INDUCTION OF CORTICAL REORGANISATION FOR REHABILITATION IN STROKE

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by

Jeric Uy, BS (Physical Therapy); MAppSc (Physiotherapy)

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Induction of Cortical Reorganisation for Rehabilitation in Stroke

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Abstract

Stroke is a cerebrovascular injury to the brain leading to neural tissue death and is the leading cause of long-term disability in the world today. My primary goal in this study was to examine the possibility that reorganisation in the stroke-affected brain could be made in a manner that supported improved motor function. To achieve this, I induced reorganisation of the motor cortex by stimulating peripheral afferents, in both normal subjects and stroke-affected patients. I also carried out a series of experiments examining the reliability of the test methods used to evaluate cortical function, and to induce functional changes in the motor cortex.

Reorganisation is possible in the neural networks of the adult nervous system following alteration of afferent inputs brought about by conditions such as motor learning or by injury. This concept of dynamic functional plasticity in the nervous system provides the foundation for the development of learning and memory throughout life and offers a potential for repair and recovery in pathological conditions. The stroke-injured brain is capable of reorganisation; hence, rehabilitation techniques should be aimed at enhancing possible mechanisms for the brain to compensate for the lesion through reorganisation or brain plasticity.

I used the technique of transcranial magnetic stimulation (TMS) to examine corticomotor function, and a series of functional tests to examine motor performance. My first series of experiments in this thesis investigated the stability of TMS map parameters over time in healthy individuals. The areas of the scalp from which responses were evoked from corticospinal cells projecting to three intrinsic hand muscles were systematically mapped with TMS at intervals of 24 hours, one week and two weeks from eight normal subjects. The area, volume and centre of gravity of these maps did not change significantly over this

period. I concluded that the conventional method for mapping the cortical representational areas of individual hand muscles gives maps that are stable over periods of up to two weeks. This validates the use of such maps for the investigation of both short-term and long-term effects of interventions that may modify the cortical representation of muscles.

I induced prolonged changes in the excitability of the motor cortex in a group of stroke patients using the technique of dual stimulation. This combines a central stimulus (TMS) with electrical stimulation of afferent nerves. The experiments described in Chapters 4 and 5 aimed to determine the effect of dual stimulation on cortical reorganisation and motor function in a group of stroke patients. Chapter 4 describes the results of my intervention on stroke-affected lower limbs and chapter 5 on upper limbs. Neurophysiological and functional changes were seen in the affected upper and lower limb muscles. Some stroke-affected individuals showed marked neurophysiological and functional changes. Furthermore, stroke-affected subjects who had the largest changes in neurophysiological measures were also the ones with the largest change in functional measures. However, the effect of the intervention was highly variable and the overall changes in the group scores were not statistically significant.

The final series of experiments described in this thesis (Chapter 6) investigated the effects of a short period of anodal direct current (DC) stimulation and peripheral nerve stimulation on corticospinal excitability. The effect of this combined DC stimulation and peripheral nerve stimulation was contrasted with peripheral nerve stimulation alone. It demonstrated that the effects of peripheral nerve stimulation on cortical excitability could be potentiated by a preceding period of DC stimulation.

DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university of other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Jeric Uy

September, 2004

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Chapter 1 A Review of Literature

1.1 Introduction

The adult nervous system is now generally viewed as a dynamic, constantly evolving system. Extensive animal and human studies have shown how the process of reorganisation is possible within the neural networks following alteration of inputs in response to stimulation or the lack thereof (Buonomano and Merzenich 1998; Donoghue 1995; Kaas 1991). This concept of functional plasticity provides the foundation for the development of learning and memory throughout life and offers a potential for repair and recovery in pathological conditions. There is also mounting evidence that supports the capacity of the brain to reorganise after injury such as a cerebrovascular accident or stroke.

