Cortical and Cerebellar Motor Processing Changes Subsequent to Motor Training and Cervical Spine Manipulation

By

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Abstract

Chronic neck pain, including subclinical neck pain (SCNP), is a significant problem that places a burden on the healthcare system. Chiropractic manipulation has shown not only to be effective in treating symptoms of neck pain, but also in providing a neuromodulatory effect on the central nervous system. The motor cortex and cerebellum are thought to be important neural structures involved in motor learning and sensorimotor integration (SMI), and are therefore key structures to investigate how SMI is changed in a SCNP group following chiropractic care. Motor sequence learning (MSL) has also been shown to provide alterations in cerebellar projections to the motor cortex. Therefore, the studies in this thesis set out to determine if it was possible to induce both cortical and cerebellar learning, and if chiropractic care could alter motor output via transcranial magnetic stimulation measures to facilitate this learning.

The study's results suggest that in a healthy group of subjects there is alteration in the intracortical inhibition of the motor cortex and no significant change in the cerebellum, following MSL. However, the results also suggest that in a SCNP group, there is a modulation of the cerebellar connections to the motor cortex but no effect specific to the motor cortex following both MSL and chiropractic manipulation. Therefore, these findings suggest that people with intermittent neck pain have concomitant changes in SMI and could manifest as clinical symptomology.

Key Terms

Sensorimotor Integration, Motor Sequence Learning, Cerebellum, Transcranial Magnetic Stimulation, Chiropractic Manipulation

Declaration

I, Julian Daligadu, declare that this thesis represents my own work, except as acknowledged in the text, and that none of this material has been previously submitted for a degree at the University of Ontario Institute of Technology or any other university. The contribution of supervisors and other to this work was consistent with the UOIT regulations and policies. Research for this thesis has been conducted in accordance to UOIT`s Research Ethics Committee.

This thesis is presented in the evolving modern style emphasizing preparation for publication. The two laboratory based studies have been reported and presented in Section Two as draft journal manuscripts to be submitted for peer review and publication in the Journal of Electromyography and Kinesiology. These articles constitute the original work performed with the approval of human subjects based on the literary and technical themes offered in Section One of the thesis manuscript.

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Thanks to Dr. Kevin Power and Dr. Paul Yielder whose guidance and knowledge assisted me in critically thinking about my thesis and the protocols used.

To all those who volunteered for my research, I am especially thankful. Cerebellar stimulation may not be the most pleasant of techniques and so I thank you for participating with such enthusiasm.

Thanks to the Ontario Government and the University of Ontario Institute of Technology for sponsoring me for the past two years of my Masters studies.

To my wonderful niece Malena, thanks for being a bright spot in my day when things were hectic.

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List of Abbreviations Used

CBI: Cerebellar Inhibition

CS: Conditioning stimulus

CSP: Cortical Silent Period

EHI: Edinburgh Handedness Inventory

EMG: Electromyography

$GABA_A$: Gamma aminobutyric acid A

ISI: Interstimulus Interval

IwF: I-wave Facilitation

LICI: Long Interval Intracortical Inhibition

M1: Primary Motor Cortex

MEP: Motor Evoked Potential

MSL: Motor Sequence Learning

MSO: Maximal Stimulator Output

RTh: Rest Threshold

S1: Stimulus 1

S2: Stimulus 2

SCNP: Subclinical Neck Pain

SICF: Short Interval Intracortical Facilitation

SICI: Short Interval Intracortical Inhibition

SMI: Sensorimotor Integration

Th: Threshold

TMS: Transcranial Magnetic Stimulation

TSC: Transcranial Magnetic Stimulation Checklist

TS: Test Stimulus

Section 1: Literature Review

Chapter 1 - Introduction to Neck Pain, Cortical Plasticity and Chiropractic Care

Chronic neck pain is a common and significant problem which affects about 30-50% of people every year and places a great burden on healthcare systems (Hogg-Johnson et al. 2008). There has recently been an increase in studies that report evidence for altered neuromuscular and proprioceptive function in patients with neck and back pain, with discussion and suggestion as to why pain becomes chronic (Gogia 1994; Bränström et al. 2001; Falla et al. 2004; Stapley et al. 2006). Chiropractic intervention is one of the most frequently applied treatments for neck and back pain, however the neurophysiological mechanisms that underlie the therapeutic effect resulting in the alteration of the pain pathways and the subjective pain experience is poorly understood. Previous research has shown that chiropractic adjustments can induce changes to the central nervous system which includes excitability, cognitive processing, sensory processing, and motor output (Murphy et al. 1995; Herzog et al. 1999; Suter et al. 1999). This combination of effects suggests that chiropractic intervention may provide a positive modulation on the neurophysiological system and this may play a role in the effect that it has on neck pain.

A mechanism proposed by Haavik-Taylor and Murphy (2007) postulates that areas of spinal dysfunction results in input that alters afferent feedback and could therefore be responsible for malign central plastic changes due to altered discordant sensorimotor integration. By implementing a high-velocity, low-amplitude manipulation technique to the area of spinal dysfunction, it is proposed that the altered afferent feedback from the spine and limbs may be normalized, thus resulting in normalized sensorimotor integration. This hypothesis and sequence of reactive changes is supported by work using

transcranial magnetic stimulation (TMS) (Haavik-Taylor and Murphy 2007), measuring the balance of motor cortical output to a defined target muscle, and also somatosensory evoked potentials (SEPs) (Haavik-Taylor and Murphy 2007; Taylor and Murphy 2010), measuring the processing of sensory information by the brain, has indicated that cervical spine adjustments can alter sensorimotor integration of the upper limb.

The cerebellum is a neural structure that is actively involved in motor learning and sensorimotor integration. Studies have shown that the cerebellum is associated with motor learning (Doyon et al. 2002; Doyon et al. 2003; Manto and Bastian 2007; Molinari et al. 2007) and is responsible for receiving and integrating the incoming signals from the joints of the neck and spine (Manzoni 2005; Manzoni 2007). There is also evidence that the cerebellum plays a role in plastic changes and the adaptation of motor circuits (Doyon and Ungerleider 2002; Apps and Garwicz 2005). Recent work has shown that there is a modulation of motor cortex excitability due to a reduction of cerebellar modulation in both patients suffering from focal hand dystonia (Brighina et al. 2009) and migraine with aura (Brighina et al. 2009). Therefore, it is fundamental that the cerebellum as a key neural structure is investigated with regard as to how chiropractic intervention alters sensorimotor integration to disclose the mechanism behind spinal adjustments. This project`s goal is to investigate if there is modulation in cerebellar output from neck pain patients, and if spinal manipulation has an effect on sensorimotor integration.

Chapter 2 - Inclusion/Exclusion Criteria for Literature Search

The contribution of chiropractic intervention in the alteration of neural components during the treatment of patients across a broad scope of neural complaints is sparsely represented in the literature. There are even fewer articles regarding these neural alterations in neck pain patients, and no known articles defining the role of the cerebellum in this process. In order to provide an unbiased and accurate review of the literature, evidence needed to be extracted, evaluated, and organized into a comprehensive representation of the current state of knowledge. This was accomplished by systematically using a set of inclusion/exclusion criteria when searching for literature. Keywords used in the literature search were developed from the research question and were: Cerebellum, chiropractic care, neck pain, motor sequence learning, and transcranial magnetic stimulation. Databases used for the search included Google Scholar and Science Direct. A "hand search" of articles was also performed following the attainment of the most significant articles from the literature by looking at the references that significantly supported their studies. Gray literature was also used as a resource to determine basic anatomy and physiology that corresponds with the motor cortex, cerebellum, and their associated pathways.

The inclusion/exclusion criteria were set to include relevant literature that would help to identify and solve the research question that was developed for this project. The article must have been written in English because that is the only language that would be comprehensible to the researchers performing this project. It was important that the data from one study not overlap another study because this would test a greater subject pool,

and therefore provide greater strength to the literature review. This analysis also specified human subjects in order to provide comparable data between different research projects. Techniques that were used to attempt to uncover the neural correlates needed were limited to TMS, somatosensory evoked potentials, electroencephalography, and/or magnetic resonance imaging because these are techniques that have been shown to accurately uncover details about the brain and its activity as specific techniques but also in relationship to each other in various research design approaches. Also, this emphasized the recency of the literature (1990-2012) as these techniques are relatively modern.

Chapter 3 - Functional Neuroanatomy

Although several areas of the brain are known to directly influence the activity of the spinal cord through their descending connections, the main pathway that is activated during voluntary movement is the corticospinal tract. The next section aims to discuss the role of the structures involved in this pathway that allow for movement to occur in the human body.

3.1 – The Primary Motor Cortex

In the early 20th century, Korbinian Brodmann distinguished 52 anatomically and functionally distinct areas of the human brain by examining these regions cyto-architecture. This led to the well-established Brodmann classification system, which identified these structurally different areas. Specifically, Brodmann's area 4 was found to be unique from other regions of the brain due to its functional capability to control motor movements and ultimately came to be known as the primary motor cortex. The primary motor cortex (M1) is located in each frontal lobe, directly anterior to the central sulcus in the precentral gyrus (Jenkins et al. 2007). Each region in the primary motor cortex controls voluntary actions of specific muscles or groups of muscles. Therefore, this region of the brain is responsible for movement initiation and coordination of movements for fine motor skills (Magill 2007). This occurs because they have motor neurons that connect axons to skeletal muscles throughout the entire body. The motor neurons act as the control center, while the axons relay the messages (or stimuli) down to the affected muscles. M1 is organized somatotopically: meaning that there is a greater representation of cortical area dedicated to highly innervated regions of the body (Magill 2007). These areas of greater representation include the hand and face regions of the body, as we use

the muscles in these parts of the body to perform finely tuned movements, such as to give a facial expression or to move your fingers to pick an object up.

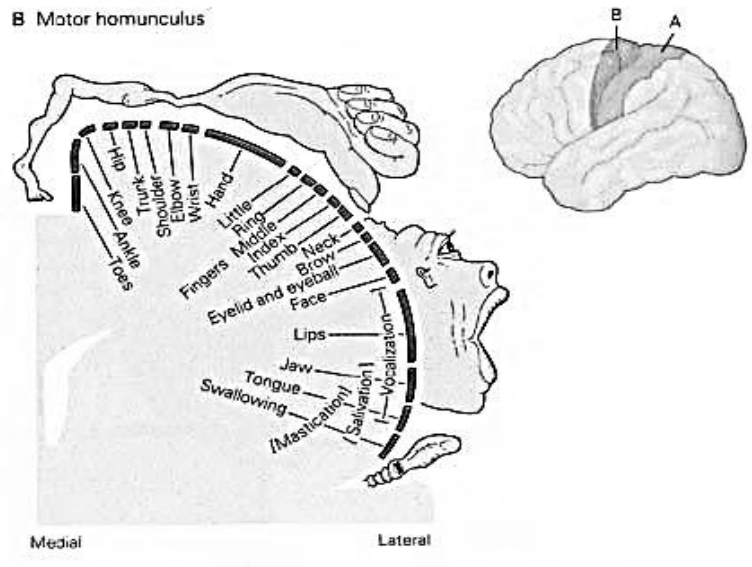

Figure 1. The motor homunculi illustrating the location and amount of cortical area dedicated to specific skeletal muscles on the body. Adapted from (Kandell et al. 2000).

3.2 – The Corticospinal Tract

The corticospinal tract (or the pyramidal tract) consists of about a million axons (DeMyer 1959), of which 60% originate from the primary motor cortex (Magill 2007), and most decussate (crosses over to the other side of the body) at the medulla. Because of the cross over in the brainstem, the muscles on each side of the body are controlled by the opposite hemisphere. The other 40% of the fibers originate from numerous other areas in the cerebral cortex. These include the premotor areas, the primary sensory cortex, and areas 5 and 7 of the parietal cortex (Porter 1993; Rothwell 1994). Therefore, due to the large amount of cortical representation that is involved in the corticospinal pathway, it is logical to accept that transcranial stimulation over a large amount of areas in the brain would result in the activation of this pathway.

Although 90% of corticospinal fibers decussate at the medulla, about 10% of the fibers do not cross until they reach the level of the spinal cord where they end (Magill 2007). In the spinal cord, some corticospinal fibers form synapses with interneurons, which allows for the coordination of larger groups of muscles to perform more gross movements (Büschges and El Manira 1998). Other fibers make single synapses with motor neurons that are involved in controlling fine movements (Pollok et al. 2006). The corticospinal tract is also modified by ascending sensory information, which includes visual and proprioceptive information. This allows for the ability to note the environment and situation one is in, and to smoothly execute movements (Doyon et al. 2003).

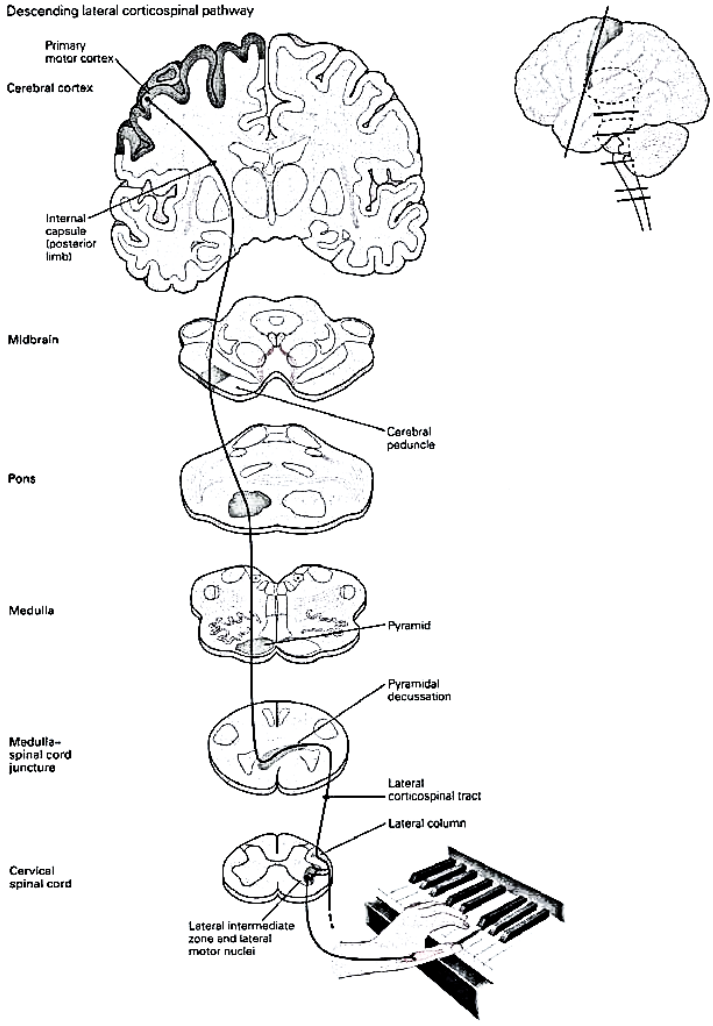

Figure 2. The corticospinal pathway illustrating the fibers originating in the primary motor cortex, decussating at the medulla, and terminating in the ventral horn of the spinal cord. Located in the ventral horn are the lower motor neurons which act as the final common pathway for transmitting neural information to skeletal muscle. Adapted from (Kandell et al. 2000).

