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Abnormal surround inhibition does not extend beyond the affected limb in people with cervical dystonia: A transcranial magnetic stimulation study

by

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled " Abnormal surround inhibition does not extend beyond the affected limb in people with cervical dystonia: A transcranial magnetic stimulation study " submitted by Laura Meghan McDougall in partial fulfilment of the requirements of the degree of Masters of Science.

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Abstract

The purpose of this study was to investigate whether dysfunction of inhibitory mechanisms in focal dystonia extends beyond the affected limb. To this end, seven participants with cervical dystonia (CD) and seven healthy age-matched individuals were asked to perform simple index finger abduction movements to the sound of a metronome (pace of 1Hz). Single-pulse transcranial magnetic stimulation was applied at time intervals from 3 - 1000ms into their movements while electromyography was recorded from the first dorsal interosseous (prime mover) and from the abductor digiti minimi (uninvolved muscle). The results showed that motor evoked potential amplitudes of the FDI were significantly greater than those of the ADM early in the movement; less than 500ms post EMG onset. The same patterns of effects were shown in both control and CD groups. These results suggest that abnormalities in surround inhibition may not extend beyond the affected limb in people with CD.

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List of Abbreviations

ADM = abductor digiti minimi

APB = abductor pollicis brevis

BSP = blepharospasm

CD = cervical dystonia

Db = decibel

ECR = extensor carpi radialis longus

EMG = electromyography

FCR = flexor carpi radialis

FDI = first dorsal interosseous

FHD = focal hand dystonia

GP_e = globus pallidus pars externa

GP_i = globus pallidus pars interna

Hz = hertz

ISI = interstimulus interval

ICF = intracortical facilitation

ICI = intracortical inhibition

LAI = long afferent inhibition

LICI = long intracortical inhibition

MEP = motor evoked potential

rMT = resting motor threshold

SAI = short afferent inhibition

SICI = short intracortical inhibition

SN_{pc} = substantia nigra pars compacta

SN_{pr} = substantia nigra pars reticulata

STN = subthalamic nucleus

TES = transcranial electrical stimulation

TMS = transcranial magnetic stimulation

Chapter 1 – General Introduction

The thousands of simple and intricate movements humans make daily require a complex interplay between and integration of many neural and muscular operations. Most of us are unaware of these mechanisms and systems; we take our ease of mobility for granted. It is not until one is unable to move that one really appreciates our reliance on a supremely complex neuromotor system.

There are a number of ways in which the movement system can be disrupted. Neural or muscular injuries and disorders can disable or render a person completely immobile. Among the many human movement disorders resulting from neural dysfunction are subgroups of movement disorders caused primarily by the dysfunction of the basal ganglia. The basal ganglia are a group of subcortical nuclei believed to support both motor and cognitive functioning. Some of the disorders thought to arise from dysfunction of the basal ganglia include Parkinson's disease, Huntington's disease and chorea, hemiballismus and dystonia. The movement disorder called dystonia is the focus of this particular paper.

Dystonia is a broad term for a varied set of dysfunctions that results in co-contraction of agonist and antagonist muscles in either single or multiple body parts. These contractions can subsequently cause abnormal and potentially painful limb postures. Dystonia has many forms, which together have been estimated to affect approximately 300 in every 1,000,000 people (Nutt et al., 1988). There is no known cure for this disorder and the existing treatments remain ineffective for the bulk of individuals with this disorder.

The characteristics of this disorder include: irregular discharge from the basal ganglia-thalamo-cortico circuit, abnormalities within the sensorimotor system, atypical muscular activation, and abnormal inhibitory mechanisms throughout the body. The focus of the present study is the inhibitory mechanisms of people with dystonia. More specifically, the study was designed to investigate a proposed dysfunction or absence of surround inhibition in the motor system in people with dystonia (Sohn & Hallett, 2004b). Of particular interest is the possibility of a poor surround inhibition mechanism in an asymptomatic limb of people with cervical dystonia (dystonia in the neck muscles). Prior to outlining the specific predictions for the study, it is necessary to develop a basic outline of the circuitry of the normally functioning basal ganglia and the nature of its dysfunction in dystonia.

1.1 The Basal Ganglia

The basal ganglia are composed of a group of nuclei (caudate, lentiform [putamen and globus pallidus], and subthalamic nuclei) along with the claustrum, substantia nigra and dopaminergic neurons of the central tegmental area. The basal ganglia are thought to be crucial structures for proper functioning of both motor and cognitive domains (Brown & Marsden, 1998). The specific role of the basal ganglia in the motor domain is complex and has yet to be fully understood. It appears that information from the frontal lobe along with information from motor and somatosensory cortices flows through a number of different pathways before it is sent back to the cortex functionally organized and ready for motor output. The following is an elementary review of the flow of information through the basal ganglia (Figure 1).

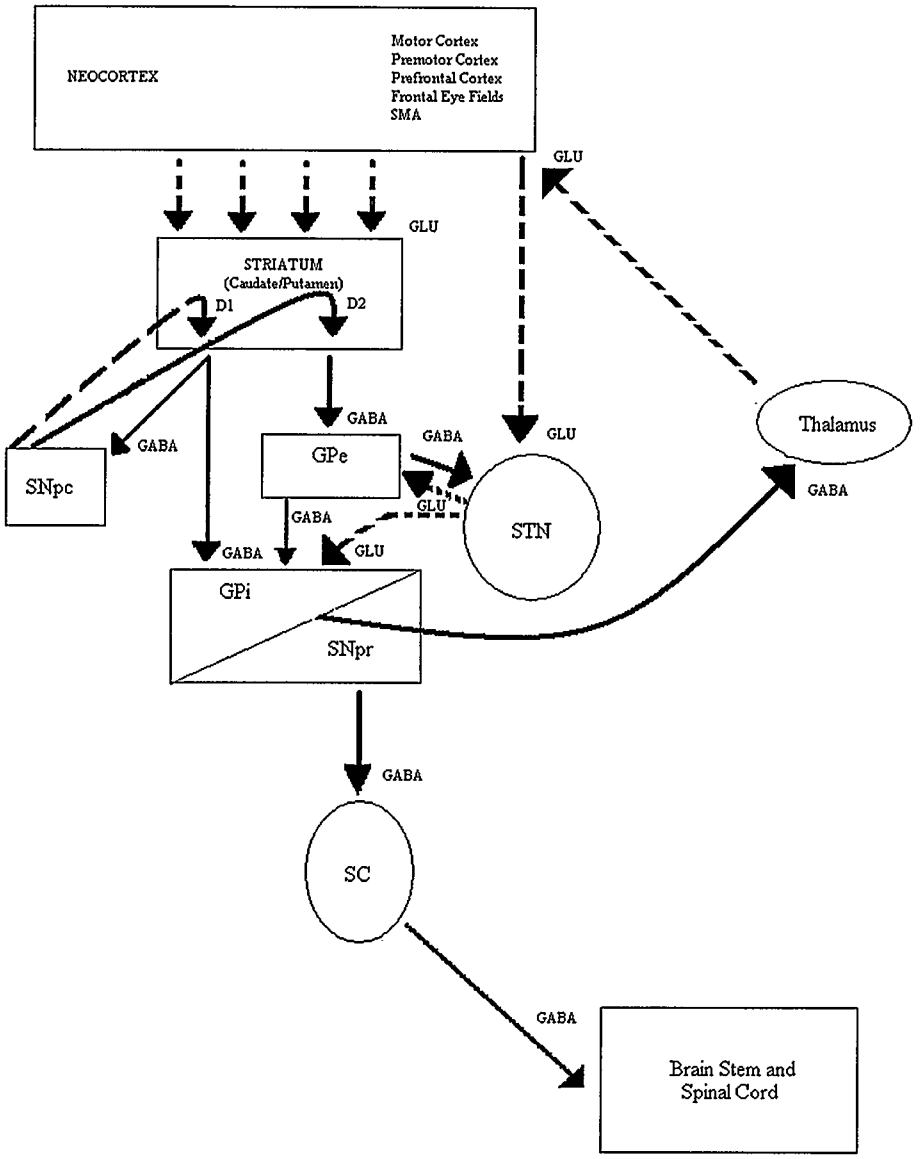

Figure 1. Simplified schematic representation of basal ganglia circuitry (adapted from Mink, 1996). GPe: globus pallidus, pars externa; GPi globus pallidus pars interna; SC: superior colliculus; SNpc: substantia nigra pars compacta; SNpr: substantia nigra pars reticulata; STN: subthalmic nucleus; D1&D2: dopamine (two receptor subtypes); GABA: gamma-amino-butyric acid; Glu: glutamate. Solid black lines indicate inhibitory projections and broken black lines indicate excitatory projections.

First, the striatum (caudate and putamen) receives excitatory input from nearly all areas of the cortex, including the somatosensory and motor cortices. The striatum is one of the two input structures of the basal ganglia (Mink, 1996). Functionally-related cortical areas project onto striatal zones in an overlapping fashion and with a clear somatotopic organization. Within the striatum, this information converges and reorganizes and is eventually sent to the output nuclei – such as the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNpr) (Mink, 1996).

In properly functioning basal ganglia, the motor circuit involving the striatum consists of two pathways that influence the thalamus and eventually the motor cortex via excitatory projections from the thalamus to motor cortex. These two pathways are the direct and the indirect pathways (Brown & Marsden, 1998). The direct pathway has inhibitory projections from the putamen onto the GPi. The GPi has inhibitory projections onto the thalamus (Figure 2). Therefore, when the striatum increases inhibitory signals to the GPi, the net effect is increased excitatory input on the cortex via the thalamus through disinhibition (Mink, 1996). There is no complete consensus on the impact of this increased excitatory input from the thalamus to the motor system, but it is generally thought that the direct pathway is involved in the facilitation of movement. What is not agreed upon is the precise role of the basal ganglia in movement. Early on, researchers thought that the direct pathway of basal ganglia was responsible for the initiation of movement, while others believed that these nuclei scaled the size and speed of movements. These are not the only roles hypothesized for this pathway, but it can be said that it sends excitatory signals to motor areas to somehow increase the likelihood of movement.

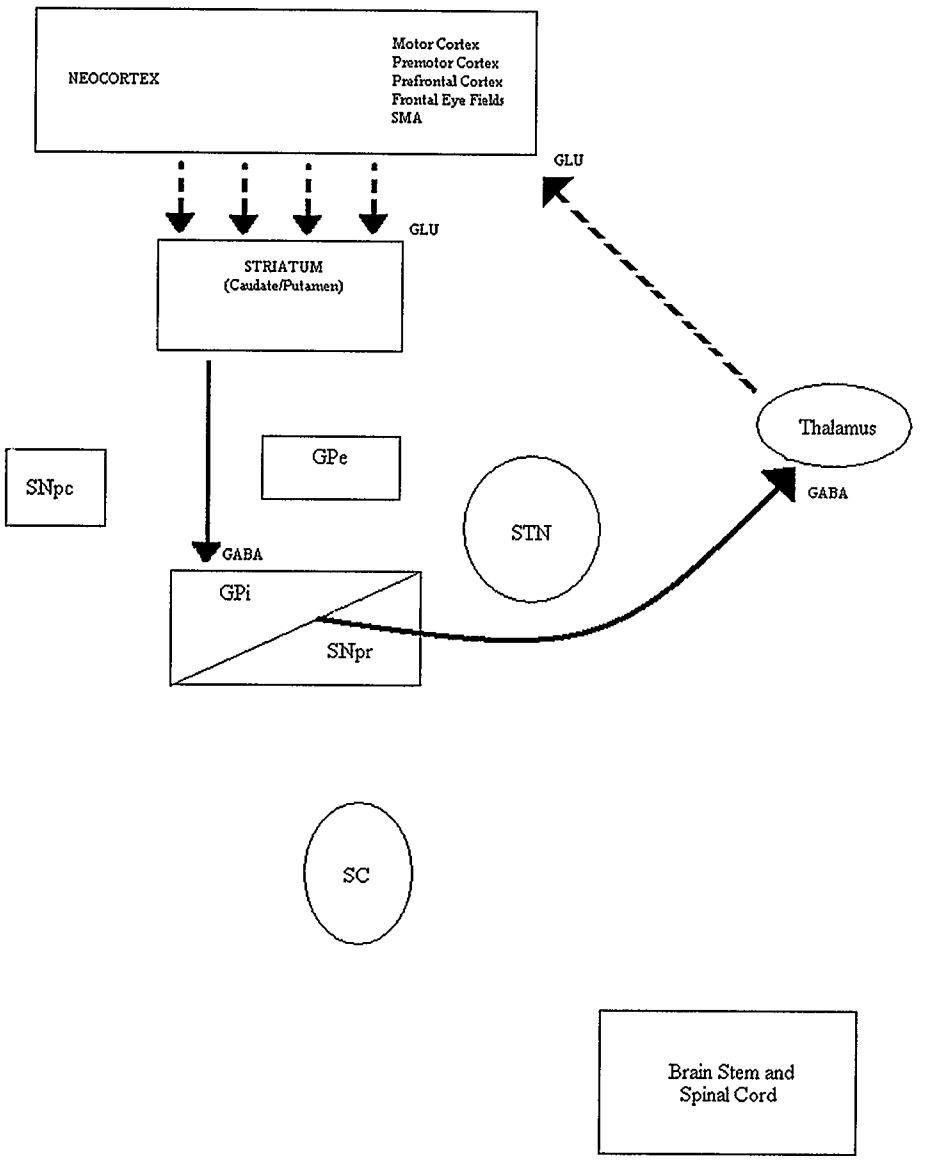

Figure 2. Simplified schematic representation of the direct pathway within basal ganglia circuitry (adapted from Mink, 1996). GPe: globus pallidus, pars externa; GPi globus pallidus pars interna; SC: superior colliculus; SNpc: substantia nigra pars compacta; SNpr: substantia nigra pars reticulata; STN: subthalmic nucleus; D1&D2: dopamine (two receptor subtypes); GABA: gamma-amino-butyric acid; Glu: glutamate. Solid black lines indicate inhibitory projections and broken black lines indicate excitatory projections.

In contrast, activation of the indirect pathway has a net inhibitory influence on the cortex. This pathway begins with inhibitory inputs from the putamen to the external segment of the globus pallidus (GPe) (Figure 3). The GPe then projects inhibitory signals onto the subthalamic nucleus (STN), which in turn sends excitatory projections onto the GPi. Thus, when the striatum increases the inhibitory signals to the GPe, the STN receives less inhibition. This decrease in inhibition leads to increased excitation of the GPi and thus, the thalamus receives more inhibitory input from the GPi and there is a net reduction of excitation on the motor cortex (Mink &Thatch, 1993). There are also direct projections from the GPe to the GPi and SNpr and projections from the STN back to the GPe (Vitek, 2002) (see Figure 1). Although some of the input to the basal ganglia is organized and focused within the striatum, it is thought that the indirect pathway further refines the information leaving the basal ganglia (Mink, 1996). Just as in the case of the direct pathway, the exact role of the indirect pathway is also unknown. However, the indirect pathway is generally thought to be a "brake" on movement, affecting either initiation or the size and speed of a movement. Other hypotheses exist for this pathway, but overall it is thought that it inhibits movement in some fashion.

