINE) (ERROR BARS REPRESENT SEM.)

Accuracy Data

Both groups showed an increase in accuracy as a result of learning. The intervention group showed 102% (±5.3%) error during the pre-testing phase, 81% (±4.5%) during the post-test and after the retention test the average error was 79% (±3.9%). For the control group had 124% (±6.8%) error at baseline, 85% (±3.6%) error following the post-test and 89% (±5.4%) error at retention. The intervention group was significantly more accurate at baseline learning ($p<0.01$) compared to the control group. Both groups also significantly increased in accuracy over the course of learning [$F(2,34)=41.04$,$p<0.0001$] with pre planned contrasts showing significant improvements from pretest to post test ($p<0.0001$)

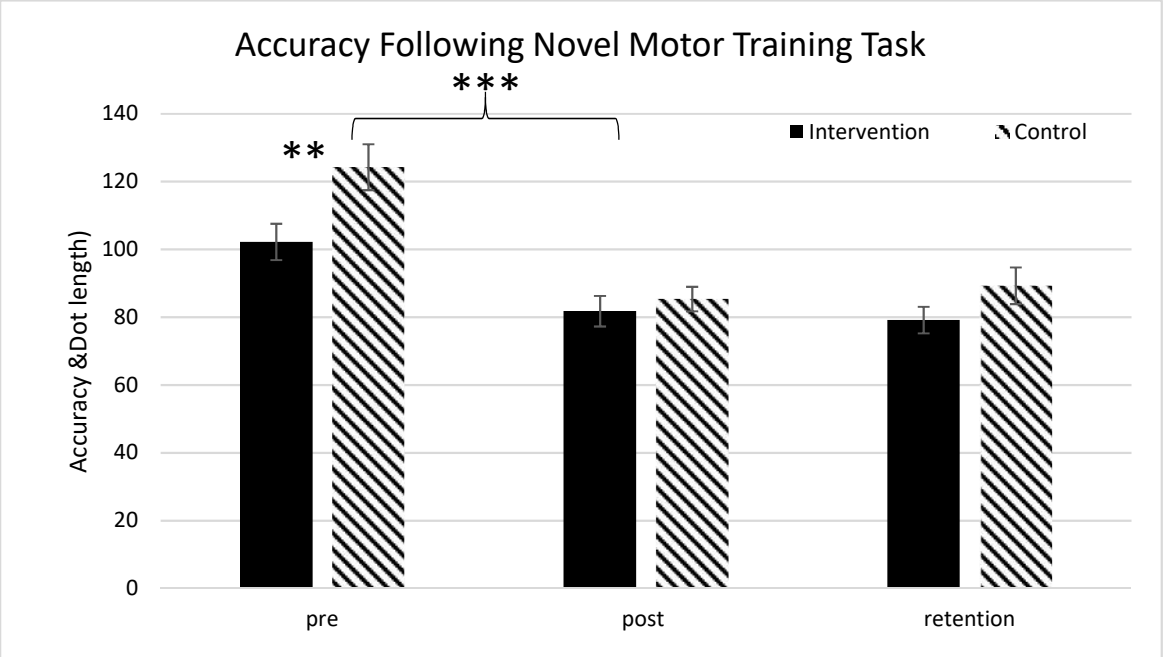

FIGURE 11: ACCURACY OF INTERVENTION AND CONTROL GROUP FOLLOWING A NOVEL TRACING TASK. ERROR BARS REPRESENT ±SEM. (**=P<0.01, ***=P<0.0001)

NPRS scores

NPRS scores were obtained on a scale of 0 to 10, with 10 being the worst sensation they could imagine. At baseline measurements the intervention groups reported no sensation. Following the application and setting time the group averaged a score of 2.72 (±1.8) and following motor training this then decreased to 1.66 (±1.1). None of the participants in the control group reported any pain at any stage of the protocol.