3.3 - The Cerebellum

The cerebellum is located in the posterior fossa of the skull, dorsal to the brainstem and below the occipital pole of the cerebral hemispheres. It is composed of a 1-mm outer layer of grey matter that composes the cerebellar cortex and forms a continuous layer over the entire outer surface. A dense mass of white matter is located internally to the cortex which contains four pairs of cerebellar nuclei in the ventral aspect: the dentate, the emboliform, the globose, and the fastigial nucleus. One identifying feature of the cerebellum is that its surface contains many parallel fissures that run transversely. Two main fissures separate the cerebellum into three lobes. The primary fissure on the dorsal surface separates the anterior and posterior lobes, while the posterolateral fissure on the ventral surface separates the posterior lobe from the flocculonodular lobe. A longitudinal band of less dense cortex, known as the vermis, forms a medial divide that separates the cerebellum into two lateral hemispheres. Each hemisphere can be further divided into intermediate and lateral regions (Kandell et al., 2000).

The cellular structure of the cerebellar cortex consists of three layers consisting of only five types of neurons. Four of these neurons are inhibitory (stellate, basket, Purkinje, and Golgi), while one is excitatory (granule cells). The two main afferent inputs into the cerebellum are mossy fibers and climbing fibers. Both types form excitatory connections with cerebellar neurons, however they terminate in different areas of the cerebellum and produce different firing patterns in the Purkinje neurons. Mossy fibers originate from nuclei in the spinal cord and brainstem and convey afferent information from the periphery and the cerebral cortex. Mossy fibers exert excitatory synapses on granule cells

within the cerebellar cortex and through the granule cells parallel fibers, they make connections with the dendrites of Purkinje cells. Climbing fibers originate exclusively from the inferior olivary nucleus and convey somatosensory visual or cerebral cortical information. Climbing fibers exert powerful excitatory influences on the Purkinje cells and deep cerebellar nuclei. Each climbing fiber synapses onto 1-10 Purkinje neurons, however individual Purkinje neurons only receive synaptic input from one climbing fiber (Kandell et al., 2000).

Purkinje cells are the main output neurons and have inhibitory connections with the deep cerebellar nuclei, which in turn provides an excitatory pathway to the motor cortex via the ventral thalamus (Allen and Tsukahara 1974). Therefore, Purkinje cell activation results in the reduction of excitatory output from the deep cerebellar nuclei to the motor cortex and it is modification to this pathway that is thought to result in the alteration of motor control (refer to chapter 4.3-4.4 for detailed description).

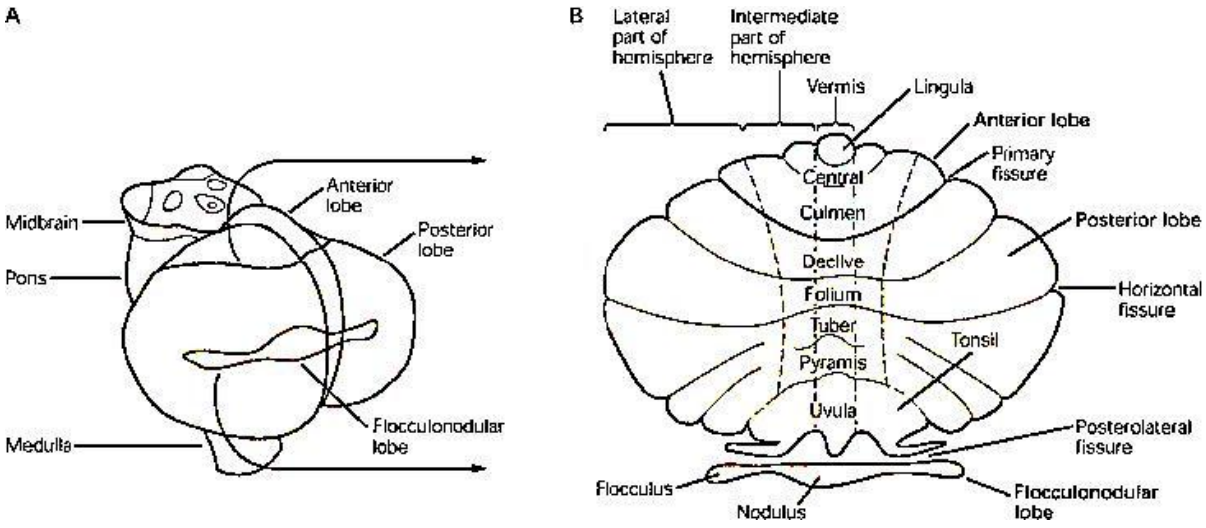

Figure 3. Anatomical divisions of the cerebellum. The vermis divides the cerebellum into two hemispheres, while the primary and posterolateral fissures divide this structure into three distinct lobes. Adapted from (Kandell et al. 2000).

Chapter 4 – Neural Plasticity

Until recently, the central nervous system (CNS) was viewed as an inflexible structure, with little capability for adaptation and modification. However, most current research exemplifies a paradigm shift with the central nervous system now being considered to be a 'plastic' or 'malleable' organ, capable of modification to account for external stressors or inputs (Celnik and Cohen 2004). This adaptive and reactive attribute of the brain has led to the term known as neural plasticity (or neuroplasticity).

4.1 – Mechanisms of Neural Plasticity

Plasticity can be defined as "any experience dependent enduring change in neuronal or network properties either morphological or functional" (Donoghue et al. 1996). It has been well documented that the central nervous system is capable of cortical reorganization following altered peripheral input (Kaelin-Lang et al. 2004; Tinazzi et al. 2004; Fratello et al. 2006). This can occur due to a decrease in behaviour or activity, such as the case in deafferentation or ischemia of the brain (Hallett et al. 1999; Murphy and Dawson 2002; Murphy et al. 2003; Tinazzi et al. 2003). It can also occur due to an increase in peripheral input, such as with repetitive muscular activity (Byl and Melnick 1997; Renner et al. 2005; Cirillo et al. 2010). This phenomenon is thought to occur because of alterations in the organization, function, and representation patterns of the neuronal connections throughout the associated areas of the brain (Cohen et al. 1999).

A fundamental consequence of neuroplasticity is that areas of the brain that are responsible for specific functions can be reorganized to move or apparently relocate to another location. This can occur within the scope of subjectively normal experience, however it also occurs during damage to, or the loss of neural tissue (Johansson 2004;

Ridding and Ziemann 2010). Conditions that cause cerebral lesions or tissue death, such as cerebral vascular accidents (stroke), are common neurologic disorders that correspond to plastic cortical changes (Ridding and Ziemann 2010). Despite permanent tissue loss, most surviving stroke patients regain various degrees of function with time (Johansson 2004). It is widely accepted that this occurs because surrounding regions of the brain develop and express association with repair processes of the functional deficits that were lost to the original insult and concomitant tissue damage. Good stroke recovery has been achieved by patients who have recruited task related areas of the brain rather than simply recruiting motor areas (Ward et al. 2003).

4.2 – Repetitive Movement and Neural Plasticity

The central nervous system and the motor cortex has demonstrated the capability to reorganize itself in response to motor performance and training, and represents an important contribution to repair processes and rehabilitative treatment (Tinazzi et al. 1998; Murphy et al. 2003; Liepert et al. 2004). Training, such as repetitive ballistic finger movements, has been shown to lead to encoding of the kinematic details of the practiced movement in the primary motor cortex (Classen et al. 1998; Takahashi et al. 2005; Cirillo et al. 2010). Further studies identified that NMDA receptor activation and GABAergic inhibition are neurochemical modulatory mechanisms operating in use-dependant plasticity of the motor cortex (Bütefisch et al. 2000). NMDA and GABA are both neurotransmitters, which act to either excite or inhibit neural activity respectively. Therefore by activating NMDA receptors to accept this neurotransmitter or by inhibiting GABA from releasing (GABAergic mechanisms), it is possible to facilitate use-dependent plasticity. While plasticity can occur via being exposed to a life-long amount of experiences and stimuli (long-term potentiation) (Tinazzi et al. 1998), it can also occur

very rapidly, within minutes to hours (Tinazzi et al. 1997). Therefore, this rapid technique can be used in order to induce motor cortical plasticity and investigate the response differences of the motor cortex to different stimuli.

4.3 - Motor Skill Acquisition

Developing novel motor skills involves the process of learning movements produced either in sequence or independently, and this trains the cortical and subcortical structures of the neural system to perform them effortlessly after repeated practice (Willingham 1998). According to Doyan & Benali (2005), there are five distinct phases when learning a motor skill. The fast (early) learning stage is when a considerable improvement in performance occurs following an initial single training session. The second stage is the slow (later) stage where following several sessions of training, there is a greater amount of improvement. The consolidation phase occurs following a latent period of more than 6 hours after the first training session and is signified by considerable improvements in performance without additional practice on the task. The fourth stage is the automatic stage and is identified when the learned skill requires minimal cognitive resources and is resistant to distraction or the effects of time. Lastly, the retention phase is the end goal of motor skill acquisition and is when the skill can be executed on command without further practice of the task.

Based on behavioural, lesion, and imaging studies investigating the neural components responsible for motor skill learning and plasticity, it has been demonstrated that interactions between cortico-striatal, cortico-cerebellar, and limbic system involvement are all necessary for motor skill acquisition. Doyon et al. (Doyon and Ungerleider 2002; Doyon et al. 2003), proposed a theoretical framework describing the plastic changes that

occur in the neural circuitry that occurs across learning stages. In the fast and consolidation learning stages, it has been shown that motor sequence tasks recruit both the cortico-striatal and cortico-cerebellar systems depending on the cognitive processes required during the task (Shadmehr and Holcomb 1997; Schendan et al. 2003; Aizenstein et al. 2004). However, in the automatic phase it has been shown that there is a shift from activity in the associative areas of the basal ganglia to the sensorimotor territories, while in the cerebellum, a shift occurs from activation of the cerebellar cortex to the dentate nucleus (Doyon et al. 2002; Floyer-Lea and Matthews 2004).

4.4 – Role of the Cerebellum in Neural Plasticity and Motor Learning

Patients with cerebellar conditions present with altered motor function and learning capabilities, and it is likely that disorders in motor learning contribute to impaired movement function for daily activities. It has been shown that the cerebellum is involved in the control of associative motor learning tasks such as the classical eyeblink conditioning response. Studies in cerebellar patients with degenerative cerebellar disorder and defined focal regions have demonstrated that the conditioning response in the eyeblink response is significantly reduced (Fortier et al., 2000; Gerwig et al., 2003, 2005). Using voxel-based lesion-symptom mapping techniques, it was shown that cortical areas of the anterior lobe may be involved in altered conditioning response timing and superior parts of the posterior lobe in stimulus association in humans (Gerwig et al., 2003, 2005).

Based on theoretical mathematical modelling of cerebellar function of Marr & Albus (Marr, 1969; Albus, 1971), it was proposed that climbing fiber input to Purkinje neurons modifies the response of these neurons to mossy fiber afferents and does so for a

prolonged period of time. This process was coined long-term depression and involves a process where climbing fibers weaken the parallel fiber-Purkinje cell synapses. According to this theory, altering the strength of mossy fiber-Purkinje cell synapses would select specific Purkinje cells to correct motor commands by integrating the afferent feedback of the movement. Therefore, each successive movement would allow the climbing fibers to weaken the parallel fiber-Purkinje cell synapses associated with an incorrect pattern of activity and allow for refinement of the appropriate movement. This theory is based off of Donald Hebb's original work on associative learning which stated that synaptic plasticity occurs during the presence of a repeated and persistent firing rate in a presynaptic neuron which subsequently stimulates a postsynaptic cell (Kandell et al. 2000). Therefore, in the cerebellum, the alterations between mossy fibers and Purkinje cells following motor training can be seen as Hebbian learning.

Chapter 5 - Transcranial Stimulation

Transcranial stimulation is a tool that is used to investigate the excitability of the motor cortex. It was first described in 1896 by Arsenne D'Arsonval (Geddes 1991) who identified that a magnetic field could stimulate certain areas of the brain to induce specific responses, such as inducing phosphenes (a sensation of light) and vertigo, when passing a current through a coil in which the subjects head was placed. This technique was rather invasive however, as patients had to be either being evaluated or undergoing surgery at the time. The next breakthrough in transcranial stimulation occurred in 1980 when Merton and Morton developed what is known as transcranial electric stimulation. They used a single high voltage shock, rather than a repetition of smaller shocks, and demonstrated that stimulation over the motor cortex could produce muscular activation of contralateral body parts (Merton and Morton 1980). However, the main problem with this procedure was that it caused a significant amount of pain as only a small amount of applied current flowed into the brain, while the rest went between the electrodes on the scalp causing local discomfort and contraction.

5.1 - Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) was created in the early 1980's (Barker et al. 1985), and is a safe way to painlessly stimulate the motor area of the brain that controls movement. This occurs due to a rapid discharge of current through a coil being placed over the scalp, which induces a magnetic field that is oriented perpendicular to the coil, and can reach values of up to 2 Tesla (Barker et al. 1985). This rapidly changing magnetic field induces stimulation of the neural tissue in the brain, namely the interneurons that synapse onto the neurons of the motor cortex. The magnetic field diminishes significantly with distance from the coil surface, which means that deeper

cortical structures in the brain (i.e. the thalamus and basal ganglia) remain inactivated (Rothwell 1997). There are many different types of TMS coils that can be used including round, figure-eight, and double cone coils. Round coils affect a large region of the brain, however are sensitive to the radius of the circle (Roth et al. 1991). Larger coils do not produce a very local stimulation, but are able to penetrate the motor cortex more deeply and can therefore activate deeper muscles (Rothwell et al. 1991). The figure-eight shape coil allows for the largest and most localized current under the intersection of both wings of the magnetic coil where the two round components merge (Cohen and Bandinelli 1988; Roth et al. 1991). TMS also allows for the study of plastic changes in cortical areas that function in motor and sensory mechanisms (Chen et al. 1998), and mechanisms of plasticity (Ziemann et al. 1998).

5.2 - Motor Evoked Potentials

Once the TMS coil stimulates the area of the motor cortex that controls the muscle being studied, it will then induce neural activity which discharges an action potential all the way down the lateral corticospinal tract to the effected muscle (Rothwell 1997; Muellbacher et al. 2000). The electromyographic (EMG) response by the muscle to these stimuli is known as a motor evoked potential (MEP). Magnetic stimulation of the motor cortex evokes EMG responses in contralateral and distal muscle (Rothwell 1997). In order to identify the area of M1 which corresponds to the target muscle a "trial and error" TMS mapping technique must occur, where the subject is stimulated along the primary motor cortex region of the brain until there is activation of the muscle (Rossini 1990). Once the area of the brain is identified, progressively increasing the intensity of the stimulation while recording EMG will allow for the development of a threshold level, which has previously been defined as the probability of evoking an MEP in 5 out of every

10 stimulations (Rossini 1990). Inter-subject variability of subjects optimal coil position for evoking a response in a muscle may vary up to 2 cm (Meyer et al. 1991), however there is a great deal of emphasis to be put on the coil orientation as well because stimulation of neural tissue is also dependant on whether or not the magnetic current is perpendicular to the motor neuron axons (Barker et al. 1985). A coil orientation with handle pointed backwards and rotated approximately 45 degrees away from the mid-sagittal line has been shown to allow for optimal activation of corticospinal neurons trans-synaptically (Werhahn et al. 1994; Kaneko et al. 1996). When performing trials, an average of 8-16 MEP's is usually taken for each stimulus parameter. In order to account for operator variability, a tight fitting cap or a neuro-navigation system is often implemented in order to accurately place the coil in the correct placement.