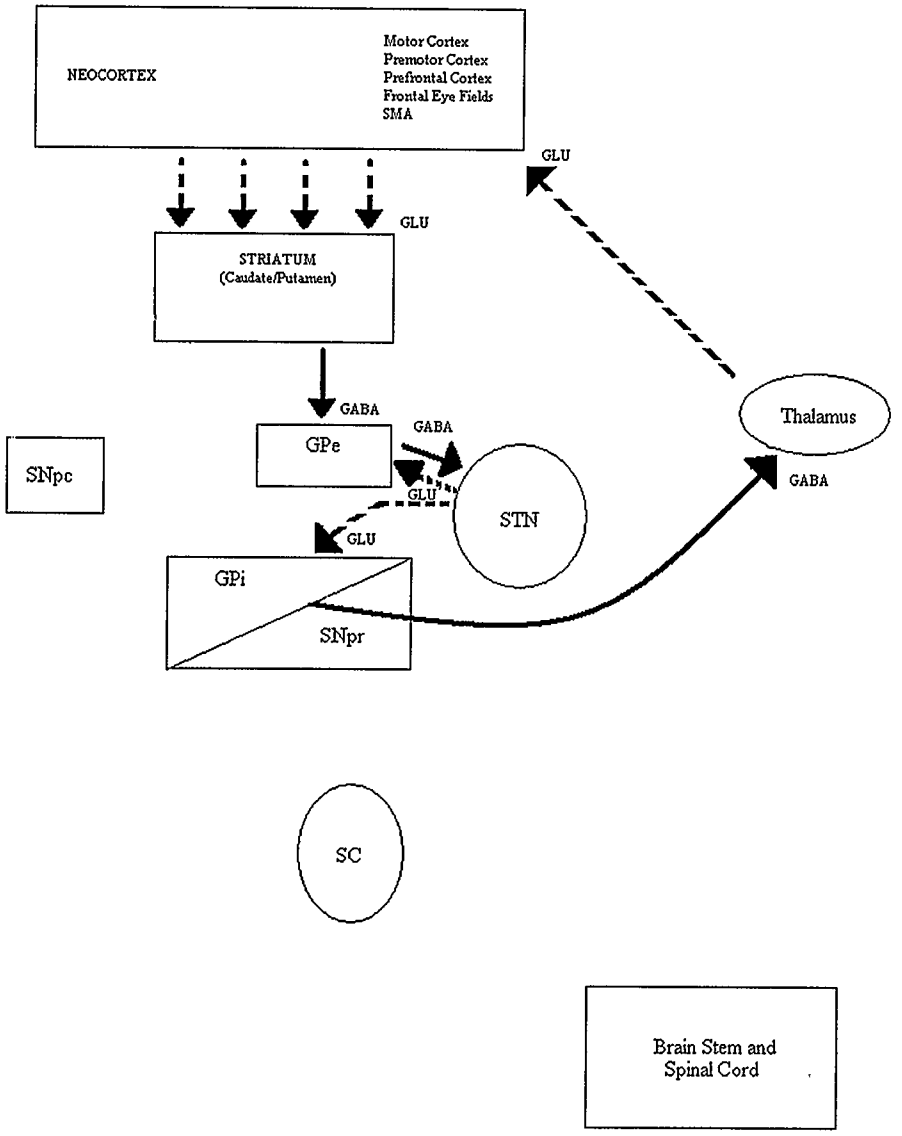

Figure 3. Simplified schematic representation of the indirect pathway within basal ganglia circuitry (adapted from Mink, 1996). GPe: globus pallidus, pars externa; GPi globus pallidus pars interna; SC: superior colliculus; SNpc: substantia nigra pars compacta; SNpr: substantia nigra pars reticulata; STN: subthalmic nucleus; D1&D2: dopamine (two receptor subtypes); GABA: gamma-amino-butyric acid; Glu: glutamate. Solid black lines indicate inhibitory projections and broken black lines indicate excitatory projections.

Researchers are beginning to support the idea that there is a second important input structure of the basal ganglia besides the striatum. Therefore, the direct and indirect pathways are not the only pathways within the basal ganglia that are responsible for the activity of the cortex. The second input structure of the basal ganglia is the subthalamic nucleus (STN) (Mink, 1996). This pathway has been termed the "hyperdirect" cortico-subthalamo-pallidal circuit (Nambu, Tokuno, & Takada, 2002) (Figure 4). The GPi and the SNpr also receive input from a fast-acting divergent pathway through the STN. The STN receives direct excitatory input from the primary, supplementary and premotor cortices. The STN then sends excitatory projections to the GPi and SNpr (Mink, 1996). It is thought that input from both the striatum and STN allows for broad excitation of the GPi from motor commands sent by the cortex as well as more focused, context-dependent inhibition of the GPi and SNpr (Mink, 1996). Thus, this "hyperdirect" pathway may work as a fast-acting and broadly excitatory signal sent to the thalamus, which results in a reduction of excitation to the motor cortex. Furthermore, it is thought that this pathway could potentially prepare the motor system for accurate movement selection (Nambu, Tokuno, & Takada, 2002).

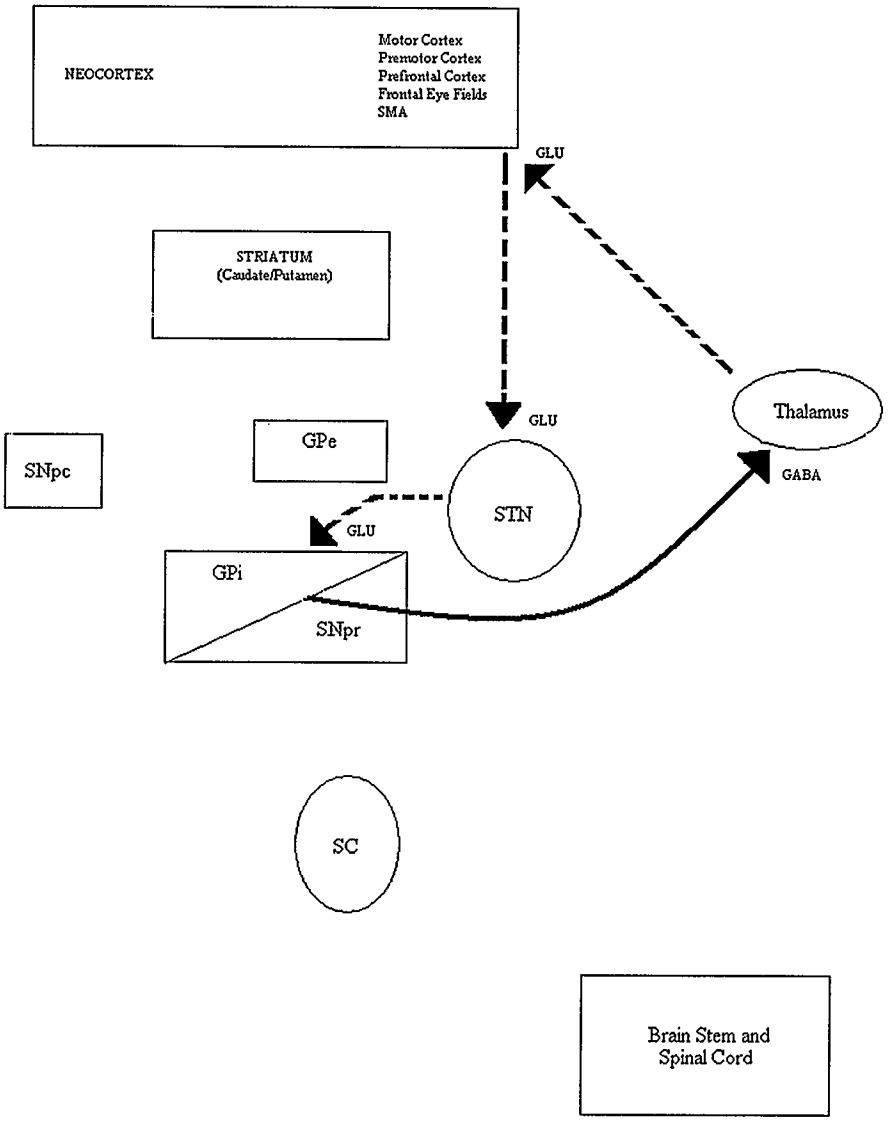

Figure 4. Simplified schematic representation of the "hyperdirect" pathway within basal ganglia circuitry (adapted from Mink, 1996). GPe: globus pallidus, pars externa; GPi globus pallidus pars interna; SC: superior colliculus; SNpc: substantia nigra pars compacta; SNpr: substantia nigra pars reticulata; STN: subthalmic nucleus; D1&D2: dopamine (two receptor subtypes); GABA: gamma-amino-butyric acid; Glu: glutamate. Solid black lines indicate inhibitory projections and broken black lines indicate excitatory projections.

A multitude of theories attempt to explain the exact purpose(s) of the basal ganglia. These theories are built mostly upon the results of research on movement disorders that are caused by dysfunction of the basal ganglia. Some of the more popular theories regarding the purpose of the basal ganglia include: movement initiation, the scaling of the size and speed of movements, and execution of automatic movement sequences (Mink & Thatch, 1991). More recently, however, Brown and Marsden (1998), Mink (1996) and Nambu et al. (2002) proposed that the basal ganglia are responsible for focusing sensory input and motor commands such that appropriate motor programs are selected while competing motor programs are inhibited. Thus, an attentional/selection mechanism for the motor system is suggested.

Whatever the true purpose of the basal ganglia, it is known that if the basal ganglia are damaged, many debilitating movement disorders can occur. Depending on the location of the damage or dysfunction, symptoms can range from the large uncontrollable movements of Huntington's disease and chorea to bradykinesia (slowing of movements), akinesia (inability to initiate movement) and tremor in Parkinson's disease. In one group of people, those with dystonia, dysfunction of the basal ganglia leads to excessive co-contraction of agonist and antagonist muscles. This co-contraction leads to twisted, tilted and contorted postures in one, or sometimes, many limbs. Because dystonia is the focus of the present study, I will provide a more thorough discussion of this disorder.

1.2 Dystonia

Dystonia manifests itself in repetitive or sustained postures, which are the result of involuntary co-contraction of agonist and antagonist muscles in one or many body

parts. The resulting postures can be painful, twisted and abnormal. There are no known cures (Fahn, 1988). Although Oppenheim studied this disorder as far back as 1911, the etiology of this disorder remains unclear. Dystonia is classified on three different characteristics: age of onset, distribution of symptoms and etiology (Fahn, 1988). The onset of dystonia may occur early (<28 years) or late (>28 years) (Fahn, 1988). According to Fahn (1988), the age of onset seems to be the best indicator of whether the dispersion of dystonic symptoms will spread and become generalized throughout the body or remain only in the body parts first affected. Early in life, if a person develops dystonia, it is more likely that the dystonia will spread throughout the body (Fahn, 1988). Whereas, after the age of 28 years, it is likely that people who develop dystonia will develop symptoms in fewer limbs and that there will be less spread than in dystonia that develops early in life (Fahn, 1988). These differing types of dystonia will be discussed below.

Dystonia is also classified based on the anatomical dispersion of the symptoms. If a single body region is affected such as the hand (writer's cramp), the eye (blepharospasm), or neck (torticollis/cervical), then it is classified as "focal dystonia" (Fahn, 1988). "Segmental dystonia" occurs when two or more adjacent areas are affected. The onset of both segmental and focal dystonia is generally later in life (Fahn, Bressman & Marsden, 1998). A classification of "generalized dystonia" means that dystonia is present in most body parts and may also be accompanied by slow and/or abnormal involuntary movements (Fahn et al., 1998). As mentioned above, generalized dystonia is more commonly associated with a very early onset and a fast progression of

affected limbs beyond the initial site and focal dystonias typically develop later in life (Fahn et al., 1998).

Finally, dystonia is classified as being of "primary or idiopathic origin" (which includes those who have genetically inherited the DYT1 gene) or of "secondary origin" (caused by an injury or lesion of the brain; Fahn et al.,1998). In both cases, it is now being proposed that people who develop focal dystonia may have a predisposition or primary abnormality, which only manifests itself after an insult to the brain or affected limb (i.e., excessive use of a limb, or injury to a limb or the effects of a stroke). Generalized dystonia has been linked to a genetic alteration of the DYT1 and DYT2 genes, but the etiology of focal dystonias is less clear, with some evidence of genetic involvement but no consistent etiology (Breakfield et al., 2008).

The prevalence of dystonia in the population is unknown as there are no large, controlled epidemiological studies on this disorder. However, a relatively small-scale study done in Rochester, Minnesota estimated the prevalence of focal dystonia to be 257 in every 1,000,000 people and a lower prevalence of generalized dystonia at 34 in every 1,000,000 people (Nutt et al., 1988). It has been shown that there is a 2:1 female to male ratio in craniocervical dystonia and a paradoxical reverse of this ratio in many of the other focal dystonias such as focal hand dystonia (Soland, Bhatia & Marsden, 1996). It is certain dystonia is not a rare disorder and its debilitating nature and apparent lack of a cure make it a clear candidate for further research.

The data and discussion outlined above show that generalized and focal dystonias each have relatively distinct attributes in terms of age of onset, etiology and dispersion of

symptoms. The target of the present study will be focal dystonias – more specifically, cervical dystonia (CD) and focal hand dystonia (FHD).

There are many common abnormalities found in focal dystonias. These abnormalities include, but are not limited to: irregular discharge from the basal ganglia-thalamo-cortico circuit (Vitek, 2002; Bhatia & Marsden, 1994), abnormalities within the sensorimotor system (Fiorio et al., 2008; Molloy et al., 2003; Abbruzzese at al., 2001), atypical muscular activation (Farmer et al, 1998; Tijssen, Marsden & Brown, 2000) and abnormal inhibitory mechanisms throughout the body (Nakashima et al., 1989; Chen, Tsai & Lu, 1995; Abbruzzese et al., 2001; Stinear & Byblow, 2004). In recent years, however, many of the common pathophysiologies associated with the affected limb in focal dystonia have been observed outside the dystonic limb – i.e., in "non-affected" limbs (Obermann et al., 2008; De Vries et al., 2008; Abbruzzese et al., 2001; Chen, Tsai & Lu, 1995; De Vries et al., 2007; Deuschl et al., 1992). This pattern of findings may suggest that all focal dystonias share an underlying systemic disturbance: that the "focal" expression of the dystonia in a single limb represents only the worst and most affected area and that the unaffected areas of the body are in a "pre-dystonic" state (De Vries et al., 2008). This conclusion may help to explain why some of the same abnormalities found within a dystonic limb are found in asymptomatic limbs as well. Each of these abnormalities will be discussed in brief below, along with the research into the asymptomatic limb. Because the overall focus of the research described in this paper is on neural inhibitory mechanisms in the motor cortex in people with dystonia, this topic will be discussed in depth later, in the surround inhibition section.

1.2.1 Abnormalities in the Basal Ganglia-Thalamo-Cortico Circuit

Dystonia can be caused by stroke or lesions (secondary causes) to the basal ganglia, particularly in the putamen or globus pallidus, or in the thalamus (Bhatia & Marsden, 1994). However, while usually there is no discernable pathological abnormality of the brain with primary (idiopathic) dystonia, functional abnormalities have been discovered within the circuits of the basal ganglia. It has been suggested that the tonic firing of the GPi is underactive in the dystonic brain (Mink, 1996). This abnormal firing would cause increases in excitatory thalamic drive to the motor cortex, which is thought be the root of excessive muscular activity (Vitek, 2002). Current thought is that, not only is the GPi underactive, but the temporal firing pattern of the GPi is also abnormal (Vitek, 2002). The abnormal temporal firing may create changes not only in the amount of excitatory drive from the thalamus, but also on the focus of the output from the basal ganglia to the thalamus. This misfiring could lead to an inability to select and inhibit competing motor programs (Vitek, 2002; Tang et al., 2007). Vitek (2002) asserts that an underactive firing rate of the GPi cannot be the only cause of dystonic symptoms. This assertion is based on the fact that a pallidotomy can relieve dystonic symptoms. If decreased firing of the GPi alone cannot be the cause of dystonia, then evidence of abnormal temporal firing patterns provides a better explanation for the symptoms seen with dystonia.

The direct pathway has also been implicated in dystonia. There is increased activity of the direct pathway so that the GPi is excessively inhibited and thus the motor areas are disinhibited (Mink, 2003). It may be the case that the interplay between

dysfunctional pathways in the basal ganglia, along with other abnormalities in the sensory and motor pathways, constitutes the root cause for the expression of dystonia.

Abnormalities within this circuit have also been found beyond the affected limb. For instance, de Vries and colleagues (2008), using an fMRI technique, showed that the activity of basal ganglia (specifically the right putamen) of patients with cervical dystonia (CD) was significantly reduced during a clinically normal wrist flexion/extension movement. Obermann et al. (2008) also found abnormalities in basal ganglia activity using fMRI during a grip force task in people with blepharospasm (BSP) and CD. However, they found increases in the activity of the putamen, thalamus and caudate nucleus rather than the reduction in activity found by de Vries et al. (2007). This discrepancy in results may be due to differences in testing parameters, sample sizes and/or task. The inconsistency of results with regard to the extent or exact area of abnormal basal ganglia activity outside the affected limb means it is not possible to draw definitive evidence-based conclusions at this time.

1.2.2 Abnormalities in the Sensorimotor System

It appears that by touching certain parts of their body or imagining doing so, some dystonic patients can temporarily relieve their symptoms. The presence of these abilities in people with dystonia, commonly referred to as 'geste antagoniste' or 'sensory tricks', may indicate a crucial involvement of sensory input and sensorimotor integration circuits in dystonia (Berardelli et al., 1998). The effectiveness of these sensory tricks may suggest that tonic sensory inflow is useful in relieving dystonic symptoms (Berardelli et al, 1998; Schramm, Reiners & Naumann, 2004).

It has also been shown that the organization of the somatotopic representation in the somatosensory cortex is disorganized and less specific than in the average population (Quatarone, 2008). People with dystonia have a decreased ability to discriminate incoming temporal, spatial and proprioceptive information (Fiorio et al., 2008; Molloy et al., 2003; Abbruzzese at al., 2001). In sum, while there is no unifying explanation of the efficacy of sensory tricks, abnormal integration of peripheral input and abnormal somatotopic organization, it appears that the sensorimotor representations in dystonia are different from those of the average population.

The sensorimotor system also seems to be affected throughout the body. In 2003, Molloy and colleagues used a spatial discrimination task in both hands to determine if people with CD and BSP had abnormalities in their sensorimotor circuits beyond their affected limbs. They found that CD and BSP participants had significantly larger spatial discrimination thresholds than the controls. Similarly, tactile temporal discrimination thresholds also appear to be significantly larger in patients with BSP (Fiorio et al., 2008). In 2008, Quatarone and colleagues used a paired-associative TMS technique to investigate the plasticity of the sensorimotor system in the arm of patients with CD. The changes in excitability were less somatotopically specific in the CD group than in controls. In the control group, only the muscle innervated by the median nerve (ADM) showed increases whereas both the FDI and ADM (muscles innervated separately by medial and ulnar nerves) showed large increases in the CD group. Therefore, it seems that both the affected and unaffected limbs of people with focal dystonia display abnormal sensory integration patterns.

