TREATMENT DURATION AND EFFICACY OF COUPLED MOTOR RECOVERY PROTOCOLS

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This document is dedicated to my mother and father

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Motor impairment is a major consequence following stroke. Recovery of movement, particularly in the upper extremity, poses a challenge for rehabilitation specialists and therefore the search to find effective modes of intervention continues. EMG-triggered neuromuscular stimulation studies have demonstrated functional improvements; however, the application of this treatment has lacked standardization. One of the major issues needing resolution is treatment duration of coupled protocols (bilateral movements and active stimulation).

The present study addressed treatment duration by comparing motor function over the course of a 4-week (12 hours) treatment period. Training involved EMG-triggered neuromuscular stimulation on the impaired limb coupled with concurrent extension of the unimpaired wrist and fingers. All participants were trained twice per week on average for 120 stimulation trials per session for a total duration of approximately 4 weeks (12 hours).

Motor functions were measured with the Box and Blocks timed manipulation task, as well as with two computerized measures of wrist extensor capabilities (reaction time and sustained contraction). Baseline testing was conducted prior to training, after 2 weeks (6 hours) of training, and following 4 weeks (12 hours) of training.

The findings of this study failed to reveal duration differences for EMG-triggered neuromuscular stimulation coupled with bilateral movements. Thus, no motor recovery inferences could be made regarding treatment duration. These results are incongruent with the current consensus on EMG-triggered stimulation and bilateral movements. Possible reasons for such differences are discussed as well as an expanded critical review of stroke motor recovery research as it relates to the influence of treatment duration on recovery.

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CHAPTER 1
INTRODUCTION

Recently, the influence of electrical stimulation on regaining motor function in the upper limb of stroke patients has been researched by several investigators (Cauraugh & Kim, 2002; Cauraugh et al., 2000; Chae et. al., 1998). This evidence suggests that neuromuscular electrical stimulation enhances motor relearning. In addition, electrical stimulation has been proposed as a therapeutic strategy for changes in muscle strength and spasticity, which in turn may positively influence motor relearning (Burridge & Ladouceur, 2001). Research has focused on both extrinsic and intrinsic measures of change that take place with active stimulation. Extrinsic measures focus on the functional effect of electrical stimulation in the ability to carry out various daily activities, and intrinsic measures offer insight into the underlying mechanisms for change (Burridge & Ladouceur, 2001). However, limitations of previous research have been noted in terms of the scientific thoroughness of many of the studies (Burridge & Ladouceur, 2001; Glanz et al., 1996). This includes a variety of problems in methodology such as the absence of a placebo, uneven group numbers, the lack of a control group, and groups that were significantly different in baseline level of function. Moreover, some of the research evidence is based on simple case studies (Chae et al., 2001).

Previous studies have used a wide variety of stimulus parameters (i.e., intensity of stimulation, duration of pulse), treatment duration, treatment frequency, and subjects (i.e., various degrees of impairment and time period since stroke). This lack of standardization in treatment administration has made it difficult to accurately compare and contrast

findings. Along with the variability in treatment protocols, different investigators have used different outcome measures. Examples of outcome measures include simple range of motion and strength testing as well as complex functional assessments such as the functional independence measure (FIM). Such a broad range can be somewhat problematic when trying to compare the efficacy of the treatment among studies.

Despite discrepancies in how various researchers have administered and measured the effect of neuromuscular stimulation, overall significant improvements in voluntary motor control have been found (Burridge & Ladouceur, 2001; Popovic et al., 2002). Such improvements have been especially pronounced in studies using stimulation at or above the motor threshold, and to an even greater extent in studies requiring volitional activation of the neuromuscular stimulation (Burridge & Ladouceur, 2001; Francisco et al, 1998; Popovic et al., 2002)

Granted, benefits from neuromuscular stimulation abound especially with volitional activation, however, optimal treatment duration has not been determined. Cauraugh and colleagues have found motor improvements in six hours of training over two weeks (Cauraugh & Kim, 2002; Cauraugh et al., 2000). Dimitrijevic and colleagues reported motor recovery progress after ten months (Dimitrijevic et al., 1996). These are two extreme treatment durations. Further, no studies have determined the time course of effectiveness of any motor improvements. Given that a treatment program of two weeks has led to significant improvements the question arises of whether additional treatment sessions provide increased benefit. The purpose of the present study was to determine an optimal treatment duration and this is consistent with conclusions in a recent critical

review of neuromuscular stimulation; optimal treatment duration has not been determined (Popovic et al., 2002).

The specific objective of the present study was to determine if motor capabilities of chronic stroke patients improve as a function of the duration of EMG-triggered neuromuscular stimulation when combined with bilateral neuromuscular movement training. In particular, does treatment duration of four weeks (12 hours) lead to significantly improved functional outcomes when compared to patients treated for only two weeks (6 hours). Based on the motor learning and control precept that additional practice would lead to enhanced motor capabilities (Winstein, Wing & Whitall, 2003), it was hypothesized that the four weeks (12 hours) of treatment would demonstrate significantly increased motor functions in the upper extremity (wrist/fingers) compared with the two weeks (6 hours) of treatment.

CHAPTER 2
REVIEW OF LITERATURE

Stroke: Causes and Classification

In general, a stroke involves the disturbance of blood supply to the brain. Due to the brain's dependence on an adequate supply of oxygen and nutrients via the blood, brain function can only be maintained for a few minutes if blood flow is reduced below a critical level (Kandel, Schwartz, & Jessell 2000). If sustained, this deprivation, leads to impaired brain cell function and often cell death. A stroke refers to the neurological signs and symptoms that result from diseases involving the blood vessels (Kandel, Schwartz, & Jessell 2000). The nature and severity of the impairments that result are directly related to the location of the brain that is affected as well as the extent of the damage.

There are two general types of stroke: (a) ischemic and (b) hemorrhagic (Kandel, Schwartz, & Jessell 2000; Popovic & Sinkjaer, 2001). An ischemic stroke involves occlusion of the brain's supply due to the closure of a vessel (i.e., blood clot). The hemorrhagic class of stroke involves a vessel rupture and consequent disruption of blood flow. Both of these forms of stroke lead to the deprivation of blood supply to the brain tissue, and when sufficiently prolonged and severe, death of neurons and other cellular elements (Kandel, Schwartz, & Jessell, 2000). This resultant death of the brain cells is referred to as an infarct and once cell death occurs the damage to this specific site is irreversible. Moreover, hemorrhagic strokes are more substantial than the ischemic strokes.

The factors that lead to stroke are diverse but tend to follow certain patterns. For example, most ischemic strokes are associated with atherosclerosis and thrombosis, while most hemorrhagic strokes are associated with hypertension or aneurysms (Kandel, Schwartz, & Jessell, 2000). In addition, other causes have been noted and include cardiac disease, trauma, infection, neoplasm, blood dyserasia, vascular malformation, immunological disorder, and erogenous toxins (Popovic & Sinkjaer, 2001). However, regardless of the cause, the end result of the stroke is death to some part of the brain and consequent impairment of function.

The functional decrements that result depend on the specific location affected by the stroke. The brain is composed of three main areas: the cerebrum, the cerebellum and the brain stem. Each of these areas is distinct in terms of function. For example, the cerebellum is responsible for movement control and coordination as well as maintaining balance. The brain stem is responsible for many automatic functions such as respiration, heart rate and blood pressure. The cerebrum is the largest part of the brain, and is responsible for many higher functions such as speech, emotion and fine movement control. The area or region is divided into a left and right hemisphere, as well as into four separate lobes including the frontal, parietal, temporal, and occipital lobes. Neural cross-over exists such that the left side of the brain controls most of the functions on the right side of the body and vise versa. Because of this crossing over of the neural tracts, a stroke that occurs in the one hemisphere will result in impairments on the opposite side of the body.

Each of these parts of the brain receives a blood supply from different arterial sources. When a certain artery is ruptured or becomes occluded, the resultant infarction

will produce characteristic impairments. Infarction that follows the disruption of blood flow through the middle cerebral artery is the most common among the various forms of stroke (Kandel, Schwartz, & Jessell 2000, 2000; Popovic & Sinkjaer, 2001). This artery supplies part of the frontal lobe and the lateral surface of the temporal and parietal lobes. The consequent stroke syndrome involves contralateral weakness, sensory loss, and visual field cut, and depending on which hemisphere is affected, either language disturbance or impaired spatial perception (Kandel, Schwartz, & Jessell 2000). Weakness and sensory loss is more profound in the face and arm as opposed to the leg.

The anterior cerebral artery supplies the frontal lobes. Weakness and sensory loss result when this arterial supply is affected and voluntary movement is compromised, especially in the distal contralateral leg (Kandel, Schwartz, & Jessell 2000). If the anterior cerebral arteries on both sides are involved then significant behavioral symptoms may result (i.e. akinetic mutism, profound apathy, urinary incontinence and motor inertia) (Kandel, Schwartz, & Jessell 2000; Popovic & Sinkjaer, 2001).

The posterior cerebral arteries supply the temporal and occipital lobes of the left cerebral hemisphere and the right hemisphere. Depending upon the location of the occlusion along this arterial branch, the clinical symptoms will vary. Some of the symptoms may include color blindness, failure to see to-and-fro movements, memory disturbance, hemisensory loss, verbal dyslexia, and hallucinations (Kandel, Schwartz, & Jessell 2000; Popovic & Sinkjaer, 2001).

In summary, the manner in which a stroke manifests itself is dependent on the region that is affected and the extent of the brain area involved. There are several factors that can lead to a stroke, and several different ways in which a stroke can occur, but the

common result is death of the brain cells that were nourished by the disrupted blood supply. The resultant impairments vary widely and frequently involve some degree of motor, sensory, and cognitive impairment.

Neurological Responses to Stroke

Following a stroke, the body undergoes neurological changes to deal with this novel insult. Neurological and functional recovery occurs with the greatest speed in the first 1-3 months after stroke (Gresham et al., 1995). As previously stated, the nature and severity of the deficits depend upon the type, location, and extent of the lesion. The deficit may be motor, sensory, or cognitive in origin, or any combination. The degree of recovery from these impairments varies, and the resolution of any one deficit may not correlate with the improvement of another. In regards to motor ability, the potential problems include muscle weakness, abnormal synergistic organization of movements, altered temporal sequencing of muscle contractions, impaired force control regulation, delayed responses, diminished range of motion, abnormal muscle tone, sensory impairments, and altered biomechanical alignment (Gresham, Duncan, Stason, et al., 1995).

With the clinical observations of outcome after stroke it is important to elucidate the underlying mechanisms. In this sense, the focus is on the intrinsic measures that lead to the observed outcome. For the first several days following a stroke, there is often a noted improvement in ability. This form of spontaneous recovery may be due to the reduction of edema or reperfusion of the ischemic penumbra (Chen et al., 2002). The penumbra is the area surrounding the infarct that is in a fragile state, yet it can be salvaged if the blood supply is stabilized within a critical period of time. Therefore, the resolution of these temporary issues may lead to improved function (Chen et al., 2002).