The MEP is usually larger in the hand and forearm region in the axial skeleton when compared to the leg, foot and pelvis regions (Rossini 1990). This is due to the positioning and the orientation of the primary motor cortex in the brain. The somatotopic position of the hand region on the motor cortex is located near the most superior and superficial part of the skull, and has the largest representation devoted to these finely skilled and complex neural pathways (Jenkins et al. 2007).

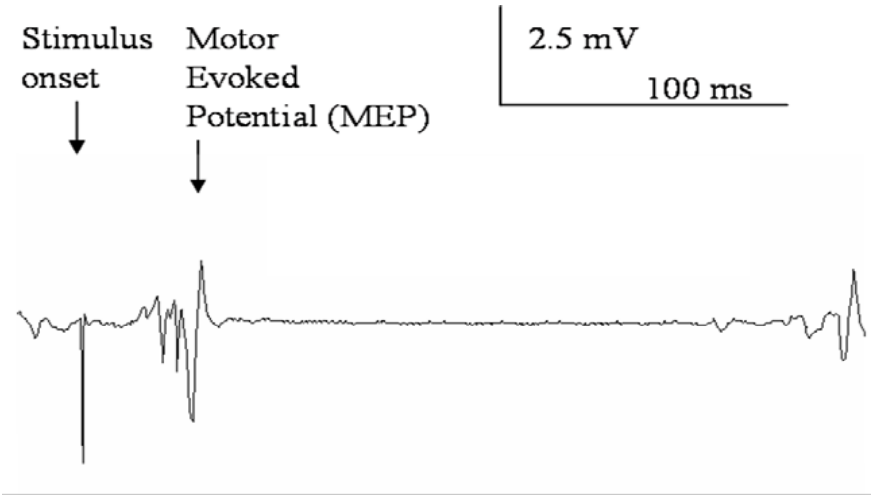

Figure 4. Example of an electromyography trace showing a motor evoked potential (Haavik Taylor 2007).

5.3 - Paired-Pulse TMS

Paired-pulse TMS (ppTMS) is produced when two distinct stimuli are outputted through the same coil at different time intervals. The initial stimuli is referred to as the conditioning stimulus (CS), while the second stimuli is called the test stimulus (TS), and the interaction the stimuli have on each other depends on the time interval between, and the intensities of both the CS and TS (Chen and Garg 2000; Ilic 2004). This method of TMS is used to non-invasively investigate inhibitory (Chen and Garg 2000; Ilic 2004; Cirillo et al. 2010) and excitatory (Chen et al. 1998; Ziemann et al. 1998; Boroojerdi et al. 2001) neural networks in the motor cortex.

5.3.1 – Short Interval Intracortical Inhibition

Short-interval intracortical inhibition (SICI) occurs when a subthreshold CS is followed by a suprathreshold TS at an interstimulus interval (ISI) of 1-6ms (Kujirai et al. 1993). The response in the motor evoked potential of the target muscle is inhibited during this phenomenon. There are two distinct phases of SICI, with one occurring at approximately at an ISI of 1ms, while the other occurs at an ISI of ~2.5-4.5 ms (Fisher et al. 2002;

Hanajima et al. 2003; Roshan et al. 2003). Studies have shown that the first phase of SICI is due to refractoriness of the neural elements that are responsible for the activation of corticospinal neurons, while the second phase of inhibition is a synaptic inhibition mediated by the gamma-aminobutyric acid A ($GABA_A$) receptor (Kujirai et al. 1993; Ziemann et al. 1996; Ziemann et al. 1996; Ilic et al. 2002). A reduction of SICI occurs prior to and during voluntary activation of motor movements (Ridding et al. 1995; Reynolds and Ashby 1999), which is thought to enhance use-dependant plasticity (Ziemann and Hallett 2001). An enhancement of SICI by $GABA_A$ receptor agonist suppresses use-dependent plasticity in human motor cortex (Tegenthoff et al. 1999).

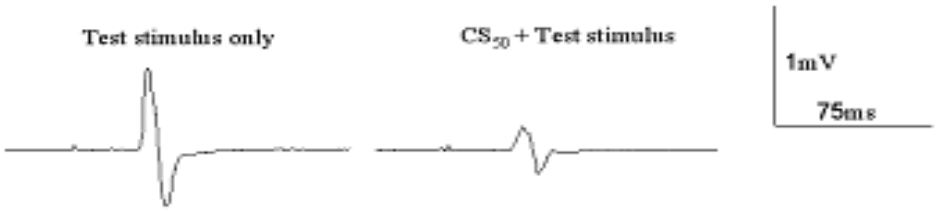

Figure 5. Example EMG trace showing SICI. The MEP evoked by the test stimulus alone is inhibited when preceded by a smaller stimulus (Haavik Taylor 2007).

5.3.2 – Short Interval Intracortical Facilitation/ I wave Facilitation

Short-interval intracortical facilitation (SICF) or I-wave facilitation (IwF) occurs when the first stimulus (S1) is above the MEP threshold and the second stimulus (S2) is below or at the level of the MEP threshold (Ziemann et al. 1998; Hanajima et al. 2002; Ilic et al. 2002). When this occurs, electromyography responses of the target muscles to the dual stimuli can be larger than responses to S1 alone. This has been shown to occur at three distinct phases of ISI at: 1.0-1.5; 2.5-3.0; and 4.0-4.5 (Ziemann 1999; Chen et al. 2008). These SICF peaks have been shown to be related to I-wave generation (Patton and Amassian 1954). There are two types of corticospinal waves following the stimulation of

the motor cortex: direct (D) and indirect (I) waves. D-waves are due to the activation of the axon of corticospinal neurons, while I-waves are due to the trans-synaptic activation of these motor neurons (Patton and Amassian 1954). In respect to SICF and IwF, this phenomenon is thought to occur because the second stimulus acts on the neuronal tissue around the motor neuron that have been partially facilitated, but have not yet reached threshold by the first stimulus, thus activating the indirect pathway (Di Lazzaro et al. 2004). I waves occur at regular "clock-like" intervals of 1.5 ms intervals, and since the three phases of SICF occur around intervals of 1.5 ms as well, it is thought that SICF is due to the interaction of I waves generated by the two stimuli (S1 and S2) (Ziemann et al. 1998).

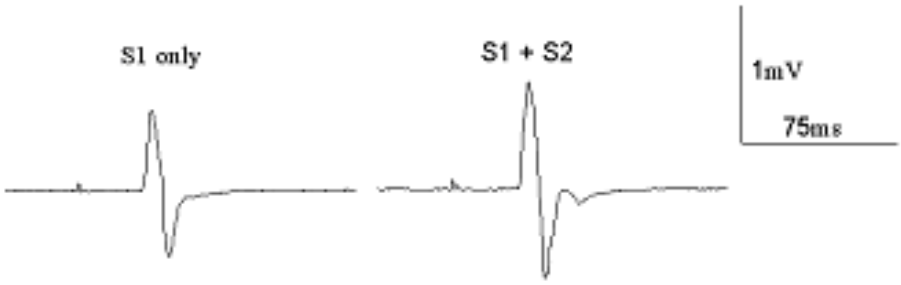

Figure 6. Example EMG trace showing SICF (or IwF). The MEP from the test stimulus (S1) alone is facilitated when followed with a smaller stimulus (S2) (Haavik Taylor 2007).

5.3.3 – Long Interval Intracortical Inhibition

In contrast to SICI, which is thought to be a $GABA_A$ mediated process, long interval intracortical inhibition is an inhibitory process that is thought to be mediated by $GABA_B$ receptors based on studies using $GABA_B$ receptor agonists (Valls-Solé et al. 1992; Wassermann et al. 1996). This process assesses intra-cortical inhibition with paired suprathreshold TMS pulses at interstimulus intervals ranging from 50-200 ms, with the optimal inhibition occurring at approximately 100 ms (Nakamura et al. 1997; Chen et al.

1999). LICI and SICI differ, as there is no relationship between the levels of SICI and LICI in different individuals, as well as the fact that with increasing test pulse strength, LICI decreases but SICI tends to increase (Sanger et al. 2001).

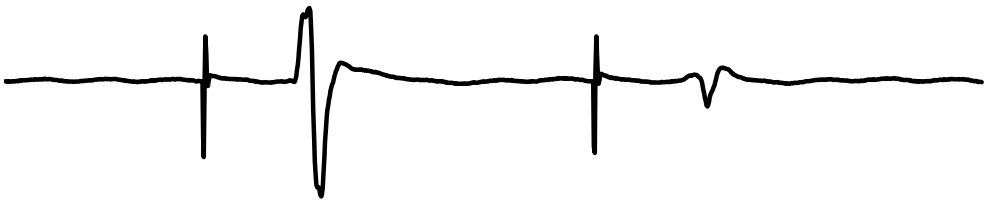

Figure 7. Example EMG trace showing LICI. The initial MEP evoked is much larger than the second MEP, which can occur at an ISI of 50-200 ms.

5.3.4 – Cerebellar TMS

Activity of the cerebellothalamocortical pathway can be revealed non-invasively in humans. It has been shown that performing either electrical (Ugawa et al. 1991) or magnetic (Ugawa et al. 1995; Pinto and Chen 2001) stimulation of the cerebellum 5-7ms before stimulation of the motor cortex results in the inhibition of this motor cortical stimulation. A double-cone coil has been shown to produce the optimal suppression using this technique (Ugawa et al. 1995). During this technique, the coil is placed over the cerebellar cortex on the contralateral side of cortical stimulation. The coil is centered to be at the midpoint on a line joining the external auditory meatus to the inion, while the current in the coil is directed downwards (induces an upward current in the cerebellar cortex). This coil position was found to be optimal for suppressing the contralateral motor cortex (Ugawa et al. 1995). The intensity of the coil has been most commonly set to 95% of active motor threshold for pyramidal tract activation, while the coil is centered over the

inion, in order to reduce the risk of activating the spinal cord (Daskalakis et al. 2004; Brighina et al. 2009).

Daskalakis et al. (2004) explored the connectivity between the cerebellum and motor cortex by using both cortical inhibitory and excitatory motor circuits to examine how cerebellar TMS interacts with these processes. The three inhibitory processes used were cerebellar inhibition (CBI), SICI, LICI, while the excitatory measure used was ICF. The first experiment showed that with increased TS intensities, CBI, LICI and ICF decreased, while SICI increased. The second experiment demonstrated that the presence of CBI reduced SICI and increased ICF. The third experiment showed that the interaction between CBI and LICI reduced CBI. Based on these results, the authors concluded that CBI results in changes to both excitatory and inhibitory neurons. The finding of reduced SICI following CBI suggests that there is activation of the Purkinje cells leading to suppression of excitatory output from the venterolateral nucleus of the thalamus, thus leading to a decreased excitatory drive to both excitatory output motor neurons as well as inhibitory (SICI) interneurons.

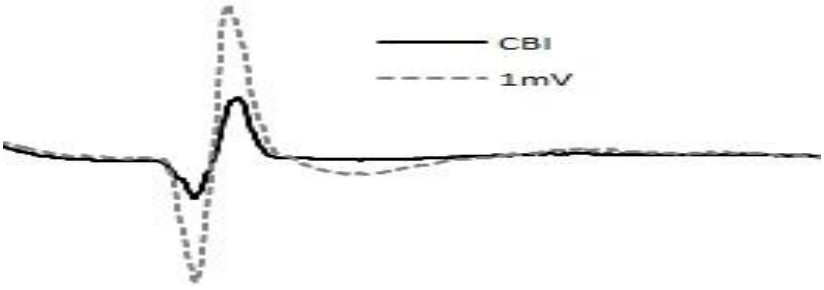

Figure 8. EMG traces demonstrating the effect of CBI. The MEP evoked by the test stimulus alone at 1mV is inhibited when a conditioning stimulus to the cerebellum 5 ms prior to cortical stimulation is given.

Chapter 6: Cervical Spine Dysfunction and Chiropractic Intervention

According to Haldeman et al (2008), a majority of the general population experiences some degree of neck pain within their lifetime. There are many prevailing factors that result in neck pain, including socioeconomic status, prior health, workplace injuries, psychological, societal, genetic, health behaviours, and sport injuries (Hogg-Johnson et al. 2008). Although neck pain is common, qualitative analysis has shown that there is marked degree of variation in the signs and symptoms that occur in the involved population. There are many reported cases of some pain, fewer cases of significant duration, less cases that need healthcare treatment, and even fewer cases that result in disability (Hogg-Johnson et al. 2008). The incidence rate of self-reported neck pain in the general population ranges from 146 to 213 per 1000 people (Croft et al. 2001; Côté et al. 2004; Ståhl et al. 2004), while the annual prevalence rate of neck pain ranged between 30% and 50% (Hogg-Johnson et al. 2008). Most studies have shown that the prevalence of neck pain increases with older age, peaking in mid-life and declining in the later years. However, the risk of developing neck pain is the same over all age groups. The younger population with neck pain have a better prognosis when compared to older persons (Carroll et al. 2008). Therefore, it may be this factor that demonstrates the difference between incidence rates and prevalence.

Chiropractic practitioners are trained to treat neuromuscular conditions through many diversified techniques such as physiological therapeutics, exercise, nutrition, and manipulation. Chiropractors place an emphasis on the latter of these techniques with the goal of correcting disorders of the neuromuscular system by improving joint alignment, range of motion, and quality of movement (Haneline 2005). Although chiropractic care is

one of the most common complementary treatment methods to neck pain, there is little understood about the neurophysiological effects that make treatment so effective. Recently, there has been evidence to suggest that patients with neck and back pain undergo neurophysiological and proprioceptive changes in function, which may lead to chronic changes (Murphy et al. 1995; Herzog et al. 1999; Suter et al. 1999). There is also evidence to suggest that chiropractic care can induce changes in nervous system functioning including cognitive processing and motor output (Herzog et al. 1999; Haavik-Taylor and Murphy 2007; Haavik-Taylor and Murphy 2007), suggesting that chiropractic treatment not only manages pain and normalizes movement, but also has the potential to modulate neural functioning.

More specifically, Haavik and Murphy (2012) have proposed an interventional approach based on the principle that high-velocity, low-amplitude spinal manipulation improves function and reduces symptoms. This novel approach suggests that altered afferent feedback caused by joint dysfunction affects ascending afferent input into cortical and subcortical neural structures, which further leads to altered sensorimotor processing. Through the use of spinal manipulation, this therapeutic treatment can facilitate normalization of the altered input and therefore return the process to its normal spectrum of perceived function (Taylor and Murphy 2010). Several studies have demonstrated altered motor control following spinal manipulation of the cervical spine by utilizing various TMS techniques(Haavik-Taylor and Murphy 2007; Taylor and Murphy 2008). TMS techniques studied have included short interval intracortical inhibition, short interval intracortical facilitation, and the cortical silent period, and each are thought to reflect different processing mechanisms within the cortex (Fisher et al., 2002; Kujirai et

al., 1993; Hanajima et al., 2002). According to Taylor & Murphy (2008) there was an increase in SICI following manipulation of dysfunctional segments in the cervical spine to the abductor pollicis brevis muscle (APB), as well as an increase in SICF for the APB muscle and a decrease in SICF for the extensor indices proprios (EIP) muscle. Therefore, these alterations in motor control appear to be targeted and specific to the muscle being utilized.