Stroke is the leading cause of long-term disability for Australian adults, affecting approximately 40,000 people every year (AIHW, 2001). Rehabilitation of stroke survivors poses a major challenge for healthcare professionals with as many as 75% of stroke survivors exhibiting functional impairments leading to disability and handicap (AIHW, 2001). The restoration of function of the affected side is the primary focus following a stroke. Although numerous techniques are available to facilitate the recovery of function after a stroke, one has yet to be proven superior over the other (Basmajian et al. 1987; Kraft et al. 1992; Johansson et al. 1993; Liepert et al. 2001). As stroke primarily causes tissue death in the brain, rehabilitation techniques should be aimed at enhancing possible mechanisms for the brain to compensate for the lesion through inducing reorganisation or brain plasticity.

Modern diagnostic tools are now readily available to study and detect plastic changes in the anatomy and physiology of the human brain. Transcranial Magnetic Stimulation (TMS) is a common technique used to activate and test the propagation of impulses from the central to the peripheral nervous system. The easy, painless and non-invasive nature of TMS makes it an attractive method in obtaining information regarding the excitability of the nervous system and the functional integrity of neural structures and connections (Hallett 2000). TMS also provides valuable, quantifiable measurements such as motor evoked potentials (MEP), conduction time and cortical maps, which offer variables such as map area, map volume and centre of gravity which have been shown to be reliable and reproducible (Wilson et al. 1993). These variables are often used to describe and detect the subtle changes associated with neural plasticity (Cohen et al. 1998; Thickbroom et al. 1999). With TMS, investigation into the recovery of the stroke-injured brain can be closely monitored with the ensuing reorganisation clearly correlated with improvements in functional performance (Cramer and Bastings 2000; Trompetto et al. 2000); however, more studies are needed to assess the potential for its use in both diagnosis and prognosis of neurological dysfunction.

The use of different forms of stimulation, more specifically afferent stimulation have generated increasing interest in influencing cortical plasticity. Experiments in normal subjects have documented cortical excitability changes associated with combining TMS with peripheral afferent stimulation (McKay et al. 2002; Ridding and Taylor 2001; Stefan et al. 2000; Stefan et al. 2002). These results provide a novel way of inducing plastic changes in the cortex and may have promising applications in inducing functional plasticity in subjects with brain injury such as stroke.

This thesis will describe an investigation in which forms of afferent stimulation were combined to induce neurophysiological and functional improvements in chronic hemiparesis. The following section will review current concepts of the process of reorganisation of the motor cortex in normal and pathological states. The review will also focus on the impact of stroke on cortical function, the different strategies available for recovery and the application of principles of neuroplasticity in stroke rehabilitation.

1.2 The Motor Cortex

1.2.1 Anatomy and Organisation

The motor cortex is a highly developed and versatile part of the central nervous system. It is divided into a mosaic of regions with distinct anatomical, physiological and functional properties. In most primate species, including humans, the regions include the primary motor cortex (M1), supplementary motor area (SMA), pre-motor cortex (PMC) and the cingulate motor area (CMA) (Nudo et al. 2001). The M1 is located in the region of Brodmann's area 4 on the convexity of the cerebral hemisphere. It spans the Sylvian fissure laterally and into the interhemispheric fissures medially (Gilman and Newman 1997). The M1 exerts a primary role in the control of voluntary movement. It influences movement through connections with pyramidal and extrapyramidal pathways, projections into the brainstem and spinal centres as well as connections to the basal ganglia and cerebellum. The M1 is also characterised by the presence of large corticospinal neurons and a relatively low threshold for eliciting movements electrically (Nudo et al. 2001). This distinctive quality of M1 has enabled scientists to describe its somatotopic organisation.

The topography of M1 has been studied using low-intensity electrical stimulation techniques as early as the middle of the last century (Woolsey et al. 1952). The resulting map revealed a somatotopic representation of the different body parts and movements. The surface of M1 is organised with a medial to lateral representation of the legs, arms, head and face. This is often represented by a cartoon-like diagram called the motor homunculus. Early studies of the motor cortex supported the existence of well-defined regions of the homunculus representing a specific body part. The functional division of M1 into leg, arm, head and face representation still holds true. However, there is growing evidence that the organised somatotopic representation within M1 may not be as precise and fixed as originally thought.