Discussion

The results of this study showed that a sensory perturbation delivered via noxious painful stimuli increases accuracy of a training task. The intervention group also showed differences in the N20 peak and the control group showed changes in the N24 SEP peak with no difference in the N30 component for either group contrary to our hypothesis.

The intervention group showed a significantly more accurate baseline test (completed in the presence of pain) as compared to the control, keeping with previous literature (Dancey et al., 2016a). A possible reason for the increase in accuracy might be that the sensory perturbation caused the participants to be closer to their optimal challenge point. This would enhance the learning process as a result of more resources being devoted to the task (Guadagnoli & Lee, 2004). Increased attention may play a role in this as well as the intervention group seemed to retain information better, which is often seen as attention increases (Wulf, 2007). Another possible explanation for this increase in accuracy has to do with the chosen motor control pattern of the non-dominant hand. The non-dominant limb usually chooses a motor control strategy that is based around impedance control and reactive mechanisms (Mutha et al., 2013; R. Sainburg & Kalakanis, 2000; Schabowsky et al., 2007). By providing sensory perturbations, we may have increased the amount of sensory feedback into a feedback system, allowing for more detailed control of fine movements. This coincides with one of the larger peak changes from the intervention group, the N20. The N20 has been shown to reflect the initial activation of the primary sensory cortex (Buchner et al., 1995; Emerson, Sgro, Pedley, & Hauser, 1988; Valeriani et al., 1998). The increase in sensory information from the sensory perturbations may have elicited this response, and with the increase in accuracy it would suggest an increase in sensory feedback into a feedback oriented system. Although there was no significant increase, this increase is contrary to previous work which used a similar perturbation technique for the dominant limb (Dancey et al., 2016a). The authors found no increase in the N20 in the intervention group following application or following motor training, and an increase following motor training for the control group, where we saw the opposite effect. This finding may suggest that early somatosensory processing in S1 may be lateralized, with differences in control strategies reflected in early somatosensory processing.

One of the peaks under close observation in this study was the N24 peak as it has been shown to change in past work using the dominant limb (D Andrew et al., 2015; Dancey et al., 2016a; Dancey et al., 2014). This peak is hypothesized to reflect the pathway from the cerebellum to S1 (Restuccia et al., 2007; Rossi et al., 2003). In the control group a 44% increase was seen following the training task. This increase might reflect an increase in inhibitory output from the cerebellum to S1 following learning. Interestingly the intervention group did not show similar changes. The group that received the sensory perturbations did show an increase in peak amplitude but to a much smaller extent that the controls. This finding is similar to the previous study which utilized similar disruptive stimuli in that no change in the intervention group was seen for the N24 (Dancey et al., 2016a). The author's hypothesis was that this type of stimulus might actually negate the changes that occur. Another possible explanation for this might be that since the cerebellum detects and corrects for errors in movement (Doyon, Penhune, & Ungerleider, 2003), the greater baseline accuracy of the intervention group may have decreased cerebellar activity. Whether this is due to increased attention or other factors is unclear, since the initial error was so low for the intervention group, the cerebellum would not have had as many corrections to produce, leading to a decrease in cerebellar activity. This is consistent with literature that suggests as task performance increases, cerebellum activity decreases (Doyon et al., 2003). This decrease in activity is seen in other studies which used a similar task, but tested the dominant hand (Danielle Andrew et al., 2015; Baarbé et al., 2014). Therefore it is speculated that the sensory perturbation delivered in this study actually caused a shift in the program utilized by the non-dominant hand to one that is similar to the dominant hand in that internal models are generated and as learning continued since there was such a high sensory input to start, the need for cerebellar input decreased (Mutha et al., 2013; R. Sainburg & Kalakanis, 2000; Schabowsky et al., 2007).