Chapter 7: Literature Synthesis and Perspective

Chiropractic treatment is one of the most common treatments for neck pain, however there is little known about the exact biological mechanism involved for its undoubted efficacy. Neck pain places a large burden on the healthcare system with approximately a 30-50% one year prevalence rate in the general population (Hogg-Johnson et al. 2008). Therefore, with the appropriate knowledge of the mechanisms involved in the therapeutic process of spinal manipulation, it may be possible to enhance treatment capabilities and provide better healthcare to clients. There is a growing amount of evidence to suggest that there is impaired proprioception and neuromuscular functions in patients with neck and back pain (Bränström, Malmgren-Olsson, & Barnekow-Bergkvist, 2001; Falla, Bilenkij, & Jull, 2004; Gogia, 1994; Stapley, Beretta, Toffola, & Schieppati, 2006). There is also evidence to suggest that chiropractic manipulation can induce changes in the central nervous system related to sensory processing and motor control (Herzog et al. 1999; Haavik-Taylor and Murphy 2007; Haavik-Taylor and Murphy 2007). Taylor and Murphy (2008) have suggested that altered afferent input to the central nervous system as a consequence of neck joint dysfunction may affect the way that the CNS processes afferent input from the neck and upper limbs and over time this may lead to altered sensorimotor integration, which can then be normalized when the dysfunctional neck joints are manipulated.

One neural structure postulated to be the integrator for this afferent information is the cerebellum. Research has shown that the cerebellum is involved in the integration of incoming signals from the joints of the neck and spine (Manzoni 2005; Manzoni 2007), and has also shown that it is associated with motor learning (Doyon et al. 2002; Doyon et

al. 2003; Manto and Bastian 2007; Molinari et al. 2007). There is no known work directly showing a relationship between the cerebellum and neck pain or chiropractic treatment. However, recent work has shown that there is reduced cerebellar modulation of motor cortex excitability in patients with focal hand dystonia (Brighina et al. 2009) and patients who suffer from migraine with aura (Brighina et al. 2009). These studies are both relevant to the field of chiropractic treatment as migraine and overuse injuries are conditions often treated by chiropractors. Given that these two conditions alter cerebellar output, it is possible that there will also be modulation in neck pain patients as well. If an alteration in motor output is demonstrated at the level of the cortex or the cerebellum, it may provide a neurological marker of whether the altered sensorimotor integration has been normalized, or if the patient is still at risk for recurrent neck pain and requires further or different care. Changes in the cerebellar output to the cortex would add to the current knowledge on the role of this neural structure on sensorimotor processing and could also contribute to future study designs to determine how prolonged these alterations are and what modes of chiropractic treatment would provide optimal care.

In order to view changes in the motor output of the cerebellum various TMS techniques can be implemented. Ugawa et al (1995) demonstrated that activity of the cerebellothalamocortical pathway can be revealed non-invasively in humans. This was revealed through stimulation of the cerebellum 5-7 ms before stimulation of the motor cortex, which resulted in the inhibition of the cortical stimulation. Recent studies (Haavik-Taylor and Murphy 2007; Taylor and Murphy 2008) have shown that manipulation of dysfunctional segments in the cervical spine alters sensorimotor integration of input from the upper limb by using cortical TMS techniques. Experimental

measures used in these studies were SICI, SICF, and CSP and all are thought to be measures of SMI processing at the level of the cortex (Fisher et al., 2002; Kujirai et al., 1993; Hanajima et al., 2002). Due to this alteration from spinal manipulation, it is necessary to investigate cortical changes, as well as cerebellar changes, in order to determine the exact neural structures which are responsible for sensorimotor changes in patients with dysfunctional spinal segments.

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Section 2: Manuscripts

Manuscript One: The Effects of Motor Learning on the Cerebellum and Motor Cortex

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Abstract

Background: The central nervous system is capable of adaptation following the development of motor skills. These changes have been shown to occur in both the cerebellum and the motor cortex following motor sequence learning (MSL). *Objectives*: To investigate the role that both the cerebellum and motor cortex play in MSL via transcranial magnetic stimulation (TMS) measures of cerebellar inhibition (CBI), short interval intracortical inhibition (SICI) and long interval intracortical inhibition (LICI). *Methodology*: Electromyographic (EMG) activity was recorded from the right first dorsal interosseous muscle in 11 healthy subjects before and after a MSL task intervention. CBI was performed and measured after applying a conditioning stimulus of 70, 80 or 90% of maximal stimulator output to the right cerebellar hemisphere prior to cortical stimulation. Cortical TMS was performed on the left motor cortex and inhibitory measures of SICI and LICI were recordedSICI and LICI measures were compared pre- to post-intervention using a paired t-test, while CBI was measured using a repeated measures ANOVA comparing the three conditioning stimulus intensities both pre- and post-intervention. *Results*: Following the motor learning task there was an improvement in task performance as indicated by a 25% decrease in reaction time ($p < 0.001$). SICI levels decreased by 32% following the MSL intervention ($p < 0.03$), while there was no change in CBI and LICI. *Conclusions*: In a healthy population, the MSL task can reduce intracortical inhibition.

Introduction

The central nervous system has been shown to be a plastic organ, capable of modification in neuronal network properties in response to altered afferent input (Donoghue et al. 1996). Such changes in neural circuitry can be a result of a decrease or increase in behaviour or activity (Hallett et al. 1999; Murphy and Dawson 2002; Tinazzi et al. 2003; Haavik Taylor and Murphy 2007), or can be a result of an increase in peripheral input, such as with an increase in motor functioning like motor skill acquisition (Byl and Melnick 1997; Cirillo et al. 2010). Motor training provides a functional method of inducing cortical and sub-cortical plasticity within the human central nervous system, and this modification can be tested in a lab setting.

Developing motor skills involves the process of learning movements produced either in sequence or independently, and this trains the cortical and subcortical structures of the neural system to perform them effortlessly after repeated practice (Willingham 1998). According to Doyan & Benali (2005), changes in cortical and subcortical structures can occur very rapidly after an initial training sessions, while further changes in neural organization can occur after repeated training sessions where the motor task can be performed on command. Although there are a plethora of studies showing the response of the motor cortex to motor skill development, (Pascual-Leone et al. 1995; Liepert et al. 2004; Takahashi et al. 2005; Cirillo et al. 2010) there are few studies demonstrating the effect on the cerebellum.

With direct and indirect anatomical connections to almost the entire central nervous system, the cerebellum is a multi-functional neural structure that is actively involved in motor learning (Bloedel 2004; Manto and Bastian 2007) and sensorimotor integration

(Manzoni 2007; Molinari et al. 2007). There is evidence to suggest that the cerebellum plays a key role in the development of motor skills, as functional brain imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) (Shadmehr and Holcomb 1997; Schendan et al. 2003; Aizenstein et al. 2004) have identified the neural networks involved with motor learning and the cerebellum. These studies have also helped to identify plastic changes that occur throughout the initial and later stages of motor learning as task performance improves with practice (Doyon et al. 2002; Doyon et al. 2003). Imaging techniques are beneficial in determining the structures and networks involved in the learning process however are unable to show the inhibitory and excitatory processes in neural circuitry and the resulting change in motor output.

Activity of the cerebellothalamocortical pathway has been revealed non-invasively in humans using both electrical (Ugawa et al. 1991) and magnetic (Ugawa et al. 1995; Pinto and Chen 2001) stimulation of the cerebellum 5-7 ms before stimulation of the motor cortex. This process has been referred to as cerebellar inhibition (CBI) (Daskalakis et al. 2004) . This conditioning stimulus resulted in the suppression of motor cortical stimulation evoked potentials in the first dorsal interosseous (FDI) muscle. There have also been reports that low frequency repetitive TMS of the cerebellum (Oliveri et al. 2005) produces modulatory effects in the motor system by facilitating motor evoked potentials (MEPs) and increasing the amount of intracortical facilitation within the motor cortex. Therefore, it is evident that the cerebellum plays a role in the modulation of motor function in relation to the motor cortex. It has been shown in previous studies that the motor cortex is highly involved in the role of motor learning by utilizing TMS techniques

(Pascual-Leone et al. 1995; Cirillo et al. 2010). However, there are no known studies reporting the response of the cerebellum to a motor sequence acquisition task while utilizing this CBI TMS protocol, although response changes have been identified using functional brain imaging technology. TMS techniques such as short interval intracortical inhibition (SICI) and long interval intracortical inhibition (LICI) can be used to investigate changes in the inhibitory processes of the motor cortex (Hallett 2007), while CBI can assess the changes in the degree of inhibitory cerebellar connections to the motor cortex. These TMS techniques therefore provide complementary measures which provide additional information on mechanism as compared to previously published fMRI investigations (Doyon and Benali 2005) and can provide a broader view on how these neural structures adapt to motor learning. Therefore, the aim of this study was to investigate the role that the cerebellum plays in motor sequence learning through the use of CBI, as well as the cortical inhibitory measures short interval intracortical inhibition (SICI) and long interval intracortical inhibition (SICI).

Methodology

Subjects

Experiments were performed on 11 healthy volunteers (mean age: 23.5; range19-33; 9 men and 2 women) after giving their written informed consent. All of the participants were right handed according to the widely used and adopted Edinburgh Handedness Inventory and none of them had any history of neurological disease (See Appendix 1 & 3 for TMS safety checklist and Edinburgh Handedness Inventory respectively). The study was approved by the local ethics committee and conducted in accordance with

regulations laid down in the Decleration of Helsinki (See Appendix 2 for project consent form).

Electromyographic Recordings

Electromyographic (EMG) activity was recorded from the right first dorsal interosseus (FDI) muscle using a pair of Ag-AgCl surface electrodes in a belly-tendon arrangement. A ground electrode strap was placed around the wrist of the right arm, between the site of stimulation and the recording electrodes. The EMG signal was amplified (1000x) and band-pass filtered (bandwidth 20-2000 Hz) with a Cambridge Electronic Design 1902 isolated amplifier (Cambridge Electronic Design, Cambridge, UK), digitizing at a sampling rate of 1 kHz (CED 1401 laboratory interface; Cambrdige Electronic Design, Cambridge, UK) and received by a laboratory computer for storage and off-line analysis. Data was analyzed using SIGNAL software version 4.08 (Cambridge Electronic Design, Cambridge, UK). Subjects were asked to maintain a relaxed position throughout the experiment, with their hand placed in a pronated position, while EMG activity was monitored to ensure that the muscle was at complete rest (Figure 9).

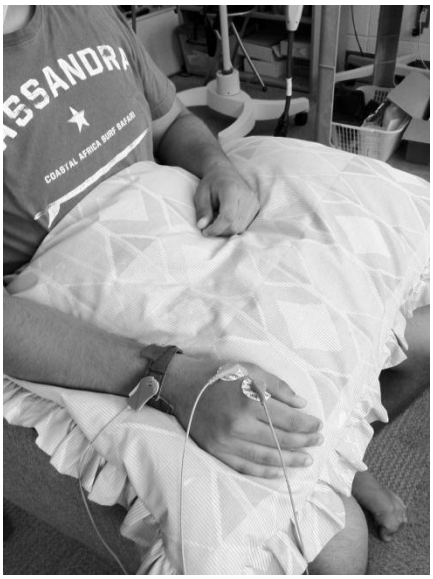

Figure 9. Electrodes were placed in a belly-tendon formation over the right FDI muscle, with ground electrode placed over the wrist and hand placed in a pronated position.

Motor Sequence Task

During the motor sequence task, the subjects were seated in a comfortable chair with their hand resting in a pronated orientation on a platform that held a modified numeric keypad. With their hand lying palm down in a relaxed position, participants were asked to place their index finger on the keypad in a comfortable position so that they could reach the 7, 8 and 9 keys, while the other three fingers and thumb were taped down in order to maintain hand orientation (Figure 10).

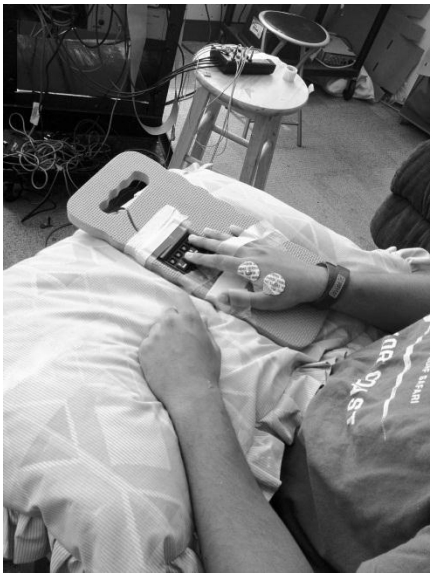

Figure 10. A custom keyboard was developed to allow the index finger to reach the 7, 8 and 9 keys of the numeric keypad. Other digits were then taped down in place to allow the proper hand orientation to allow the index finger to move freely and optimally activate the FDI muscle through abduction.

A custom program was made using E-Prime 2.0 software (Psychology Software Tools, Sharpsburg, PA) which prompted the participants to enter randomized sequences of the keys 7, 8 and 9 in six letter blocks being displayed on a screen. This side to side movement of the index finger allowed optimal activation of the FDI muscle by performing its primary action of abducting the index finger. Subjects were asked to

perform the action of pressing the sequence as quickly and accurately as possible. The task was separated into three parts: a pre-section, complex task, and a post-section. The task was the same for all three parts. Accuracy and reaction time data were calculated from two blocks of 15 trials performed at the beginning and end of the complex task, whereas the complex task itself contained 225 trials performed over a 20 minute period.

Transcranial Magnetic Stimulation

For cortical stimulation, a figure-of-eight coil (outer diameter 10 cm) was applied over the hand region of the left motor cortex. Magnetic stimulation was applied to the target site via the use of two Magstim 200 stimulator units (Magstim Co., Whitland, Dyfed, UK) given in BiStim mode. The coil was held with the handle pointed backwards and rotated approximately 45 degrees away from the mid-sagittal line, with the current flowing posteriorly. This specific coil orientation has been shown to allow the induced current to be perpendicular to the central sulcus, which allows for optimal activation of corticospinal neurons trans-synaptically (Kaneko et al., 1996; Werhahn et al., 1994). The optimal coil position for inducing motor evoked potentials (MEPs) in the FDI muscle was determined as the site where stimulation at just above threshold intensity which consistently produced the largest MEPs. The optimal site was then marked with a felt tip pen on a cloth cap that the subject was asked to wear throughout the entire experiment, in order to maintain consistent coil placement. TMS was delivered at a frequency of 0.2 Hz with a 20% variance in order to account for anticipatory effects in all trials.