Within M1, muscle representations overlap (Nudo et al. 1997; Sanes et al. 1995). Animal models have shown that single descending M1 neurons have projections that extend over multiple segments of the spinal cord and span motor pools across joints and limbs (Shinoda et al. 1979; Shinoda et al. 1986). Intracortical stimulation techniques uncovered vast interconnecting sites within the upper limb representation area of the macaque monkey (Huntley and Jones 1991). Spike-triggered averaging also revealed that single M1 neurons in the arm representation area influence motor neuron pools of multiple arm muscles (Buys et al. 1986; Fetz et al. 1989; Sessle and Wiesendanger 1982). Modern imaging techniques like positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) also confirm the overlapping patterns of activation within M1 in response to upper limb movements (Grafton et al. 1991; Sanes et al. 1995). An analogous, discrete, overlapping internal organisation has also been shown in the face (Huang et al. 1989) and the lower limbs (Gould et al. 1986). Although there exists a fairly organised division between larger body parts within M1, the internal networks seem to reveal features of divergence and convergence.

Stimulation and imaging studies have disputed the hypothesised orderly topographic representation of the body on M1. It is now proposed that cortical representation areas overlap, intermingle and share networks within the internal circuitry. These emerging features of M1 provide for a widespread area that is functionally flexible and malleable and may be the underlying substrate for its capacity for plastic change.

1.2.2 Cortical Control of Movement

Cortical activation elicits coordinated and complex movements and it is suggested that the cortical control of movement is organised in terms of behaviourally useful actions aimed towards a goal posture (Graziano et al. 2002). Using spike triggered averaging in monkeys, it was shown that stimulation of a cortical neuron not only elicited a demonstrable change in multiple muscles, but also showed increased activity in one muscle group and a simultaneous decrease in activity in another (Cheney et al. 1985). Graziano et al., (2002) demonstrated an even more complex relationship between the cortex and muscles when electromyographic (EMG) activity was found to vary considerably depending on arm starting positions. The EMG activity depended on whether the starting position required the muscles to assume either an agonist or antagonist role. This sensitivity reflects the influence of cortical neurons over intrinsic variables such as muscle force and joint angle (Cabel et al. 2001; Scott and Kalaska 1997). Similarly, velocity of movement (Reina et al. 2001) and position of movement (Caminiti et al. 1990) have also been correlated with cortical neuronal activity. It seems that the cortex acts to mediate the different and complex factors associated with movement and facilitate the necessary adjustments.

Micro stimulation of the primate motor cortex has been used to establish a complex map of postures. The final specific posture elicited was found to have behavioural

significance as the stimulation-evoked movements assumed positions such as those that resemble putting food in the mouth or a protective stance, and followed a muscle activation pattern observed in normal movement (Graziano et al. 2002). The movements and postures were also found to be repeatable and consistent. Furthermore, the stimulation sites that produced the movement and final posture were arranged in a rough map across the pre-central gyrus. The map showed some degree of discontinuity and covered areas in both the primary motor cortex and adjacent areas from the pre-motor cortex to the arcuate sulcus. There was no clear separation between the cortical areas that evoked the movement, providing further evidence of the overlapping nature of the cortex and how different areas are involved in the execution of movement.

It is clear that other areas besides M1 are involved in the network for the execution and control of movement. The PMC is topographically adjacent to M1. The PMC plays a substantial role in the preparation and sensory guidance of movements (di Pellegrino and Wise 1993; Kurata and Wise 1988) and in the organisation of motor sequences (Sadato et al. 1996). Single cell recording techniques during a training task also revealed the PMC contains predominantly directionally selective, preparation related neurons (Riehle and Requin 1989).

Another area that may contribute to movement is the SMA. Activity in the SMA has been shown to increase during the conception and execution of movement as revealed by cerebral blood flow studies (Orgogozo and Larsen 1979). Subsequent studies have also demonstrated the SMA to be involved in the initiation of movement regardless of task complexity and in relation to sensory cues (Deecke et al. 1985). These studies support the important function of the SMA in the planning and programming of motor tasks.