1.2.3 Abnormalities in Patterns of Muscle Activation

It has been noted that people with FHD have significantly more 'common input' to opposing muscle groups (e.g., Farmer et al., 1998). 'Common input' can be defined as groups or pairs of motor units that share the same presynaptic input (Sears & Stagg, 1976). Researchers examining this phenomenon, typically look at measures of coherence and synchrony in EMG patterns to gain insight into the degree of common input between different motor units. The higher the coherence and synchrony between motor units, the greater the probability of a common presynaptic input. Evidence for this increased common input has come from a study of the extensor and flexor carpi radialis muscles during an object grip task that required participants to maintain 20-50% of maximum voluntary contraction in both muscles. Thus, common input was being evaluated during co-contraction. Using frequency domain and cross-correlation analysis, it was found that there were significantly higher levels of coherence and motor unit synchronization in FHD (Farmer et al., 1998). Furthermore, Tijssen, Marsden and Brown (2000) found that, whereas control subjects had a significant peak in EMG at 10-12 Hz, CD patients showed coherence in their affected muscles (sternocleidomastoid (SCM) and splenius capitus (SPL)) in a 4-7 Hz bandwidth. These authors also noted that the SCM and the SPL were in phase with each other and that these patients' display of short-term synchronization suggests a common presynaptic drive to motor neurons of the SCM and SPL. Common input and presynaptic drive can also be thought of as divergence within the motor system. This divergence increases the likelihood that two motor units, possibly in two different muscles, will fire together. It may, in fact, be that the co-contraction in dystonia is caused by changes in common input to both agonist and antagonist groups of muscles.

It is interesting to note, however, that high levels of common input were not found in the asymptomatic limb in people with dystonia, which may suggest that this is not a systemic issue in focal dystonia and may be a result of the persistent co-contraction commonly associated with focal dystonias (Farmer et al., 1998). The absence of this abnormality outside the affected limb suggests that not all symptoms are present elsewhere in the body.

1.2.4 Abnormal Inhibitory Mechanisms

Spinal Cord

Reduced inhibitory mechanisms are the hallmark of dystonia. Over time, research has revealed that there may be a lack of inhibition throughout many different areas of the brain and spinal cord. A spinal reflex known as reciprocal inhibition, which is tested using the Hoffman-reflex (H-reflex) technique, is reduced between the hand extensors and flexors in the affected hand of people with FHD (Nakashima et al., 1989; Chen et al., 1995). This reflex is thought to enable movement by inhibiting antagonist muscles during a movement that would otherwise interfere with performance of the agonist muscles. Specifically, when one muscle is activated, an inhibitory interneuron synapses on motor neurons of its antagonist pair. This inhibitory action allows for the contraction of one muscle and the relaxation of the opposing muscle thus reducing the likelihood of co-contraction during movement (Nakashima et al., 1989). Reduced reciprocal inhibition seems to be one mechanism by which co-contraction of agonist and antagonist pairs comes about in focal dystonia, which is a primary distinguishing expression of dystonia (Berardelli et al., 1998).

The spinal cord and spinal reflexes also seem to be affected in a global manner. As outlined previously, dystonia tends to be associated with decreases in reciprocal inhibition within the affected limb. Just as in the experiments mentioned above, a conditioning stimulus of the radial nerve was used to look at the size of the reciprocal inhibition in the median nerve. It was found that the unaffected hand of those with FHD and CD had significantly reduced reciprocal inhibition (Chen et al., 1995; Deuschl et al., 1992). Therefore it seems that the problems in reciprocal inhibition were apparent in the asymptomatic hand of people with FHD and in the forearms of patients with CD (Chen et al., 1995; Deuschl et al., 1992). Furthermore, De Vries et al. (2007) looked at the levels of co-contraction in the asymptomatic limb (arm) of people with CD. Although people with CD did not have any overt co-contraction in their forearms, they did show a significantly prolonged extensor activation causing overlap between flexor and extensor activity. These two pieces of data taken together add to the evidence linking reciprocal inhibition and co-contraction and also provide evidence that another dystonic abnormality extends beyond the affected limb.

Sensory System

Studies using paired associative TMS, a technique using peripheral nerve electrical stimulation followed by TMS stimulation, have revealed that both long- and short-latency afferent inhibition are reduced in people with dystonia (LAI and SAI) (Abbruzzese et al, 2001). This same method showed that peripheral stimulation reduces the size of TMS evoked MEPs in healthy individuals and that these effects are dependent on the interstimulus interval (ISI) (Sailer et al, 2003). There seems to be interaction between human sensory and motor systems that may reflect gating and/or an updating of

information coming into and leaving the cortex. The interaction between these two systems requires a degree of integration of information in order to work effectively, which is why this method is thought to reflect sensorimotor integration (Sailer et al., 2003). Abbruzzese and colleagues (2001) found that people with focal dystonia had facilitation of MEPs after peripheral stimulation (a paired associative TMS paradigm) rather than inhibition, as is found in healthy subjects. This pattern of effects suggests that people with dystonia may not be able to integrate sensory information they receive from their surroundings. If this is the case, the ability to organize and generate subsequent movements based on that information would be compromised.

People with dystonia display decreased inhibition in the motor system after peripheral stimulation; this may imply that the communication between these two systems is somehow compromised. This disconnection may contribute to the observed symptoms. Abbrezzese and colleagues (2001) did investigate both the symptomatic and asymptomatic hand and found similar patterns of results, which may suggest that abnormal sensory inhibition may be a systemic issue.

Motor Cortex

Research with paired-pulse TMS has also revealed that people with dystonia have significantly lower levels of short intracortical inhibition (SICI) (Stinear & Byblow, 2004). In paired-pulse TMS studies, a test stimulus is provided 2-200 ms after a subthreshold conditioning stimulus. The amplitude of the test MEP is the critical variable and the relative amplitudes and timings of the two stimuli vary from study to study. Since paired-pulse TMS is considered to preferentially assess the activity of GABA-mediated inhibitory interneurons in the primary motor cortex, it is thought that lower

levels of SICI in people with dystonia indicate a lack of inhibition in the motor cortex itself and that this may contribute to the symptoms of dystonia (Stinear & Byblow, 2004). Beck et al. (2008) followed up on the work done by Stinear and Byblow (2004). They looked more specifically at the time course of the abnormal changes in ICI levels found by Stinear and Byblow (2004). This study revealed that the control group showed a reduction in the size of MEPs in the APB and constant levels of SICI during FDI movement initiation. People with FHD on the other hand, showed no modulation of MEP amplitude in the APB and reduced SICI during FDI movement initiation. Based on these findings, Beck and colleagues argue that the circuitry underlying SICI is integral to the ability to inhibit unwanted muscle activity. Moreover, these authors found that this inhibition happens early in movement initiation and tapers off as the movement is maintained. This information and the sensorimotor integration data suggest that a lack of inhibition in both the motor and sensory input may contribute to dystonic symptoms. Since this sort of investigation has only been conducted in the affected limb, there is no evidence to determine how levels of ICI are affected throughout the body.

Sohn and Hallett (2004a) coined the phrase "surround inhibition in the human motor system" to denote the idea that groups of muscles involved in an action are selectively activated, while muscles that would compete with that action are inhibited. It is further suggested that this inhibition is mediated by inhibitory interneurons and intracortical inhibitory mechanisms discussed above (Sohn &Hallett, 2004; Stinear & Byblow, 2004; Beck et al., 2008). Some evidence for this connection lies in the findings that, along with lower levels of SICI, people with FHD also exhibit less surround inhibition in their motor system (Sohn &Hallett, 2004b). Neither ICI, nor inhibition in

the motor system has been investigated beyond the affected limb. This gap in our knowledge has inspired the present investigation. Inhibition in the motor system (surround inhibition) and its role in both the average and dysfunctional human motor system will be discussed at length in the following section.

1.3 Surround Inhibition

Surround inhibition (a.k.a lateral inhibition, center surround or on-center off-surround) is a mechanism found in a number of different systems throughout the body and is thought to focus information coming into or leaving a system. In the visual system, the retina contains ganglion cells which are responsible for this center-surround mechanism (Famiglietti & Kolb, 1974). These cells become most active when light falls on the center of their receptive fields and these cells have inhibitory connections to surrounding ganglion cells. It is thought that this mechanism allows the visual system to sharpen visual images, edges and spatial locations (Famiglietti & Kolb, 1974). In the tactile sensory system, slowly adapting type 1 (SA1) cells ending in Merkel cells specialize in the representation of spatial information. These cells use changes in sensitivity of strain energy density receptors to emphasize particular information and suppress surrounding areas in the receptive fields (Johnson, 2001).

Although a surround inhibition mechanism was first discovered in the sensory systems, it seems that a similar system could be at work in the motor system. It may work to activate groups of muscles involved in a movement and inhibit groups of muscles either not involved or competitive with a desired movement (Mink, 1996; Hallett, 2004). Since the discovery of possible surround inhibition in primate motor pathways, researchers have been investigating the same phenomena in the human motor system.

1.3.1 Surround Inhibition in the Non- Human Primate Motor System

Prior to human research, primate models were used to study both the properly functioning movement system and a dysfunctional movement system (among many other neural systems). Due to less restrictive protocols in primate research, single neuron recording is possible. This technique allows researchers to get a much more detailed look at the exact flow of information and activation in the cortical and subcortical systems. Much of the research done on the function of the basal ganglia was done using primate models (Mink, 1996). Georgopoulos (1995) investigated the motor cortex in non-human primates and concluded that cells in the motor cortex are directionally tuned. When a movement needs to be made, the cells that preferentially fire in the "preferred direction" are most active and have excitatory synaptic interactions with other cells with similar preferred directions. Cells that do not fire in the preferred directions are inhibited and have inhibitory synaptic interactions. From this work Houghton and Tipper (1996) proposed that there was a selection mechanism in the motor system, such that competing motor programs are inhibited and motor programs involved in movement are "selected". Mink (1996) would support these conclusions and would suggest that these mechanisms and the patterns of activation seen in the motor cortex are at least partly due to the patterns of basal ganglia output onto the motor cortex.

1.3.2 Surround Inhibition and Transcranial Magnetic Stimulation

The most commonly used tools for the neurophysiological investigations of surround inhibition in the human motor system are single-pulse, paired-pulse and paired-associative TMS. Barker, Jalinous, and Freeston (1985) described TMS as a useful neurophysiological tool. They found that this technology could induce EMG activity in

stimulated human muscles that were analogous to those of the homunculus. Prior to this discovery, a painful technique known as transcranial electrical stimulation (TES) was the only option. TMS is much less invasive, painless, and is considered a safe tool in neuroscientific research. It has all but replaced the use of TES and expanded the scope of human experimentation (Barker et al., 1985; Rossini et al., 1994; Capaday, 1997; Hallett, 2007).

A TMS stimulator unit consists of a capacitor containing a large amount of stored electrical energy. When discharged, it produces a flow of current through a highly conducting copper coil (Rothwell et al., 1997). The maximum voltage produced by the capacitor is approximately 4000V and when the capacitor is discharged it produces a maximum magnetic field of 2.5 Tesla with a rise time of 50-200 microseconds (Rossini, 1994). The coil itself contains tightly wound copper wires and can come in many different shapes (i.e. cone, circle or butterfly) (Hallett, 2007).

TMS technology is based on the principles of electromagnetism and its induction across the skull. A large electrical current is released through a series of copper coils that are held outside the skull. This brief, but intense electrical current produces a magnetic field at a right angle to the flow of the electrical current. Because the magnetic field developed outside the scalp can pass across the skull with little resistance, electrical currents can be produced directly in the extracellular fluid of the cortical neural tissue. The pain receptors are located in the skull and skin and are oriented parallel to the induced electrical currents: magnetic stimulation does not activate pain receptors. So TMS is a painless technology.

When the TMS unit is discharged any nearby electro-conductive medium, the intra- and extra-cellular fluid of the brain in this case, is excited. This induced current is parallel and in the opposite direction of the stimulation (Rossini, 1994). Therefore, when the coil is oriented at an angle of approximately 45 degrees to the midline and tangential to the scalp, it induces a posterior-to-anterior flow of current to the primary motor strip (Rossini et al., 1994). This positioning has been shown to activate corticospinal neurons indirectly via activation of cortical interneurons (Rossini et al., 1994). Once the corticospinal neurons are activated, the signal is passed down the pyramidal tract and action potentials are elicited in the targeted areas of contralateral extremities. Muscle potentials created using electrical or magnetic stimulation are commonly referred to as "motor evoked potentials" (MEPs) (Figure 5).

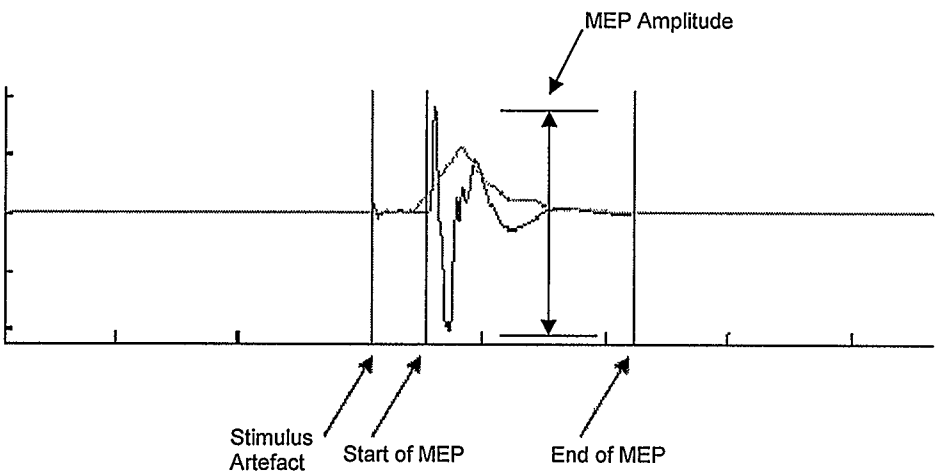

Figure 5. A single motor evoked potential (MEP). Arrows indicate different events that occur during a MEP. These include: a stimulus artefact, start of the MEP and end of the MEP. Also depicted are two measures used when analyzing an MEP. The amplitude, which is measure in volts, is the difference in voltage between the highest peak and the

lowest trough. The root mean square (RMS) is the grey line and represents the area of the MEP.

Early work with TES showed that when animals were stimulated, two distinct responses were elicited. One of those responses was a short latency D-wave, which was thought to be caused by the direct activation of the neurons of the pyramidal tract (Hallett, 2007). The second of these two responses has a longer latency and was referred to as an I-wave. The I-wave was thought to be caused by the indirect activation of the neurons of the pyramidal tract via cortical interneurons (Hallett, 2007). Early TMS research found only the I-wave response following stimulation. It was thought, because of the vertical alignment of the pyramidal neurons and the nature of the magnetic field and induced electrical current, that a D-wave could not be produced by TMS stimulation. However, it was later found that, by manipulating the angle and position of the coil, D-waves can indeed be produced (Hallett, 2007). When the coil is oriented at an angle of approximately 45 degrees to the midline and tangential to the scalp, it induces a posterior-to-anterior flow of current and this produces an I1-wave (approximately 1.5 ms after the D-wave) (Hallett, 2007). The fact that all responses using TMS are at longer latencies than TES is thought to be due to the indirect nature of magnetic stimulation (Hallett, 2007).

Prior to any single- or paired-pulse TMS testing procedure, the motor "hot spot" (area optimal for eliciting motor evoked potentials in the target muscles) and the resting motor threshold (rMT) must be located (Rossini et al., 1994). To find the motor "hot spot", the motor cortex (M1) must be found. This is done by first locating the vertex. One must mark the middle of nasion to inion and the top of pina to pina. A point six

centimetres lateral and two centimetres anterior to the vertex is then identified. This area is the approximate area of the motor cortex that represents the hand and forearm. The optimal scalp position on the motor cortex for the targeted muscles is the location where the largest MEP amplitudes are evoked following TMS. By moving the coil over the motor cortex in incremental one centimetre steps until maximal amplitudes are recorded from the target muscle, the optimal location can be identified (Rossini et al., 1994). rMT is then measured over this optimal scalp position and is defined as the minimum stimulus intensity to be able to evoke five of 10 MEP's of at least 50 μV (Rossini, 1994).

The most common types of TMS techniques used to investigate surround inhibition are single-pulse, paired-pulse and paired-associative stimulation. In single-pulse TMS experiments, the stimulator is turned up above rMT and one pulse is given at a time. This technique is thought to indirectly excite corticospinal neurons of the pyramidal tract via excitatory interneuron synaptic inputs (Hallett, 2007). The resultant MEP in the contralateral extremity is thought to represent the summation of all excitatory and inhibitory influences from the cortex, brain stem and spinal cord that act on the alpha-motorneurons (Hallett, 2007). In essence, TMS is a tool that allows researchers to magnify the activity of the system. The magnitude of the resultant MEP provides useful information about modifications of the motor system by different tasks and inputs.