RTh and 1 mV MEP

In order to determine the correct parameters needed for the paired-pulse TMS techniques being utilized in this experiment (SICI and LICI), it was necessary to find the stimulus

intensity that elicited a MEP of approximately 1 mV as well as the subjects resting motor threshold (RTh). The 1 mV MEP was calculated by determining the level of stimulator output that would elicit approximately a 1 mV MEP in peak to peak amplitude after averaging 14 pulses. RTh was calculated by determining the lowest stimulus intensity needed to elicit a MEP of approximately 0.05 mV in at least five out of ten trials, while the subject was at rest.

Paired Pulse TMS

Short interval intracortical inhibition (SICI) and long interval intracortical inhibition (LICI) were assessed using paired-pulse TMS paradigms. The SICI protocol consisted of a subthreshold conditioning stimulus (set to 80% of RTh) that is followed by a suprathreshold test stimulus (TS) by 2.5 ms (Kujirai et al., 1993). The test stimulus intensity was monitored before and after the motor training intervention in order to ensure that it was still similar to the pre-trial peak-to-peak amplitude and adjusted accordingly. Each data block consisted of sixteen stimuli. The conditioned MEP amplitude was expressed as a percentage of the suprathreshold 1 mV amplitude.

Long interval intracortical inhibition (LICI) was assessed by applying a suprathreshold stimulus preceded by another suprathreshold stimulus and separated by an interstimulus interval (ISI) of 100 ms (Nakamura et al. 1997; Chen et al. 1999). The two suprathreshold stimuli were set to the 1 mV value of stimulator output and the inhibition was measured as a ratio between the first and second MEPs.

Cerebellar TMS

The cerebellar conditioning stimulus (CCS) was delivered over the right cerebellar hemisphere with a double cone coil (110 mm mean diameter). This coil has previously

been found to be the most effective in applying an inhibitory stimulus to induce cerebellar brain inhibition (CBI) (Ugawa et al. 1995). The coil was positioned in the midpoint of a line joining the external auditory meatus to the inion and the coil was oriented downwards to produce an upwards current in the cerebellar cortex (Ugawa et al. 1995; Daskalakis et al. 2004; Brighina et al. 2009). The coil was held by a stand and was strapped around the participants' heads in order to maintain a close fit and proper coil orientation (Figure 11).

Figure 11. Cerebellar coil was positioned over the right hemisphere of the subjects cerebellum, and strapped in place around the subjects head to maintain a close fit.

The intensity of the stimulator was pseudo-randomized to stimulate at 70, 80, or 90% of the combined output of the two Magstim units connected by a BiStim Unit. These intensities were chosen based on pilot data (Daligadu et al. 2012) which showed that an inhibitory modulation could be demonstrated at these three intensities without the contamination of brain stem or nerve root stimulation. The test stimulus over the motor cortex was set to a stimulus intensity that evoked a MEP of approximately 0.8 mV, as

CBI has been demonstrated to be most effective when MEP amplitudes were below 1 mV (Daskalakis et al. 2004). The interstimulus interval between the CCS and the test stimulus of the motor cortex was set to 5 ms. This ISI was chosen because it has been previously shown to induce CBI and the effects are thought to be related to cerebellar stimulation as opposed to stimulation of peripheral nerves or muscles (Ugawa et al. 1995; Daskalakis et al. 2004).

Experimental Design

This experiment looked to examine the effects of a motor sequence learning task on the cerebellar and motor cortices. The cortical measures used were SICI and LICI, while CBI was used to measure the inhibitory effect of the cerebellum. These were measured both before and after a 20 minute motor sequence learning task that was used to specifically activate and train the FDI muscle. SICI and LICI were performed after the attainment of the 1 mV MEP and the RTh (Bistim set-up), and both measures were averaged over 16 stimuli. CBI was performed following the attainment of the 0.8 mV MEP (single Magstim set-up) and was averaged over 10 stimuli. An additional 4 stimuli were given at each of the three intensities used in order to monitor for brainstem and nerve root activation.

Statistical Analysis

Once data was acquired, the peak-to-peak amplitude for each trial was measured off-line using a customized Signal configuration (Cambridge Electronic Design, Cambridge, UK) and the average amplitude was calculated for each session using Microsoft Excel. SICI and CBI were measured as a ratio of conditioned MEPs to unconditioned MEPs, while LICI was measured as a ratio of the first MEP to the second MEP. Paired t-tests were run

between the pre- and post-intervention MEPs in order to compare the mean peak-to-peak amplitudes using IBM SPSS Statistics (Version 19) for SICI and LICI. Performance on the motor sequence task was analyzed based on the measures of reaction time and accuracy of the keystrokes. The effects of cerebellar inhibition were evaluated through repeated measures ANOVA with Time (two levels: pre- and post-intervention) and between conditioning stimulus intensity (three levels: 70%, 80%, and 90% MSO), with appropriate post hoc tests as required.

Results

None of the subjects reported side effects from the experimental measures. A total of 11 subjects completed the study, however 1 subject found the cerebellar stimulation too uncomfortable and two subjects had large artefacts from the high intensity cerebellar stimulation that swamped the EMG signal and could not be suppressed, even with efforts to further decrease impedance of the skin overlying the FDI. Therefore there were 11 data sets for SICI and LICI and 8 data sets for the CBI analysis.

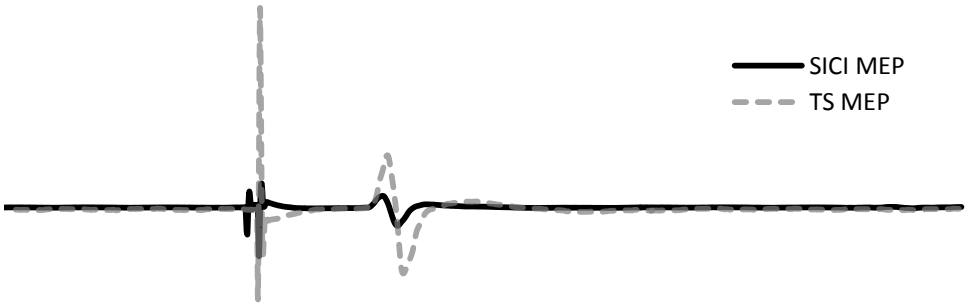

Figure 12. Raw EMG data illustrating the effect of SICI on the test stimulus. This paired-pulse technique results in the suppression of the test MEP from a conditioning stimulation that occurs 2.5 ms prior to the TS.

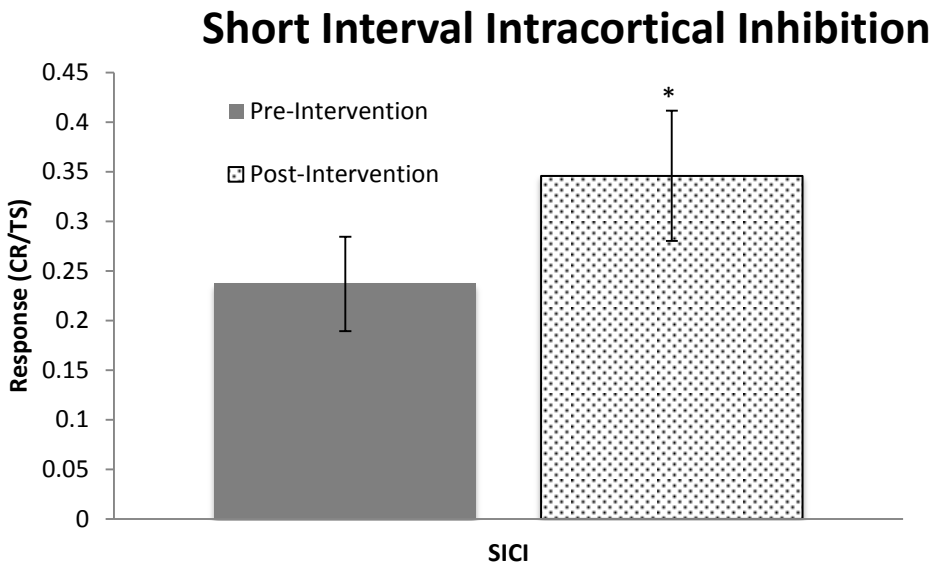

Figure 13. Averaged results for pre- and post-intervention SICI, with the conditioned response (CR) being averaged to the TS. The motor sequence learning intervention led to a 32% decrease in the effect of SICI.

For the SICI data, a significant effect was observed when comparing pre- to post-intervention results. The mean amplitude of the pre-intervention SICI measure was 0.237 ± 0.47 SE, compared to the post-intervention SICI which was 0.346 ± 0.66 SE ($p < 0.03$) (Figure 12 & 13). LICI showed no significant change from pre-intervention (mean ratio 17.98 ± 6.19 SE) compared to post-intervention (mean ratio 16.48 ± 5.84 SE; $p = 0.831$) (Figure 14). For the CBI measure, repeated measures ANOVA evidenced a significant effect for the factor of stimulus intensity ($F = (6,2)$ 31.64 ($p < 0.001$)), however none for the factor of time (Figure 15).

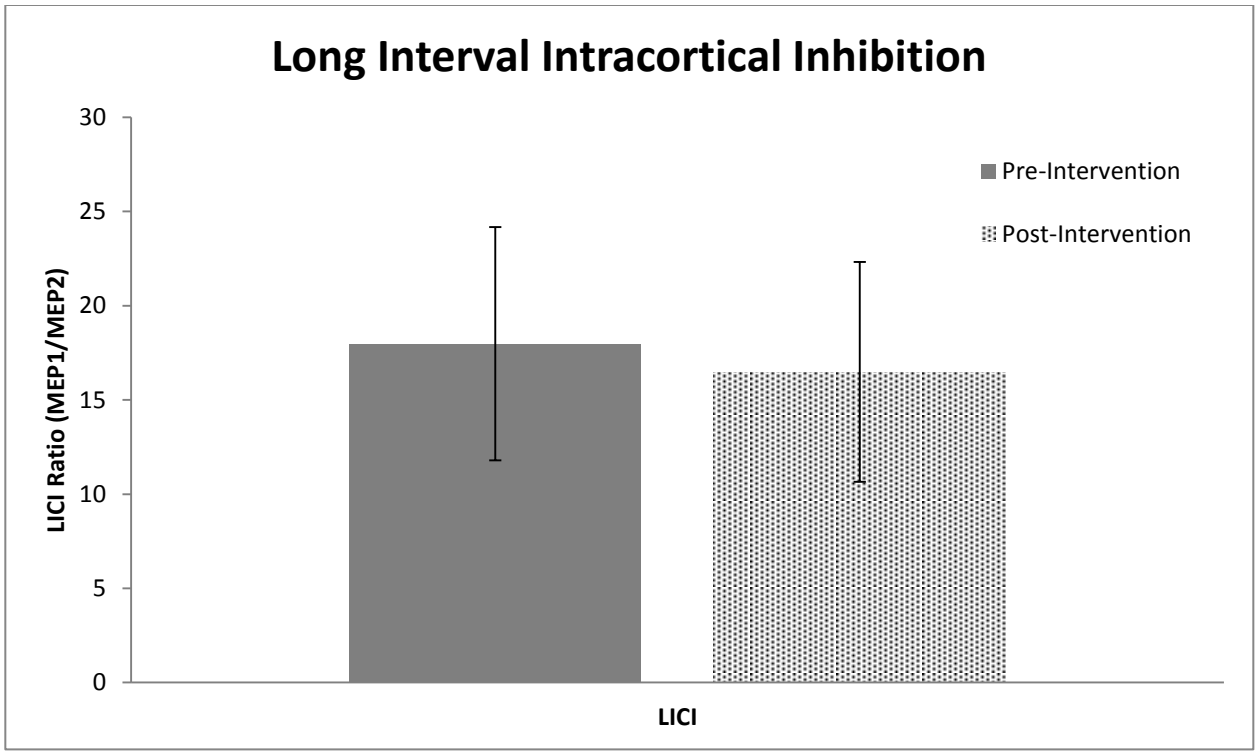

Figure 14. Averaged ratios for pre- and post- intervention LICI. The motor sequence learning showed no significant differences between pre- and post-intervention LICI values when investigating the ratio between the first conditioning MEP to the second test MEP.

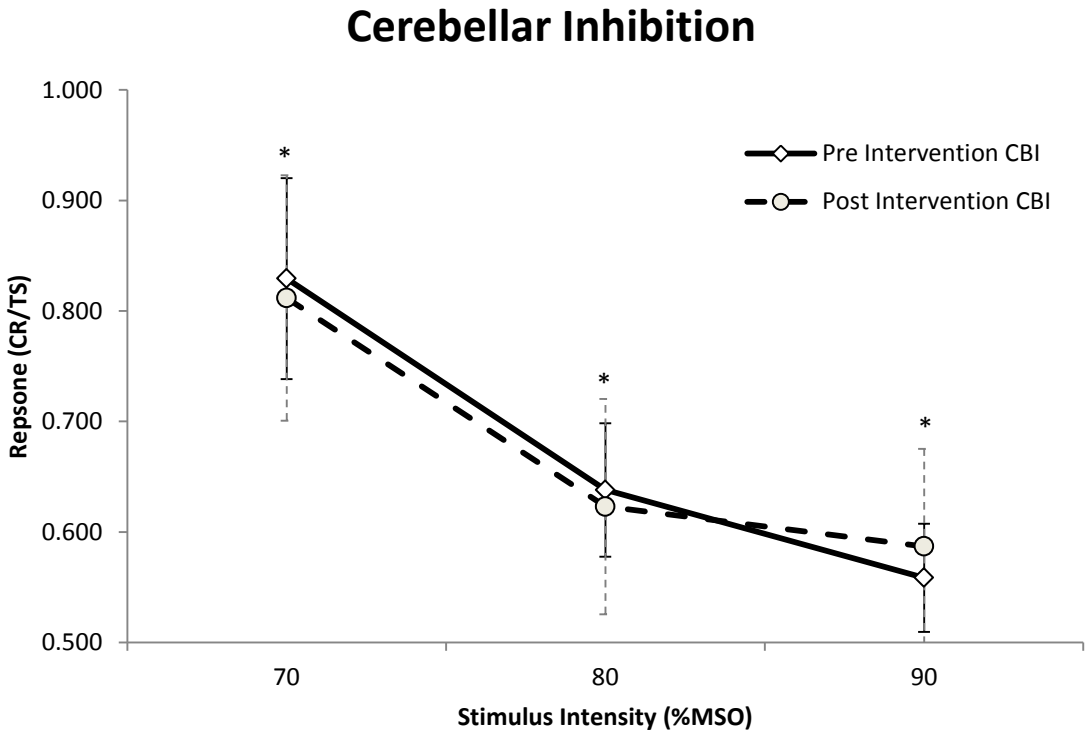

Figure 15. Conditioned response magnitude for CBI averaged according to the TS (where 1.00 indicates TS amplitude). There was greater inhibition as the conditioning cerebellar stimulation was increased. However, there was no significant difference between the pre- and post-intervention responses at all three levels of stimulus intensity.

The motor training task showed that following the motor sequence learning intervention, the reaction time improved significantly (from 493.1 ms to 367.29 ms, $p = 0.001$). As reaction time decreased, task accuracy also decreased significantly following the intervention (97.6% to 95.2%, $p = 0.024$). However, this was only a 2.5% decrease in accuracy.