Situated on the medial surface of the cerebral hemisphere are the CMA. The CMA receives afferent inputs from the limbic and prefrontal structures and sends efferent outputs to the primary and secondary motor areas, as well as the brainstem and spinal cord (He et al. 1995; Morecraft and Van Hoesen 1993). By virtue of its anatomical connections, the CMA plays an important role in motivation and the cognitive evaluation of the environment (Vogt and Gabirel 1993), as well as processing information necessary for the selection of voluntary movements when presented with a variety of motor tasks (Picard and Strick 1997; Shima and Tanji 1998).

The cortical control of movement is not exclusively executed by M1. The anatomical and physiological connections of the PMC, SMA and CMA show direct or indirect contributions to the execution of movement. Axons from these areas have been found to terminate in the spinal cord and have interconnections with spinal motor neurons in a manner similar to M1 (Dum and Strick 2002). This unique motor network functions to produce complimentary commands that initiate, generate and guide movement (Picard and Strick 1997; Shima and Tanji 1998). The organisation of the motor areas provides an excellent framework for the acquisition and mastery of new skills and may prove useful for the process of recovery when faced with injury or damage.

1.3 Cortical Plasticity

There is much evidence that demonstrates that the adult nervous system is capable of undergoing dynamic changes in response to hormonal, pharmacological, environmental and sensory stimulation. This process of change is termed "neuroplasticity" and can be observed at molecular, morphological, synaptic, cortical and functional levels. Neuroplasticity provides the foundation for the development of learning and memory

throughout life. Plastic changes have been demonstrated in the hippocampus (Castro-Alamancos and Connors 1997; Kirkwood et al. 1993; Teyler et al. 1995) in the visual (Antonini et al. 1999; Berardi et al. 2003; Kind 1999), auditory (Jancke et al. 2001; Pantev et al. 1999) and the human motor cortex (Donoghue 1995; Hamdy et al. 1998; Karni et al. 1995).

The function of the motor cortical areas has evolved constantly. The dynamic and flexible organisation of the motor cortex makes it not only involved in the planning and execution of movement but gives it an active role in learning and CoGnition as well (Sanes and Donghue 2000). The mechanism for this capacity for plastic changes has been attributed to the system of horizontal connections spanning M1. The cerebral cortex has been shown to possess neurons that have a system of substantial collateral branches that project horizontally from M1 (Ghosh and Porter 1988; Hess and Donoghue 1994; Huntley and Jones 1991). These horizontal connections function to integrate information from distant or neighbouring cortical and subcortical zones (Canedo 1997). This makes them an attractive substrate for cortical plasticity, as reorganisation in response to sensorimotor stimulation seems to rely on the substantial horizontal connections of the cortical areas (Buonomano and Merzenich 1998). The balance of inhibitory and excitatory inputs within its system also influences the plasticity of the M1 circuitry. Organisation of the M1 representational map has been shown to change following local blocking of the inhibitory neurotransmitter gamma-amino butyric acid (GABA). Iontophoretically releasing a GABA antagonist, (-) bicuculine methobromide (bid) in the cortex of adult rats after peripheral nerve transection revealed significant map changes (Jacobs and Donoghue 1991). Adjacent cortical regions expand as the feed-forward inhibition is blocked and pre-existing horizontal connections are unmasked.

Restructuring of cortical maps also involves excitatory intra-cortical connections. The excitatory horizontal connections are mediated by postsynaptic calcium [Ca^{2+}] entry, activation of metabotropic glutamate receptors and the generation of diffusible intercellular messengers (Bear and Malenka 1994; Keller 1993). This excitatory property of the synaptic circuitry of M1 together with the unmasking brought about by the release of GABAergic control provide the basis for the immediate changes observed in the functional organisation of M1. Persistent changes in the synaptic properties of the horizontal connections, however, would require a more stable form of modification.