After a period of approximately two weeks a large degree of the recovery that takes place is because of mechanisms of plasticity (Chen et al., 2002). The type of mechanism and the degree of plasticity have a high correlation with the degree of recovery that is noted in patients (Hallett, 2001). The mechanisms that are involved with plasticity involve unmasking of inhibitory influences on regions surrounding the infarct, strengthening or weakening of existing synapses (i.e. long-term potentiation or depression), or alteration of neuronal membrane excitability (Chen et al., 2002; Hallett, 2001). Because of the existence of redundant circuitry in the brain, the possibility exists that these previously dormant circuits may now be used. These processes work along a relatively rapid time course. Another mechanism, which requires a longer duration to manifest, involves anatomical changes such as sprouting of new axon terminals and the formation of new synapses (Hallett, 2001).

An important point to remember when considering the concept of plasticity and how it leads to cortical reorganization is that plasticity can take place at multiple sites throughout the nervous system. This means that reorganization may occur at a cortical level as well as at the sub-cortical, brainstem and spinal cord levels (Chen et al., 2002). Moreover, the spinal cord, which was at one time thought of as only a hard-wired and immalleable system has demonstrated the ability to remodel function in relation to afferent input (Whelan & Pearson, 1997).

For remodeling of the nervous system to occur there must be some impetus for change. One possibility is the brain's inherent propensity for resource competition. Reorganization studies on the motor and sensory cortex following de-afferentation of a limb reported that the deafferented cortex did not remain unused. Instead, body part

representations that were adjacent to that of the deafferented body part appropriated the cortical region (Hallett, 2001). Other studies have shown similar results with the brain displaying an ability to remold itself according to input stimulation or a lack of it (Chen et al., 2002). Indeed, the enlarged cortical representation of the first dorsal interosseus muscle in proficient Braille readers is a testament to use-dependent molding of the nervous system (Hallett, 2001).

Of particular interest to stroke rehabilitation is the issue of how the area surrounding the damaged tissue can take over some of the function that was lost. This concept is referred to as peri-infarct reorganization (Abo et al., 2001). The other mechanisms that may have importance in post-stroke rehabilitation include the activation of the hemisphere contralateral to the damaged region leading to ipsilateral influence over the affected limb, as well as plasticity and dendritic branching in the opposite hemisphere (Abo et al., 2001).

Treatment Induced Reorganization: Principles Governing Rehabilitation

The Clinical Practice Guideline on Post-Stroke Rehabilitation (Gresham et al., 1995) outlines three major philosophies that direct treatment choices for sensorimotor deficits: remediation or facilitation, compensation, and motor control. Remediation, is traditional therapeutic exercise using forced sensory stimulation modalities, exercises and resistive training to enhance motor recovery. In this form of treatment, some degree of volitional limb movement is a requisite. Compensation is essentially self-explanatory in that it implies using means of accomplishing a task other than with the impaired limb (i.e., using the unaffected limb to perform an activity). Finally, motor control rests on the premise that a complex interaction exists between the neurological and musculoskeletal systems and the environment, and that rehabilitation must occur in a task-specific manner

to be effective. Most likely, some combination of the above approaches would be optimal and the specific recipe for treatment would vary with the type and severity of the impairment involved.

An important consideration when reviewing the variety of treatments for motor recovery is that the best methods of achieving maximal recovery remain uncertain (Feys et al., 1998; Gresham et al., 1995; van der Lee et al., 2001). Although several studies have been implemented that compare some form of intervention with a standard physiotherapy regimen, overall there is little to indicate one treatment as being superior to another (Francisco et al., 1998; van der Lee et al., 2001). The issue is further clouded when one considers the large assortment of ways in which treatments are administered, to whom and how these interventions are measured. This makes for imprecise comparison. However, a general framework of knowledge is starting to build and illuminate several factors that appear important to motor recovery. Thus, at this point, it is appropriate to present the general basis behind most forms of treatment, and their use to capitalize on the body's resource for healing and sensorimotor adaptation.

The nervous system is a highly malleable substrate that can be modified by external input. Post-stroke treatment essentially attempts to capitalize on the inherent capacity for plasticity and improve beyond spontaneous recovery. Currently, techniques for rehabilitation include biofeedback, functional electrical stimulation, balance training, different types of exercise (i.e., isokinetic, active resisted etc.), sensory retraining, and active neuromuscular stimulation (Gresham et al., 1995).

One of the basic premises behind several rehabilitation techniques is that actual limb use is vital for re-acquiring and maintaining cortical representation, and hence

function (Braun et al., 2001; Hallett, 2001). This supports the recommendation that patients with at least some degree of voluntary control of limb movement should be encouraged to use the limb in functional activities (Gresham et al., 1995; van der Lee et al., 2001). This reacquisition of function through repeated use can actually be hindered by many of the forms of treatment where compensation for the impaired limb is the opted strategy (Nudo, 1999). In this case, the continued disuse of the impaired limb would only exacerbate the limited ability of the limb (Gresham et al., 1995).

Using activity dependent recovery as a foundation, the practice of constraint-induced movement therapy was initiated by Taub and colleagues (Taub et al., 1993). The main tenet of this therapy is that constraining the unaffected limb would force the patients to use the affected one and therefore lead to improved ability for that limb. A typical scenario in stroke is the impairment of motor function on one side of the body contralateral to the affected cortical hemisphere. In the early stages following a stroke, or any neurological injury, there is a resultant shock to the central nervous system and an inability to use the affected extremity (Taub et al., 1993). As the individual passes out of this phase there is a return of capacity, at least in some latent fashion, for motor ability in the impaired limb. However, a major problem is that the individuals have learned a non-use pattern, or what is referred to as a learned suppression for the affected body part.

Just as activity tends to lead to a positive influence, inactivity tends to have deleterious effects on motor ability. In the case where the initial shock prevented movement, another consideration is how this lack of activation leads to reduced cortical representations (Byrnes et al., 2001; Johansson, 2000; Rossini et al., 1998). This form of remodeling of the nervous system has been shown to occur within minutes in studies

involving deafferentation via anesthesetic (Chen et al., 2002). The neural shock is followed by a learned suppression of movement with consequent reorganization in the cortex that would amplify the diminished capacity for movement.

Previous research has demonstrated use-dependent cortical re-organization, as well as functional changes that correlate with such change (Nudo, 1999). Liepert and colleagues (Liepert et al., 2000) found that the area of excitable cortex almost doubled as a result of constraint induced movement treatment, and more importantly, this increased area was paralled by improvements in performance measures.

Moreover, massed practice with the impaired limb has led to a specific pattern of cortical re-arrangement. Specifically, the adjacent spared cortex tends to take over the function of the damaged area (Nudo, 1999). In addition to an alteration of the adjacent spared cortical tissue, changes occur in more remote cortical regions as a means of adaptation. However, recovery is highly use-dependent. When one body area is rendered inactive the general trend within the nervous system is for neighboring brain representations to take over functions for the damaged area (Muellbacher et al., 2002). In this sense, the proximal muscle representations will often take over the territory previously occupied by the distal muscles if they are unused. Therefore, the maintenance of cortical space is contingent on use (Johansson, 2000).

Pharmacological Interventions

A common theme behind successful treatments for motor recovery in stroke is that there must be some degree of active involvement (Hallett, 2001; Johansson, 2000; Liepert et al., 2000). Actively initiating motor actions helps to preserve the cortical territory and further strengthens the connections within the neural network (Byrnes et al., 2001). In addition, pharmacological interventions have demonstrated an improved functional

outcome in stroke patients. Pharmacological interventions can exert their influence acting either alone as plasticity-promoting agents or in concert with physical training to create an enriched effect (Johansson, 2000).

Drugs that have been shown to aid in recovery work in two basic ways: (a) in the short term by means of "damage control" and (b) in the long term with plasticity. In the short term, there have been found several trophic factors that are able to rescue neurons in the acute stage of a stroke and therefore this can be of benefit during the early ischemic period (Johansson, 2000). At present, it is unknown if these trophic factors exert any direct influence during the rehabilitation phase, but there are other drugs such as amphetamines that have proven effective in long term influences. Norepinephrine, amphetamines, and other alpha-adrenergic stimulating drugs have demonstrated the ability to enhance motor performance (Johansson, 2000; Nudo, 1999). Some of the effects linked with these drugs are increased neural sprouting and syaptogenesis and coincident increases in motor performance with humans (Nudo, 1999).

Regardless of the isolated effects of these pharmacological agents themselves, the greatest improvements have been noted when other environmental factors are added. In this sense, the coupling of drug treatments with directed movement interventions has been shown to lead to superior gains, over either one used independently. The fact is noteworthy that the positive influence of amphetamines on motor recovery is not observed when subjects are prevented from moving their impaired limb (Francisco et al., 1998). Thus, behavioral intervention is a vital aspect of the optimal recovery protocol.

Electrical Stimulation as a Means of Treatment for Motor Recovery

Of the many treatments that are used to regain motor control in stroke patients, electrical stimulation therapy has proven effective in a variety of forms. However, there

is no objective data to suggest any one form of rehabilitation is superior to all others (Gresham et al., 1995; van der Lee et al., 2001). Electrical stimulation as a treatment involves sending some form of electrical signal into the body for conduction through the nervous system. The clinical practice guidelines set out by the U.S. Department of Health and Human Services defines functional electrical stimulation as follows: "Bursts of electrical stimulation applied to the nerves or muscles affected by stroke, with the goal of strengthening muscle contraction and improving motor control." (Gresham et al.,1995). This signal can be administered either through direct nerve contact or by means of cutaneous electrodes. Furthermore, this signal can take on a variety of pulse durations, intensities and other characteristics that may lead to different outcomes.

As an historical overview, electrical stimulation has been used to map certain aspects of the nervous system such as the topographical arrangement of body part representations in the sensory and motor cortices. Additionally, stimulating particular regions in the brain can create certain motor responses (Velasco, 2000). This ability of externally applied electrical current to modify brain responses has been used for several treatment purposes such as regulating seizures and behavior disorders, as well as modifying the rigidity and tremor that is associated with conditions such as Parkinson's disease (Velasco, 2000).

Electrical stimulation has been used since the 1960's for functional motor recovery (Kraft et al., 1992). There are two basic categories under which the clinical application of electrical stimulation fall: orthotic, and therapeutic (Burridge & Ladouceur, 2001). The orthotic use of electrical stimulation implies that the stimulation activates the appropriate muscles (of the hand for example), to accomplish a particular task, without subject

volition. An example of this type of stimulation has been carried out in other studies where pre-programmed muscle activity sequences from the subject's normal limb are captured and used as a means of stimulating the affected limb (Kraft et al., 1992). The therapeutic application of stimulation involves using the electrical current as a means of creating neuromuscular adaptations in order for the patient to regain independent motor function.