Discussion

This research project looked to identify neural changes in the motor cortex and cerebellum following a motor sequence learning task. The motor cortex was investigated using paired-pulse TMS measures of SICI and LICI, while the cerebellum was investigated using CBI. A significant decrease in SICI was found following the intervention, while no changes were found using the LICI and CBI measures. It was also noted that a significant improvement in reaction time occurred during the intervention, and a significant decrease in accuracy.

Motor sequence learning tasks have been demonstrated to have the capacity to induce structural plastic changes in both the motor cortex (Pascual-Leone et al. 1994; Pascual-Leone et al. 1995; Cirillo et al. 2010) and the cerebellum (Doyon et al. 2003). However, few studies have used this technique to show plastic changes in the motor cortex with TMS measures following motor sequence learning, and no known studies have used it to show cerebellar changes with CBI.

It has been previously shown that motor cortex representations change when humans perform and learn sequences in response to sensory cues. These motor sequences often require participants to press a sequence in order, and with repetition the reaction time to start the button gradually decreases (Nissen & Bullemer, 1987). This decrease in reaction time is thought to reflect implicit (or learning) knowledge, and has been shown to induce a larger representation of the finger muscles in the motor cortex using TMS mapping techniques (Pascual-Leone et al. 1994). In the present study, we found that from the beginning of the intervention to the end, there was a 25% decrease in the time needed to react to the motor sequence. Therefore, this decrease in reaction time is interpreted as implicit knowledge learning.

This increase in implicit knowledge was reflected in a 32% decrease in SICI following the intervention. Previous studies have also demonstrated a decrease in SICI following motor learning of both simple and complex tasks (Gallasch et al. 2009; Cirillo et al. 2010), and reflects the current findings in this study using motor sequence learning. SICI is thought to be reflective of the excitability in $GABA_A$-ergic circuitry within the human cortex, and it is therefore suggested that the decrease in intracortical inhibition plays an important role in motor skill learning and motor cortical plasticity. LICI is also a measure of intracortical inhibition, however it is thought to be reflective of the excitability in $GABA_B$-ergic circuitry. Since there was no modulation of LICI following the intervention, it is suggested that this inhibitory pathway does not play a role in motor adaptation.

Previous imaging studies have shown that there is activation of cerebellar structures such as the cerebellar cortex and the deep cerebellar nuclei in the process of motor learning

(Doyon et al. 2002). However, in the present study there were no such changes as indicated by the TMS measure of CBI. This could be due in large to a couple of reasons. Firstly, we did use a novel motor sequence learning intervention in order induce cortical and potentially cerebellar plasticity and learning modulations. This was based on similar methodologies previously studied, which were shown to induce plasticity in the cortex using cortical TMS (Pascual-Leone et al. 1994), and cerebellum using neuroimaging (Doyon et al. 2002). However, the slight modifications made to this motor learning task may have led to a greater amount of recruitment from motor cortex as opposed to the cerebellum, as demonstrated by the decrease in SICI following the intervention. It may also have been that the task we selected was not complex enough to require large amounts of cerebellar involvement for learning to occur. Previously published work on motor training, via pressing the numbers 7,8,9 repeatedly in sequence on a keypad, has been shown to cause changes in somatosensory evoked potential peaks related to sensorimotor integration (Haavik Taylor and Murphy 2007), however this task reflected simple motor training as opposed to the more complex task of motor sequence acquisition which has been shown to involve the cerebellum (Doyon et al. 2002). It was thought that by randomly generating the number sequences, that we would be better testing skill acquisition as opposed to motor training, however the random nature may have favoured motor skill acquisition requiring changes in cortical inhibition reflective in the SICI changes but requiring fewer cerebellar changes for improvement to occur.

Secondly, we used a modified CBI protocol from that of Ugawa et al. (1995) who originally developed it. The original protocol involves stimulating the cerebellum at a stimulus intensity that is sub-threshold to posterior fossa stimulation (cervical medullary

evoked potentials or CMEP). However, it is not possible to evoke a CMEP in all people, and we therefore found that it was difficult to find subjects that could perform the protocol. Also, the stimulus from the cerebellar coil is rather uncomfortable for the participant to undergo numerous sweeps. Therefore, the modifications made to our protocol were made in order to allow all screened subjects to participate in the study and to shorten the amount of exposure to CBI. It is possible however, that this modified CBI protocol may have not had the capacity to determine changes within the cerebellar cortex, or even possibly have activated complementary neural structures which would have led to the suppression of the conditioned CBI MEPs. However, EMG was monitored throughout the experiment and while eliciting conditioning CBI stimuli alone, in order to ensure that there was no cortical output to the FDI that would have been interfering with the CBI. Therefore, it would be unlikely that activation of the corticospinal tract directly would have resulted in the suppression of the MEP responses.

Future studies should aim at further fine tuning the motor sequence learning task to elicit a greater response from the cerebellum. The sample size of the cerebellar group was also small and therefore further research should include a greater sample size to enhance the statistical power.

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Manuscript Two: Alterations in Cortical and Cerebellar Motor Processing in Neck Pain Patients Following Chiropractic Manipulation

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Abstract

Background: Chiropractic manipulation is one of the most common treatment methods for neck pain, however little is understood about its neurophysiological effects. Previous work has shown that spinal manipulation affects sensorimotor integration (SMI), and it is thought that structures involved in this process include the motor cortex and cerebellum. *Objective*: To investigate if there is modulation in cerebellar output from subclinical neck pain patients, and if spinal manipulation and motor sequence learning (MSL) has an effect on SMI with respect to the cerebellum and motor cortex. *Methodology*: Electromyographic (EMG) responses were recorded from the right first dorsal interosseous muscle in 10 volunteers who experienced subclinical neck pain (SCNP), before and after a combined intervention of chiropractic treatment and MSL. Transcranial magnetic stimulation (TMS) was performed on the left motor cortex and included the inhibitory measures of short interval intracortical inhibition (SICI) and long interval intracortical inhibition (LICI). Cerebellar TMS was performed over the right cerebellar hemisphere using the inhibitory measure of cerebellar inhibition (CBI), with conditioning stimulus intensities at 70, 80, and 90% maximal stimulator output (MSO). SICI and LICI measures were compared pre- to post-intervention using paired t-tests, while CBI was measured using a repeated measures ANOVA. *Results*: Following the intervention there was an improvement in task performance as indicated by a 19% decrease in mean reaction time ($p < 0.0001$). There was a significant decrease in CBI following the combined spinal manipulation and MSL intervention ($F = (7,2)\ 7.92$ ($p < 0.05$)). No changes were seen in the inhibitory cortical measures. *Conclusions*: Altered SMI in SCNP patients may play a role in the modulation of cerebellar output to the motor cortex. Chiropractic treatment may potentially be able to modify this defunct SMI.

Introduction

Chiropractic treatment is one of the most common treatments for neck and back pain, however there is little understood about the neurophysiological mechanism that results in its efficacy to deter pain. Neck pain is a common and significant problem which affects about 30-50% of people every year and places a great burden on healthcare systems (Hogg-Johnson et al. 2008). Subclinical neck pain (SCNP) falls under this category and is defined as recurring neck dysfunction, such as mild neck pain, ache, and/or stiffness in individuals who have not sought any treatment for their maladies (Haavik and Murphy 2011). Recent studies have provided a growing body of evidence for altered neuromuscular and proprioceptive function in patients with neck and back pain which may explain why pain becomes chronic (Bränström et al. 2001; Falla et al. 2004; Stapley et al. 2006). There is also accumulating evidence to suggest that chiropractic manipulation can result in changes to the central nervous system function including reflex excitability, cognitive processing, sensory processing, and motor output (Murphy et al. 1995; Herzog et al. 1999; Haavik-Taylor and Murphy 2007; Haavik-Taylor and Murphy 2007). This is also evident in individuals that fall under the category of SCNP, as chiropractic manipulation has led to alterations in cortical somatosensory processing (Haavik-Taylor and Murphy 2007), and in elbow joint position sense (Haavik and Murphy 2011). This evidence suggests that chiropractic manipulation may have a positive neuromodulatory effect on the central nervous system and this may play a role in the effect it has on neck pain.

One mechanism proposed by Haavik-Taylor and Murphy (2007) suggests that areas of spinal dysfunction alters sensory feedback and could therefore be responsible for

improper sensorimotor integration (SMI) due to central plastic changes. The use of appropriate chiropractic care and spinal manipulation to the areas of spinal dysfunction would therefore normalize the afferent input, thus resulting in appropriate SMI. Previous work using paired-pulse transcranial magnetic stimulation (TMS) of the motor cortex has indicated that cervical spine manipulation can alter sensorimotor integration of the upper limb by decreasing the amount of short interval intracortical inhibition (SICI) (Haavik-Taylor and Murphy 2007).

The cerebellum is neural structure that is actively involved in both motor learning (Doyon et al. 2002; Doyon et al. 2003; Manto and Bastian 2007; Molinari et al. 2007) and SMI of afferent input from the joints of the neck and spine (Manzoni 2005; Manzoni 2007). It has also been suggested that the cerebellum is a plastic structure resulting in the modulation of motor circuitry (Doyon and Ungerleider 2002; Apps and Garwicz 2005). More recently, studies have shown that the cerebellum is also involved in the modulation of motor cortex excitability due to a reduction of cerebellar inhibition in patients suffering from migraine with aura (Brighina et al. 2009) and patients with focal hand dystonia (Brighina et al. 2009). These findings are highly relevant as they provide support for the concept that changes in the excitability of cerebellar projections may occur in individuals who suffer from overuse injuries and migraine, two conditions commonly treated with neck manipulation. Therefore, the effect of chiropractic manipulation on cerebellar function and its contribution to SMI, as well as its interactions with the motor cortex needs to be investigated in order to further understand the role and mechanisms underlying the efficacy of spinal manipulation. This research study therefore aims to investigate if there is modulation in cerebellar output to the motor cortex in SCNP

patients, and if spinal manipulation and motor sequence learning has an effect on SMI with respects to the cerebellum and subsequently the motor cortex. This will be performed using the cortical TMS measures of SICI and long interval intracortical inhibition (LICI), as well as the cerebellar TMS measure known as cerebellar inhibition (CBI) following spinal manipulation and a motor learning task.

Methodology

Subjects

Experiments were performed on 10 volunteers (mean age: 23.8; range: 20-35; 7 males & 3 females) each of which experienced recurring neck pain classified as SCNP, as assessed by the neck disability index (refer to appendix 4), and by a registered chiropractor, after giving their informed written consent. All of the participants were right handed as assessed by the Edinbugh Handedness Inventory (EHI), and none had any history of neurological disease as assessed by the TMS Safety Checklist (TSC) (refer to appendix 1 & 3 respectively). The study was approved by the local ethics committee and conducted in accordance with regulations laid down in the Decleration of Helsinki (refer to appendix 2 for consent form).

Electromyographic Recordings

Electromyographic (EMG) activity was recorded from the right first dorsal interosseus (FDI) muscle using a pair of Ag-AgCl surface electrodes in a belly-tendon arrangement. The ground electrode was placed around the wrist of the right arm, in a location that was located between the stimulating coil and the surface electrodes. The EMG signal was amplified (1000x) and band-pass filtered (20-2000 Hz) with a Cambridge Electronic

Design 1902 isolated amplifier (Cambridge Electronic Design, Cambridge, UK) digitizing at a sampling rate of 1kHz (CED 1401 laboratory interfacel Cambridge Electronic Design, Cambridge, UK) and received by a laboratory computer for off-line analysis. Data was analyzed using SIGNAL software version 4.08 (Cambridge Electronic Design, Cambridge, UK). Subjects were asked to maintain a relaxed position throughout the experiment, while their hand was placed in a pronated position. EMG activity was monitored during the protocol to ensure that the muscle was at rest.

Motor Sequence Task

Throughout the motor sequence learning (MSL) task, subjects were asked to sit in a chair with their arm supported by a soft pillow with a modified numeric keypad lying on top. With their hand palm down in a relaxed position, participants were asked to place their index finger on the keypad in a comfortable position so that they could reach the 7, 8 and 9 keys, while the other three fingers and thumb were taped down in order to maintain proper hand orientation. A custom program was created using E-prime 2.0 software (Psychology Software Tools, Sharpsburg, PA) which prompted the participants to enter randomized sequences of the keys 7, 8 and 9 in six letter blocks being displayed on the screen. This side to side movement of the index finger allowed optimal activation of the FDI muscle by performing its primary action of abducting the index finger. Each participant's performance was measured by accuracy and reaction time to the task. Due to the long duration of the task (~20 min), the task was separated into three parts: a pre-section, the complex task, and a post-section. The task was the same for each section, however the pre- and post-sections only consisted of 15 trials, while the complex task itself consisted of 225 trials.

Chiropractic Treatment

Participants received high velocity, low amplitude spinal manipulation immediately following the pre-intervention measures. Manipulations focused on the cervical and upper thoracic spine, in treatment of neck pain, and were targeted on dysfunctional cervical joints, which were determined by a registered chiropractor. Clinical evidence of joint dysfunction includes restricted intersegmental range of motion, palpable muscle tension at the intervertebral level, and tenderness to palpation of the joint (Hubka and Phelan 1994; Fryer et al. 2004). Myofascial trigger points in the cervical muscles were also treated if determined necessary by the chiropractor. The high velocity, low amplitude manipulation consisted of thrusts to the spine held in lateral flexion, with slight rotation and slight extension. This is a standard manipulation common to physiotherapists, physicians, and chiropractors. Previous research has shown that reflex EMG only occurs after this specific type of manipulation, rather than that of low-amplitude manipulations, and would thus be more capable of modulating afferent input to the central nervous system (Herzog et al. 1995).

Transcranial Magnetic Stimulation

Cortical stimulation was performed using a figure-of-eight coil (outer diameter 10mm) and was applied over the hand region of the left motor cortex (to elicit a response in the right FDI). Magnetic stimulation was given via the use of two Magstim 200 stimulator units (Magstim Co., Whitland, Dyfed, UK) connected together with a BiStim unit. The coil was held with the handle pointed backwards at approximately 45 degrees away from the mid-sagittal line, with the current flowing posteriorly. This coil orientation has been previously shown to allow the induced current to be perpendicular to the central sulcus,

which allows for the optimal activation of corticospinal neurons trans-synaptically (Werhahn et al. 1994; Kaneko et al. 1996). The optimal coil position for inducing a motor evoked potential (MEP) in the right FDI muscle was determined as the site where a slightly suprathreshold stimulus consistently produced the largest MEPs. This location was then marked with a felt tip pen onto a cap that the subject was asked to wear throughout the entire procedure. TMS was delivered at a frequency of 0.2 Hz with a 20% variance in order to account for anticipatory effects.

RTh and 1mV MEP

In order to determine the correct parameters used in the paired-pulse measures being utilized in this study (SICI and LICI), it was necessary to attain the correct stimulus intensity that elicited a MEP of approximately 1 mV and the subjects resting threshold (RTh). The 1 mV MEP was calculated by determining the stimulus intensity that would elicit MEPs of approximately 1 mV in peak to peak amplitude after averaging 14 sweeps. RTh was determined by finding the lowest level of stimulator output that would elicit a MEP of approximately 0.05 mV in at least 5 out of 10 trials, while the subjects hand was at rest.