1.3.1 Long Term Potentiation and Long Term Depression

Extensive studies have shown how the brain continually organises throughout life. Fundamental to this plastic property is a mechanism based on Hebbian principles wherein changes in synaptic efficiency underlie learning and memory formation (Buonomano and Merzenich 1998). A prototypic mechanism of changing synaptic efficiency that is widely accepted is long-term potentiation (LTP). LTP is defined as a sustained increase in synaptic strength brought about by high-frequency stimulation of excitatory afferents (Asanuma and Pavlides 1997; Maren and Baudry 1995). The process of LTP follows Hebb's postulate wherein simultaneous pre- and post-synaptic activity provide multiple inputs to a cell and results in the strengthening of synapses in the activated pathway. Thus the three requirements for LTP are cooperativity, associativity and specificity. LTP is a form of activity-dependent plasticity that has been shown to persist for several days and has been implicated in the formation of memory and learning. The process of LTP was first discovered in the hippocampus (Bliss and Lomo 1973) and has since been documented in several other sites in the brain including the motor cortex (Aou et al. 1992; Baranyi et al. 1991; Iriki et al. 1989; Sakamoto et al. 1987; Ziemann et al. 1998b). This capacity for persistent synaptic

modification has been shown to occur within the broad horizontal connection network of M1 (Hess and Donoghue 1994). However, in the adult cortex, LTP of the horizontal connections requires a transient reduction of inhibition during the period of stimulation together with the simultaneous tetanisation of the vertical pathways (Hess et al. 1996). This would suggest the contribution of vertical inputs coming from the cerebello-thalamocortical pathways in the cortical organisation and restructuring of M1 (Buonomano and Merzenich 1998; Hess et al. 1996).

Another form of activity-dependent plasticity is long-term depression (LTD). The role of LTD in cortical plasticity has been less extensively studied than LTP. LTD induces rapid, activity-dependent reduction of responses in relation to irrelevant sensory stimuli (Bear et al. 1987; Rittenhouse et al. 1999). It is easily induced in the vertical connections of the visual cortex (Kirkwood and Bear 1994) and the horizontal connections of the motor cortex (Hess and Donoghue 1996). Different types of LTD, namely, homosynaptic (Dudek and Bear 1992; Kirkwood and Bear 1994); heterosynaptic (Cummings et al. 1996; Lynch et al. 1977) and associative LTD (Artola and Singer 1990; Fregnac et al. 1994) have been described in the literature. Heterosynaptic LTD, in which a second pathway is activated to produce a depression in the inactive pathway, has been suggested as the possible mechanism involved in the reorganisation of cortical representational maps (Buonomano and Merzenich 1998).

The capacity of LTP and LTD to induce a bi-directional change in synaptic efficiency is influenced by the arrangement and organisation of the synaptic activity in the cortex, with the adjustment of the strength of the synaptic connections dependent on parameters such as frequency, timing and intensity of inputs (Dinse et al. 1993; Sjostrom et al. 2001). Generally, high frequency stimulation induces LTP (Bliss and Lomo 1973) and

lower frequencies eliciting LTD (Dudek and Bear 1992; Kirkwood et al. 1993). The mechanisms involved in the induction of LTP and LTD in the cortex are similar to that observed in the CA1 area of the hippocampus. M1 plasticity is NMDA-receptor-dependent and is usually accompanied by a downscaling of the activity of inhibitory circuits (Artola and Singer 1987; Hess et al. 1996; Ziemann 1998). In addition, the potentiation and depression of synaptic strength also depends on the level of free calcium in the post-synaptic cell (Bennett 2000; Yang et al. 1999). No definite system has been identified to explain how post-synaptic calcium concentration can selectively induce LTP or LTD. Yang et al. (1999) observed how specific post-synaptic [Ca^{2+}] elevation patterns influence the induction of either LTP or LTD. A brief increase of [Ca^{2+}] with relatively high magnitude elicited LTP, while a prolonged, modest increase produced LTD.

Comprehensive animal studies have provided solid evidence that long-term plasticity is possible in M1. M1 most certainly possesses the likely substrate, via the horizontal connection system and the mechanisms, for LTP and/or LTD (Buonomano and Merzenich, 1998). Although human studies have not been as extensive as those in animals, the concept of synaptic plasticity in the human motor cortex is ever evolving with the continued development of more sophisticated techniques and equipment.

1.4 Induction of Cortical Plasticity

It is now widely acknowledged that plastic change of the human brain continues throughout life. The M1 region has been shown to reorganise following alteration of inputs brought about by social, sensory or environmental interactions in both the intact and injured motor cortex.