Perhaps the best known example of orthotic or functional electrical stimulation, involves gait applications. Favorable effects were reported using this form of stimulation in regaining the ability to walk in stroke patients and those with traumatic brain injury (Oostra et al., 1997). The common use for electrical stimulation in this sense is to correct the problem of spastic footdrop. The stimulation unit is worn as an orthotic device on a daily basis, and works by stimulating the peroneal nerve to produce appropriately timed dorsi-flexion of the foot during walking (Oostra et al., 1997). Upper extremity examples of this form of stimulation can also be found in terms of orthotic grasping units such as the "Bionic Glove" (Popovic et al., 2002).

Within the realm of therapeutic electrical stimulation there is further breakdown into different categories. The stimulation intensity may be set at an assortment of levels. For example, sub-sensory threshold stimulation was used in the study by Golaszewski et al., and Dimitrijevic et al., as a means of observing the influence of afferent stimulation that falls under the perceptual limit of the subject (Dimitrijevic et al., 1996; Golaszewski et al., 1999). Other protocols have used stimulation levels that are within the limits of perception; however they do not create movement, and are therefore classified as sub-

motor threshold level. Finally, stimulation that is strong enough can create movement at the joint and would be considered at or above the motor threshold.

All of these forms of stimulation have been shown effective in aiding motor recovery, however, they tend to exert their influence in slightly different ways. One commonality amongst the various applications is that some degree of afferent input is present, whether it is perceived or not. It has been found that effective motor learning and re-learning require afferent input to the CNS (Burridge & Ladouceur, 2001). Indeed, following a stroke a relationship exists between damage in the sensory cortex and motor recovery (Burridge & Ladouceur, 2001).

Golaszewski et al. (Golaszewski et al., 1999), used a mesh glove to provide whole-hand afferent stimulation on the impaired side. This stimulation was set just below the conscious sensory threshold and was set to produce tonic, synchronous input to the CNS. The purpose was to see if this form of stimulation could elicit changes in cortical brain activity, and the results supported this contention. The benefits of this treatment included suppression of muscle hypertonia, increased awareness of the affected hand, and the augmentation of residual voluntary movement. The connection between the improved performance measures and the alteration in cortical activity, is that this form of stimulation leads to an increase in the responsiveness of the somatosensory system and motor cortices during a voluntary motor task. Furthermore, the mesh glove leads to a modification of some of the abnormally active proprioceptive responses that are consequent to stroke such as amplified tendon reflexes and resistance to passive stretch (Dimitrijevic et al., 1996).

In the midst of this spectrum of stimulation types, there is as of yet no evidence to indicate which one is best, for what situation, or optimal duration (Burridge & Ladouceur, 2001; Popovic et al., 2002). Although many studies have used a variety of stimulation parameters and effectiveness has been demonstrated, there is rarely any comparison made between the treatments. For example, Kraft et al. (Kraft et al., 1992), separated treatment conditions across rehabilitation centers and compared performance against a control group. The three treatment conditions were proprioceptive neuromuscular facilitation (PNF), EMG-triggered stimulation, and bias/balance treatment (i.e., low intensity stimulation that is just under the motor threshold combined with voluntary effort to move the limb). The EMG-triggered stimulation involves a volitional attempt at moving the limb by the subject leading to EMG activity in that muscle. When the degree of activity reaches a pre-established threshold the stimulation is initiated. The results of this study showed EMG-triggered stimulation to be the most effective of the three treatment protocols, however, the advantage was only statistically significant when compared to the PNF treatment. Although there was a lack of significance in the difference between the two forms of electrical stimulation, it should be noted that the sub-motor stimulation that was applied in the B/B group involved the added component of volitional movement. Therefore the results should not be taken as a measure of the effectiveness of sub-motor stimulation.

This lack of adequate comparison among various modes of treatment is a problem throughout stroke rehabilitation in general, with an assortment of interventions used without any clearly defined parameters (Feys et al., 1998; Gresham et al., 1995). This is equally true in electrical stimulation where there are many levels of stimulation and even

different ways of administering the same stimulation. Most importantly, the lack of comparison between the various interventions and the manner in which they are applied hinders the elucidation of an optimal treatment strategy. This is perhaps exemplified best in the unresolved issue of treatment duration.

Neuromuscular Stimulation Involving Movement

With the knowledge that the nervous system is constantly adapting and learning, the use of active neuromuscular stimulation to produce movement provides an additional element over sub-motor threshold settings. There is evidence that repetitive active movement, mediated by neuromuscular stimulation, can enhance motor re-learning after CNS damage (Burridge & Ladouceur, 2001; Popovic et al., 2002). The additional component of movement provides augmented sensory feedback and proprioceptive afferent stimulation that is a direct consequence of the movement and muscle activation (Burridge & Ladouceur, 2001).

As indicated previously, there is a reorganization of cortical representations for body parts based upon the afferent input that they contribute as well as the amount of motor activation they undergo. With electrical stimulation there is evidence that it equally influences this reorganization (Golaszewski et al., 1999). This can be highly advantageous in limbs that are impaired to such a degree that voluntary movement would be impossible. Because of the significant amount of hemiparesis that is caused by stroke, the use of electrical stimulation to generate movement provides a means of inducing positive motor changes associated with motion (Chae et al., 1998; Chae et al., 2001). Thus, the introduction of movement, even if supplemented by an external means can provide the impetus for motor improvements. Likewise in stroke patient's who have retained some degree of voluntary movement control following stroke, this intervention

can expand the pre-existing abilities and act as a catalyst to improve and regain daily functioning activities (Burridge & Ladouceur, 2001).

Studies have demonstrated cortical reorganization as a result of peripheral stimulation, and that this reorganization relates to functional change (Burridge & Ladouceur, 2001; Golaszewski et al., 1999). The functional changes that have been noted to improve with stimulation include passive and active range of motion, EMG activity, muscle strength and torque, and a reduction in spasticity (Burridge & Ladouceur, 2001; Glanz et al., 1996; Popovic et al., 2002).

Application and Underlying Principles of Electrical Stimulation

The application of electrical stimulation can take place either indirectly through cutaneous electrodes or directly by contacting the nerve itself. Although many animal studies use direct nerve stimulation (Baar & Esser, 1999; Timson, 1990; Wong & Booth, 1988) the majority of human studies focus on cutaneous stimulation. Granted, impedance can be a factor during indirect current application, however, this tends to be less of an issue with superficial muscles (Prentice, 1994).

The typical protocol for stimulation in humans involves placing cutaneous electrodes over the target muscle. More specifically, the electrodes should be placed over an area referred to as the motor point to give the optimal individual muscle contraction (Prentice, 1994). This point is the region where motor nerve fibers are most numerous. Stimulating at motor point regions maximizes the muscular response while limiting the amount of current applied. This is important because of the potential for pain at electrode sites associated with increasing levels of stimulation intensity.

Each of the surface electrodes possesses a different charge, one positive and the other negative, therefore creating an electrical current. This current passes through the

underlying tissues and upon reaching the nerve leads to a series of electro-chemical events that initiates an action potential. The electrical impulse that arrives at the nerve must be of sufficient intensity to reach the nerve cell membrane's voltage threshold level. Upon meeting or exceeding this threshold an action potential is created; a rapid interchange of charged elements across the cell membrane, immediately followed by propagation of a depolarization wave down the length of the nerve cell. This propagation continues until the terminal end of the nerve cell contacts another nerve cell, or reaches an effector organ (such as the muscle). In the case of neuromuscular stimulation the end result is excitation of the corresponding muscle tissue and movement, if intensity is sufficient (Prentice, 1994).

An important feature of signal transmission in nerve cells is the all-or-none manner in which they fire. Once a stimulus is strong enough to reach the threshold level the motor neuron will react with an action potential of full strength. Force gradation produced in the muscle occurs through one of two ways: (a) recruiting more nerve cells, or (b) increasing the frequency of firing for individual cells, as opposed to modifying the size of a given impulse (Kandel, Schwartz, & Jessell 2000). Therefore, with electrical stimulation, more nerve cells will fire as the strength or duration of the current increases.

A major distinction between volitional versus electrically induced neural stimulation involves the recruitment order of motor unit firing. A motor unit consists of a large alpha motor neuron that originates from the ventral horn of the spinal cord, and supplies a number of muscle fibers (Popovic & Sinkjaer, 2001). Under normal voluntary recruitment conditions there is an asynchrony of motor unit firing as some units are used and others remain inactive. In particular, this takes place in an ordered progression

dependent on size of the units, referred to as the *size principle,* with recruitment of the smallest fibers during low levels of activation and increasingly large fibers as the strength of activation rises (Kandel, Schwartz, & Jessell 2000). In contrast, during an external electrically induced muscle contraction, there is evidence suggesting a reversal of this recruitment order possibly due to differences in nerve axon impedance (Basmajian & De Luca, 1985; Feiereisen, Duchateau, & Hainaut, 1996). There is a lack of consensus as to this proposed recruitment reversal, since several human studies have produced conflicting results. Feiereisen et al., compared voluntary and electrically induced recruitment order in humans and concluded that some degree of reversal did occur. However, given that reversal did not occur to the expected extent, suggested that factors other than axon impedance were involved (Feiereisen, Duchateau, & Hainaut, 1996).

Another difference between these modes of induction involves synchronization of the motor units. During voluntary conditions, the firing of motor units is asynchronous, meaning that some motor units are used while others are not. Electrical stimulation leads to synchronization, with essentially the same motor units responding every time the stimulus is applied. For this reason, voluntary contractions tend to have a later onset of fatigue relative to electrically induced contractions (Prentice, 1994).

Volitionally Activated Stimulation

A final important distinction in the way that stimulation is provided involves the idea of volitional control of movement. In addition to various levels of stimulation (i.e. sub-sensory threshold vs. motor threshold), there are different ways of inducing the stimulation. In this sense, the stimulation can either be passive in nature or instigated by some measure of the subject's own volition. The passive protocol simply involves applying stimulation, usually in a cyclical manner, to the subject to produce a movement.

On the other hand, volitional muscle stimulation involves some degree of activation voluntarily attempted by subjects, and then stimulation is triggered. The typical manner in which this is accomplished is through EMG activated stimulation, although other related protocols have been used, such as positional feedback-based electrical stimulation (Bowman et al., 1979). In positional feedback-based stimulation situations, subjects are required to achieve a particular threshold value of movement to initiate the stimulation. Once the subject achieved the pre-set value of joint range the stimulator would be activated resulting in a full movement at the joint.

With EMG-triggered stimulation, muscle activity is measured at the motor points for the preferred movement. When subjects reach the desired threshold, the stimulation begins, and the movement is completed. EMG activation that serves as a pre-requisite for stimulation adds a cognitive component to the standard stimulation protocol. Each movement is "time locked" with subject volition and sensory feedback (Chae et al., 2001). Studies have demonstrated that cyclical stimulation (stimulation without volition on the part of the subject) may not be the best way to deliver neuromuscular stimulation and that the stimulation, when produced under the control of the patient, tends to be better related to improvements in motor function of the stroke patients (Burridge & Ladouceur, 2001; Chae et al., 2001).