The N30 peak, is suggested to represent activity in sensorimotor integration pathways (Rossi et al., 2003; Valeriani et al., 1998; Waberski et al., 1999). More recent work has localized the N30 to the frontal and prefrontal areas of the cortex (Lelic et al., 2016). Studies which used similar tasks saw changes in the N30 peak which would reflect increasing level of sensory motor integration (SMI) (Danielle Andrew et al., 2015; Dancey et al., 2016a), however we did not see

this to the same extent. In both of our groups there were slight increases in the peak amplitude following the training task but these were not significant. This does suggest an increase in SMI following the task and follows a trend from previous work using similar sensory perturbations (Dancey et al., 2016a). One possible explanation for this is that due to the nature of the task, there may have been a gating effect on the N30 peak. Literature has shown that opposing movements of the thumb or hand ”gate” or attenuate the N30 peak (A. M. Cebolla et al., 2009; Kaňovský et al., 2003). This gating effect during these finger movement has been hypothesized to originate from the motor cortex (Waberski et al., 1999). Another reason might be that the task itself is too simple. With technology the way it is today, the use of both thumbs is much more common, meaning the level of complexity needed to change SMI may not have been reached in this task.

The rate of learning was slightly different between the groups. The intervention group began with 102% error and decreased to 81% at post-test measurements. The control group decreased from 124% to 85% in the same time. The control group made more errors initially but learned better from the task. In a previous study using a similar task except using a different intrinsic hand muscle (first dorsal interosseous) of the dominant hand there was a similar drop from around 170% to 140% (L. Holland et al., 2015). This would suggest that the control group learning was similar to that of other controls who experienced no altered sensory input.

An important question to ask is whether sensory perturbations delivered via painful stimuli strong enough to perturb the sensory system. Based on the outcome of this study the results are mixed. No significant interactive effects were observed for any of the SEP peaks. This might suggests that unlike visuomotor rotations, the change in sensory stimulus was not strong enough to elicit a true perturbation to the system (Mutha et al., 2013). This reflects in the scores of the NPRS where the intervention group only achieved a rating of 2.72 out of 10 prior to motor training. The effect may not of lasted long enough either, since following motor training the group average was down to 1.66 out of 10. However it has been reported that a change in 2 points on the NPRS represents clinically meaningful changes (Childs, Piva, & Fritz, 2005). This differs from a previous study by Dancey et al (2016) which showed average NPRS ratings of 4 following application and 3 following training. The level of pain in the present study

appeared to be strong enough to increase learning, as seen by the increased accuracy, but not strong enough to promote neurological changes that have been seen to accompany this increase in performance (Dancey et al., 2016a; Dancey et al., 2014). The cream itself was applied over the lateral aspect of the left elbow as opposed to the working APB muscle of the left hand. This was done to avoid interrupting the working muscle and to ensure the task itself did not cause the participants pain. This may explain why some of the effects were not as large as previous studies involving the dominant hand.

Strengths

The major strength in this study is its one of the first of its kind to utilize a pain induced perturbation to the non-dominant hand. This study keeps with other literature in that perturbations cause an increase in accuracy, and also sheds new light on to the understanding of the nervous system in response to a new type of perturbation.

Limitations

A major limitation to this study is sample size and it is quite likely that type II errors occurred as a result of this. Some datasets had unstable peripheral conditions (N9 variance greater than ±10%) and had to be excluded. The application of the cream causes the movement of the upper arm away from the baseline recording position more often than with other protocols. This increases the likelihood of the N9 peripheral volley being disturbed, despite careful repositioning. Future work should consider restraining the arm during the application process to avoid any unnecessary movements of the arm.

Conclusions

The results of this study may suggest that perturbations evoked by painful stimuli are enough to stimulate learning and increase accuracy. However, they appear to be too weak to elicit significant changes in processing within the cortex. Future research should look to increase the level of sensory perturbations and observe the effects following movement and motor training.