1.4.1 Enriched environment

Numerous studies in animal models have demonstrated the positive effect of environmental enrichment on the brain. Increases in brain weight (Bennett et al. 1969) and cortical thickness (Diamond et al. 1964) after environmental enrichment have been reported. Synaptic plasticity has also been reported after exposure to an enriched environment with studies demonstrating increased synaptogenesis (Turner and Greenough 1985), synaptic strengthening (Nakamura et al. 1999), neurogenesis (Nilsson et al. 1999) and increased dendritic branching, length and density (Diamond et al. 1976; Globus et al. 1973). The influence of an enriched environment has also been positive in the injured brain. Rats given experimental brain lesions and housed post-operatively in enriched environments were shown to perform significantly better than rats housed in impoverished environments (Ohlsson and Johansson 1995). The enriched environments comprised of opportunities to perform different activities and social interaction with other rats. The social interaction component when combined with an enriched environment was shown to result in the best outcome (Johansson and Ohlsson 1996). The mechanism behind the beneficial effects of an enriched environment in post-injury outcome has been attributed to the increased synthesis of neurotrophic factors (Johansson 2000). Neurotrophic factors are thought to be capable of promoting the neuronal survival and are also likely to be involved in synaptic reorganisation and alteration in receptor expression (Johansson 2000; Klintsova and Greenough 1999).

However, there is still no evidence that shows the value of neurotrophic factors and related functional outcomes, either in animal or human models. As neuronal changes in response to an enriched environment have been documented in the cortex, hippocampus, cerebellum and the striatum, future studies should look into its therapeutic benefits. Stimulation from an enriched environment may prove to be an important causative factor in enhancing functional plasticity following neuronal injury and damage.

1.4.2.Learning-Dependent Plasticity

Emerging experiences that bring about motor learning can also drive plastic changes in the motor cortex. Reorganisation of the motor cortex in relation to physical training has led to the belief that M1 has a role in not just the execution of movement but also in the learning of movement. Anatomical and physiological changes within the M1 of animal models secondary to exposure and manipulation of various experiences have been extensively demonstrated. Rats that were trained to complete a complex motor task had significantly more synapses compared with controls (Kleim et al. 1996). Similarly, trained rodents showed longer dendritic lengths and extensive dendritic branching compared with non-trained ones (Greenough et al. 1985; Withers and Greenough 1989). Squirrel monkeys trained on a small object retrieval task showed an expansion of the digit topography in their primary motor cortex (Nudo et al. 1996). The expansion was attributed to the highly skilled use of the digits when performing the task. This functional expansion of the motor cortex was likewise demonstrated in the rodent M1 following motor skill learning in experiments employing standard microelectrode stimulation techniques (Kleim et al. 1998). A relevant, related finding to these studies is that repetitive, unskilled movements that did not induce motor learning failed to show changes in the motor representation of the cortex. Plasticity of M1 appears to be skill-

dependent as adaptive changes in the motor cortex are driven by learning a new motor skill and not just by motor use (Nudo et al. 1996).

The acquisition of skills has also been shown to influence plastic changes in the human motor cortex. In studies using TMS, cortical representation areas of the muscle controlling the Braille-reading finger in humans were found to exhibit a significant expansion over the sensorimotor cortex compared with the non-Braille reading finger and controls (Pascual-Leone et al. 1993). Analogous results were seen in a group of elite badminton players. The corticomotor projection of the skilled, playing hand was shown to have increased MEP amplitudes and larger shifts in the representation maps as revealed by TMS (Pearce et al. 2000). These studies illustrate how functional reorganisation of M1 is evident in the long-term acquisition of motor skills. Motor cortex representation can likewise be modified by short-term experiences. Changes in M1 can appear after as little as 5-10 minutes of rapid, repetitive thumb movements (Classen et al. 1998). Combined, synchronised thumb and foot movements performed over 40 minutes also showed reorganisation, with the thumb representation shifting medially towards the foot area (Liepert et al. 1999). Similar results were shown when thumb movements were combined with face (Cohen et al. 1996) or shoulder (Cohen et al. 1995) movements. Rapid motor learning of ballistic contractions of the muscles involved in pinching revealed significantly bigger MEPs for the muscles involved in pinching (flexor pollicis brevis) compared with non-pinching muscles (abductor digiti minimi) (Muellbacher et al. 2001). This study showed the involvement of M1 in learning related changes in force generation and movement acceleration.