In Krafts' study, the greatest improvement in function among the various forms of treatment resulted from EMG-triggered stimulation (Kraft et al., 1992). Although this was not found significantly greater than the low-intensity stimulation protocol it should be noted that the overall trend on all measures was for the greatest functional improvement with EMG-triggered stimulation. In addition, the group receiving the low-

intensity stimulation that was below the motor threshold, was also attempting voluntary movement of the limb. Therefore, this protocol was still using the concept of volition, only with a lower degree of stimulation for re-enforcement.

Six studies have shown volitionally activated neuromuscular stimulation to produce positive results over and above standard rehabilitation (Bowman et al., 1979; Cauraugh & Kim 2002; Cauraugh et al., 2000; Chae et al., 2001; Francisco et al., 1998; Kraft et al., 1992). These studies have demonstrated effectiveness with this form of treatment through a wide variety of treatment measures. Most of these treatment variables have involved measures of spasticity, range of motion, strength (isometric and isotonic), impairment and overall disability (i.e., performance of activities of daily living).

Cauraugh and colleagues (Cauraugh & Kim, 2002; Cauraugh et al., 2000) demonstrated improved motor function in the impaired wrist and fingers of chronic stroke patients. These improvements were found in reaction time, sustained muscle contraction ability, and in the Box and Block timed manipulation test. An important aspect of these studies is that all subjects were chronic stroke survivors (at least one year post stroke), with hemiparesis (partial paralysis) in the upper extremity. Thus, spontaneous regeneration was an unlikely explanation for the functional improvements later in stroke recovery.

Francisco and colleagues (Francisco et al., 1998) noted that most research with EMG-triggered stimulation had only used impairment measures when testing for treatment effectiveness. They attempted to address the issue of motor function and it's impact on physical disability (i.e., does the increased function noted in a motor ability such as isometric strength have a positive influence on the performance of everyday

activities?). Their results indicated that EMG triggered stimulation led to significant improvements in motor ability and functional recovery.

A noteworthy finding in the studies by Chae and colleagues (Chae et al., 1998), and Powell and colleagues (Powell et al., 1999) where cyclic neuromuscular stimulation was used, was an increase in the motor function of patients without significant functional benefits. Both studies used the Functional Independence Measure as an indicator of disability and observed no effect from their stimulation protocols upon it. These findings reveal that a close relationship does not necessarily exist between disability and neurological impairments in stroke patients. In a comprehensive review by Burridge and Ladoucer (Burridge & Ladouceur, 2001), the general trend among studies using passive and cyclical application of electrical stimulation, is that functional improvement in everyday activities did not parallel impairment reduction. The absence of this problem in the study by Francisco et al. (Francisco et al., 1998) may attest to the superior nature of combining volition with regular neuromuscular stimulation.

Voluntary initiation of movement by the stroke patient appears to be of practical significance because this is the route that movements would have to draw from when the external aid is removed. A recent review by Woldag and Hummelsheim (2002) contends that neuromuscular stimulation triggered through subject volition is superior to passively induced stimulation due to the additional component of subject volition. Studies with motor imagery have shown an increase in motor evoked potentials that coincided with simple imagery focusing on that muscle group (Burridge & Ladouceur, 2001; Woldag & Hummelsheim, 2002). The evidence tends to point towards cortical level changes as the source for these effects. Therefore, with the introduction of volition into the electrical

stimulation procedure, higher-end re-structuring of the nervous system should be invoked.

Searching for an Optimal Treatment Duration

In general, we have established that electrical stimulation treatment has demonstrated positive improvements on motor re-acquisition following a stroke. More specifically, stimulation that produces movement that is initiated by subject volition has proven effective in improving various measures of motor performance. In reviewing all of the research that has been published on this topic a general conclusion is that the application of this intervention is somewhat erratic. A wide variety of treatment protocols have been used in terms of stimulus intensity, types of subjects used for testing, and testing durations. This lack of standardization in how treatment is applied reflects an absence in the knowledge base for what constitutes an optimal treatment strategy.

In addition, the issue of establishing optimal treatment is further clouded by many different ways of measuring performance (Duncan et al., 2000). This makes comparison among treatments, intensities, and durations difficult. In general, the outcome measures that have been used tend to fall into four general categories: strength, range of motion, measures of impairment, and measures of global disability (i.e., the extent to which the impaired body part affects overall function in everyday-type activities). In the present study, there was no intention to resolve the issue of outcome measure standardization. Rather it has been presented as a further issue that needs to be addressed in regards to the overall assessment of stroke rehabilitation outcome in general.

In an attempt to clarify the issue of developing an optimal treatment strategy this paper attended to the issue of treatment duration. Some authors have argued that we need more knowledge in the area. For example, Chae and colleagues (Chae et al., 1998) stated

that future studies should measure and "define the dose effect" as a means of guiding the intervention. Of further note was the recent review by Popovic et al. (2002). They stated that the most important questions currently needing attention involve when and to whom therapy should be applied and what is the optimal treatment duration of the therapy. The context for this comment was specifically tailored for functional electrical therapy (FET); However, the comment equally applies to all forms of electrical stimulation and in particular for EMG-triggered stimulation.

Why Treatment Duration?

In reviewing the available literature on active neuromuscular stimulation, among the inconsistencies and blurred application of treatment, the issue of how long the treatment period lasts is clearly unguided and lacks consensus. The broad range over which treatments have been applied tends to reflect an almost arbitrary assumption of what constitutes an effective period of time. The various studies have comprised a range of two weeks (Cauraugh & Kim, 2002; Cauraugh et al., 2000) up to 10 months (Dimitrijevic et al., 1996). The 10 month long study primarily used an afferent stimulation below sensory threshold, thus a different form of electrical stimulation (Dimitrijevic et al., 1996). However, this is still a means of using electrical stimulation to assist motor recovery; Furthermore, even within studies that use motor-threshold stimulation, a wide range in treatment times exists (Cauraugh & Kim, 2002; Kraft et al., 1992; Chae et al., 1998).

An obvious question arises when one examines all of the studies that have been completed to this point: Does treatment efficacy vary as a function of treatment duration, and if so to what extent? If motor improvements are found in two weeks, then will four weeks further differentiate groups? Intuition suggests that the more treatment is always

better and therefore using this intervention for four weeks versus two weeks should provide enhanced performance measures. This appears to be an expansion of a principle in general motor learning whereby the level of a skill is increased in proficiency in relation to the amount of repetitive practice. However, there exists the possibility that stimulation need only be applied to elevate the subject's function to a certain level at which point the new functional abilities are incorporated into daily activities. In this sense, the resolution of the limb impairment could lead to a re-introduction of the limb into daily use thereby promoting the type of continued repetition needed to maintain function, and providing a successful transfer of gains within the lab to a real world setting. Thus, stimulation can be viewed as a catalyst to aid in motor re-learning (Burridge & Ladouceur, 2001). In either case, it is possible that the optimal treatment duration could be dependent upon the baseline function of the patient being treated. Several studies have reported that the most promising degree of recovery occurs in patients that enter treatment with the highest level of motor function (Burridge & Ladouceur, 2001; Glanz et al., 1996). Perhaps patients that have a certain level of impairment would need a corresponding period of electrical stimulation to improve.

The Selection of Time Periods for Comparison

In the studies by Cauraugh and colleagues (Cauraugh & Kim, 2002; Cauraugh et al., 2000), significant improvements were observed in the motor performance of chronic stroke patients. The first study involved two treatment sessions of 30 successful movement trials that lasted approximately one hour, and this was performed three days per week for two consecutive weeks. This led to a total of 360 trials over 12 treatment sessions. The second study administered treatment protocols for 90 minutes twice a week for two weeks. Given that both studies showed functional improvement after only six

hours of treatment, one could conclude that six hours provides a sufficient base for evaluating time course effectiveness. By this it was assumed that two weeks (six hours) represents an adequate minimal point of comparison for a treatment model because of the reported demonstrated effectiveness.

The second treatment time for comparison was four weeks (90 minutes per session, twice a week for four weeks). While the selection of this time frame was somewhat more arbitrary than the baseline model, an important point to remember is that this research question was exploratory in nature. In essence, this study attempted to answer the question of whether active NMES training varies in effectiveness as a function of treatment duration. This proposal tested if doubling the time involved with the baseline model influenced motor improvements. Furthermore, bilateral movement training was added in to the training equation, since this form of treatment has already established its' value (Cauraugh & Kim, 2002). The issue of bilateral training will be addressed presently.

Bilateral Movements Coupled with Active Stimulation

Cauraugh and colleagues (Cauraugh & Kim, 2002) investigated bilateral movements of the forearm extensors while the impaired limb underwent EMG-triggered stimulation. The concept behind bilateral movements is that the two limbs working as a coordinated unit provides a means of recruiting alternate pathways in the nervous system and thus enhances movement. Bimanual coordination theory as described in dynamic systems theory provides the theoretical basis for including both arms as a behavioral intervention. Evidence suggests that both arms share a central link as a coordinated whole, with the upper limbs functioning in a homologous coupling of muscle groups on both sides of the body. Coordinated movement patterns emerge spontaneously from the

constraints on the system including the inherent characteristics of muscles, as a function of dynamics (Cauraugh & Kim, 2002).

Researchers argue that bilateral movements trigger interhemispheric disinhibition. Three alternative recruitment pathways have been suggested to result from this disinhibition, namely, (1) cortical motor neurons within the damaged hemisphere that remain intact, (2) corticospinal pathways running ipsilaterally from the undamaged hemisphere, and (3) ipsilateral corticospinal pathways that work indirectly. These proposed means of neural plasticity were reviewed earlier as adaptive measures undertaken by the nervous system in response to damage. In this particular case, bilateral movement training activates an inherent capacity for neural reorganization that is dependent on movement as a coordinated whole.

Studies using bilateral action as a treatment, have demonstrated motor improvements beyond standard physical therapy. Therefore, the purpose of the study by Cauraugh and colleagues, was to couple bilateral activity with EMG-triggered neuromuscular stimulation (Cauraugh & Kim, 2002). In this sense, two scientifically established interventions were coupled to determine potential advantages of combination effects. The results of the coupled motor recovery protocols, showed a significant improvement in motor ability on several outcome measures over the control group (no treatment given), as well as the group receiving stimulation with unilateral activation only. Because the coupling of interventions demonstrated improvements beyond either one separately, the selection of a baseline treatment for the presently proposed study used this combination. Therefore, the application of treatment involved EMG-triggered

stimulation of the impaired wrist and fingers along with simultaneous bilateral activation of the unimpaired wrist and fingers.

CHAPTER 3
METHODS

The method and procedures for this study have been described in detail in two recent publications by Cauraugh and colleagues (Cauraugh & Kim, 2002; Cauraugh et al., 2000). The current method and rationale are summarized here.