Paired Pulse TMS

SICI and LICI were assessed using paired-pulse TMS paradigms. SICIs protocol consisted of a subthreshold conditioning stimulus (set to 80% of the RTh) preceded by a suprathreshold test stimulus at an interstimulus interval (ISI) of 2.5 ms (Kujirai et al. 1993). The test stimulus for SICI was set to the stimulator intensity that elicited an approximate 1 mV MEP. The test stimulus was monitored both before and after the intervention in order to ensure that the peak-to-peak amplitude was within 15% of each

other. If this value was outside of this 15% allowance, the stimulator intensity was raised until it was back within range. Each data block consisted of sixteen stimuli. The conditioned MEP amplitude was expressed as a percentage of the suprathreshold 1 mV amplitude.

LICIs protocol was assessed by applying a suprathreshold stimulus preceded by another suprathreshold stimuli and separated by an ISI of 100 ms (Nakamura et al. 1997; Chen et al. 1999). The two suprathreshold stimuli were set to the stimulator intensity that elicited the 1 mV MEP and the inhibition was measured as a ratio between the first and second MEPs.

Cerebellar TMS

The cerebellar conditioning stimulus (CCS) was delivered over the right cerebellar hemisphere with a double cone coil (110 mm mean diameter). This coil has been previously shown to be effective in applying an inhibitory stimulus to induce CBI (Ugawa et al. 1995). In order to position the coil with correct placement the coil was set at the midpoint of a line joining the external auditory meatus to the inion and the coil was oriented downwards, in order to produce an upwards current within the cerebellar cortex (Ugawa et al. 1995; Daskalakis et al. 2004; Brighina et al. 2009). The coil was placed in a stand and was strapped around the head of the participant in order to maintain a close fit and proper coil orientation. The intensity of the stimulator was pseudorandomized to stimulate at 70, 80, or 90% of the combined maximal stimulator output (MSO) of the two Magstim units connected by a BiStim unit. These intensities were chosen based on pilot data which showed that an inhibitory modulation of the test MEP could be attained at these levels, without the contamination of brain stem or nerve root stimulation . The test

stimulus, which was placed over the left motor cortex, was set to a stimulus intensity that elicited an MEP of approximately 0.8 mV, as CBI was demonstrated to be most effective when MEP amplitudes were below 1 mV (Daskalakis et al. 2004). The interstimulus interval between the CCS and the test stimulus of the motor cortex was set to 5 ms as it has been previously shown to induce CBI (Ugawa et al. 1995; Daskalakis et al. 2004). The inhibition was expressed as a percentage of the 0.8 mV test stimulus.

Experimental Design

This experiment looked to examine the effects of chiropractic treatment and a MSL task on the cerebellar and motor cortices. The cortical measures used were SICI and LICI, while the cerebellar measure used was CBI. These were measured both before and after a combined intervention of the chiropractic treatment and MSL task. These two tasks were combined as it was necessary to keep the experimental procedure under 3 hours in order to prevent the subjects tiring and thus decreasing their excitability levels. SICI and LICI were performed after the attainment of the 1 mV MEP and the RTh (Bistim set-up), and both measures were averaged over 16 stimuli. CBI was performed following the attainment of the 0.8 mV MEP (single Magstim set-up) and was averaged over 10 stimuli. An additional 4 stimuli were given at each of the three intensities used in order to monitor for brainstem and nerve root activation.

Statistical Analysis

Once the data was acquired, the peak-to-peak amplitude for each sweep was measured off-line using a customized Signal configuration (Cambridge Electron Design, Cambridge, UK) and the average amplitude was calculated for each session using Microsoft Excel. SICI and CBI were measured as a ratio of test MEPs, and LICI was

measured as a ratio of the first to second MEPs. Paired t-tests were run between the pre- and post- intervention groups in order to compare the mean peak-to-peak amplitudes for SICI and LICI. CBI was analyzed using a repeated measures ANOVA test with time (two levels: pre- and post-intervention) and between conditioning stimulus intensity (three levels: 70, 80, and 90% MSO), with appropriate post-hoc analyses as needed using IBM SPSS Statistics (Version 19). The MSL task was analyzed based on the measures of reaction time and accuracy of the keystrokes using a paired t-test between the pre- and post-intervention trials, which was also performed in IBM SPSS Statistics.

Results

SICI and LICI were performed on all participants both before and after the spinal manipulation and MSL task. However, only 7 participants were able to complete the CBI measure, as 3 of the subjects had large artefacts from the high intensity cerebellar stimulation that swamped the EMG signal and could not be suppressed, even after repeated abrading of the skin overlying the FDI muscle. Therefore, there were 10 data sets for SICI and LICI and 7 data sets for the CBI data analysis.

The MSL task showed that following the training intervention, the subjects reaction time improved significantly (from 451.63 to 364.14 ms; $p < 0.0001$) (Figure 16), while the participants accuracy of the task remained unchanged ($p = 0.55$).

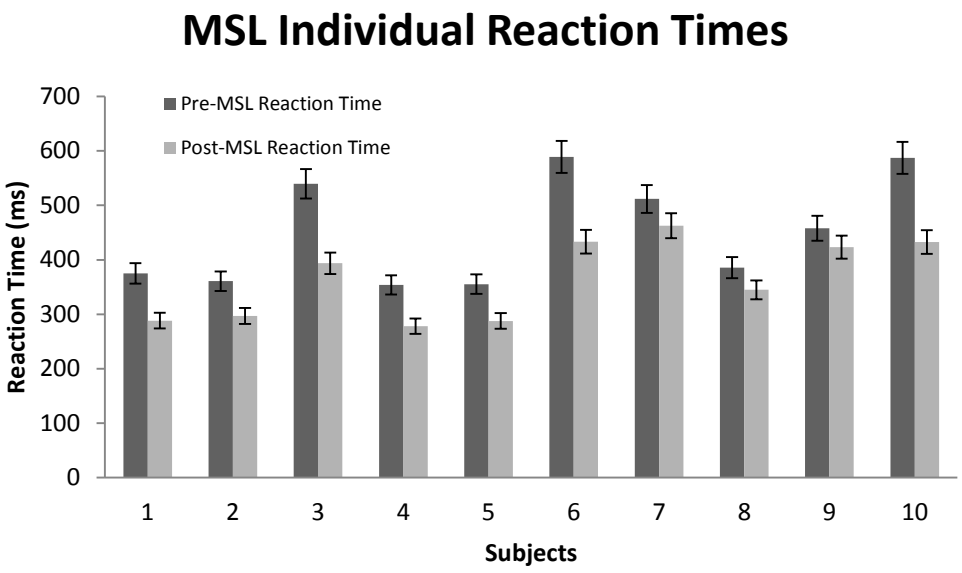

Figure 16. Motor sequence learning reaction times for all subjects. The MSL task resulted in a significantly decreased reaction time to the intervention for all subjects.

For the CBI measure, a significant difference was seen when comparing pre- and post-intervention with respects to the factor of time ($F = (6,2)\ 7.92$ ($p < 0.05$)), and with the factor of conditioning stimulus intensity ($F = (6,2)\ 6.56$ ($p < 0.05$)). However, there was no reported interactive effect between the two factors. A priori contrasts revealed that there was significant difference between pre- and post-intervention at both 70 ($p < 0.0001$) and 80% ($p < 0.05$) MSO, however no significant difference at 90%.

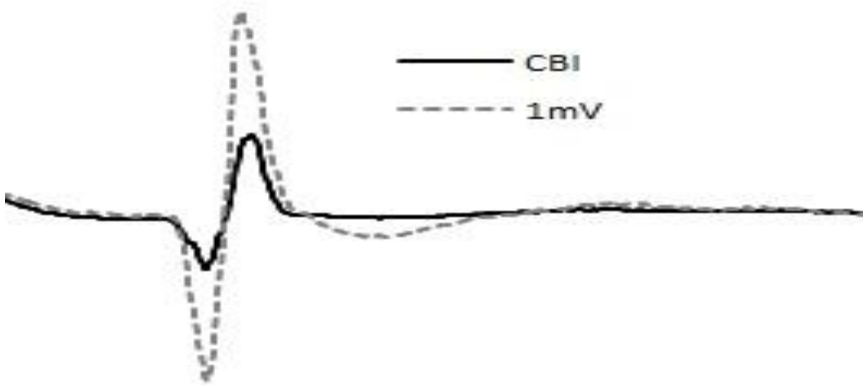

Figure 17. Raw EMG demonstrating the effect of CBI on cortical stimulation. When a conditioning stimulus is presented over the posterior fossa 5 ms prior to a cortical stimulus, it results in the suppression of the MEP.

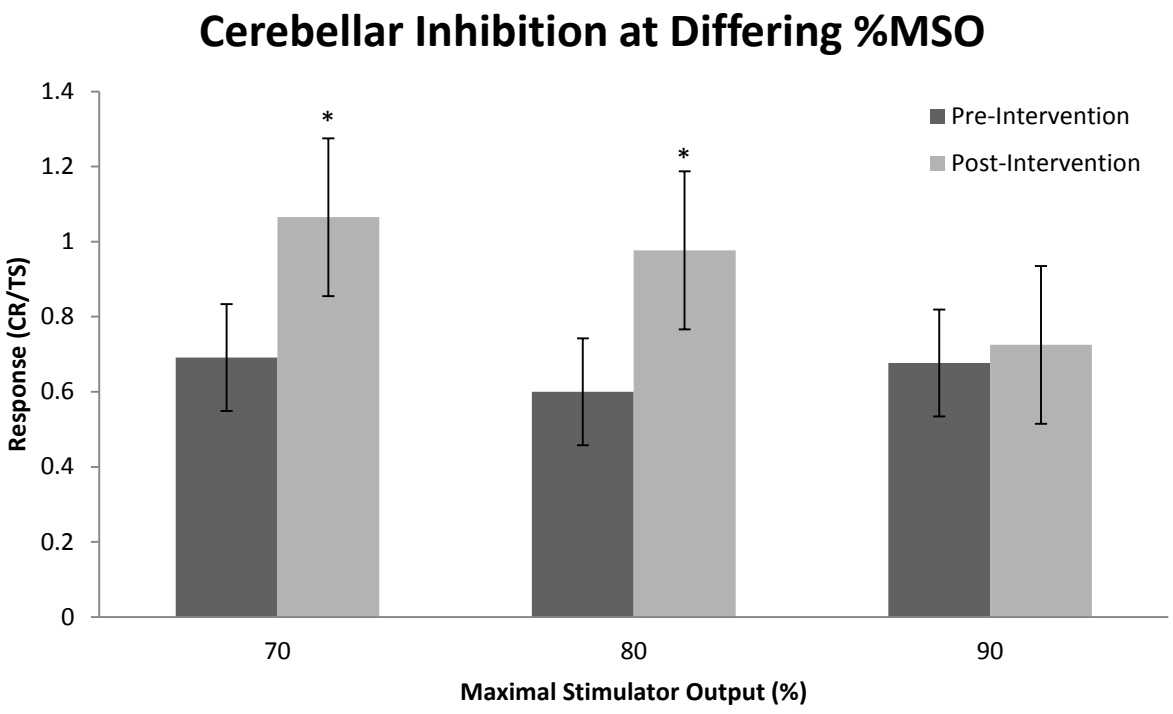

Figure 18. Responses for CBI at all conditioning stimulus intensities compared pre- to post-intervention, with the conditioned response (CR) being averaged to the test stimulus (TS). At 70 and 80% of MSO there was a significant change in the conditioned response, however no change at 90%.

Both SICI and LICI remained unchanged when comparing from pre- to post-intervention.

Discussion

The aim of this research project was to identify if there was modulation in cerebellar output in SCNP patients following spinal manipulation and MSL. Cortical TMS was used to measure the level of inhibition included SICI and LICI, while CBI was used to measure the inhibitory effect of the cerebellum on the motor cortex. A significant decrease in CBI was found following the intervention, while no change was found in the cortical measures of SICI and LICI. Significant improvement in reaction time occurred after the MSL segment of the intervention, while there was no change in the accuracy of the task.

MSL tasks have been previously shown to induce plasticity within the circuitry of both the motor cortex (Pascual-Leone et al. 1994; Pascual-Leone et al. 1995; Cirillo et al. 2010) and the cerebellum (Doyon et al. 2003). The decrease in mean reaction time as demonstrated in this study reflects implicit learning, which has been previously reported to induce altered representations of finger muscles in the motor cortex (Pascual-Leone et al. 1994). Neck manipulation has also been shown to provide a modulatory effect on the motor cortex by reducing the amount of intracortical inhibition (Haavik-Taylor and Murphy 2007). However, there are no known studies that have demonstrated the effects of neck manipulation alongside MSL using TMS to measure cortical and cerebellar output.

It has been previously demonstrated that cerebellar modulation is present in certain patient groups including focal hand dystonia (Brighina et al. 2009) and migraine with aura (Brighina et al. 2009). This study further adds to the literature by demonstrating an

alteration to cerebellar output in neck pain patients when they received a manipulation based chiropractic treatment prior to performing MSL. In manuscript one, there was no change seen following MSL alone in a healthy patient population, however in this study there was a change following the combined intervention in a SCNP group of subjects. It may be possible that these results occurred because of altered sensorimotor integration as proposed by Haavik Taylor & Murphy (2012), which was remedied following treatment. However, a limitation to these results is that due to the time limit being placed on the protocol, we had to perform the chiropractic treatment and MSL task one after another. Therefore, the design did not allow us to attribute whether the changes were due to the chiropractic intervention or the MSL task.

It is interesting to note that there was no significant effect on SICI following chiropractic treatment and the MSL. Referring back to manuscript one in this thesis, it was found that after MSL alone there was a significant decrease in the amount of intracortical inhibition as determined by SICI, while in another previous study by Haavik-Taylor & Murphy (2007) there was also a decrease in SICI following chiropractic treatment. It has also been shown that spinal dysfunction, as assessed by simultaneous median and ulnar stimulation divided by the arithmetic sum of somatosensory evoked potentials obtained from individual stimulation of the median and ulnar nerves, altered sensorimotor processing whereas chiropractic care resulted in changes to this ratio (Haavik-Taylor and Murphy 2007). Therefore, the lack of a significant change in SICI can be seen as uncharacteristic to the past literature.

This lack of results may have occurred due to numerous reasons. Firstly, there may have been an interaction between the spinal manipulation and the MSL task which may have

potentially cancelled out the effect observed from strictly the MSL task alone. Secondly, the previous study by Haavik-Taylor & Murphy (2007b) was shown to produce changes in the abductor pollicis brevis muscle, rather than the FDI which was used in the current study. Therefore, the FDI may not be susceptible to changes in excitability following spinal manipulation. Lastly, a SCNP group was used in the current study, and their altered sensorimotor integration may have led to insignificant changes in cortical excitability pre- to post-intervention.

Daskalakis et al. (2004) demonstrated that there is an interaction between CBI and SICI. This study postulated that if TMS of the cerebellum activated inhibitory Purkinje cells, the output from the deep cerebellar nuclei to the motor cortex via the ventrolateral nucleus of the thalamus would be reduced. Furthermore, if the cerebellothalamocortical pathway terminated on inhibitory neurons within the motor cortex, it would be expected that the cerebellum would also have the potential to reduce local intracortical inhibition. If the MSL task had a significant effect on the cerebellum in this group of subjects due to their neck pain and altered sensorimotor integration, then it is possible that a decreased level of CBI output to the motor cortex would result in an increase in SICI. However, with previous studies demonstrating that both chiropractic care and MSL tasks decrease SICI levels, the combined effects may have negated one another resulting in the lack of change seen in this study.