Changes in the primary motor cortex associated with skill acquisition have also been demonstrated in humans using PET. A progressive increase in M1 activation was

evident as skill developed in the motor tracking of a moving target (Grafton et al. 1991). Sequential right-hand finger movements performed by healthy volunteers and mapped using PET revealed a consistent task-specific activation and significant increase in regional cerebral blood flow (rCBF) in the left primary sensorimotor cortex (Schlaug et al. 1994). In addition, other areas of the brain were also shown to be involved with motor learning, with PET scans displaying increases in rCBF in the cerebellum, limbic and paralimbic structures, pre-motor areas, cingulate areas as well the frontal cortex, thalamus and the basal ganglia (Schlaug et al. 1994; Seitz et al. 1990).

Functional magnetic resonance imaging following a complex finger-tapping task showed learning-related changes in the primary motor cortex of piano players (Hund-Georgiadis and von Cramon 1999). Short-term motor learning in piano players was associated with significantly increased activation of the M1 contralateral to the trained hand compared with non-musicians. Persistent changes in M1 activation, as revealed by fMRI, were also shown following practice of rapid sequence finger movements (Karni et al. 1995). After four weeks of training, the extent of activation of M1 was larger for the practised movement compared with the unpractised sequence. Consistent with the findings in the PET scans, the fMRI studies also showed involvement of the secondary motor areas including the somatosensory, parietal and inferior frontal cortex, the thalamus and cerebellum, during the process of motor learning (Hund-Georgiadis and von Cramon 1999).

Thus, imaging studies using PET and fMRI as well as TMS studies have shown how motor learning influences short and long-term plasticity in the human motor cortex. In addition, other areas surrounding M1 have also been implicated in the skill acquisition process; however the complex interaction between M1 and these different structures is

yet to be fully understood. Anatomical and physiological changes in relation to cortical reorganisation brought about by skill training and acquisition provide further support that M1 does not have an exclusive movement executory function, but does play a vital role in motor learning.

1.4.3 Mechanisms of Learning-Dependent Cortical Plasticity

Functional reorganisation of the cortex has been associated with the modification of synapses. The phenomenon of LTP has been widely accepted as the synaptic mechanism involved in learning and memory. Skill learning in rats showed larger amplitude field potentials in the contralateral motor cortex of the trained forelimb (Rioult-Pedotti et al. 1998). Similar plastic changes in intra-cortical horizontal connections have also been demonstrated in monkeys (Mitz et al. 1991) and cats (Aou et al. 1992). It has been proposed that the acquisition of new skills is dependent on the cortico-cortical projections from the somatosensory cortex to the motor cortex (Pavlides et al. 1993). Changes in dendritic and synaptic morphology have also been shown after motor learning. Dendritic arborizations after motor learning have been observed in the pyramidal cells in Layer II/III and V of the motor cortex of rats trained in a reaching task (Greenough et al. 1985; Withers and Greenough 1989). An increased synapse-per-neuron count was also shown in rat sensorimotor cortex after acrobatic training (Jones et al. 1999; Kleim et al. 1996). This increased number of synapses has been implicated in an increase in synaptic efficiency brought about by enhanced post-synaptic responses after motor learning (Yi and Greenough 1994). These studies show that plastic changes associated with motor learning are distributed across different layers of the motor cortex utilising different mechanisms. Such distribution may be important in the adaptive changes that occur after cortical damage. The plasticity of the motor cortex at these different levels would provide a critical link for functional recovery and would provide

a physiological basis for the improvements in function brought about by rehabilitation and training.