Paired-pulse and paired-associative TMS protocols are both conditioning paradigms. That is, at different latencies prior to the test TMS pulse, a conditioning stimulus (either sub- or suprathreshold) is applied (Hallett, 2007). The conditioning stimulus in a paired-pulse paradigm is another stimulation of the motor cortex. This technique is thought to provide an index of interneuron influence in the cortex (Hallett,

2007). Paired-associative stimulation involves applying a conditioning stimulus to a peripheral nerve followed by a testing pulse in the cortex (Hallett, 2007). This technique is thought to provide information as to how sensory information is integrated and how it influences the motor system. Taken together, the data from all of these techniques has been used in surround inhibition literature to examine the cortical activity related to the influence of movement on surrounding musculature. Furthermore, these techniques may provide insight into the mechanisms which lead to the modulations in cortical activity.

1.3.3 Surround Inhibition in the Human Motor System

Researchers such as Mink (1996; 2003) and Nambu, Tokuno and Takada (2002) who have studied the basal ganglia, suggested the idea of a center surround mechanism in the human motor system. Patterns of activation in the intrinsic circuits of the basal ganglia may act to stimulate patterns of muscles in the motor cortex involved in the appropriate motor program while inhibiting those muscles involved in competing motor programs (Mink & Thatch, 1993; Mink, 1996; 2003; Nambu, Tokuno & Takada, 2002). This action may occur via convergent, context-specific and long latency activation from the striatum (giving rise to the direct and indirect pathways) and a fast, divergent, and broadly exciting activation from the STN. Nambu and colleagues (2002) propose a "hyperdirect" cortico-subthalmo-pallidal pathway that acts to quickly and broadly reduce excitation sent to the motor cortex in a non-context specific manner. The striatum then sends slow convergent signals to the GPi and GPe via the direct and indirect pathways. The direct pathway is thought to disinhibit the thalamus and thus, excite the groups of muscles premotor and primary motor cortices involved in the motor program to be

executed. The indirect pathway, on the other hand, inhibits specific groups of muscles that would compete with the intended motor program (Mink, 2003) (Figure 6).

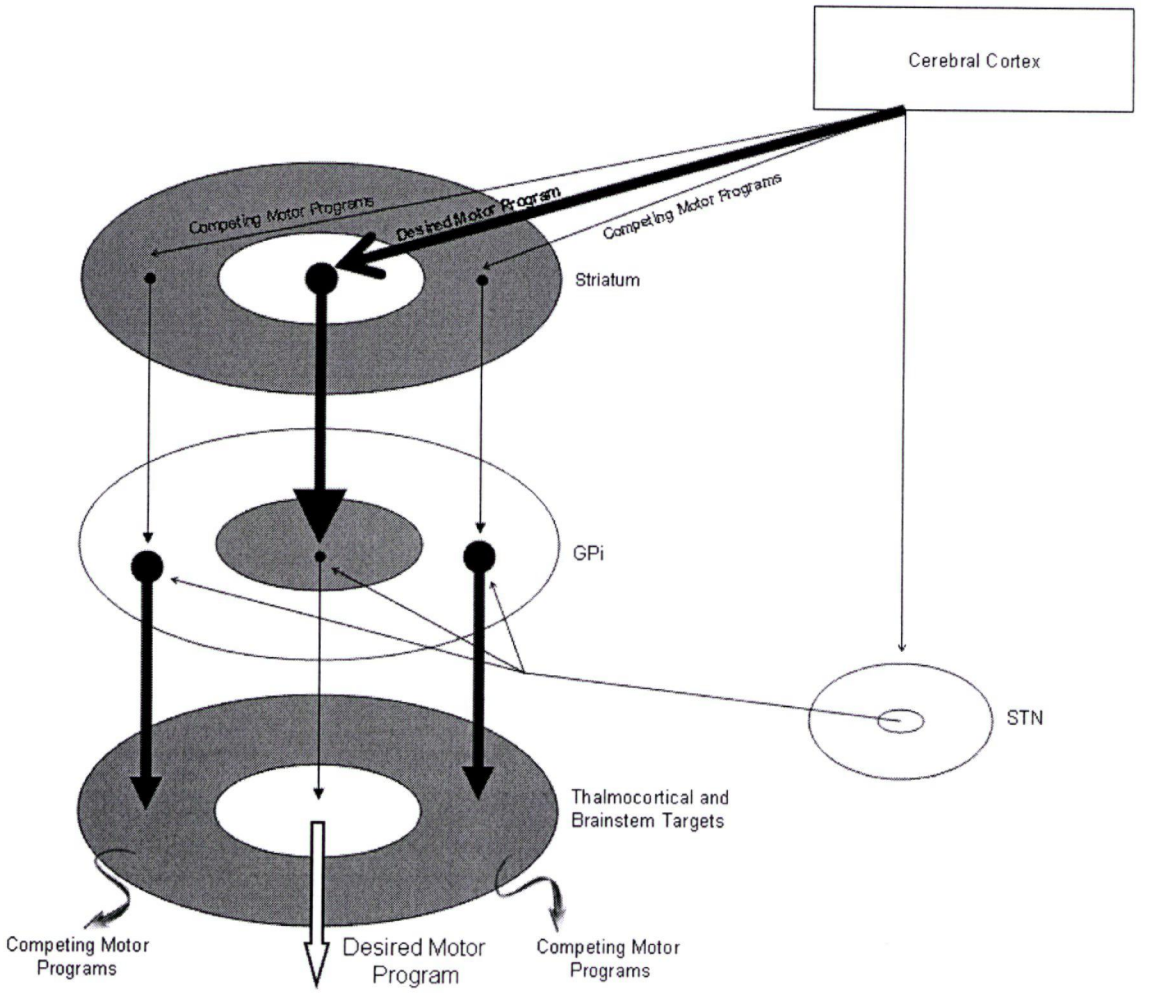

Figure 6. Simplified functional organization of the basal ganglia for surround inhibition and selective facilitation (a model adapted from Mink, 2003). Open arrows represent excitatory projections; filled arrows, inhibitory projections. Arrow thickness represents relative magnitude of activity. GPi: globus pallidus pars interna; STN: subthalamic nucleus.

There have not been many behavioural or neurophysiological studies conducted on the specific phenomena of surround inhibition, but investigations into this issue have been attempted recently and the body of literature continues to grow. Sohn and Hallett

(2004a) discovered what they believe to be the functional expressions of the neural phenomenon known as surround inhibition [as hypothesized by Mink (1996)], in the average human population. In this investigation, the authors used both single- and paired-pulse TMS techniques to look at the inhibition of muscles during a number of different muscle contraction tasks. They hypothesized that the MEPs in non-synergistic muscles (muscles not directly involved with the movement task) would be inhibited due to a surround inhibition mechanism.

During the single-pulse TMS task, participants were asked to perform self-paced movements. TMS pulses (at 140% of rMT) were delivered randomly at various time intervals (3, 15, 40, 80, 200, 500, and 1000 ms) after the onset of EMG. The triggering muscles used were the index finger (flexor digitorum superficialis [FDS]), the mouth (risorius [RS]) and the leg (tibialis anterior [TA]). EMG responses were recorded from the abductor digiti minimi (ADM), FDS and extensor indicis proprius (EIP) when the FDS was the triggering muscle and the ADM and the abductor pollicis brevis (APB) when the RS and TA were the triggering muscles. The results suggested that during index finger flexion, muscles involved in finger flexion were significantly enhanced while ADM excitability was suppressed compared to rest (at 15, 40 and 80 ms intervals after EMG onset). F-wave amplitudes (used to investigate activity at the level of the spinal cord) were increased during this time. The authors suggest that the spinal cord was not the source of the inhibition and if anything, the excitability at the level of the spinal cord would have to be suppressed by descending commands in order to see the inhibition in the ADM. The ADM and APB MEP amplitudes were not significantly different from rest when the mouth and leg were the triggering areas.

Sohn and Hallett (2004a) then used a paired-pulse TMS paradigm to investigate possible pathways and mechanisms mediating what they found. The paired-pulse experiment involved the same tasks as the single-pulse (except no use of mouth movements as one of the triggers). This part of the study was designed such that a stimulation of the motor cortex at a subthreshold stimulating intensity (which preferentially excites interneurons in the motor cortex) was given 10 ms after the onset of muscle activity. A time period of ten milliseconds was chosen for the delivery of the conditioning stimulus because this was the time in the single pulse task that the ADM showed the greatest amount of suppression. This was followed by a suprathreshold test stimulus at two or ten ms (creating short intracortical inhibition (SICI) and intracortical facilitation (ICF) respectively) after the conditioning stimulus of an intensity sufficient to produce > 1 mV MEPs. Long intracortical inhibition (LICI) was also investigated. A suprathreshold conditioning stimulus was followed after 70 ms by a test stimulus (with an intensity enough to produce > 1 mV MEPs). The results indicated that the conditioned MEPs of the ADM in both SICI and ICF were unchanged during both index finger and leg movements. MEPs during LICI in contrast, were significantly enhanced during both finger and leg movements. This may suggest that the GABA-mediated inhibitory mechanisms in SICI may be partly or completely responsible for surround inhibition in the human motor system. Stinear and Byblow (2004) and Beck and colleagues (2008) would agree with this assertion as they found enhanced levels of SICI in the APB during a FDI selective activation task.

It is important to note that the exact location of the inhibitory drive in the human motor system is as yet unknown. Most researchers investigating surround inhibition

would argue that the cortical and subcortical areas are responsible for producing this inhibition. However, because most of these studies use TMS and the TMS-evoked motor commands must travel through the spinal cord and out the final common pathway, there is a possibility that inhibition may occur because of differences in common input to the muscles and/or spinal cord inhibitory interneurons. Investigations of the F-wave have been used to support the cortical origins of surround inhibition and other cortical phenomena when using TMS. F-waves are usually elicited in the fibres of a peripheral nerve in close proximity to the muscle of interest (Rossini et al., 1994). This nerve is stimulated by a supramaximal stimulation, which creates an antidromic volley. This antidromic volley travels back toward the spinal cord and if the timing is right, it can "re-excite" efferent motor neurons, which ultimately results in a late excitation of the muscle (Rossini et al., 1994). This late wave is known as the "F-wave". By comparing the F-wave amplitude at rest and during the same experimental task as in the TMS protocol, it is assumed that this measure will provide an indication of spinal cord contribution during the task. However, F-waves methods do not conclusively rule out the spinal cord, common input or a spinal cord/cortical interaction as contributors to this inhibitory phenomenon.

Sohn and Hallett's (2004a) investigation lacked a methodological description, making it difficult to reproduce. The methods section did not detail the positioning of participant's hands, arms, legs or head throughout the various tasks. The tasks were only vaguely described as a request to "move their triggered muscle briefly". The timing, monitoring and control of the task were not described in any depth; the threshold for detecting movement onset was imprecise. The lack of clear methodological description

makes this study difficult to understand and evaluate in a critical manner; it is next to impossible to replicate identically. These deficiencies must be considered when examining the conclusions of the authors.

1.3.4 Surround Inhibition and Dystonia

Soon after their original surround inhibition study, Sohn and Hallett (2004b) used their experimental paradigm to look at the same inhibitory mechanisms in people with FHD. In this study, only single-pulse TMS was used in both healthy participants and FHD patients. The triggering muscle used was the FDI and the muscle of interest was the ADM. Seven FHD participants and seven age-matched control participants were asked to make self-paced index finger flexion movements. Surface EMG was recorded from the FDI and the onset of muscle activity in the FDI was determined. TMS pulses that evoked MEPs from FDI and ADM were then triggered at randomized time intervals after EMG onset (same time intervals as in Sohn and Hallett, 2004a). The results indicated that people with FHD had significantly larger MEP amplitudes in the ADM than the control group during the first four time intervals of movement (TMS pulse triggered 3, 15, 40 and 80 ms after EMG onset). Sohn and Hallett (2004b) suggested that these results suggest lower levels of surround inhibition in people with FHD.

In another study, Stinear and Byblow (2004) had subjects perform a task similar to that done in the paired-pulse component of the Sohn and Hallett (2004) experiment. They discovered that, in the average population, levels of SICI, believed to be mediated by GABA, did not change in the FDI (the muscle involved in movement) and were significantly increased in the APB during the index finger task. Furthermore, these authors found that people with FHD did not show modulation of their SICI levels. These

results further confirmed these authors' hypothesis that SICI is responsible for inhibiting unwanted muscular activity. Not only does SICI increase when unwanted muscle activity is suppressed, but in a group that has an apparent inability to inhibit muscle activity, SICI levels do not change.

It must be restated that it is important to remember that there is no conclusive proof that surround inhibition originates in the basal ganglia and the motor cortex. It is also important to note that Sohn and Hallett's (2004b) task and methods were ill defined and controlled with questionable consistency in the performance of the task. These problems need to be addressed in the future in order to draw appropriate and valid conclusions about inhibitory mechanisms in the human motor system.

Although the studies reviewed in this section have provided some insights into the possible problems with surround inhibition in the affected limb of people with focal dystonias, the question yet to be investigated is whether the problems in surround inhibition persist beyond the symptomatic limb. As reviewed earlier, many of the other symptoms have been found outside the affected limb (e.g., basal ganglia dysfunction, Obermann et al., 2008; reciprocal inhibition, Chen, Tsai & Lu, 1995 & Deuschl et al., 1992; co-contraction, De Vries et al., 2007; sensorimotor integration, Abbruzzese et al., 2001). The present investigation was conducted to determine if problems in surround inhibition exist beyond the affected limb of people with CD. This was done with a group of people with CD and adapting the methods used by Sohn and Hallett (2004b). If it is found that the lack of inhibition indeed persists in the hand of those with CD, we may be able to add to the growing weight of evidence that has found abnormalities in the asymptomatic limb.

1.4 Purpose and Hypotheses

Based on the existing literature, it is clear that more work needs to be done to untangle the various pathophysiologies of focal dystonia and to make a solid case for a link between the different expressions of focal dystonia. It appears that many of the abnormalities found in the dystonic limb have been found in an asymptomatic limb as well. These findings may support the idea of a "pre-dystonic state" that links all focal dystonias. It is important to note that, to my knowledge, surround inhibition in a focal limb dystonia has not been evaluated in this way. Therefore, the present investigation was designed to determine if abnormal surround inhibition is a common underlying systemic irregularity in focal dystonias by investigating whether the lower levels of inhibition previously found within the dystonic limb (Sohn & Hallett, 2004b) persist beyond the affected limb.

The present investigation had two specific purposes:

1. The first objective was to determine whether a healthy control group inhibits muscle activity in a non-synergistic muscle during an index finger abduction task. To this end, the level of cortical and spinal activity of the ADM was evaluated using TMS in 17 control subjects while they completed an index finger abduction task (a slight variation on the Sohn and Hallett (2004b) task).

2. The second objective was to investigate integrity of the same inhibitory mechanism in the asymptomatic limb of people with dystonia. The present study employed an adapted protocol of Sohn and Hallett's (2004b) investigation of surround inhibition in individuals with CD or FHD and in a control group. In this way, the levels of surround inhibition could be investigated in the hand of people with dystonia in their

necks and compared to a number of control groups to provide insight into inhibition in an unaffected limb.

There were two specific hypotheses:

1. First, it was predicted that the average population would show significant surround inhibition in their hand muscles. Specifically, the control participants would have significantly smaller MEP amplitudes in their ADM muscles than in their FDI muscles during FDI activation.

2. Second, it was hypothesized that people with CD, like those with FHD, would have reduced surround inhibition in the non-active muscles of the hand (their non-affected limb). This decreased inhibition would be reflected in a non-significant difference between MEP amplitudes in the ADM and FDI muscles during FDI activation for both the FHD and CD groups. Such a result would suggest that surround inhibition, as Sohn and Hallett (2004a) have described and tested it, is a systemic issue in focal dystonia and that non-affected limbs may be in a "pre-dystonic" state. If decreased surround inhibition mechanisms are not systemic and are contained within the affected limb, then the CD group would show significantly smaller MEP amplitudes in their ADM muscles than in their FDI muscles during FDI activation. In this possibility, only the FHD patients will show a lack of inhibition in their hand.

Chapter 2 – Main Investigation

****Note that this section has been written in a format that will allow easy conversion to a submittable paper****

2.1 Introduction

Dystonia manifests itself in involuntary co-contraction of agonist and antagonist muscles resulting in painful, twisted and abnormal postures for which there are no known cures (Fahn, 1988). There are many different types of dystonia, which are primarily distinguished by age of onset, etiology and dispersion of symptoms. Primary focal dystonias in particular usually have an onset later in life, are of idiopathic origin and are contained within one limb (Fahn, Bressman & Marsden, 1998; Fahn, 1988). Primary focal dystonias are commonly associated with abnormal basal ganglia output to the motor areas. Mink (1996) proposed that one of the primary functions of the basal ganglia is to focus motor output in a center-surround (on-center/off-surround) fashion such that motor programs necessary for the goal movement are activated while competing motor programs are inhibited. Furthermore, he proposed that dysfunction of this system might be the cause of many of the symptoms seen in people with dystonia.