Subjects

All subjects were volunteers that had experienced a stroke at least one year before the onset of testing. Stroke survivors who had chronic hemiparesis, partial paralysis of their impaired upper extremity, were recruited. Because spontaneous processes are a highly probable cause for recovery during the first year following a stroke, the influence of any interventions used during this period may be hard to distinguish. For this reason, the most compelling evidence in stroke rehabilitation research is derived from studies that use chronic patients as their treatment group (Gresham et al., 1995). Mean length of time since the stroke and age of the sample were calculated.

The degree of upper extremity chronic hemiparesis was monitored during the initial assessment period to determine baseline function. Participants were evaluated on their ability to extend at the wrist and/or fingers from a flexed position. To assess this function the impaired hand was draped over the edge of a counter with the wrist joint slightly off the counters' edge to allow for an unobstructed pivot. Participants were required to demonstrate a minimum of 10 º extension in the wrist and/or fingers of the impaired limb during this assessment to qualify for the study.

To understand the reason for focusing on the upper limb in this study, one must appreciate the typical sequence of functional recovery following a stroke. In general, reacquisition of arm function following a stroke poses far greater of a problem than regaining leg function (Feys et al., 1998; Volpe et al., 2000). This could be for a number of reasons including the majority of strokes occur in a region supplied by the middle cerebral artery leading to consequent impairment of hand function (Feys et al., 1998). A further likelihood is that because of the complex nature of the hand, functional recovery is more difficult when compared to the leg (Kraft et al., 1992). Given that the upper extremity is such a weak link in motor recovery, improvement in this area serves as a sensible starting point. Further, the hand has such a profound impact on daily activities that recovery is vital to returning to everyday activities.

Inclusion Criteria

The criteria for admission included: (1) diagnosis of at least one stroke (2) the cutoff point in terms of motor recovery was set at 80% as an upper limit. This was determined by using rectified EMG activation patterns and sustained force contractions while comparing the impaired and unimpaired limbs; (3) the cutoff point in terms of a lower limit, was 10 º of voluntary wrist or finger extension against gravity from a 90 º flexed position. The requirement for some pre-existing capacity for movement is important because the stimulation unit needs a certain amount of muscle activation before turning on; (4) no other severe neurological deficits were present, including the use of a pacemaker. Subjects needed to have a degree of cognitive capacity that allowed them to participate in the various tests. This was necessary because some of the performance measures involved recognition of a stimulus followed by an appropriate motor response; (5) there was no use of drugs for the purpose of treating spasticity. The exclusion of

subjects on spasticity medication was important to isolate the influence of the stimulation treatment, especially since a reduction in spasticity was one of the possible effects of the treatment; (6) participants were not involved in any other motor recovery rehabilitation protocol. Prior to testing, an *informed consent was signed by all subjects. (*Institutional Review Board approved).

Experimental Design

This study tested 13 subjects using a completely within-subjects design. All participants underwent four weeks of total treatment, and therefore experienced both levels of the treatment (two weeks and four weeks). Testing was performed prior to treatment to establish a baseline, after two weeks of treatment (6 hours), and at the end of four weeks (12 hours). The first treatment level consisted of six hours of treatment (four days) completed over a period of two weeks. The second treatment level doubled the duration (twelve hours of treatment/eight days, over a period of four weeks). Results from the first level were compared with those from the second level.

Figure 1. Experimental Design

Instrumentation and Procedures

To measure motor function in the upper extremity, three separate types of performance measures were used. These measures have been used and outlined in the studies by Cauraugh and colleagues (Cauraugh & Kim, 2002; Cauraugh et al., 2000). The first measure was the Box and Blocks timed manipulation test. This was a test of manual

dexterity that has age-based normative data available. The task required subjects to grasp and transport small wooden blocks from one compartment to another that was directly beside it. Participants were given 60 seconds to perform this task, and instructed to move as many blocks as possible. This test was used to provide an index of overall hand function in relation to reaching, grasping, transporting, and releasing.

The next two measures were force generation tasks that used the same instrumentation. The first task measured reaction time in the wrist/finger extensors. The purpose was to evaluate the speed of information processing and rapid muscle onset. The second force generation task involved sustained muscle contraction in the wrist extensors as a measure of force modulation. For both of these tasks, participants had their hands placed into an apparatus designed to measure the force of wrist/finger extension. Load cells with a capacity for 34.1 kg of force, were located in each of the two arm devices. Force and EMG signals were recorded online for both arms. The EMG activity of wrist/finger extensor muscles were recorded using surface electrodes (silver-silver chloride electrodes with an epoxy-mounted preamplifier).

During the reaction time task, participants were instructed to respond as quickly as possible to an auditory cue by means of wrist/finger extension against the load cells. Ten trials were performed on each arm separately and 10 trials were performed using both limbs together. During the sustained muscle contraction task, participants were instructed to gradually increase their wrist/finger extension force to a maximal point and then hold this isometric contraction for a period of 6.5 seconds. The experimenter provided the signal to initiate and then cease force production. Three trials were performed for each arm and both arms acting together. For both force generation tasks, testing was

administered in a random order with a rest period of approximately five minutes between tasks.

Training Protocol

As noted previously, all participants received a total of 12 hours of treatment (24 treatment sheets over 4 weeks). Initially they received EMG-triggered neuromuscular stimulation coupled with bilateral movement training for 6 hours of treatment (12 treatment sheets), which they completed over a period of approximately 2 weeks. This constituted the first level of the treatment, after which, all participants were posttested (posttest 1). The second level involved an additional two weeks of the same treatment, resulting in double the duration (twelve hours of treatment and 24 treatment sheets, over a period of four weeks). All participants were again tested at this point (posttest 2). A treatment sheet consists of 30 separate stimulation trials.

During each training day, most participants completed four sets of thirty successful EMG-triggered neuromuscular stimulation trials (four treatment sheets). Some participants requested lower training volumes due to fatigue. Throughout training, participants were instructed to perform wrist/finger extension with the unimpaired limb as well as the impaired limb. However, only the impaired limb had the stimulation unit attached. This process took approximately 90 minutes each training day.

At the beginning of each training session, surface electrodes were attached to the extensor communis digitorum and extensor carpi ulnaris muscles of the impaired limb. The electrodes were attached to an Automove (AM 800) EMG Facilitation Stimulator microprocessor. This device functions to provide electrical stimulation once a target threshold level of activity is reached with EMG. The electrical stimulation was provided by a one second ramp up, followed by five seconds of biphasic stimulation at 50 Hz,

pulse width of 200 microseconds, and finally a one second ramp down. The mA range spanned 16-29 mA. Stimulation was adjusted so that it assisted the subjects in attaining a full range of movement in the wrist.

The initial threshold for the stimulation unit was set at 50 microVolts. When the subjects successfully reached this level the stimulator automatically adjusted the threshold to a slightly higher point. This unit works in a feedback sensitive manner and as such it adjusted the threshold level down if the subject was unable to reach it. The threshold in this sense dropped down to a point that approximated the level of effort that the subject was able to produce. Each trial was separated by 25 seconds of rest.

Data Reduction

The initial data reduction step was to rectify and smooth the reaction time EMG data at 100, which was followed by determining the fractionated components (premotor and motor). The premotor reaction time, a central component, was operationally defined as the time from stimulus onset until EMG activity in the extensor muscles reach 30% of peak activity. Motor reaction time, a peripheral component, was operationally defined as 30% of peak force amplitude. This component began immediately following premotor reaction time, and ended with the initiation of movement.

The ability to maintain a certain level of force was determined through the sustained contraction task. Root mean square error was the response variable, providing an overall measure of bias and variability in peak force amplitude across the sustained contraction interval. Root mean square error was calculated for a five second period, one and a half seconds after the stimulus onset to allow for the gradual increase to peak force.

Data Analysis

The number of blocks moved in the Box and Blocks test was analyzed in a within-subjects design, one-way repeated measures ANOVA with three levels of test session (pretest, posttest 1, and posttest 2). The reaction time and sustained contraction tasks were analyzed separately using a within-subjects 2 x 3 repeated measures ANOVA (Hand – unilateral vs. bilateral condition x Test Session – pretest, posttest 1 and posttest 2). All statistical tests were conducted with alpha level set at 0.05. The Tukey-Kramer procedure was used as a multiple comparison follow-up test. Conservative degrees of freedom adjustments were used for any sphericity violations.

CHAPTER 4
RESULTS

Reaction Time

Total reaction time along with its' fractionated components of premotor and motor time were analyzed in separate 2 (Hand) x 3 (Test Session) ANOVAs with repeated measures on the last factor. The levels of test session refer to the pretest, posttest 1, and posttest 2. Hand represents whether the test is performed in a unilateral or bilateral condition. The bimanual condition refers to the fact that both hands are involved in the reaction trial, however, only the response of the impaired limb was evaluated. The underlying purpose was to test for any differences that may result in the impaired arms' performance when movements are coupled with the unimpaired arm.

Previous research with the same reaction time protocol indicated that median reaction times provided a more accurate representation of the data (Cauraugh & Kim 2002). Therefore, median values were calculated from the individual trials for each of the reaction time conditions (impaired limb only, unimpaired limb only, and both limbs together). Prior to generating the median values, outliers were removed (i.e., values outside 3 standard deviations). Mean values were calculated for each of the reaction time condition median values. The resultant mean values were then analyzed using the above 2 x 3 ANOVAs. The median values for the individual subjects are presented in Table 1 for the unilateral condition, and Table 2 for the bilateral condition. Note that subject 6 failed to produce reliable data for post-test 1 and therefore was excluded from further reaction time analyses.

Total reaction time failed to yield significant differences in the main effects or interaction, hand: F (1, 8) = 2.95, $p < 0.12$; test session: F (2, 16) = 2.57, $p < 0.11$; hand x test session: F (2, 16) = 0.20, $p < 0.82$. Total reaction time is displayed in Figure 1.

In addition, premotor time, the central component of reaction time, revealed no significant differences in the main effects or interaction, hand: F (1, 8) = 0.35, $p < 0.57$; test session: F (2, 16) = 0.55, $p < 0.57$; hand x test session: F (1.19, 9.54) = 0.15, $p <$ 0.75. Premotor reaction time is displayed in Figure 2.

Analyses of the third reaction time component, motor time, revealed a significant hand main effect, F (1, 8) = 5.485, $p < 0.047$. Faster motor reaction times were found during the unilateral condition compared with the bilateral condition. No significant differences for the interaction or the test session main effect were identified, test session: F (2, 16) = 1.10, $p < 0.36$; hand x test session: F (2, 16) = 0.98, $p < 0.39$. Motor reaction time is displayed in Figure 3.