Future studies should individually investigate the effects of MSL and chiropractic manipulation on neck pain patients. By performing CBI and SICI protocols in separate experiments, the design could include an immediate post-manipulation measure prior to the MSL which would allow us to more clearly attribute changes to the either

manipulation or MSL effects. Also, a control condition, such as a passive head movement group, should be included to act as a control for the non-specific physiological effects that occur with a neck manipulation such as the application of pressure over a joint and head movements that occur during a neck manipulation. This comparison should be performed in that of a healthy age- and gender-matched control group.

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Thesis Summary

Subclinical neck pain is a substantial problem that affects numerous people each year, and places a burden on the healthcare system. Altered afferent input to neural structures, as a result of neck pain, results in defunct sensorimotor integration within the motor cortex, however it is unclear if there is modulation that occurs within the cerebellum as well. Motor sequence learning has also been shown to induce sensorimotor and plasticity changes within the cerebellum, and therefore these two mechanisms may alter the cerebellum similarly in order to induce plastic changes within the structure. Two studies were performed in order to determine if it was possible to induce both cortical and cerebellar learning, and if chiropractic care could alter motor output, via transcranial magnetic stimulation measures, to facilitate this learning.

Study one set out to determine if motor sequence learning could result in altered cerebellar and cortical processing and motor output. Results showed that following the motor learning intervention, there was an alteration in intracortical inhibition of the motor cortex, however no significant change in cerebellar output. Study two investigated if subjects with subclinical neck pain had altered sensorimotor integration within the cerebellum and motor cortex, and if chiropractic intervention could remedy this alteration. Results from this study demonstrated that following a combined intervention of motor sequence learning and chiropractic intervention, there was a modulation of cerebellar output to the motor cortex with no modulation within cortical inhibitory mechanisms.

There have been no known studies to have reported cerebellar processing changes following chiropractic manipulation, and few that have reported changes following motor sequence learning. The combined results of these two studies indicate that people who have subclinical neck pain have some form of altered sensorimotor integration which is changed when receiving chiropractic treatment. It is also evident that there is a change in cortical connections following MSL in the normal population, however a change in cerebellar processing in SCNP patients following chiropractic treatment. Therefore, it is evident that there is a modulation effect that occurs following chiropractic manipulation in the cerebellum, and that the cerebellum plays a role in those patients with altered afferent input. This is highly significant to future work in the field as this dysfunctional cerebellar processing may have potential as a measurement tool to determine those SCNP patients with disordered cerebellar integration and who may therefore be at risk of developing chronicity.

Section 3: Appendices

Appendix 1: 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 2: Project Consent Form

Associate Professor Bernadette Murphy
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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

Research Information for participants

Title: ***The neurophysiological effects of spinal manipulation- TMS April, 2008.*** **This study has received ethical approval from the UOIT ethics commitee (REB# 07-073)**

This is a multi-centre research study being conducted by Dr Bernadette Murphy from the Faculty of Health Sciences at the University of Ontario Institute of Technology (UOIT), in Oshawa, Ontario, Canada and Dr. Heidi Taylor from the New Zealand College of Chiropractic in Auckland, New Zealand. We are investigating how joint manipulation alters neurophysiological function in the central nervous system. In order to do this we will need to collect some information about the way your brain processes information and how it controls your hand and forearm muscles before and after a period of chiropractic care. We will also get you to complete some questionnaires, which will provide information regarding your current functional capacity, level of neck pain (if any), and general well being.

You are invited to participate in our research and we would appreciate any assistance you can offer us. Your participation in this study is entirely voluntary (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 future chiropractic care and/or academic progress, irrespective of whether or not payment is involved. We are seeking people with no neck or arm problems as well as those who have had a history of chronic neck pain for at least three months and are aged between 18 and 50. To participate in this study you must complete an eligibility checklist in conjunction with one of the researchers, to ensure you are eligible to participant in this research. You will also need to complete a TMS safety checklist.

Measurement sessions

Should you agree to participate, we will need you to attend up to two different evaluation sessions. If you are taking part in the spinal manipulation component, you will be screened by Dr Bernadette Murphy in order to determine and document if there is evidence of restricted joint movement in the joints of your neck. During each 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. If grant funding is obtained, we may be able to provide you with a $10 gasoline voucher for attending the measurement sessions.

Manipulation

If you are in the group receiving spinal manipulation one of the researchers will fill in an eligibility questionnaire with you to ensure you are a suitable candidate to receive spinal manipulation. If for any reason, you are not an appropriate candidate for this study, we will withdraw you from the study. However, this will not impact in any way on your chiropractic care.

Risks and benefits

The benefits of participating in this study is that you will learn more about your neck and arm pain and you will receive a free treatment session. You will also be aiding our understanding of these costly and disabling

conditions. Only safe conventional low amplitude spinal manipulation techniques will be employed in this study. These have been used by our research group in previous studies and no participant has reported any ill effects at all. Most participants have had very positive improvements in their outcome measures. On occasion, some participants may experience soreness the day after their first treatment, but this is only transient. If any participant experiences an unexpected worsening of their condition as a result of their care they will be withdrawn from the study and encouraged to return to their medical practitioner for further advice. The surface EMG techniques have low risks such as the person getting a skin irritation from the alcohol swab or electrode gel, but these again are uncommon and not serious. Magnetic stimulation is a safe procedure that allows us to study the nerve pathways that go to the muscles of the hand. The stimulator produces a clicking sound and then a mild twitching feeling can sometimes be felt in the scalp muscles as well as the hand muscles. Occasionally, some people experience mild, transient scalp discomfort, due to the activation of the scalp muscles by the stimulator. Some people may also experience experience nausea or a mild headache. Both these reactions are uncommon and not serious. If you experience any of these effects for longer than 24 hours after the experiment please contact the principal investigator. Both these reactions are uncommon and not serious. There are no other specific risks associated with the procedures and the equipment used in the study. Because the magnetic field discharges so quickly there is far less electromagnetic radiation than that from a television or mobile phone. At any time during the experiment, at your request we will stop the stimulation immediately.

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 filing cabinet at the New Zealand College of Chiropractic for 10 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 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, 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 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).
Phone (09) 526 6789 ext 207 Fax (09) 526 6788

The data from this research will be submitted to scientific conferences and peer reviewed journals. At the completion of the study, you will be sent a summary of the research findings and any place where the data has been published. All published data will be coded so that your data is not identifiable.

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

- I understand that taking part in this study is voluntary (my choice) and that I am free to withdraw from the study at any time without giving a reason and that this will in no way affect my future chiropractic care and/or academic progress, irrespective of whether or not payment is involved.
- This consent form will be kept in a locked filing cabinet at UOIT, Oshawa, Ontario for a period of seven years before being destroyed.
- The data collected in this study will be kept in a locked filing cabinet, separate to consent forms, at UOIT, Oshawa, Ontario for a period of seven years before being destroyed.

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

- I have read and I understand the information sheet dated April 2008 for volunteers taking part in the study designed to investigate the neurophysiological effects of spinal manipulation. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.
- I will be attending up to two sessions where measurements will be taken of the electrical activity in my hand and forearm muscles following magnetic stimulation of my brain
- 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 or the study.

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

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

Signed ..... Date .....

Contact numbers of main researchers:
Dr Bernadette Murphy, Phone: + 905 721-8668 ext 2778
Dr Heidi Haavik-Taylor, Direct Dial Phone: + 64 9 526-2104 (New Zealand)

RESEARCHER TO COMPLETE

Project explained by: _____

Project role: _____

Signature: _____ Date: _____

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.

	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: Neck Disability Index (NDI)

Neck Disability Index

THIS QUESTIONNAIRE IS DESIGNED TO HELP US BETTER UNDERSTAND HOW YOUR NECK PAIN AFFECTS YOUR ABILITY TO MANAGE EVERYDAY -LIFE ACTIVITIES. PLEASE MARK IN EACH SECTION THE ONE BOX THAT APPLIES TO YOU.
ALTHOUGH YOU MAY CONSIDER THAT TWO OF THE STATEMENTS IN ANY ONE SECTION RELATE TO YOU, PLEASE MARK THE BOX THAT MOST CLOSELY DESCRIBES YOUR PRESENT -DAY SITUATION.

SECTION 1 - PAIN INTENSITY

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

SECTION 2 - PERSONAL CARE

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

SECTION 3 – LIFTING

- ☐ I can lift heavy weights without causing extra neck pain.
- ☐ I can lift heavy weights, but it gives me extra neck pain.
- ☐ Neck pain prevents me from lifting heavy weights off the floor but I can manage if items are conveniently positioned, ie. on a table.
- ☐ Neck pain prevents me from lifting heavy weights, but I can manage light weights if they are conveniently positioned
- ☐ I can lift only very light weights.
- ☐ I cannot lift or carry anything at all.

SECTION 4 – READING

- ☐ I can read as much as I want with no neck pain.
- ☐ I can read as much as I want with slight neck pain.
- ☐ I can read as much as I want with moderate neck pain.
- ☐ I can't read as much as I want because of moderate neck pain.
- ☐ I can't read as much as I want because of severe neck pain.
- ☐ I can't read at all.

SECTION 5 – HEADACHES

- ☐ I have no headaches at all.
- ☐ I have slight headaches that come infrequently.
- ☐ I have moderate headaches that come infrequently.
- ☐ I have moderate headaches that come frequently.
- ☐ I have severe headaches that come frequently.
- ☐ I have headaches almost all the time.

SECTION 6 – CONCENTRATION

- ☐ I can concentrate fully without difficulty.
- ☐ I can concentrate fully with slight difficulty.
- ☐ I have a fair degree of difficulty concentrating.
- ☐ I have a lot of difficulty concentrating.
- ☐ I have a great deal of difficulty concentrating.
- ☐ I can't concentrate at all.

SECTION 7 – WORK

- ☐ I can do as much work as I want.
- ☐ I can only do my usual work, but no more.
- ☐ I can do most of my usual work, but no more.
- ☐ I can't do my usual work.
- ☐ I can hardly do any work at all.
- ☐ I can't do any work at all.

SECTION 8 – DRIVING

- ☐ I can drive my car without neck pain.
- ☐ I can drive my car with only slight neck pain.
- ☐ I can drive as long as I want with moderate neck pain.
- ☐ I can't drive as long as I want because of moderate neck pain.
- ☐ I can hardly drive at all because of severe neck pain.
- ☐ I can't drive my care at all because of neck pain.

SECTION 9 – SLEEPING

- ☐ I have no trouble sleeping.
- ☐ My sleep is slightly disturbed for less than 1 hour.
- ☐ My sleep is mildly disturbed for up to 1-2 hours.
- ☐ My sleep is moderately disturbed for up to 2-3 hours.
- ☐ My sleep is greatly disturbed for up to 3-5 hours.
- ☐ My sleep is completely disturbed for up to 5-7 hours.

SECTION 10 – RECREATION

- ☐ I am able to engage in all my recreational activities with no neck pain at all.
- ☐ I am able to engage in all my recreational activities with some neck pain.
- ☐ I am able to engage in most, but not all of my recreational activities because of pain in my neck.
- ☐ I am able to engage in a few of my recreational activities because of neck pain.
- ☐ I can hardly do recreational activities due to neck pain.
- ☐ I can't do any recreational activities due to neck pain.

PATIENT NAME _____ DATE _____

SCORE _____ [50]

Appendix 5: Chiropractic Patient Examination Form

Subject #: _____ Date:_____

Name:_____ Code:_____

Age:_____ DOB:_____ Ph#: _____

Sex: M / F Mobile: _____

VBI test: Left side_____ Right side_____

Current problem area (Neck/shoulder/elbow/forearm/wrist/hand)

Location _____

Onset _____

Palliative/provocative _____

Quality _____

Region/radiation _____

Severity out of 10 _____

Timing (when does it occur)_____

(how long have you had this problem)_____

Previous episodes (if reoccurring, how often)_____

_____

Previous treatments for this conditions and outcomes _____

_____

_____

Previous head/neck injury: Y / N

_____

_____

_____

_____

_____

_____

Previous chiropractic treatments: Y / N

If yes, details:_____

_____

_____

_____

Previous trauma: Y / N _____

Previous surgery: Y / N _____

Known conditions: Y / N _____

Current medication: Y / N _____

Orthopedic tests:

Tinels

Phalens

Bracelet

Trigger points present:

Upper limb Reflexes:

C5

C6

C7

Upper limb muscle strength (note if pain on testing):

Lateral deltoid

Supraspinatus

Anterior deltoid

Teres minor

Subscapularis

Biceps

Triceps

Wrist extensors

Wrist flexors

Supination

Pronation

Triceps

Triceps

Chiropractic Pre-check notes and care plan

Additional problem area (Neck/shoulder/elbow/forearm/wrist/hand)

Location _____

Onset _____

Palliative/provocative _____

Quality _____

Region/radiation _____

Severity out of 10 _____

Timing _____

Previous episodes _____

Previous treatments for this conditions and outcomes _____

_____

_____

_____

_____

_____

_____

Additional problem area (Neck/shoulder/elbow/forearm/wrist/hand)

Location _____

Onset _____

Palliative/provocative _____

Quality _____

Region/radiation _____

Severity out of 10 _____

Timing _____

Previous episodes _____

Previous treatments for this conditions and outcomes _____

_____

_____

_____

_____

_____

_____

_____

Table 1 Diagnostic criteria for upper limb disorders proposed by the HSE Workshop (adapted from Harrington et al, 1998[1])

Disorder	*Diagnostic criteria*
Rotator cuff tendinitis	History of pain in the deltoid region *and* pain on resisted active movement (abduction - supraspinatus; external rotation - infraspinatus; internal rotation - subscapularis)
Bicipital tendinitis	History of anterior shoulder pain *and* pain on resisted active flexion or supination of forearm
Shoulder capsulitis (frozen shoulder)	History of pain in the deltoid area *and* equal restriction of active and passive glenohumeral movement with capsular pattern (external rotation > abduction > internal rotation)
Lateral epicondylitis	Epicondylar pain *and* epicondylar tenderness *and* pain on resisted extension of the wrist
Medial epicondylitis	Epicondylar pain *and* epicondylar tenderness *and* pain on resisted flexion of the wrist
De Quervain's disease of the wrist	Pain over the radial styloid *and* tender swelling of first extensor compartment *and either* pain reproduced by resisted thumb extension *or* positive Finkelstein's test
Tenosynovitis of wrist	Pain on movement localised to the tendon sheaths in the wrist *and* reproduction of pain by resisted active movement
Carpal tunnel syndrome	Pain *or* paraesthesia *or* sensory loss in the median nerve distribution *and one of*: Tinel's test positive, Phalen's test positive, nocturnal exacerbation of symptoms, motor loss with wasting of abductor pollicis brevis, abnormal nerve conduction time
Non-specific diffuse forearm pain	Pain in the forearm in the absence of a specific diagnosis or pathology (sometimes includes: loss of function, weakness, cramp, muscle tenderness, allodynia, slowing of fine movements)

The subjects diagnosis based on the above criteria

_____

_____