In 2004a, Sohn and Hallett found what they believe to be evidence for the functional expression of the neural phenomenon known as surround inhibition, as hypothesized by Mink (1996), in an average human population. They applied single-pulse TMS over the area of the motor cortex that represents the abductor digiti minimi (ADM) and found that the motor evoked potentials (MEPs) were significantly smaller than baseline during the execution of a movement involving a non-synergistic muscle (the first dorsal interosseous - FDI). These authors believe that this decrease in MEP

amplitude reflects the inhibition of non-synergistic muscle actions, which serves to focus goal movement and select appropriate responses.

Sohn and Hallett (2004b) used this experimental paradigm to investigate the same inhibitory mechanisms in people with focal hand dystonia (FHD). This investigation revealed that people with FHD did not demonstrate the same decrease in MEP amplitude in the ADM suggesting that there was significantly less inhibition in uninvolved muscles than a group of healthy individuals. Since dystonia is at least partially caused by basal ganglia dysfunction, the fact that they show less ability to inhibit unwanted motor programs supports both Mink (1996) and Sohn and Hallett's (2004b) assertion that the basal ganglia may mediate surround inhibition.

Since the publication of these two studies, there have been a number of studies designed to look at the physiological mechanisms responsible for the presence of surround inhibition. One such study found that short intracortical inhibition (SICI), likely mediated by GABA-ergic intracortical inhibitory interneurons, decreased in the FDI during movement (Stinear & Byblow, 2004). In contrast, SICI was found to increase in the abductor pollicis brevis (APB) – a muscle that was to remain quiescent throughout the movement. The authors suggested that the SICI present in the APB might reflect the inhibition of unwanted movements. In support of their conclusions, there was no modulation of SICI in patients with focal hand dystonia (FHD) during the same task even though resting levels of ICI were similar between the two groups. Beck and colleagues (2008) followed up on this study looking at the time course of this inhibition and found that SICI seemed to be important in inhibiting movement of non-synergistic muscles during movement initiation but not during the maintenance phase of movement. While

controls showed constant SICI resulting in APB inhibition, FHD patients actually showed reduced SICI and associated increases in the MEP amplitude of the APB during movement initiation. In sum, the data suggest that people with FHD have a dysfunctional surround inhibition mechanism.

Over the last ten years or so, researchers have begun to investigate if problems associated with dystonia exist in the asymptomatic limb. Abnormal basal ganglia activity (Obermann et al., 2008), co-contraction (De Vries et al., 2007), sensorimotor integration (Abbruzzese et al., 2001), plasticity (Chen et al., 1995) and spinal reflexes (Deuschl et al., 1992) have all been found in the asymptomatic hand/arm of people with FHD, blepharospam (BS) (dystonia in the muscles of the eye), and/or cervical dystonia (CD). These findings may suggest that there is a common pathology underlying all focal dystonias and that asymptomatic limbs actually exist in almost like a "pre-dystonic" state. The limb affected by dystonia is just the most extreme expression of a systemic problem, which is why dystonia can spread to another limb (De Vries et al., 2008). Surround inhibition, as Sohn and Hallett (2004b) have defined it, has yet to be investigated in an asymptomatic limb. Such an investigation would add to the growing evidence of a systemic "pre-dystonic" state in focal dystonias.

The purpose of the present investigation was to determine whether people with CD exhibit abnormal inhibition outside their affected limb and thus, to determine whether this issue is more systemic or local in nature. Recently, Sohn and colleagues (2004b) have reported significant decreases in the MEP amplitudes of non-synergistic muscles in neurologically-normal, but not in a group of people with FHD. They have suggested that this pattern reflects the integrity of the surround inhibition mechanism in these groups. In

the present study, an adaptation of the Sohn and Hallett (2004a, b) protocol was used with a group of individuals with CD and a group of age-matched control participants to provide some insight into the neurological abnormalities underlying CD. If people with CD have abnormal inhibition in their unaffected limbs, then the MEP amplitudes in their ADM would be significantly greater than those of the control group. Furthermore, the CD group would have MEP amplitudes in their ADM muscles that were not different from the MEP amplitudes in their FDI muscles. In contrast, if people with CD do not have abnormal inhibition in their unaffected limbs, then the pattern of MEP amplitudes should be similar across groups and the MEP amplitudes of their ADM muscles will be significantly smaller than those of their FDI. It is hypothesized that the disturbed surround inhibition will extend beyond the affected limb in people with CD suggesting that surround inhibition may be a systemic disturbance rather than a local one as many other abnormalities seen in dystonia appear to be.

2.2 Methods

2.2.1 Subjects

We recruited 16 subjects with cervical dystonia and 17 healthy age-matched controls. Dystonia patients were recruited from a convenience sample of a movement disorders clinic and the Dystonia Society and the controls were recruited from around the community. A physician who specializes in movement disorders assessed all dystonia subjects (see Table 1 for all patient details). To be included in the CD group, participants had to be diagnosed with primary focal cervical dystonia with no evidence of focal hand dystonia. Participants were also excluded if they had tremor affecting their hands, if they were unable to perform the task, and/or if they had a personal or family

history of epilepsy. All patients that were being treated with botox injections were tested at least 12 weeks after their last injection. Some of the patients were also being treated with centrally acting drugs and were not asked to stop their course of treatment because of possible adverse health complications that abruptly stopping the drugs could cause. Of the 16 subjects recruited with CD, only 7 participants were tested. Four patients eventually declined to participate. Of the remaining 12, an additional 5 people were eliminated. One had underlying essential tremor, 1 had a history of epilepsy, and 3 participants could not complete the task due to neck pain and/or lack of relaxation.

The main between-group comparison in the current study included the 7 remaining CD patients (6F, Mean Age: 59.4 yrs, Age Range: 49-75) and 7 controls (6F, Mean Age: 58 yrs, Age Range: 47-72 yrs) that were closely matched for age and gender. In addition to the two small groups, all 17 of the healthy controls were tested and were used for a large control group analysis (including the 7 used in the sub-analysis). All of the participants included in the study were right-hand dominant except for one of the CD participants who was left hand dominant who had a stroke affecting his left hemisphere. This participant was asked to perform all tasks with their left hand and TMS was applied to their right hemisphere. (See Table 1 for all patient details)

Age (yr)	Diagnosis	Duration (yr)	Affected Muscles	Main Dystonic Movement	Treament(mo from last injection)	Other Medications
75	Cervical dystonia	26	SCM[r/l],TRAP[r],SC[r/l]	head rotation left, tilt right	None	
65	Cervical dystonia	33	SCM[r],TRAP[r],SC[l]	head rotation left	Myobloc (3mo)	Amitriptyline
64	Cervical dystonia	15	SCM[r],SC[r/l]	head rotation left, tilt right	None	Clonazapam
51	Cervical dystonia	9	SCM[l]	head rotation right, tilt left	Botox(3mo)	
51	Cervical dystonia	7	SCM[l],SC[r],TRAP[r]	head rotation right,extension	Botox(3mo)	
61	Cervical dystonia	6	SCM[l],SC[r/l],TRAP[r/l]	head rotation right,extension	Botox(3mo)	Clonazapam
49	Cervical dystonia	22	SCM[r],TRAP[l],SC[l],LS[l], CORRUGATOR[r/l]	head rotation left, tilt left	Botox(3mo)	
48	Writer's dystonia	18	FPL[r],FPB[r],FDS[r]	thumb, finger and wrist flexion	Botox(3mo)	
51	Writer's/musician's dystonia	4	FDS[r],FDP[r],FPL[r]	finger flexion	Botox(4mo)	

Table 1. Patients' characteristics. SCM: sternocleidomastoid; TRAP: trapezius; SC: splenius capitis; LS: levator scapulae; FPL: flexor pollicis longus; FPB: flexor pollicis brevis; FDS: flexor digitorum superficialis; FDP: flexor digitorum profundus

In order to verify Sohn and Hallett's (2004b) findings, an attempt was made to recruit participants with FHD as well. Unfortunately, due to a small subject pool and due to the fact that many people with FHD do not seek medical attention for their condition, only three people with FHD volunteered for the study. Of those three, two were able to complete the experimental protocol. One person was excluded due to their inability to perform the required finger movements and their inability to relax without tremor at rest. Although 2 people is an inadequate sample size to show meaningful differences, these two participants were run through the experiment and evaluated individually to see if they behaved in a different manner than the control group.

2.2.2 The Task, TMS and EMG Procedures

The Task

Figure 7 provides a timeline for the experimental session, the task and the individual trials. Participants were given an informed consent form and were asked to fill out a medical history questionnaire upon their arrival. Participants were then given instructions verbally by the experimenter explaining the TMS and procedural details. They were then asked to sit comfortably with their right hand in the pronated position on a desk 20cm away and their left hand resting in their lap. Instructions were then given to remain relaxed and as still as possible (other than the movement required with their index finger) throughout the experiment.

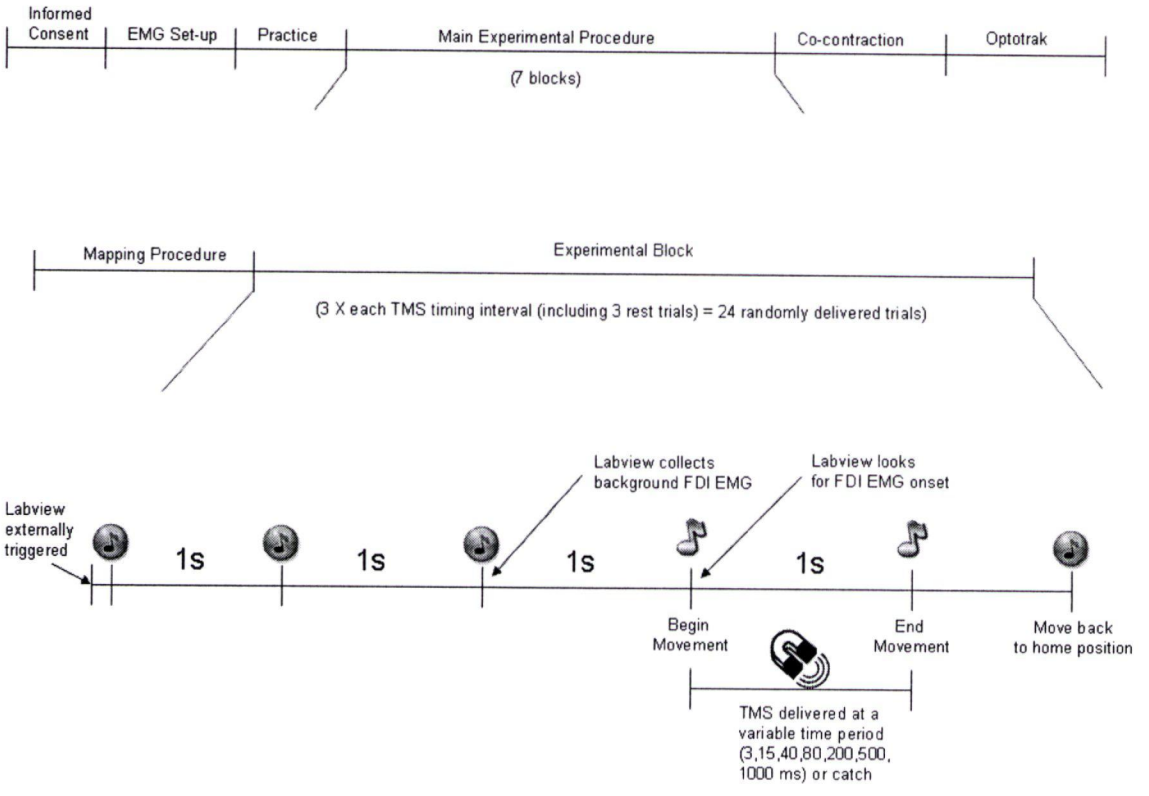

Figure 7. A timeline of experimental procedures. The top row is an overall session timeline. The middle row represents the events during an experimental block and the last row represents events during an individual trial.

Before the experimental session began, subjects were asked to practice isolated index finger abduction movements to the pace of a metronome (at a pace of 1Hz) until they felt comfortable performing that movement (approximately 5-10 trials). After the practice, subjects performed seven blocks of 24 individual index finger abduction movements (following the same metronome pace as in the practice session). Each trial consisted of three preparation tones (74 Db) followed by a higher tone (80 Db), which indicated participants were to begin moving. This "go" tone was followed by another high tone (80 Db) one second later, which was the moment they were to end and hold their movement. A final tone (74 Db) one second later indicated the participants were to

return to the starting position. There were eight trial types defined by when the TMS pulse was presented after the onset of the EMG burst. The time intervals were: 3, 15, 40, 80, 200, 500, 1000 ms (see Sohn and Hallett, 2004a) and a catch trial in which the "go" signal was replaced by a TMS pulse. This later trial type was used to asses the baseline level of motor system activation. Each trial type was randomly presented 3 times in a single block of trials.

A custom program written in Experimenter Builder software on a Dell computer with an Intel Pentium 2 processor initiated the experimental procedure by sending a signal to a custom Labview program. The metronome (1 Hz), timing of the TMS pulses, and timing of EMG recordings were all controlled using the custom Labview software. Due to Labview programming errors, some trials were saved over and lost (~17% of the data). These data were lost randomly across the trials and no time bin was affected more than another. Therefore, the data were not lost in any systematic way. Errors in which Labview failed to record movement and/or the TMS pulse were eliminated and constituted 4% of the data.

Electromyography

Electromyographic (EMG) activity of the ADM and FDI of the right hand were recorded throughout the experiment (Delsys Systems, model Bagnoli-8EMG System) (Figure 8). The recording area was shaved and cleaned and the electrodes were placed on the skin prior to the experimental procedure. EMG was recorded at 8000 Hz. from onset of FDI activity, which was defined as the point at which muscle activity in the FDI crossed a threshold of 2 SD above the RMS of resting FDI activity for 400 consecutive samples (at least 50ms). After detection of FDI activity above threshold, TMS was

activated at one of the 7 different randomized delays. Data was stored in the computer hard drive for offline analysis.

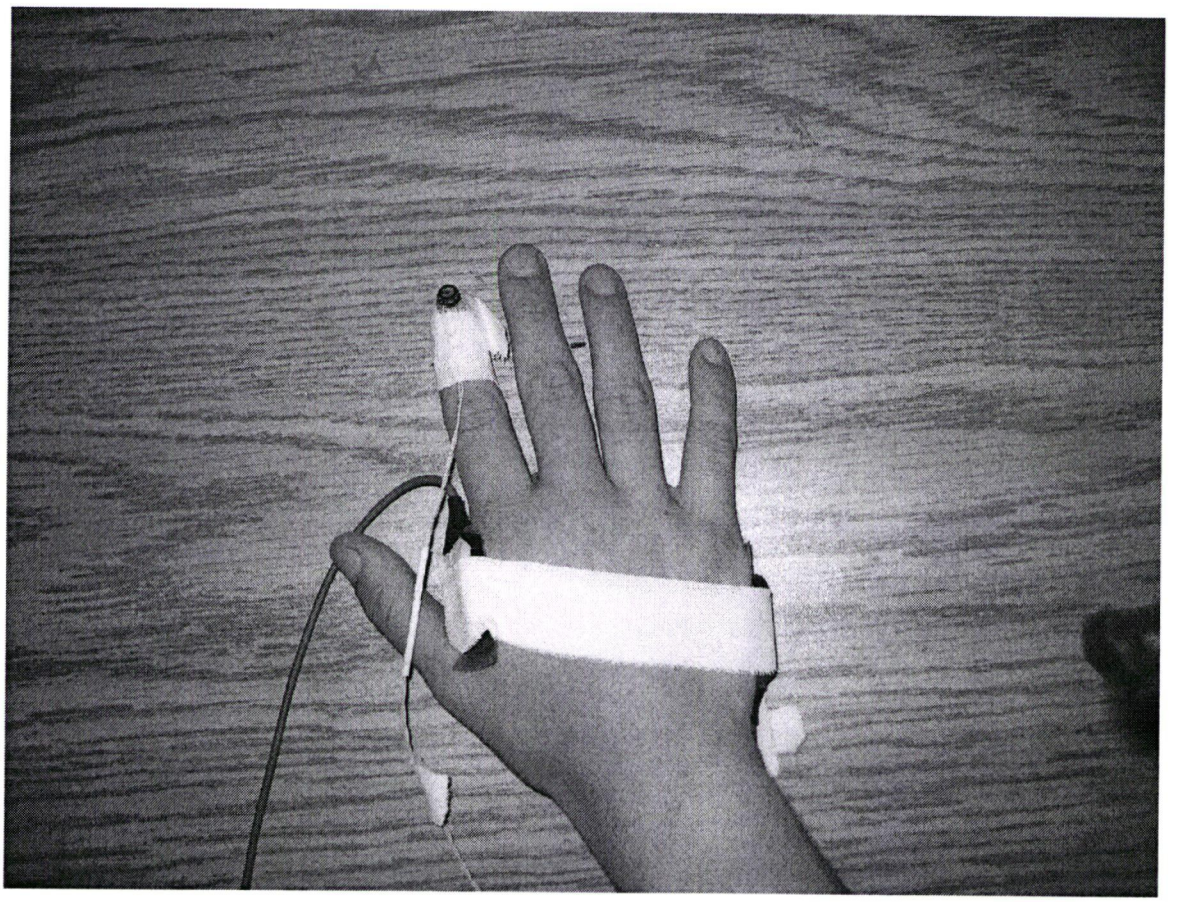

Figure 8. EMG and IRED set-up and participant hand placement.