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Thesis Summary

The first study of this thesis showed significant differential SEP peak changes in the dominant and non-dominant limbs, accompanied by significantly greater accuracy at performing the motor task by the non-dominant limb. Taken together these results present evidence for underlying neurological differences in the dominant and non-dominant hemisphere with respect to somatosensory processing during motor control. This expands on research in the area of laterality by linking our understanding of cortical and hemispheric differences first brought about by early brain studies (Broca, 1861, 1863) with our understanding that when completing a motor task, there are visually observable differences in the way our limbs complete these tasks (Mutha et al., 2013; R. Sainburg & Kalakanis, 2000; Schabowsky et al., 2007; Vivek Yadav & Sainburg, 2014).

A potential explanation for the results above is that the neural generators associated with the SEP peaks that represent areas of sensorimotor integration and pathways from the cerebellum are active at different levels for the dominant and non-dominant upper limbs. This is evident from the results of manuscript 1. The greater accuracy of the non-dominant hand may have a couple of explanations as well. The first being that the predominant control strategy utilized by the non-dominant limb is based around reactive mechanisms (feedback). This is known in literature to be a more accurate control strategy at the effect of an energy cost, as it uses much more energy (R. Sainburg & Kalakanis, 2000). The second is the level of attentional resources that are dedicated to the non-dominant limb. Much of the world is designed for right handed people, so when asked to use the left hand (non-dominant hand) greater attention may need to be given to the task, making it more accurate. More research is needed to determine if these pathways are what cause the rise of different motor control patterns between the limbs, or if it has to do with development of preferred handedness which leads to adaptation of the nervous system.

When a sensory perturbation was introduced to the non-dominant hand in manuscript two, differential SEP peak changes were observed, as well as a significantly greater accuracy for the intervention group. Though the neurophysiological data did not reflect changes to the same

degree, there is suggestion that there are some lateralized differences in early somatosensory processing when compared to previous research that used a similar task and protocol with the dominant hand (Dancey et al., 2016a). The intervention group was more significantly accurate at baseline, keeping with this literature as well. This might be explained by the use of a reactive mechanism, in that there is increased sensory input to a feedback system, making it more active, or creating an environment that stimulates greater attention. The results of manuscript 2 specifically show that sensory perturbations may not be as effective at disrupting motor control or stimulating adaptation as mechanical perturbations are, but there are differences in somatosensory processing during motor learning in the presence of altered sensory input for the non-dominant hand as compared to previously published work in the dominant hand.

Together, both manuscripts add new insight into the literature on laterality and motor control. There are underlying neurophysiological differences between the hemispheres that may partially reflect the neural substrate responsible for the observable differences in motor performance and adaptation between the hemispheres. This becomes important in a rehabilitation setting where lateralized disruptions to motor control can be seen (ie. Stroke). Stroke patients often show deficits in each hemisphere that follow the lateralized control mechanisms seen in a healthy population (Schaefer, Haaland, & Sainburg, 2007). The use of rehabilitation plans that can train the limbs in their preferred motor control state might have the potential to increase the gains made in recovery. The other implication could be dependent on which limb was injured. Loss of dominant limb function would be detrimental to the individual, so rehabilitation which assists the non-dominant limb to convert to more of a dominant control mechanism (predictive based movements), this might prove more beneficial for the patient in the long run. Ultimately, there is more research needed to determine if these suggestion are viable. In our age of increased bilateral technology use, a better understanding of the differences in control mechanisms between the hemispheres could aid the design of technology to make it more user friendly and less likely to lead to injury.

In conclusion, the results of this thesis show that the differences in motor control between the limbs is reflected in neurophysiological measures, specifically early SEPs; , and the introduction of altered sensory input in the form of cutaneous pain causes changes to early

somatosensory processing, but actually improves motor performance, similar to previous studies involving the dominant limb.

Future work should use explore different perturbations and directly compare perturbations that will affect feedback and feedforward control mechanisms to better understand laterality differences in mechanisms of motor control and learning. Coupling this with whole head EEG analysis would allow for the evaluation of cortical neural generators that may be difference between the hemispheres, as well as evaluations of the pathways associated with them and ultimately lead to better understanding of lateralized control mechanisms in the upper limbs.