Table 1. Reaction Time and Fractionated Components (Unilateral Condition)

	Pre-Motor Time			**Motor Time**			**Total Time**		
Subject	Pre-test	Post 1	Post 2	Pre-test	Post 1	Post 2	Pre-test	Post 1	Post 2
1	287	292	339	140	80	94.5	450	347	453.5
2	219.5	248	249	63.5	69	67	300.5	318	317
3	402	254.5	373	40	51	112.5	442	300.5	440.5
4	260	266.5	209	56	53.5	52	310	311	273
5	289.5	294	276.5	124	101	138	418.5	389.5	411.5
6	302.5	NA	247	98	NA	131	417	NA	384
7	187.5	186.5	212	43	61	51	240	245.5	266
8	315.5	265	230	50.5	32	22	361.5	293	259
9	151	138	155	36	33	30	191	171	188
10	244.5	296	289.5	97.5	28	117	336	324	400
Mean	265.9	248.94	258	74.85	56.5	81.5	346.65	299.94	339.25
SD	70.96	53.51	64.32	37.30	24.27	42.47	87.75	62.15	90.54

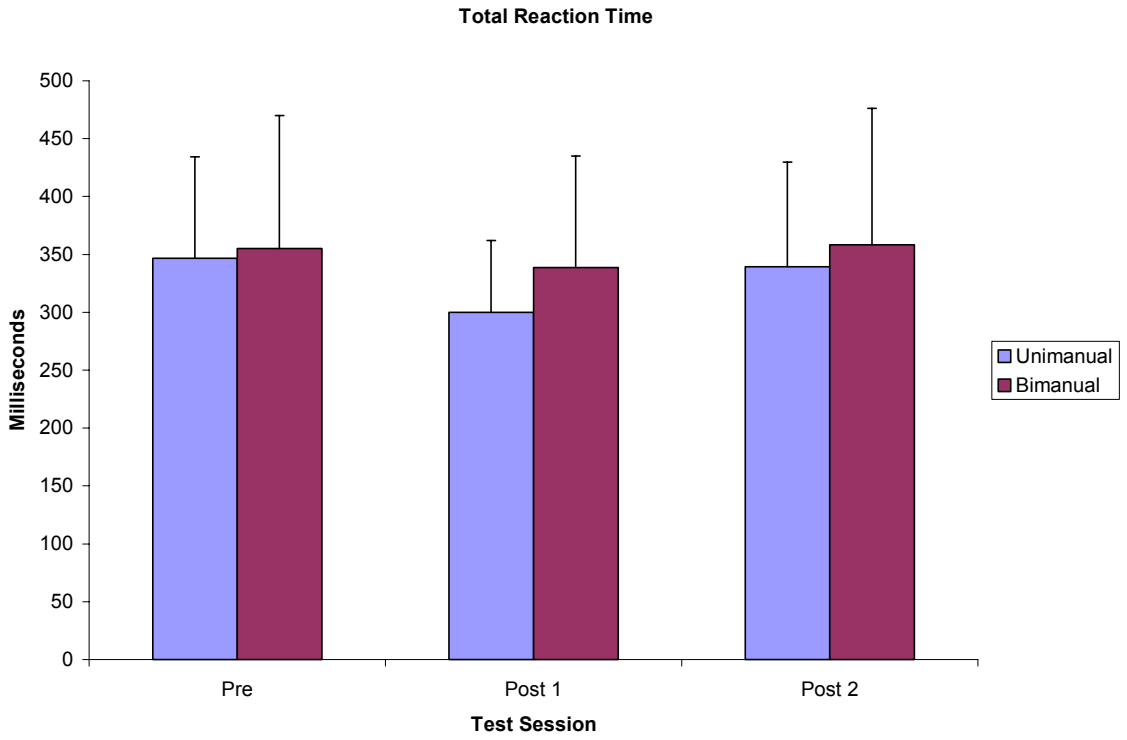

Figure 2. Total reaction time

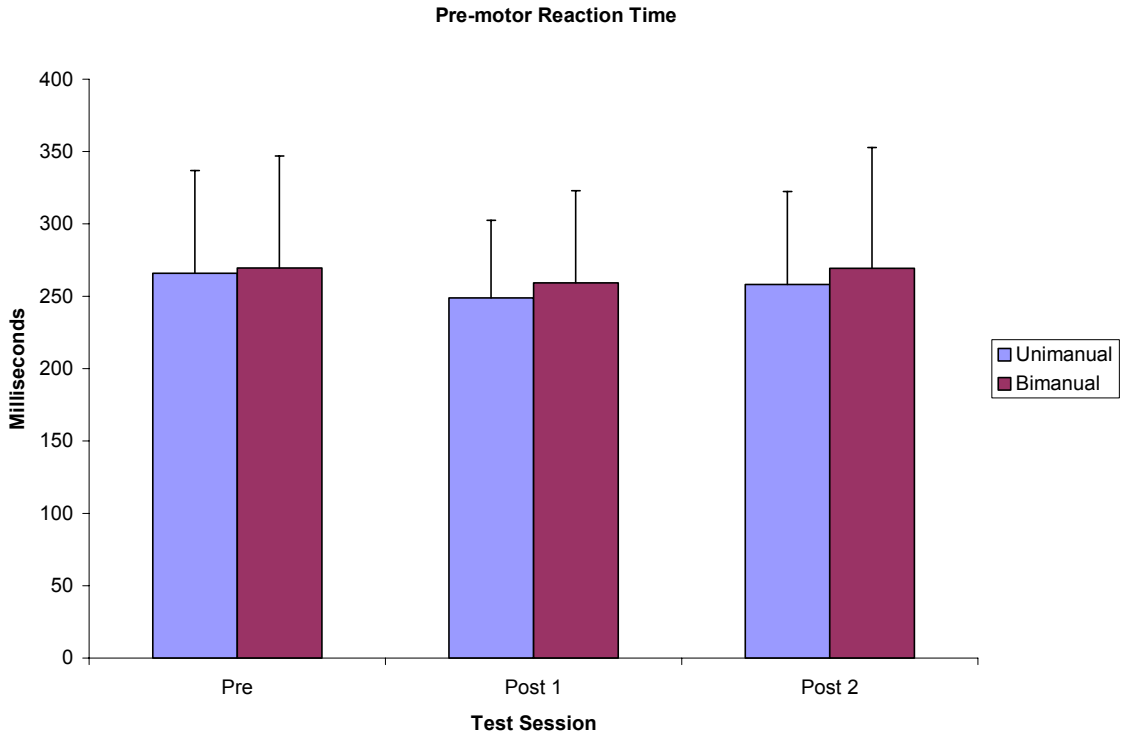

Figure 3. Pre-motor reaction time

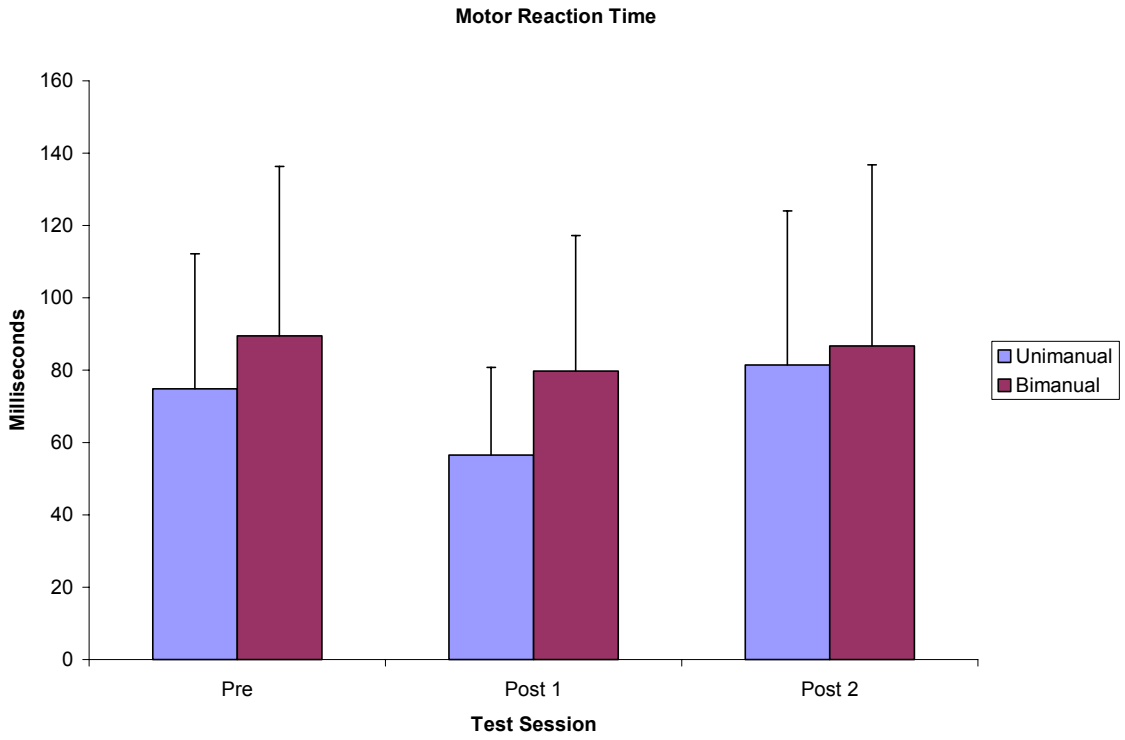

Figure 4. Motor reaction time

Table 2. Reaction Time and Fractionated Components (Bilateral Condition)

	Pre-Motor Time			Motor Time			Total Time		
Subject	Pre-test	Post 1	Post 2	Pre-test	Post 1	Post 2	Pre-test	Post 1	Post 2
1	332	356	417	172	117	127	471	482	536
2	231.5	240.5	254.5	45	42.5	66.5	283.5	280.5	326.5
3	290.5	285	396	104	111	81	408	396	498
4	264.5	263	257	63	56	53	326.5	322.5	310
5	354.5	327	289	118.5	116	163.5	468.5	443	454.5
6	334	300.5	255	113	128	148.5	377	428.5	406.5
7	147.5	183.5	186	45.5	97.5	40	193	274.5	225
8	258	232	232	55.5	52	26	338	272	268
9	141	143	144	36	28	38	175	172	178
10	342	261	262	142	50	124	510	317	381
Mean	269.55	259.15	269.25	89.45	79.8	86.75	355.05	338.8	358.35
SD	77.45	63.84	83.61	46.91	37.43	50.05	114.75	96.17	117.83

Sustained Muscle Contraction Task

As with reaction time, the sustained muscle contraction task was analyzed with a mixed design, hand x test session, (2 x 3) ANOVA with repeated measures on the last

factor. Indeed, the factors of hand and test session have the same meanings as in the reaction time task.

The response variable for sustained muscle contraction is operationally defined as root mean square error. The purpose of this task is the maintenance of wrist extension force over a 5 second time period. Therefore, root mean square error provides a marker for consistency where lower values indicate more consistent force modulation. This replicates the procedure and intermediate analysis outlined by Cauraugh and Kim (2002).