Transcranial Magnetic Stimulation

Magnetic stimulation was delivered by a MagStim 200 stimulator (The Magstim Company, Carmarthenshire, Wales, UK) via a figure-of-eight coil (external wings 7 cm in diameter) to the hemisphere contralateral to the test limb. The motor cortex (M1) was found by locating the vertex by marking the middle of nasion to inion and top of pina to pina. The point 6 cm lateral and 2 cm anterior from that location was then identified as the rough location of the hand area of the motor strip. The optimal scalp position on the

motor cortex for the targeted muscles was then defined as the location at which the largest MEP amplitudes are evoked in the targeted muscle (ADM) following TMS. This "hot spot" was located by moving the coil over the motor cortex in incremental 1 cm steps until maximal amplitudes are recorded from the ADM. This spot was then marked on the scalp with non-permanent pen to maintain TMS position consistency. The coil was oriented at an angle of approximately 45 degrees to the midline and tangential to the scalp. This coil orientation induced a posterior to anterior flow of current in the primary motor strip (Rossini et al., 1994). This positioning has been shown to activate corticospinal neurons indirectly via excitatory synaptic inputs (Rossini et al., 1994).

Resting motor threshold (rMT) was measured over the optimal scalp position and was defined as the minimum stimulus intensity to be able to evoke five of 10 MEPs of at least 50 μV. Test stimulus was set at a stimulator output of 140% of individual rMT (Sohn & Hallett, 2004).

2.2.3 Co-Contraction

To examine the possibility of a missed diagnosis of FHD in CD patients and contamination of the experimental groups, degree of co-contraction of the wrist flexors and extensors was evaluated. Electromyographic (EMG) activity from the flexor carpi radialis (FCR) and extensor carpi radialis longus (ECR) of both the controls and CD patients (Delsys Systems, model Bagnoli-8EMG System) was recorded after the main experimental procedure was conducted. The recording area was shaved and cleaned and the electrodes were placed on the skin prior to the experimental procedure. EMG was recorded at 1000 Hz. and data were collected and recorded by a custom Delsys analysis program and stored for examination offline.

EMG activity of both muscles was collected for 2 blocks of 20 seconds. During the first 20-second period participants were asked to perform self-paced maximal wrist flexion and extension movements. During the second 20-second period they were asked to perform maximal wrist flexion and extension movements as quickly as possible. These procedures were completed in order to ensure that there was little to no co-contraction in the CD to ensure that a diagnosis of FHD was not missed in this group of subjects.

2.2.4 Kinematics

Following the experimental procedure, participants were fitted with an infrared light-emitting diode (IRED) on the tip of their right index finger. They were then asked to perform 5 more finger abductions to the sound of the metronome exactly as they had done throughout the experiment. A custom program written in Experimenter Builder software on a Dell computer with an Intel Pentium 2 processor initiated the experimental procedure by sending a signal to a custom, NDI First Principles, program controlling the Optotrak system. The Optotrak system recorded the position of the IRED at a rate of 500 Hz. All kinematic data during the index finger abduction movement was analyzed to ensure movement consistency across all participants.

2.3 Data Processing and Reduction

EMG data was recorded and examined offline using custom Labview and Matlab software, respectively (for a typical trial view see Figure 9). Time markers were manually placed at the beginning of the TMS artefact (created by interaction between the TMS output and the EMG electrodes) and at the beginning and end of the MEP (refer to Figure 5). The interval from the onset of the FDI EMG to the onset of the TMS artefact, MEP peak-to-peak amplitudes, and root mean square (RMS) area were then calculated

based on those time markers. MEP amplitudes for each of the stimulus onset asynchronies (SOAs) were normalized to rest (MEPs on the catch trials) to account for individual resting activity and presence of environmental factors and any external differences during collection. This normalization procedure was performed for each block separately to account for any between-block variability in overall MEP amplitude due to subtle changes in coil placement.

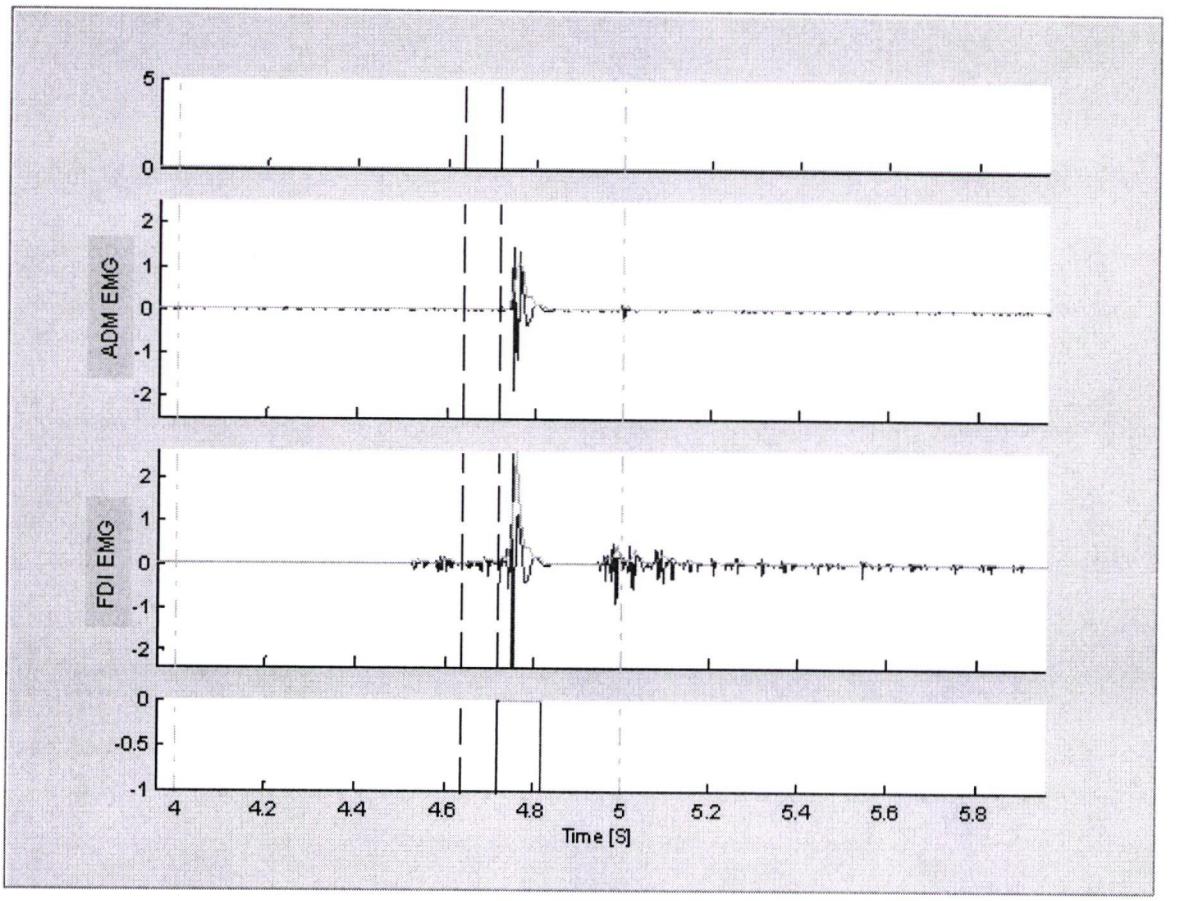

Figure 9. Typical trial view used during cleaning and data processing (typical trial with 80ms TMS SOA). Images would be enlarged and event markers would be placed on the image and saved for further processing.

EMG data was cleaned offline using the same custom Labview software. Cleaning the data consisted of discarding those trials with background activity (85-5ms

prior to TMS pulse) greater than 3SD above the mean in the ADM preceding the TMS pulse. The reason for the exclusion of these trials is that MEP amplitude increases during active contractions and it is important to ensure that any modulation of MEP amplitude is due to surround inhibition or lack thereof and not due to active muscle contractions. These data made up less than 1% of the total data.

For CD patients, levels of co-contraction were analyzed compared to the control group to ensure proper grouping. The data from the second 20-second collection period (movement as fast as possible) was used for analysis because of the great number of data points this procedure afforded. Voltages of both muscles activities were then outputted to Excel software. A threshold decision criterion was set for muscle onset based on visual inspection of the data and placement of an onset marker on the y-axis where each muscle onset began. The percentage of time that participants were in co-contraction could then be determined by dividing the number of time points in co-contraction by the total number of time points collected (20,000).

Finally, the displacement data recorded by Optotrak were analyzed using a custom Matlab program to identify the time of movement onset (point at which instantaneous velocity surpassed 30 mm/s for more than 70 ms) and the time of movement offset (point at which instantaneous velocity fell below 30 mm/s for more than 70 ms). Reaction time was calculated as the interval from the "go" signal to movement onset. Movement time was calculated as the interval between movement onset and movement offset. Peak velocity was defined as the highest instantaneous velocity achieved by the finger tip during the movement time period.

2.4 Statistical Analysis

Due to some variability in the consistency of the TMS triggering program, the TMS data were binned according to the time interval between FDI onset and TMS artefact as identified during data reduction. The data were then binned according to the following criteria: 0-30 = 15 ms bin, 30-75 = 40 ms bin, 75-175 = 80 ms bin, 175-480 = 200 ms bin, 480-950 = 500 ms bin and anything greater than 950 = 1000 ms bin. A catch trial was identified as having a negative difference between TMS pulse and EMG onset. Note that there is no 3 ms bin because, after examining the data and the time between FDI EMG onset and the TMS pulse, it was recognized that the program controlling the delivery of the TMS during the study was unable to consistently produce a TMS pulse after 3ms. Therefore, the data were combined from the 3ms and 15ms time bins so that we would have similar numbers of trials in each time bin.

Different subsets of the mean normalized MEP amplitudes were then submitted to a series of different analyses to test specific hypotheses. First, the mean normalized MEP amplitudes from the large control group (N=17) were submitted to a 2 (muscle: FDI: ADM) X 6 (time: 15, 40, 80, 200, 500, 1000) repeated measures ANOVA to determine if our control group demonstrated the same pattern of MEP amplitudes the healthy individuals in the initial Sohn and Hallett (2004a) showed (see Objective #1 in Section 1.4 of Introduction). Next, mean normalized MEP amplitudes from the two smaller groups were submitted to 2X2X6 mixed ANOVA with Group (control, cervical dystonic) as a between-subjects factor and Muscle (ADM, FDI) and Time (15, 40, 80, 200, 500, 1000) as within subjects factors. This between group analysis was conducted to determine if there were any differences in the patterns of MEP amplitudes of the CD or

healthy control group (see Objective #2 in Section 1.4 of Introduction). Post hoc analysis of any significant effects revealed in the ANOVAs was performed using Tukey's Honestly Significant Difference (HSD).

A chi-square test was used to determine whether the mean percentage of time in co-contraction differed between the CD and control groups. This analysis was performed to attempt to identify any undiagnosed FHD in the CD group. Kinematic data and group characteristics were analyzed using paired t-tests to ensure consistency of movement time and all relevant kinematic markers such as time to peak velocity, peak acceleration and peak deceleration and to ensure the two groups did not differ in age. Alpha was set at $p < 0.05$ for all statistical and posthoc tests.

Finally, to determine if the two individuals with FHD differed from the control group, a series of individual analyses were performed. Specifically, mean and standard deviation values for the normalized MEP amplitudes for both the ADM and FDI were calculated at each time point for the large (n=17) control group. Z-scores were calculated for each participant with FHD's mean MEP amplitude at each time point using the mean and standard deviation values of the control group. By convention, z-scores larger than ±1.96 were taken to indicate values that were not consistent with normal distribution of the control group.

2.5 Results

2.5.1 TMS and EMG Results – Large Control Group

There was a significant muscle x time interaction, $F(5, 80) = 2.78, p<0.05$ (Figure 10). Tukey's HSD posthoc analysis revealed that differences between the MEP amplitudes of the ADM and FDI existed at time bins of 15, 40, 80 and 200ms such that

MEP amplitudes of the ADM were reliably smaller that those of the FDI at those 4 time bins.

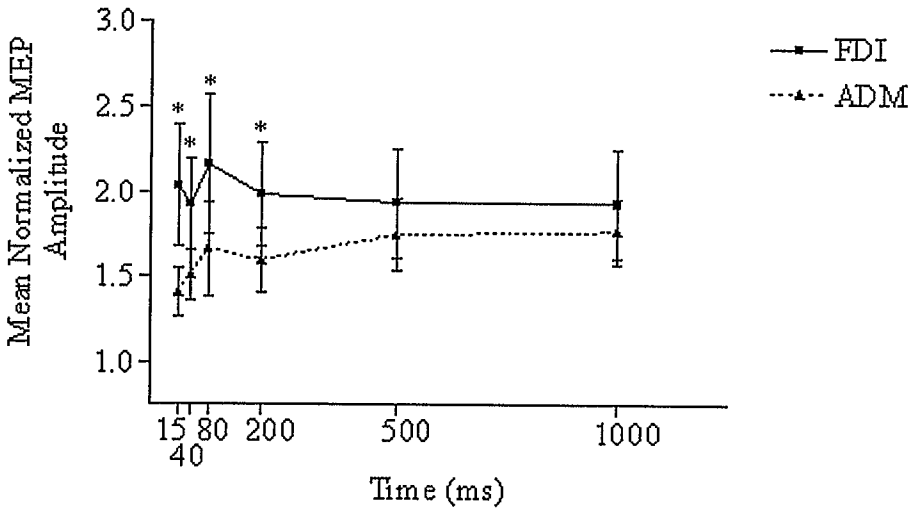

Figure 10. Large control group (N = 17). Changes in mean motor evoked potential (MEP) amplitude of the first dorsal interosseous (FDI) and the abductor digiti minimi (ADM) muscles at each interval (15, 40, 80, 200, 500, 1000 ms) from electromyography (EMG) onset of the FDI, compared to resting state (catch trials). * Significant differences between FDI and ADM MEP amplitudes ($p < 0.05$). Error bars indicate standard error of the mean.

2.5.3 TMS and EMG Results – FHD Participants

By convention, any z-score +/- 1.96 SD or greater from the mean is considered to be reliably different from the population. Each z-score calculated for each individual with FHD were well within these boundaries, which suggests that it is reasonable to conclude that their data were the not different from the average population. In fact, none of their z-scores fell outside of the range of +/- 0.2 SD from the control population mean (Figure 11).

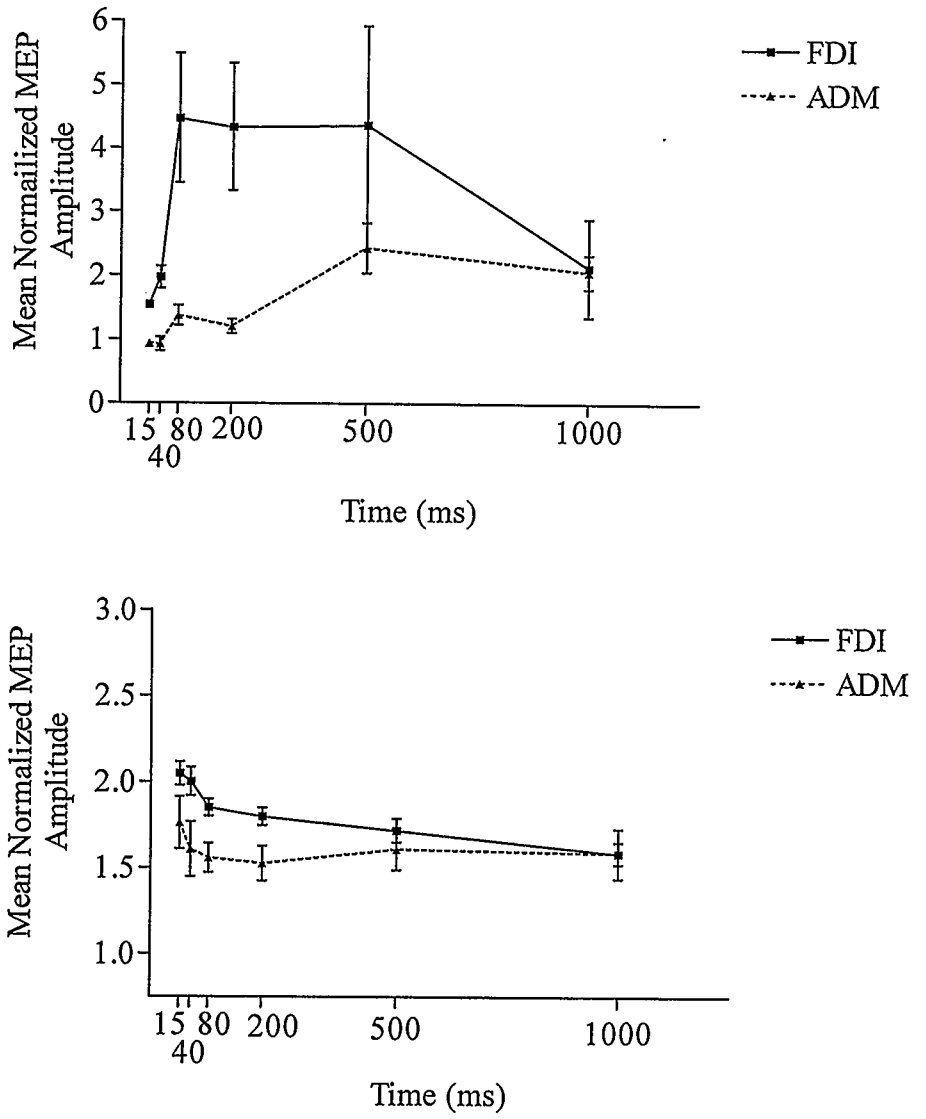

Figure 11. Individual motor evoked potential amplitudes of each focal hand dystonia participant. Changes in motor evoked potential (MEP) amplitude of the first dorsal interosseous (FDI) and the abductor digiti minimi (ADM) muscles at each interval (15, 40, 80, 200, 500, 1000 ms) from electromyography (EMG) onset of the FDI, compared to resting state (catch trials). Error bars indicate standard error.