Section 3: Appendix

Appendix 1: Manuscript 1 Consent Form

Professor Bernadette Murphy

University of Ontario Institute of Technology

Faculty of Health Sciences

2000 Simcoe St. North

Oshawa, Ontario

CANADA L0B 1J0

Email: Bernadette.Murphy@uoit.ca

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

Title: ***Exploring lateralized somatosensory processing using Somatosensory Evoked Potentials (SEPs) – January 2016.*** **This study has received ethical approval from the UOIT ethics committee (REB# 07-072 & 07-073)**

This study is being conducted by Dr. Paul Yielder and Dr. Bernadette Murphy, in conjunction with MHSc candidate Ryan Gilley and fourth year practicum research students from the Faculty of Health Sciences at the University of Ontario Institute of Technology (UOIT), in Oshawa, Ontario, Canada.

Rationale for Research: Research has found that neck pain is a significant burden and affects 30 to 50% of people every year. Research is also showing that neck pain affects the way that people move and their awareness of head and upper arm positioning.

The research we are doing is showing how the brain responds to neck pain. We want to show how neck pain affects movement, as well as the ability to properly respond to outside sources of stimuli.

The other reason we are completing this research is because chronic conditions have become increasingly a problem. Our hope is that this research will show responses of healthy participants. This will provide important clues to how the brain functions normally which is important to know how the brain may be re-wired because of neck pain. This will help us to know why neck pain is a chronic problem and how interventions may work to prevent or reverse the cycle of chronic pain for normal function and improved health outcomes.

Information for participants: To complete this research, we will perform a Pre-Test SEPs measurement, and then each participant will be randomly sorted into one of two groups: one group using the LeapTrace

tracing task, and the other group using the Unity trajectory task. Each group will then have a Post-Test SEPs measurement taken.

We are seeking people with no known neurological conditions who are between 18 and 50 years of age. To participate in this study you must complete an eligibility checklist in conjunction with one of the researchers to ensure you are eligible to participate. You will also be given a chance to review the details of the study and ask any questions you may have.

Each evaluation session will take approximately 2-3 hours and you will be given a chance to ask questions. We will provide you with a bonus 1% in one of your classes, selected from a pre-determined list of classes.

Your participation in this study is entirely voluntary (your choice), and you are free to decline taking part in this study. You may also withdraw from the study at any time without giving a reason. This will in no way affect your academic progress. Questions about your rights as a volunteer can be made to the Compliance Officer at 905 721 8668 ext. 3693 or compliance@uoit.ca .

Measurement sessions: Should you agree to participate, we will need you to attend one measurement session, which will last 2-3 hours.

Measurement procedures:

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 or elbow, and over your neck, shoulder and scalp. You may experience some mild discomfort as your skin is prepared for the electrodes by gently shaving and then wiping the area with alcohol. The electrodes over your neck, shoulder 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 and/or forearm muscles by passing mild electrical current through them. This creates a mild tingling sensation on the skin over the nerve. This is not painful but may feel quite strange 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.

We will also ask you to complete a task that involves tracing an image or displayed on a computer screen. We will ask that you complete this activity as accurately and quickly as possible, and once you are finished, if you would like we can give you a progress report on your performance.

Risks and benefits

The benefits of participating in this study is that you will learn more about research techniques at UOIT and the somatosensory systems in the CNS. You will also be aiding our understanding of hand dominance and laterality.

The surface EMG techniques have low risks such as the person getting a skin irritation from the alcohol swab or electrode gel. These are uncommon and not serious. You may also experience mild discomfort as your skin is prepared for the electrodes by shaving the skin with a razor, or lightly abrading with special tape, and then wiping the area with alcohol. If irritation persists, we recommend that students go to campus health services (and contact the researcher). 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.