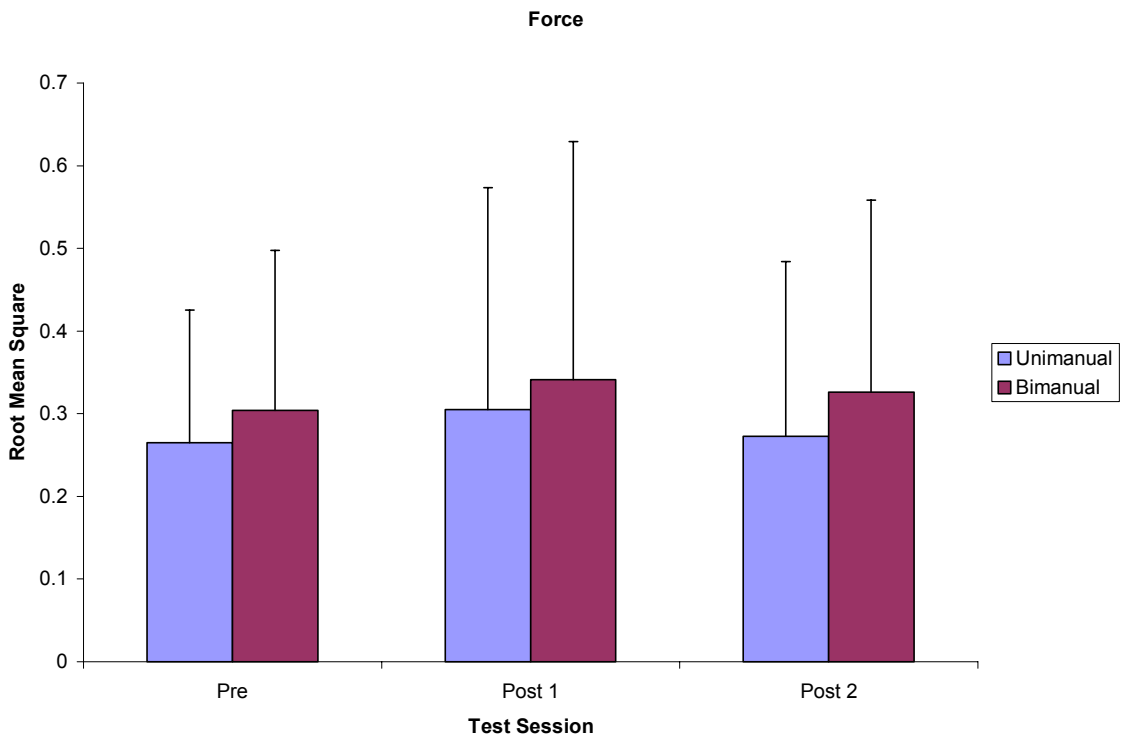

Figure 5. Sustained Muscle Contraction Task

Results from the two-factor mixed design analysis indicated no significant differences in the interaction or the test session main effect, test session: F (2, 18) = 0.164, $p < 0.850$; hand x test session: F (2, 18) = 0.048, $p < 0.954$. However, a strong trend was found with the hand main effect, F (1, 9) = 4.481, $p < 0.063$, with the unilateral condition demonstrating a tendency towards greater force modulation. The results of the

sustained muscle contraction task are displayed in Figure 4 and individual subject values are reported in Table 3.

Table 3. Sustained Muscle Contraction Task Results (root mean square error)

	Unilateral Condition			Bilateral Condition		
SUBJECT	Pre-test	Post 1	Post 2	Pre-test	Post 1	Post 2
1	0.37	1.03	0.72	0.52	0.97	0.89
2	0.15	0.18	0.55	0.13	0.1	0.57
3	0.44	0.32	0.1	0.28	0.71	0.25
4	0.3	0.31	0.26	0.69	0.36	0.27
5	0.47	0.37	0.36	0.39	0.41	0.28
6	0.46	0.18	0.18	0.4	0.2	0.24
7	0.14	0.21	0.17	0.18	0.19	0.18
8	0.07	0.18	0.19	0.09	0.2	0.19
9	0.09	0.18	0.11	0.14	0.18	0.28
10	0.16	0.09	0.09	0.22	0.09	0.11
Mean	0.27	0.31	0.27	0.30	0.34	0.32
SD	0.16	0.27	0.21	0.19	0.29	0.23

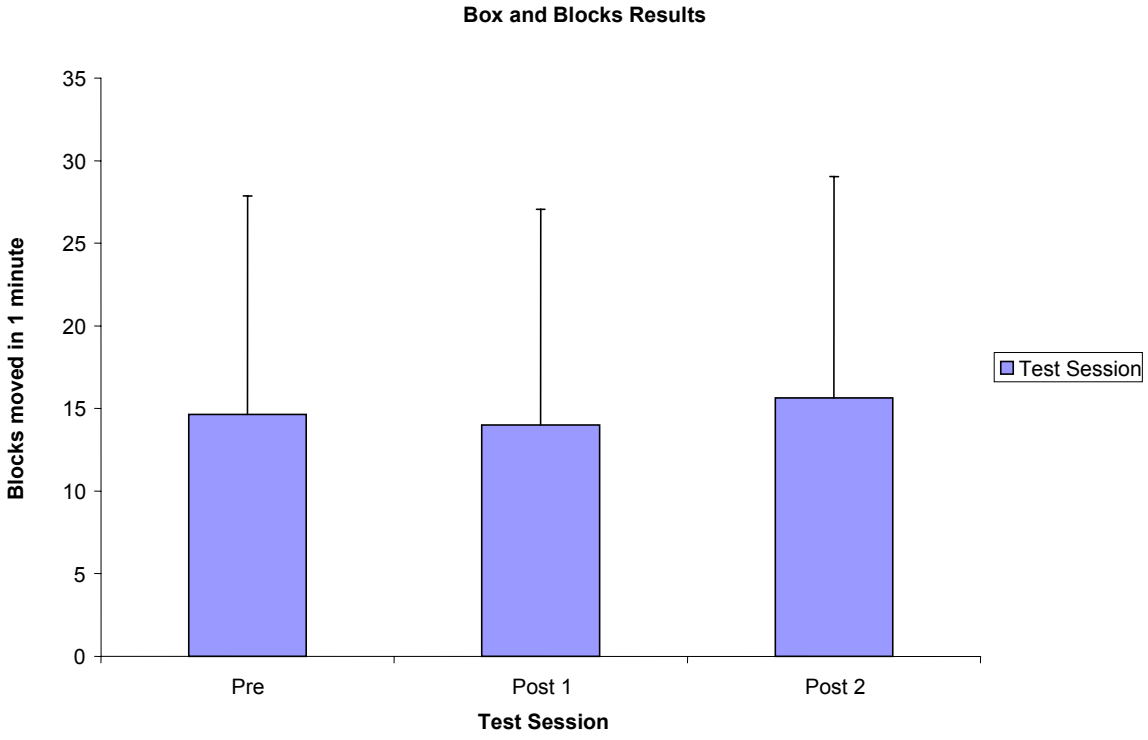

Figure 6. Box and Blocks results

Box and Blocks Test

For the Box and Blocks test, a 1-way ANOVA with 3 levels of test session was performed. The response variable for this test was the number of blocks moved in a 1 minute period. Analysis revealed no significant differences between the levels, F (2, 20) = 0.987, $p < 0.390$. The results are displayed in Figure 5 and the number of blocks moved is recorded in Table 4.

Table 4. Box and Block Test Results (number of blocks moved by the impaired arm in 60 seconds)

Subject	Pre	Post 1	Post 2
1	11	3	5
2	12	13	14
3	20	14	18
4	2	9	3
5	3	3	2
6	47	48	47
7	0	0	1
8	26	23	25
9	11	13	20
10	14	13	20
11	15	15	17
Mean	14.64	14	15.64
SD	13.22	13.05	13.39

CHAPTER 5
DISCUSSION AND CONCLUSIONS

The results of this study fail to support the hypothesis that chronic stroke patients would demonstrate greater improvements in upper limb function after 12 hours (24 treatment sessions) compared with only 6 hours (12 treatment sessions) of treatment. Moreover, the results of this study did not indicate that EMG-triggered electrical stimulation was an effective means of improving motor function of the hand and wrist in chronic stroke patients. There were no significant differences between the three testing sessions in any of the three measures used to assess motor function in the hand and wrist.

These surprising results are inconsistent with previous studies using EMG-triggered electrical stimulation (Cauraugh et al., 2000; Cauraugh & Kim, 2002; Francisco et al., 1998; Hummelsheim et al., 1996; Kraft et al., 1992). These other studies were performed using a similar form of active electrical intervention all finding significant improvements on various measures of motor function. Moreover, two of these studies were conducted in the same laboratory as the present study, using similar procedures (Cauraugh et al., 2000; Cauraugh & Kim, 2002). From this collective pool of research, the resultant consensus is that volitionally induced neuromuscular stimulation has a pronounced positive effect on progress toward motor improvements in chronic stroke patients (Burridge & Ladouceur, 2001; Woldag & Hummelsheim, 2002).

When the outline and purpose for the present study were originally created the published research in stroke motor recovery was considered strong evidence for a treatment effect. From this general framework the present study worked under the

assumption that treatment was effective, and therefore it was only a matter of determining if any duration related changes in efficacy took place. Failure to replicate motor performance improvements with the coupled protocols (bilateral movement training and active stimulation) was unexpected. Much of the ensuing discussion focuses on possible reasons for the results of the present study and why they fail to coincide with the previous studies.

Throughout stroke research a common concern is how reliably any advances in function can be attributed to a particular intervention. As previously noted, chronic stroke patients tend to offer a better opportunity for assessing treatment-related changes (Gresham et al., 1995). Consequently, the present study used chronic stroke patients as a participant base. The converse side to preventing possible contamination of treatment effects via spontaneous recovery is that producing motor gains now falls onto less fertile ground for recovery. The acute phase following stroke may afford a greater opportunity for treatments to manifest in motor improvements. Independent of the confounding associated with spontaneous regeneration, the acute phase following stroke may provide a medium in which treatment effects are amplified (Turton & Pomeroy, 2002). Several of the studies involving active electrical stimulation have used chronic stroke patients and have demonstrated significant motor improvements with training (Cauraugh et al., 2000; Cauraugh & Kim, 2002; Fields, 1987; Kraft et al., 1992). This includes two studies previously performed in the same lab as the present study (Cauraugh et al., 2000; Cauraugh & Kim, 2002). However, a point to consider is that the focus on chronic stroke patients makes the advancement of function a tougher task.

Focusing on the specific patients involved in the present study reveals several issues that deserve attention. Out of 13 participants that participated in the study, only 10 were able to reliably produce a full set of data to be included in the analyses. From this group of 10 participants, 5 had previously participated in EMG-triggered stimulation protocols in the same laboratory as the present study. Further, 3 of the participants were involved in this additional training immediately prior to the current study. Perhaps some of the participants reached a plateau hindering further improvement. The possibility exists that for participants to advance to a higher level of function, treatment intensity would need to rise in a corresponding manner. Intensity could be adjusted through higher work volumes, reduced rest between stimulations, greater frequency of sessions, or perhaps even complimentary modes of treatment.