2.5.2 TMS and EMG Results – CD and Small Control Groups

The analysis revealed only one significant interaction between muscle and time, $F(5,60) = 5.16, p<0.001$. Thus, FDI activation and ADM activation differed across time

in both groups. It is important to note that there was no main effect of group ($F<1$) and no significant interaction involving group and any other factor ($Fs<1$).

Although the absence of any group effects suggests that there were no differences between the groups, it does not follow that the muscle by time interaction observed in the omnibus analysis and with the larger group (see section 2.5.2) is significant in each group. Due to the theoretical importance of this interaction, the data for each group were subsequently submitted to separate 2 (muscle: FDI, ADM) X 6 (time: 15, 40, 80, 200, 500, 1000) repeated measures ANOVAs. These analysis revealed a significant muscle by time interaction in the CD group, $F(5,30) = 3.85$, $p<0.05$, but not in the control group, $F(5,30) = 1.85$, $p>0.05$ (Figures 12 and 13, respectively).

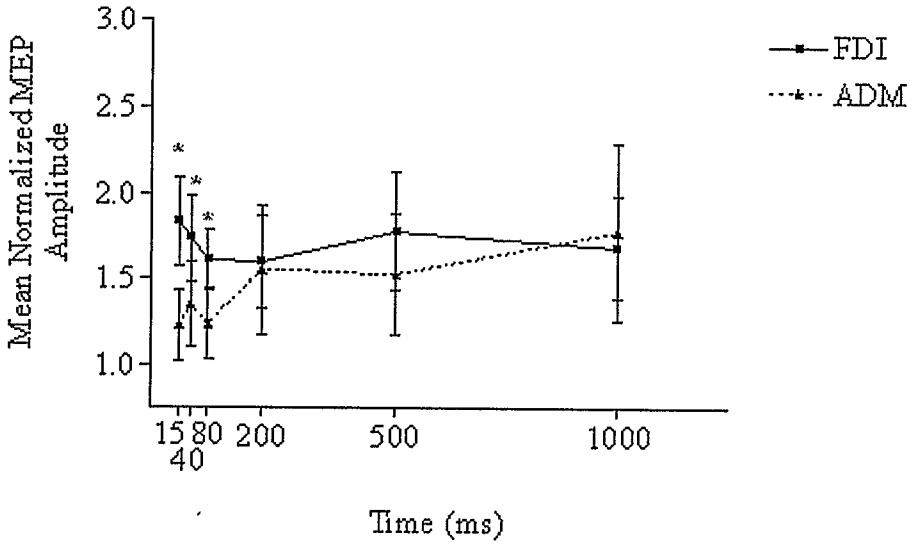

Figure 12. Cervical dystonia (CD) group (N = 7). Changes in mean motor evoked potential (MEP) amplitude of the first dorsal interosseous (FDI) and the abductor digiti minimi (ADM) muscles at each interval (15, 40, 80, 200, 500, 1000 ms) from electromyography (EMG) onset of the FDI, compared to resting state (catch trials). *

Significant differences between FDI and ADM MEP amplitudes ($p < 0.05$). Error bars indicate standard error of the mean.

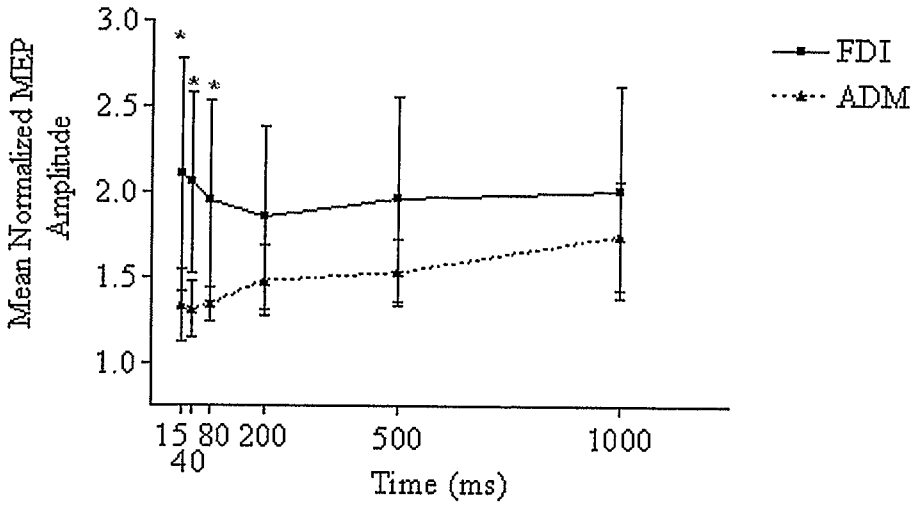

Figure 13. Small control group (N = 7). Changes in mean motor evoked potential (MEP) amplitude of the first dorsal interosseous (FDI) and the abductor digiti minimi (ADM) muscles at each interval (15, 40, 80, 200, 500, 1000 ms) from electromyography (EMG) onset of the FDI, compared to resting state (catch trials). * Significant differences between FDI and ADM MEP amplitudes ($p < 0.05$). Error bars indicate standard error of the mean.

These effects were subsequently analyzed using Tukey's HSD ($p < 0.05$) because differences between muscle activation at individual points in time were of greatest theoretical interest in the current investigation. These posthoc analyses revealed significant differences between in the FDI and the ADM activation at 15, 40, and 80ms time bins in both the control and CD groups suggesting that FDI muscle activation was significantly greater than the ADM muscle activity early in the movement and as time went on, the two muscles activations were not different from each other. Also, this

pattern of effects suggests that the control and CD groups were not behaving differently from each other during the task.

The same statistical analyses were performed on the RMS area of the normalized MEPs and these analyses revealed the same pattern of effects.

2.5.4 Co-contraction Results

The results from this analysis showed that there was a significant difference in the amount of time that the control group (5%) and the CD group (12%) spent in co-contraction, $\chi^2(6) = 32.47, p<0.001$. This may suggest that some individuals in the CD group may have subclinical dystonic symptoms in the tested hands.

2.5.5 Group and Kinematic Results

The control and cervical dystonia groups were matched closely for age and gender. There were no significant differences in average age of the groups, $t\ (12) = 0.285$, $p>0.05$. In addition, the groups of people executed their finger movements in a similar fashion. Specifically, there were no group differences in reaction time, $t\ (12) = 0.347$, $p>0.05$, movement time, $t\ (12) = 1.419, p>0.05$, and peak velocity, $t\ (12) = 0.436$, $p>0.05$.

2.6 Discussion

The main aim of the current study was to investigate whether disturbed inhibitory mechanisms were present in the asymptomatic limb of people with CD. To this end, participants completed a protocol adapted from studies by Sohn and Hallett (2004a, 2004b). Participants were asked to perform 1-second index finger abduction movements to the beat of a metronome. During this movement, a single TMS pulse was delivered over the finger area of motor cortex and the resultant MEPs from the FDI and ADM

muscles were recorded and analysed. It was hypothesized that, in the controls, the muscles of the little finger (ADM) and other surrounding musculature should receive inhibitory influences because these muscles were not involved in the goal task. Such inhibition would be revealed by smaller MEP amplitudes in ADM than in FDI. In contrast, because it has been suggested that the surround inhibition mechanism may be dysfunctional in people with CD, neurons that activate ADM may not receive inhibition and thus there might not be any differences between MEP amplitude in FDI and ADM.

Consistent with the predictions regarding the control group, the analysis of the MEP data with the large sample of control participants (Section 2.5.1.) revealed significant differences between the MEP amplitudes of the FDI and ADM during the 15, 40, 80 and 200ms time bins. The FDI had significantly larger changes in MEP amplitude during movement than did the ADM. This pattern of results is generally consistent with the original findings of Sohn and Hallett (2004a). One major difference, however, was that the control group in the current investigation did not show inhibition below rest; the normalized MEP amplitudes did not decrease below "1". Although not strictly consistent with the predicted inhibitory mechanism, the findings may not mean that inhibition was not at play. This conclusion will be discussed in detail below.

For the between-group analysis it was hypothesized, based on an abundance of literature showing dystonic abnormalities in an asymptomatic limb, that a lack of surround inhibition would also extend beyond the affected limb. Such an absence of surround inhibition would have been indicated by significantly larger normalized MEPs in the ADM of the CD group compared to the control group and/or a non-significant muscle x time interaction in the CD group. This hypothesis was not supported by the

results. Specifically, the pattern of MEP amplitudes observed in the group with CD was not different from the pattern of MEP amplitudes observed in the control group. In fact, both groups showed the same pattern of results in that both the control and CD groups displayed differences in MEP amplitude between the ADM and FDI early in the movement (up to and including 80 ms) and no differences later in the movement. These data seem to suggest that there were no between-group differences in cortical circuitry and that abnormal inhibition (measured in this way) does not extend beyond the affected limb in people with CD. Moreover, even though there were only two FHD participants, the findings of this group also followed the same patterns of cortico-spinal excitement in their affected limbs. This is inconsistent with the results of Sohn and Hallett (2004b). Obviously, because this was such a small group, any conclusions about their activation and neural circuitry versus other groups must be drawn with caution. This is an inconsistency, however, that deserves attention and possibly a follow-up investigation confirming Sohn and Hallett's (2004b) findings in the group with FHD.

Although the main hypothesis of an absence or reduction of surround inhibition in an asymptomatic limb of people with CD was not supported, it should be noted that the broader literature investigating dystonic abnormalities in asymptomatic limbs is somewhat inconsistent and lacks cohesiveness. Therefore, the findings of the present study should not come as too much of a surprise. Some of the literature would suggest that the abnormalities found in dystonia from increased co-contraction to sensory deficits, extend beyond the affect limb (Obermann et al., 2008; De Vries et al., 2007; Abbruzzese et al., 2001; Chen et al., 1995; Deuschl et al., 1992). Other researchers would assert, however, that other abnormalities such as increased common input are not found outside

the affected dystonic limb (Farmer et al., 1998). The results of the present study are consistent with the latter conclusions because it appears that decreased inhibition or "surround inhibition", as Sohn and Hallett (2004a, 2004b) have defined it, does not extend beyond the affected limb.

A few questions remain then about focal dystonia. Do all abnormalities found in focal dystonia extend beyond the affected limb, but some tests are not sensitive enough to detect them? Are there some abnormalities underlying the expression of dystonia (can be observed prior to the overt expression of dystonia) and other abnormalities that come about as a result of the dystonic postures (would only be present after dystonia is expressed in a limb)? Or perhaps, is it possible that the investigations that found abnormalities outside the affected limbs actually had contaminated groups in which members had dystonia in multiple limbs, but had not yet been diagnosed? As stated above, the literature in this particular area is somewhat inconsistent and has not yet been evaluated in such a way (large literature review/meta-analysis) so that cohesive conclusions can be drawn about focal dystonias and a potential link between all of the various expressions of the disorder.

One interesting result of the present study relating to surround inhibition was that most of the participants in the control and CD groups showed MEP amplitudes in their ADM larger than baseline (a normalized value greater than 1; see Figures 11 and 12). Furthermore, although Sohn and Hallett (2004b) did not report whether ADM activity was significantly less than "rest", their graphs suggest that none of the normalized amplitudes fall below 100% (rest). This is an important distinction because, in their earlier study, Sohn and Hallett (2004a) reported that normalized ADM MEPs were

significantly lower than rest when they eliminated trials with background activity. Based on this subset of results, they suggested that the motor system actively inhibits surrounding non-goal muscular activity. However, even within this same study they do mention that without the removal of these trials, ADM activity was near and slightly above resting levels. These discrepancies have not been discussed in detail. In addition, it should be noted that a similar screening procedure was also completed in the present study in that MEPs in the ADM that had background activity prior to the MEP were eliminated prior to data analysis.

Observing normalized values above 100% may not mean that surround inhibition does not exist. Instead, it may just mean that this mechanism needs to be conceptualized in a slightly different way. Specifically, during movement there is a general non-specific increase in activity in the motor cortex. Furthermore, Sohn and Hallett (2004a, 2004b) also found that spinal activity (assessed by F-waves) of both muscles increased during movement as well. Because of this increase in spinal excitability, the MEP amplitudes above 1 may reflect the fact that this non-specific cortical and spinal facilitation is being attenuated, thought not completely inhibited, during movement. Thus, from a functional point of view, non-goal muscles might not need to be inhibited to below rest (revealed through MEP amplitudes that are below rest), but instead that they would only need to be inhibited below a level that would cause overt movement.

The investigation into a so-called surround inhibitory mechanism in the motor system is in its infancy and as such, the methodology used to investigate it has not been fully developed and controlled. In the current investigation, we chose to modify the methodology used by Sohn and Hallett (2004a; 2004b). As such, we used an index finger

abduction movement instead of an index finger flexion movement. Both movements were pilot tested and it appeared that we were able to get larger, more discernable bursts in the FDI and that people were able to perform those abduction movements without overt activity in the ADM. In addition, the movement in the present study took more time to complete (1s versus 200-300ms) and used a metronome to decrease the movement variability across participants. The task was actually very difficult for some of the subjects. It appeared that some people had little difficultly isolating index finger movements while others struggled. These difficulties and the methodological changes may be a part of the reason for the lack of difference between our two groups. Although these methodological differences may have contributed to some of the different patterns of effects, the results from the control group mirrored those of Sohn and Hallett (2004a) in that their control group demonstrated significantly smaller normalized MEP amplitudes in the ADM than in the FDI during index finger flexion from 3ms – 200ms. The consistency in the patterns of effects in the control groups suggest that these small methodological changes were not the main contributor to the results and that the absence of difference between the two groups has more to do with the way dystonia affects (or does not affect) the human motor system.

It is important to note that we had a relatively small sample size compared with literature using the average population. However, our sample size was no smaller than most other clinical research in this area including Sohn and Hallett (2004b; n=7). Furthermore, it is important to note that the majority of the critical non-significant effects involving group had F ratios of less than one. Finally, the pattern of effects of both of Sohn and Hallett's work (2004a; 2004b) were replicated in our control group, and in our

CD group. In sum, there was sufficient power to detect differences and it is unlikely that a small sample size was responsible for the null group effects.

Finally, because we did not include F-wave analysis in our protocol and analysis we can neither confirm nor dispute the assertion that this inhibition is cortical or spinal in nature. It is simply our assertion that the surround inhibition mechanism does not seem to be different in the average population or in people with CD.

In conclusion, when both control and CD subjects performed index finger abduction movements, there was significant facilitation of FDI MEP amplitudes above those of the ADM in the early stages in the movement (up to 80ms into the movement). This finding suggests that abnormalities in this inhibitory mechanism that have been seen in FHD do not extend outside of the affected limb in people with CD. This finding may suggest that a lack of inhibition measured in this way is not a systemic issue in dystonia and that it is contained within an affected limb. Lack of inhibition throughout the nervous system in focal dystonia is seen as a major contributor to the disorder and as such, deserves further attention and methodological scrutiny to ensure there is a full understanding of both a properly functioning motor system and a dysfunctional one (Hallett, 1998). Furthermore, investigating the asymptomatic limb in dystonia may provide us with a link between all of the focal dystonias and a better understanding of the disorder therefore it is important to continue investigating these issues.