If the information you provide is reported or published it is done in a way that does not identify you as its source. The data will be stored in a locked area at UOIT for seven 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. Once you have completed the chiropractic care, your data cannot be withdrawn. Taking part in this study is voluntary and your decision to take part

in this study (or not) will in no way influence your academic progress or relationship with your chiropractor and/or teacher.

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 Dr Bernadette Murphy, a Professor at the University of Ontario Institute of Technology, Faculty of Health Sciences, 2000 Simcoe St North, Oshawa, Ontario, L1H 7K4

Phone (905) 721-8668 ext 2778 Fax (905) 721-3179

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 academic progress, irrespective of whether or not payment is involved.

- This consent form will be kept in a locked area at UOIT, Oshawa, Ontario for a period of seven years before being destroyed.

- The data collected in this study will be coded so that it is confidential from the consent form and stored in a locked area at UOIT, Oshawa, Ontario for a period of seven years before being destroyed.

I, ……..... agree to take part in this research.

- 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 January 2016 for volunteers taking part in the study designed to investigate the comparison between motor learning tasks. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

- I will be attending one session where measurements will be taken of the electrical activity in my brain following electrical stimulation of the muscles in my hand/forearm

- I have completed an eligibility checklist to ensure I am eligible to participant in this research.

- I have completed a TMS safety checklist.

- 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 chiropractic care portion of the study.

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

(tick one)

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

Signed …… Date ……..

Contact numbers of main researchers:

Dr Bernadette Murphy, Phone: + 905 721-8668 ext 2778

RESEARCHER TO COMPLETE

Project explained by: _____

Project role: _____

Signature: _____ Date: _____

Appendix 2: Manuscript 2 Consent Form

Professor Bernadette Murphy

University of Ontario Institute of Technology

Faculty of Health Sciences

2000 Simcoe St. North

Oshawa, Ontario

CANADA L0B 1J0

Email: Bernadette.Murphy@uoit.ca

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

Central sensitization evokes changes in the properties of nerve conduction

Purpose of the Study

The physiologic mechanisms of pain are poorly understood. Central sensitization in an important, if not fundamental, mechanism in expression of pain yet there is currently no objective measure of central sensitization. Central sensitization is defined as an 'increased excitability' of nerves in the central nervous system. The purpose of this study is to investigate the effect of central sensitization on the characteristics of nerve conduction in humans. Specifically, we are interested in finding out what, if any, changes occur to the properties of nerve impulses after sensitization as it may provide insight into novel methods of quantifying sensitization. We are also interested in understanding if sensitization affects motor performance, that is, the way your muscles perform when learning a novel task. You are invited to participate in this study being conducted by Dr Bernadette Murphy (Faculty of Health Sciences, University of Ontario Institute of Technology). It has received Ethical Approval from the University of Ontario Institute of Technology (REB# 11-067).

Procedure

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

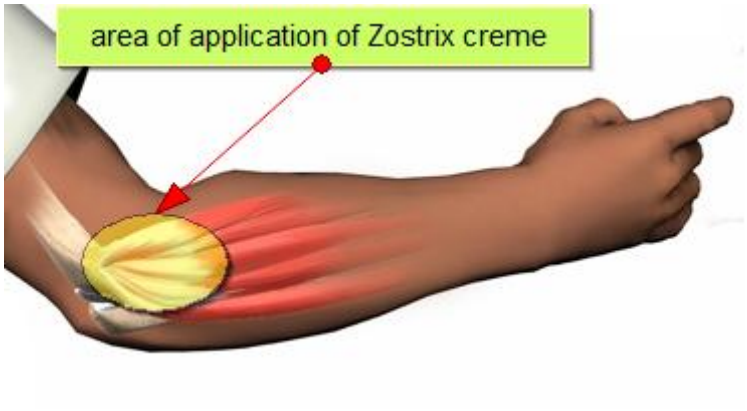
We will require access to your arm, shoulder, upper back and neck regions; please wear appropriate clothing that allows for exposure of these areas. In the event you do not have such clothing, you will be provided appropriate gowns for this study. In addition, you will have complete and sole privacy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