An additional point to consider that may have influenced the results of the current study involves the frequency of treatment. The protocol outlined in the methods section initially called for two treatment sessions per week for 4 weeks. Each session consisted of 90 stimulation trials (3 training sheets with 30 trials each). However, because most participants traveled significant distances to the lab (i.e., greater than 2 hours round trip on average), this was altered to 2 sessions per week at 120 stimulation trials per session (4 training sheets). This compromise was made in response to requests by participants aimed at limiting the number of visits to the laboratory. Moreover, scheduling conflicts occasionally arose where standardized treatment sessions were skipped, therefore, reducing the training frequency to one visit over a week. In the case of one participant, the time required for commuting was prohibitive enough to reduce training frequency to once per week over the entire study. Another participant was only able to complete 60

stimulation trials per session because of fatigue. Such concessions were not ideal, however, they were deemed necessary on the basis of increasing the sample size for this study. Therefore, although the application of this intervention was standardized (i.e., work/rest ratio, stimulation impulse time etc), frequency of treatment occasionally varied across participants. Certainly this increased variability, thus possibly hindering any training effect by diluting the training intensity over a longer time period.

Further, study design concerns may have contributed towards the lack of significant treatment effects. A pre-experimental design was employed for the current study, therefore, no control group was required, nor was any additional baseline period taken into account except for a single pre-test. At the outset of the study a control was opted against for two reasons. First, all studies from different laboratories using active neuromuscular stimulation in the past have demonstrated significant motor functional improvements with treatment. Second, because subject recruitment imposed such an obstacle in this study, the division into two groups and hence a reduction in the sample receiving treatment seemed unnecessary. Indeed, the combination of these two factors appeared to militate against the notion of dividing the participant pool. The original judgment was to run all subjects through the training protocol because the primary question for this study was if treatment efficacy varied with total treatment duration; as opposed to whether or not the treatment was effective. Adherence to the rigorous constraints of a traditional research design has been questioned by previous research, especially in the rehabilitation arena where participant recruitment and withholding treatment from a group of patients poses practical and ethical problems (Ottenbacher & Hinderer, 2001). In summary, although exclusion of a control group appeared to be a

reasonable assumption going into the study the consequent major disadvantage is the absence of a true comparison group.

In addition to some of the aforementioned points, there is a distinct challenge in recovering motor functions in the upper limb of stroke patients (Feys et al., 1998; Volpe et al., 2000). This is particularly pronounced in wrist and finger extension because of the presence of an uncontrolled flexion synergy in the impaired upper limb (Cauraugh et al., 2000). Consequently, improvement in wrist and finger extension ability offers an excellent indication of therapeutic efficacy, thus, providing the rationale for an upper limb focus in the current study. However, a disadvantage with an upper limb focus, is that eliciting gains in this area can be onerous, therefore imposing an additional obstacle for treatment gains. This is similar to the problem associated with limiting the study to chronic stroke participants whereby improvements are more difficult to produce.

Another unexpected result from this study was the impact of unilateral versus bilateral testing conditions. Reaction time and sustained contraction testing was performed under three separate conditions; impaired arm only, unimpaired arm only and both arms concurrently. Analysis was limited to the impaired limb, however the bilateral condition was imposed to monitor for possible influences from the coupling. Cauraugh and Kim (2002) demonstrated faster reaction times with total reaction time and the fractionated components during the bilateral condition. Results from the present study did not show a significant difference for total and premotor reaction times, and even revealed faster motor reaction times for the unilateral condition. The sustained contraction task, which also revealed an advantage during the bilateral testing condition for Cauraugh and Kim (2002), indicated a trend favoring the unilateral condition in the current study. A

possible explanation for performance decrements in the bilateral condition may be elevated demands in attention related to a divided focus on two limbs. However, it is unknown how these differences could have occurred between the two studies since such similar training and testing methods were involved.

An additional issue that tends to plague therapeutic rehabilitation trials in general is that of sample heterogeneity (Lincoln et al., 1999; Pomeroy & Tallis, 2002; van der Lee et al., 2001). Because the impairments rendered by stroke widely range in severity, the problem of heterogeneity is introduced as participants of various ability levels collectively represent the influence of treatment. The exact nature of this influence is currently unknown because contrasting results have been produced in stroke research. Feys et al (1998) used a repetitive rocking action to treat the upper limb of stroke patients and noted that the greatest improvements occurred in those subjects with higher levels of impairment. Conversely, the review by Burridge and Ladouceur (2001), revealed a trend in electrical stimulation treatment whereby subjects retaining some residual motor control demonstrated a superior response. A possible explanation for such a discrepancy may be that subjects within different impairment classes may respond favorably to different types of treatment (Lincoln et al., 1999; Pomeroy & Tallis, 2002). Lincoln et al (1999) conceded how the inclusion of a broad spectrum of impairment levels can possibly conceal treatment effects that may vary according to the patient sub-group. To narrow the functional range of participants, the present study imposed inclusion criteria with both upper and lower limits of acceptability. However, even within this truncated range it is possible that the level of impairment could influence the effect of treatment. For example, the number of blocks moved during the Box and Blocks pretest range from 0 to 47

therefore indicating a broad range in functional ability in the participants. Stratification of participants into appropriate categories and the corresponding effects of treatment have been put forth as important areas of future research (Popovic et al., 2002).

The failure of this study to demonstrate any significant improvements associated with active neuromuscular stimulation rendered further examination of the primary research question a moot point. Directly addressing the issue of time-related treatment effects via the current study was impossible. This issue remains unresolved in stroke motor recovery in general and is not simply a problem with neuromuscular stimulation (Lincoln et al., 1999; Kwakkel et al., 1997; van der Lee et al., 2001). The results of the present study fail to offer any insight into this issue, therefore, the remainder of this discussion will focus on related stroke research and what it can tell us about the influence of treatment duration.

A research synthesis by Kwakkel et al. (1997) indicated that a small, but statistically significant functional improvement corresponded with higher intensities of treatment, where intensity was defined as the amount of time in therapy. For their study, stroke rehabilitation was viewed in general terms without a focus on any one specific intervention and results were then pooled and analyzed using a meta-analysis. Another meta-analysis performed by Ottenbacher and Jannell (1993) likewise addressed stroke rehabilitation in general terms to determine if it was effective overall in improving functional outcomes. Their results indicated that focused rehabilitation programs may be helpful in improving function, however, they found that this improvement was unrelated to the duration of treatment.

Nugent et al. (1994) examined the relationship between the amount of weight-bearing exercise and walking characteristics. The results indicated that a dose-response was present, but only for those subjects that had an initial capacity in the impaired limb for single limb support during walking. Those subjects who were initially unable to stand or step forward did not exhibit this relationship with additional exercise repetitions. This re-emphasizes the influence of impairment level on the outcome of therapy. In this case a treatment-duration effect was contingent upon a higher baseline level of function.

Further, Kwakkel and Wagenaar (2002) investigated the connection between time spent in rehabilitation and walking ability. Their aim was to reveal any influence training duration may have on walking speed and the underlying walking mechanics (i.e., coordination between hemiplegic and non-hemiplegic sides). The results indicated that longer treatment durations involving the lower extremities were associated with small increases in comfortable walking speed compared to controls. Not surprisingly, longer treatment duration for the group emphasizing upper extremity rehabilitation had no impact on walking outcome. This would appear consistent with principles of training specificity. In regards to interlimb coordination between hemiplegic and non-hemiplegic sides, additional therapy provided no benefit relative to controls.

One theme that does appear to be arising from the literature is that treatment duration influence is certainly not a universal effect. Different participants may respond in a correspondingly different manner to a particular type of treatment and any dose-relations may be reliant upon this impairment level. Furthermore, even within a given class of impairment, dose-effects may be specific regarding how or if they influence a particular variable.

Relating treatment duration to efficacy with active neuromuscular stimulation, Fields (1987) indicated that improved outcomes were associated with higher treatment frequency. An important qualification on these results, however, is that EMG activity in affected muscles served as the primary endpoint, therefore, leading to possible difficulties in comparisons with practical function. Although Field states how improvements were reflected in functional measures these measures involved ambulation (for the lower limb) and range of motion; not upper extremity function. As noted by Lincoln et al. (1999), hand and wrist function imposes a greater challenge for recovery, thus highlighting an important distinction (Lincoln et al., 1999).

Given that massed repetition has been suggested as an important factor in motor recovery following stroke (Turton & Pomeroy, 2002), a logical assumption is that a greater degree of repetition would make increased contributions to motor recovery. Short and long term neural transformations occur in the nervous system in relation to the activation frequency of respective pathways (Hallet, 2001). Based on this information, an intuitive inference is that a positive link exists between the volume of training and therapeutic effectiveness. Due to the value of repetition and cortical re-structuring, a further question could be asked regarding what amount of repetition is needed to notice improved ability and does this rate of improvement vary as a function of the treatment time? It is possible that a threshold level of repetition must be exceeded for improvement to occur. At the other extreme is the potential of diminishing returns where continued treatment may fail to provide gains beyond a certain point. Both of these issues represent important information for clinical application of treatment.

Muelbacher et al. (2002) demonstrated improved hand motor function as a result of regional anesthesia of the upper arm coupled with motor practice. The premise behind this procedure was to remove the influence of the competitive input of the upper arm in the motor cortex, thereby allowing more cortical substrate area to be available to the hand. A significant increase in performance occurred following the initial practice session and the follow-up session, combined with retention of these improvements. However, following the second practice session no further improvements took place indicating a plateau in this training effect. Thus, an important application of the above results may be that stroke interventions can produce improvements to a limit at which point further treatment application is no longer effective. Discovering if and where such a point exists in active neuromuscular stimulation would be valuable to clinicians where cost and time efficiency are highly regarded directives.

An important qualification to this simple question is repeating how any impact is likely influenced by the patients' functional level and the specific outcome variable in question. Consensus throughout the stroke motor recovery literature tends to indicate that a larger amount of treatment will generate greater benefits (van der Lee et al., 2001). Specific populations of patients based on impairment may respond disproportionately to various types of intervention (Lincoln et al., 1999), therefore several implications are made for active neuromuscular stimulation. Future motor recovery studies may increase the accuracy and treatment applicability of their effects if participants are stratified based on impairment level. Therefore, treatment effects can be determined relative to these specific populations. Further, creating such homogenous groups could increase the chance of exposing possible differences in regards to treatment duration effects.

In conclusion, the current results failed to support the hypothesis that a greater duration of active neuromuscular stimulation would generate increased measures of motor performance in the wrist and finger extensors of chronic stroke patients. Furthermore, the findings did not support EMG-triggered neuromuscular stimulation as an effective means of motor recovery. Possible reasons for this failure to replicate previous research results include participant heterogeneity, lack of a control group, focus on a complex area of motor recovery (i.e., wrist/finger extension), and the use potentially gain-resistant participants.

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BIOGRAPHICAL SKETCH

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