Chapter 3 – General Discussion

The aim of this master's thesis was to answer two main questions. The first question was: do healthy, neurologically intact individuals inhibit muscle activity in a non-synergistic muscle during an index finger abduction task? To answer this question, participants were asked to perform brief and isolated index finger abductions while keeping their other fingers relaxed. TMS was applied over the motor cortex at different times during this movement and the size of the normalized MEP amplitudes in both the FDI and ADM were compared. Previously, Sohn and Hallett (2004a; 2004b) investigated inhibition in a similar way in both a control group and in a group of individuals with FHD. They found that that the healthy control group demonstrated inhibitory effects, whereas the people with FHD were not able to inhibit activity in their ADM during an index finger flexion task. Many abnormalities in people with focal dystonia have also been found in an asymptomatic limb. This led to the second question. Do people with CD have abnormal inhibition outside their affected limb? This question was evaluated in the same way as the first. The following sections address the results and implications of these questions. Some of the limitations and conclusions will then be discussed.

3.1 Inhibition in Healthy Controls

First, would a healthy control group show inhibition in their ADM muscles during index finger abduction task? This question served the purpose of attempting to replicate previous findings suggesting that there is an inhibitory mechanism present in healthy individuals that allows them to perform movements with ease and specificity (Sohn & Hallett, 2004a). The answer to this question may be very important to motor control research in that it may allow for a better understanding of inhibition in the motor system

which is notoriously difficult to evaluate since one is looking at an absence of activity rather than a presence of it.

The analysis of the large control sample revealed that the amplitude of the average MEPs seen in the ADM were significantly less than in the FDI. Because the MEP amplitude is generally used as an index of cortico-spinal excitability, these data suggest that the neural circuits that innervate ADM were not as highly activated as the circuits that innervate FDI. Furthermore, it has been suggested that there is a broad overall excitation of the motor cortex and spinal cord during movement. Thus, significantly smaller MEP amplitudes in the ADM may suggest that inhibition is occurring somewhere in the motor system in order to suppress unwanted movements. Since there is no true way of determining whether excitation or inhibition occur cortically, sub-cortically or at the spinal cord using the TMS technique, it is very difficult to make the assertion that this is purely a cortical inhibitory mechanism. However, there are many other systems in the body that have a cortically-driven surround inhibition mechanism, such as the visual and tactile systems (Famiglietti & Kolb, 1974; Johnson, 2001). It would be reasonable to suggest that this inhibitory circuitry is found in the motor system and, hence, the lower ADM MEPs may be a cortically-driven phenomenon.

Although surround inhibition is a typical cortical mechanism, it may also be possible that this inhibition is occurring at the level of the spinal cord or both the spinal cord and the cortex. The spinal cord is responsible for regulation of other inhibitory processes such as reciprocal inhibition. Therefore, this process may involve inhibitory interneurons in the cortex or may utilize interneurons at the level of the spinal cord to bring about quiescence. Regardless of the location, there is significant activation of

muscles involved in a movement and what looks like an inhibition of activation in muscles that are not involved in an action.

The results of the present study did not show, however, inhibition in the way Sohn and Hallett found and explained in their initial 2004a paper. In that study, these authors found that the MEP amplitude of the ADM was significantly suppressed below resting during a finger flexion task. In the present investigation, MEP amplitudes were not significantly different from rest in the ADM but were never close to falling below rest. This may be explained by the task. Sohn and Hallett (2004) used an index finger flexion task in order to evaluate inhibition in the ADM. The little finger is rarely ever abducted while a person performs an index finger flexion unless it is specifically practiced. This may explain why the motor system was able to so significantly inhibit unwanted little finger activity. Our task however, involved index finger abduction. It is more likely that index finger abduction and little finger abduction would be performed together during any movement that involved finger spreading. Therefore, it makes sense that the motor system could still inhibit this movement, but there was still a greater level of activation in the little finger.

3.2 Inhibition and Dystonia

The second, and arguably the question of greatest theoretical significance for the paper, question this thesis attempted to answer was: do people with cervical dystonia display reduced inhibition in the ADM muscle during the task described above or do they follow the same pattern of inhibition as a healthy control group? This question was developed from a review of a number of key papers. First, Sohn and Hallett (2004b) found that people with FHD seem to lack this inhibitory mechanism and show greater

cortical activation for non-synergistic muscles. Second, the literature described some other abnormalities of dystonia found in an asymptomatic limb (e.g., Basal ganglia dysfunction, Obermann et al., 2008; Reciprocal inhibition, Chen et al., 1995 & Deuschl et al., 1992; Co-contraction, De Vries et al., 2007; Sensorimotor integration, Abbruzzese et al., 2001). If abnormalities seen within the affected limb in focal dystonias are also seen outside the affected limb, it might suggest that there is a common set of abnormalities among all focal dystonias and that they are not distinct disorders but multiple manifestations of the same disorder. Furthermore, finding these abnormalities in the asymptomatic limb could suggest that certain abnormalities are underlying causes of dystonia and are necessary for dystonia to develop. Abnormalities that do not extend beyond the affected limb on the other hand, may arise as a result of the dystonic posture and are secondary to the disorder itself.

The results of the current work suggest that a lack of inhibition measured in this way does not extend beyond the affected limb in people with cervical dystonia. There are many reasons that this result could have come about. For instance, the findings could indicate that abnormal surround inhibition is not common to all dystonias and that perhaps there is not a common link between all focal dystonias. This would mean that the other abnormalities found beyond the affected limb might simply be many similarities among separate and distinct focal dystonias. This is possible, but it seems unlikely due to the number of common abnormalities seen in focal dystonias. One or two common abnormalities may be explained this way, but the fact that sensory deficits, increased plasticity, abnormal basal ganglia activity, increased co-contraction and abnormal reciprocal inhibition have all been found beyond the affected limb seems suggests that

there is a set of underlying conditions that are common to all focal dystonias. Thus, there is a large amount of evidence in the favour of an underlying common dystonic condition in focal dystonia. Beyond this evidence, the fact that dystonia often spreads to other body parts also lends itself to the idea that there is an underlying systemic issue in people with focal dystonias and that some kind of provocation causes the disorder to manifest in a limb.

On the other hand, the present findings might mean that abnormal inhibition of this kind is strictly an abnormality found in FHD patients. If this abnormality is unique to FHD, one would not expect it to show up in another focal dystonia and one would certainly not expected it to extend beyond the affected limb in any other focal dystonia. Since this abnormality has not been investigated in other focal dystonias, it is not possible to know whether this is a common abnormality in many different focal dystonias. The hand is a very unique part of the body, which allows researchers to analyze very controlled and isolated movements due to the number of specialized and distinct intrinsic muscles. It may be difficult to achieve this level of separation anywhere else in the body. Therefore, finding this phenomenon measured in this way may be next to impossible. However, if one thinks about this mechanism theoretically, it makes more sense that this is the body's means of selecting certain groups of muscles for an action and turning off other groups of muscles that may interfere with an action throughout the body and not just a specific adaptation of the hand. It seems that the hand is merely an eloquent example of this neural mechanism due to its very specialized and distinct muscle groups.

Another possibility is that abnormal surround inhibition only arises as a result of dystonia. More specifically, the manifestation of dystonia in a limb may over time

change the circuitry of the brain or nervous system such that inhibition becomes increasingly more difficult to achieve. Therefore, only when dystonia manifests itself in a limb will this abnormality be present. This possibility is a reasonable explanation for why abnormal inhibition was not found in this CD group. The nervous system is very plastic and can be affected in both directions. Not only can higher-order disorders cause changes downstream but so too can changes seen peripherally change the system upstream. The only way to truly know if this is the case is to evaluate inhibition throughout the lifespan of the disorder. Because age and time of onset is very difficult to ascertain from individuals due to self-report bias and if and when people chose to get treatment, this would be very difficult to look at. To my knowledge, abnormalities in dystonia have never been looked at in this way.

A final but less likely reason that abnormal inhibition may not have been seen is that the measure and methodology used in this study was not sensitive enough to pull apart a between-group difference. This does not seem likely because if this were the case, one would think that you might see a slight trend in the data suggesting that the CD group had less inhibition than the control group. This was not the case and in fact the opposite was true, the CD group showed slightly more inhibition than the control group. A more sensitive test would need to be created in order to combat this problem. To date however, no such technique exists since this is a relatively new way to look at inhibition in this way.

Looking at all of the possible explanations of the current findings, it seems that the most likely candidate is that this abnormality simply does not extend beyond the affected limb and thus, it would be likely that a lack of inhibition found in FHD came

about as a result of the dystonic posture. Of course, until all of the other explanations are ruled out it would be difficult to make a case for any one of these explanations.

3.3 Limitations

The present study is not without limitations. One limitation of this investigation is the degree of generalizability. First, a cross-sectional study approach was used for this investigation. The present study is one snapshot in time and it can only really be asserted that at this point in time with the two specific groups used, abnormal inhibition was not found in either group. Because a cross-sectional design was used it is necessary to understand that it is difficult to look at causation or extend the findings beyond the two groups that were used. Furthermore, we used such a controlled and simple task that it is very hard to generalize the findings to a more ecologically relevant task such as movements that would be seen in a "real-world setting".

Another possible limitation of this investigation was the size of the groups that were used for between-group comparisons. It is important in any study using between-group comparisons to ensure that groups are large enough to allow for an adequate amount of power in the study. That is, there needs to be enough people in each group so that if true differences do exist between the groups, an investigator will be able to statistically find them. A sample size calculation was conducted prior to this investigation using data from Sohn and Hallett (2004) and that calculation yielded 11 people as the number needed to have significant power. Having said this, Sohn and Hallett (2004b) were able to find statistically reliable differences between their two groups with 7 participants in each group, which is the same number used in the current investigation. Furthermore, statistically reliable differences were seen between muscles

in each group and the trends seen in both groups mirrored that seen in the analysis of the larger 17 person control group. These findings suggest that the investigation was powerful enough to yield statistically significant differences.

For this investigation a group of CD patients was used. This group had many characteristics that made it difficult to carry out the experimental protocol. One characteristic in some of the CD patients that made the protocol difficult was dystonic tremor. When using TMS it is important that the magnetic coil remains in the same location on the scalp throughout a block. Because some of the patients had dystonic tremor, coil placement consistency was difficult to maintain. Most of the participants with tremor had somewhat mild tremor and because of the blocked design rest was provided which often helped each participant rest and relax. However, it was still an issue with some of the participants and this may have affected the reliability of the results for his group. Furthermore, even if some of the patients did not have tremor, sometimes patients had a significant head tilt or rotation due to their dystonia. This also made it difficult to maintain coil consistency while ensuring participant comfort. Again, having a blocked design allowed for a coil placement check to ensure accurate placement (see methods) and time for participants to rest. In addition, significant effects were observed. Problems in maintaining coil placement would have only been an issue if there were no differences and if MEPs were not observed (the coil was not placed consistently enough to evoke MEPs). Such was obviously not the case.

The use of different medications in treating dystonia may have potentially affected the outcome of this experiment. Most of the participants were on botox for their cervical dystonia and this was fairly easy to control for by ensuring that these participants

were tested in the last week before their next botox injection. This ensured a wash out period of 13 weeks, which is consistent with much of the literature using patients with dystonia. Some of the patients had discontinued botox treatments and were being treated with a centrally-acting benzodiazepine called clonazopam. Benzodiazepines are a class of drugs used to treat muscle spasms among other things and work by enhancing neurotransmitters GABA and $GABA_A$ receptors, which causes a depression or calming effect of the central nervous system. It is typically not recommended to discontinue the use of these types of medication without being weaned off them very slowly. Because of this precaution, participants taking this medication were not asked to discontinue their use for this experiment. This could mean that these two individuals may have behaved differently than other CD patients. It would be likely that their levels of excitation and responsiveness to the protocol may have been diminished throughout the system and that the affect of their dystonia may not be similar to other CD patients. Based on an individual inspection of their data, however, these two patients did not appear to be behaving consistently different from the other members of the group. This type of medication can also cause difficulties in the motor system and in memory. This too may have been a problem if they were not able to understand or carry out the protocol. Great care was taken however, to ensure that every participant was performing the task adequately and consistently and feedback was given throughout the experiment to ensure continued understanding. These two participants did not seem to have any more or less difficulty than anyone else performing the task. One other participant was taking amitriptyline, which is a trycyclic antidepressant and an anticholinergic agent that acts to inhibit serotonin and noradrenalin uptake. Because this is a centrally acting drug it too

could potentially affect an individual's performance or brain chemistry to alter their outcome. The side affects of this drug could affect an individual's ability to complete the protocol because these types of drugs can cause ataxia, memory loss and confusion. Again, all participants were closely monitored for their task performance and the data from this participant showed a similar pattern of effects as each of the other CD participants. (Compendium of Pharmaceuticals and Specialties, 2009)

A final but important potential limitation was the task choice. Index finger abduction was chosen for a number of different reasons. This type of movement was easy to control, it is the primary movement of one of the muscles of interest (FDI) and during pilot testing this movement was fairly easy to perform without much difficulty and without involvement from the ADM. As participants came in, it became apparent that the task was difficult for some individuals. The difficulty was not unique to any one of the groups and one of the main problems that people had was a difficulty isolating the index finger, which meant activity was seen in the ADM during FDI activation when it should have been quiescent. This problem was combated in a number of different ways. First, participants practiced the movements until they felt comfortable. If necessary during this time, participants were given biofeedback and were asked to watch the EMG display until they were able to keep the ADM still. Second, ADM activity was monitored throughout the study and trials were recollected if ADM activation was observed. Finally, if any trials with significant ADM activity were missed during the experiment, an outlier procedure was performed to eliminate these trials during the data analysis stage.

Another difficulty people had with the task was listening to the metronome and moving for the whole one-second-time period. Again numerous practice sessions were

allowed and trials were redone if participants did not perform a movement correctly. The analysis of the post experiment movement times were consistent and were very near to 1000ms, so we are confident that the task was performed correctly. Having said this, the task remained very difficult for many individuals and it may be useful to pilot test a number of different isolated finger movements to eliminate the difficulties and the time consuming process of ensuring correct task performance.

3.4 Conclusions, Implications, and Future Directions

It is clear after looking at the different conclusions that could be drawn from the present results and the limitations of this study, that there is much more research to be done in these areas. The two areas that should be followed up with in the future are the basic phenomenon of "surround" inhibition in the body and the investigation of dystonia outside the affected limb. The future for these lines of research is bright and full of potential.

Of utmost importance in continuing the inhibition research is creating a reliable and consistent task and protocol for testing this phenomenon. The task needs to be more closely controlled and looked at across many different parts of the body. As was previously stated, the hand is uniquely adapted to perform fine isolated movements, but more investigation involving more body parts is required to really determine if this inhibition is a more widespread principle of the human movement system. It may also be interesting to follow up on the finding that inhibition may not necessarily result in cortico-spinal activation that is below rest. In the current investigation, ADM MEP amplitudes were well above rest but were significantly smaller than those in the FDI. It is difficult to conclude that inhibition was occurring in the ADM. However, because of

previous findings showing increased spinal excitation in the FDI and ADM during isolated finger movements (Sohn & Hallett, 2004 a,b) and because there is wide spread throughout the motor cortex during movement, it may still be concluded that inhibition, at some level, may have been taking place. In Sohn and Hallett's investigation (2004a) however, AMD MEP amplitudes were inhibited below resting levels. These discordant findings may be due to task differences, but it is still important to investigate why there were discrepancies between these two studies.

The investigation looking at the abnormalities beyond the affected limbs and the possibility for an underlying common connection among all focal dystonias must continue. In order to understand primary focal dystonias fully, abnormalities leading to the manifestation of dystonic symptoms must be identified more clearly and links between them must be established. It may be useful to follow up the present study with an investigation of inhibition in the asymptomatic hand of those with FHD to see if similar contralateral body parts (both hands) are affected differently than more dissimilar ipsilateral body parts (the neck and the hand). It may be useful to use this group as well to eliminate one of the limitations of the current study, which was the difficulty performing TMS on a group with CD. To combat some of the other potential limitations of this study, larger sample sizes could be tested although this is difficult when dealing with a limited clinical population. Also, it may be interesting to investigate these inhibitory phenomena on and off peripherally and centrally acting drugs to determine what role they may play in inhibition in dystonia. Dystonia is a complex disorder and any possibility that there is of finding a common link between many different forms of

focal dystonia could have a large impact on future treatment and research of focal dystonias.

In conclusion, a group of healthy controls were found to inhibit non-synergistic muscle activity during an index finger abduction task. This was demonstrated by the fact that MEP amplitudes (an index of cortical excitability) of the ADM were significantly smaller that those in the FDI the muscle performing the movement. Of greater theoretical interest was the finding that the group with CD demonstrated the same pattern of MEP amplitudes. This finding did not support the hypothesis that impaired inhibition in people with dystonia would extend beyond the affected limb in people with CD. Thus, the results of the present study suggest that a the type of abnormal inhibition seen in FHD may be contained only within the dystonic limb and may suggest that this impairment is caused by the presence of dystonia, and that it is not a root cause of dystonia.

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