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

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

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

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



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

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

~~**Typing task intervention**~~

~~Some experiments will include a typing task which will take place after the cream has been applied. The intervention will consist of a repetitive typing task where you will be required to press keys on an external numeric keyboard with your thumb for a period of 20 minutes. There will be sequences of four letters arranged in random order that come up on a computer monitor and you will be asked to reproduce them with the numeric key pad. We will be monitoring the typing rate and number of errors to determine the effects of capsaicin on your ability to type these sequences.~~

Tracing task intervention

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

~~**Cortisol**~~

~~Cortisol is a steroid hormone released during stressful episodes such as acute pain. Cortisol elevation is a normal part of the physiological response to stress. Elevations in cortisol production is linked with changes in the way the brain functions which can affect task performance. The researchers will use swabs under your tongue to collect your saliva three times throughout the experiment. These samples of your saliva (spit) will then be put in the freezer and will be later tested at a laboratory for the stress hormone cortisol.~~

Potential Risks and Discomforts

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

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

Potential Benefits to Participants and/or to Society

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

☐ email_____

☐ fax_____

☐ written _____

Compensation for Participation

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

Confidentiality

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

Participation and Withdrawal

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

Rights of Research Participants

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

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

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

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

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

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

(tick one)

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

_____ __ _____

(Name of Participant) (Date)

_____ _____

(Signature of Participant)/ (Signature of Researcher)

Appendix 3: Edinburgh Handedness Inventory

Edinburgh Handedness Inventory

Please indicate your preferences in the use of hands in the following activities *by putting a check in the appropriate column*. Where the preference is so strong that you would never try to use the other hand, unless absolutely forced to, *put 2 checks*. If in any case you are really indifferent, *put a check in both columns*.

Some of the activities listed below require the use of both hands. In these cases, the part of the task, or object, for which hand preference is wanted is indicated in parentheses.

Please try and answer all of the questions, and only leave a blank if you have no experience at all with the object or task.

Task	Left		Right	
1. Writing				
2. Drawing				
3. Throwing				
4. Scissors				
5. Toothbrush				
6. Knife (without fork)				
7. Spoon				
8. Broom (upper hand)				
9. Striking Match (match)				
10. Opening box (lid)				
Total (count checks in both columns)				

Difference	Cumulative TOTAL	Result

Scoring:

Add up the number of checks in the "Left" and "Right" columns and enter in the "TOTAL" row for each column. Add the left total and the right total and enter in the "Cumulative TOTAL" cell. Subtract the left total from the right total and enter in the "Difference" cell. Divide the "Difference" cell by the "Cumulative TOTAL" cell (round to 2 digits if necessary) and multiply by 100; enter the result in the "Result" cell.

Interpretation (based on Result):

below -40 = left-handed

between -40 and +40 = ambidextrous

above +40 = right-handed

Appendix 4: TMS Safety Checklist

TMS safety checklist:

The following questions are to ensure it is safe for you to have TMS applied. If you answer yes to any of the questions below, we may need to exclude you from TMS experiments.

QUESTION	ANSWER	
1. Do you suffer from epilepsy, or have you ever had an epileptic seizure?	Yes	No
2. Does anyone in your family suffer from epilepsy?	Yes	No
3. Do you have any metal implant(s) in any part of your body or head? (Excluding tooth fillings)	Yes	No
4. Do you have an implanted medication pump?	Yes	No
5. Do you wear a pacemaker?	Yes	No
6. Do you suffer any form of heart disease?	Yes	No
7. Do you suffer from reoccurring headaches**?	Yes	No
8. Have you ever had a skull fracture or serious head injury?	Yes	No
9. Have you ever had any head surgery?	Yes	No
10. Are you pregnant?	Yes	No
11. Do you take any medication or use recreational drugs (including marijuana)*?	Yes	No
12. Do you suffer from any known neurological or medical conditions?	Yes	No

Comments _____

_____

_____

Name _____

Signature _____

Date _____

*Note if taking medication or using recreational drugs please read through the medication list on the next page to see if you use contraindicated drugs or medications. You do not need to tell the researcher which medications or drugs you use, unless you wish to. However, all researchers have signed

confidentiality agreements and this information will not recorded in writing, if you do wish to discuss this issue.

**Dr. Murphy will meet with participants who answer yes to this question to seek further information.

Medications contraindicated with magnetic stimulation:

1) Tricyclic antidepressants

Name	Brand
amitriptyline (& butriptyline)	Elavil, Endep, Tryptanol, Trepiline
desipramine	Norpramin, Pertofrane
dothiepin hydrochloride	Prothiaden, Thaden
imipramine (& dibenzepin)	Tofranil
iprindole	-
nortriptyline	Pamelor
opipramol	Opipramol-neuraxpharm, Insidon
protriptyline	Vivactil
trimipramine	Surmontil
amoxapine	Asendin, Asendis, Defanyl, Demolox, Moxadil
doxepin	Adapin, Sinequan
clomipramine	Anafranil

2) Neuroleptic or Antipsychotic drugs

A) Typical antipsychotics

Phenothiazines:	Thioxanthenes:
o Chlorpromazine (Thorazine)	o Chlorprothixene
o Fluphenazine (Prolixin)	o Flupenthixol (Depixol and Fluanxol)
o Perphenazine (Trilafon)	o Thiothixene (Navane)
o Prochlorperazine (Compazine)	o Zuclopenthixol (Clopixol and Acuphase)
o Thioridazine (Mellaril)	• Butyrophenones:
o Trifluoperazine (Stelazine)	o Haloperidol (Haldol)
o Mesoridazine	o Droperidol
o Promazine	o Pimozide (Orap)
o Triflupromazine (Vesprin)	o Melperone
Levomepromazine (Nozinan)	

B) Atypical antipsychotics

Clozapine (Clozaril)	Quetiapine (Seroquel)
• Olanzapine (Zyprexa)	• Ziprasidone (Geodon)
Paliperidone (Invega)	• Amisulpride (Solian)
• Risperidone (Risperdal)	

C) Dopamine partial agonists: Aripiprazole (Abilify)

D) Others

Symbyax - A combination of olanzapine and fluoxetine used in the treatment of bipolar depression.

Tetrabenazine (Nitoman in Canada and Xenazine in New Zealand and some parts of Europe

Cannabidiol One of the main psychoactive components of cannabis.

Regular Cannabis use more often than once per week and/or cannabis use in the past 4 days.

Regular use of other recreational drugs, or single episode within the past three weeks.

Appendix 5: Confidential Health History

UOIT
CHALLENGE INNOVATE CONNECT

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

RESEARCH STUDY CONFIDENTIAL HEALTH HISTORY

Subject CODE: _____

How old are you?

You are: Male □ Female □

Are you: Left Handed □ Right Handed □

Do you play a musical instrument Yes □ No □

If yes, how many times a week?

Do you play competitive sports? Yes □ No □

If yes, please indicate what sport and how often?

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

How long have you had the above pain?

Is your pain getting: better □ worse □

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

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

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

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

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

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

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

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

Yes □ no □

Do you have a history of:

-Use of anticoagulant medication or therapy yes □ no □

-Stroke or transient ischemic attacks yes □ no □

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

-Whiplash within the last year yes □ no □

-Cervical spine surgery yes □ no □

-Clinically important hypertension yes □ no □

-Connective tissue disorders yes □ no □

-Focal neurological symptoms such as:

Dizziness/vertigo	yes □ no □
Tinnitus (ringing in ears)	yes □ no □
Blurred vision	yes □ no □
Sensory/motor disturbance	yes □ no □