1.4.4 Afferent Stimulation and Cortical Plasticity

Considerable evidence is available on how different forms of manipulation can produce organisational changes in the sensorimotor cortex. Plastic changes in numerous areas of the brain have been observed in relation to exposure to an enriched environment, learning and skill acquisition and to different forms of afferent stimulation. The use of various patterns of afferent stimulation to produce distinct changes in the organisation of the sensorimotor cortex has been extensively reported. Manipulation of sensory feedback, through denervation (Donoghue et al. 1990), deafferentation (Brasil-Neto et al. 1993; Cohen et al. 1993; Ziemann 1998) and prolonged positional adjustments (Sanes et al. 1992), has been shown to bring about changes in representational areas of M1. These show that the manipulation of sensory inputs can reorganise the representational areas in the cortex and that the changes induced can be reversed as soon as sensation is restored.

More persistent cortical reorganisation has been induced by sensory afferent stimulation. Following 10 minutes of repeated electrical pharyngeal sensory stimulation, a significant increase in motor cortex excitability and cortical representational area of the pharynx was reported to persist for at least 30 minutes (Hamdy et al. 1998). There was also a reduction of the oesophageal representation and the changes were cortical, as no changes in excitability were seen in the brainstem-mediated reflexes. Prolonged repetitive stimulation of either ulnar or radial nerves has also been shown to induce persistent changes in corticomotor representations of intrinsic hand muscles. A significant increase in cortical excitability and centre of gravity shift in the cortical maps of the stimulated muscles was induced by two hours of

stimulation (Charlton et al. 2003; Ridding et al. 2000; Ridding et al. 2001) with the cortical changes persisting for at least two hours post-stimulation (Charlton et al. 2003). Further refinement of this technique using a paired associative stimulation paradigm gave similar results. A one-hour randomised stimulation protocol designed to minimise habituation and adaptation, significantly increased corticospinal excitability for the stimulated muscles compared with the control stimulation paradigm group (Ridding and Uy 2003). Afferent stimulation not only induces a response in excitatory inputs but can also alter the activity of inhibitory circuits in the cortex. Using TMS, it has been demonstrated that single digital nerve stimuli, when appropriately timed, are capable of inducing a transient reduction in intarcortical inhibition (Ridding and Rothwell 1999). Therefore, there is compelling evidence that different forms of peripheral afferent stimulation are capable of inducing plastic changes in the motor cortex.

The cortical reorganisation following afferent stimulation has been of great interest in understanding the plasticity of the motor cortex and in developing novel ways of promoting these changes for potential functional use. Studies have recently combined peripheral afferent stimulation with low frequency transcranial brain stimulation in order to fulfil the criteria for associative or Hebbian plasticity and shorten the time required to bring about enduring cortical excitability changes (Stefan et al. 2000). Central cortical stimulation is usually accomplished by using TMS, which preferentially activates the horizontal intracortical fibres (Rothwell 1997). Persistent plastic changes have been shown to occur within these horizontal fibres (Hess and Donoghue 1996). A period of median nerve stimulation synchronously paired with low frequency TMS over the optimal cortical activation site for abductor pollicis brevis (APB) resulted in significantly larger MEPs being evoked in APB (Stefan et al. 2000). The increase in MEP amplitude was conditionally dependent on the relative timing of the afferent

stimulation and the TMS. In addition, the plastic changes induced by synchronously pairing stimulation evolved rapidly. The changes persisted, were reversible and remained topographically specific, features that show a signature for LTP. Similar findings were seen when electrical motor point stimulation was paired with TMS of the first dorsal interosseous (FDI) hotspot for a period of 30 minutes (Ridding and Taylor 2001). Using a similar dual stimulation protocol, significant changes in excitability were seen together with cortical expansion of the scalp representation area for FDI (McKay et al. 2002). The expansion was accompanied by a significant movement of the centre of gravity (CoG) of the cortical map taken from FDI and the changes observed persisted for up to five days without further stimulation. It has been suggested that the immediate neuroplastic changes associated with a dual stimulation intervention may be analogous to mechanisms that involve the fast learning of a motor task (Karni et al. 1998). With repeated sessions of dual stimulation, these changes were found to be more long-lasting. The changes observed indicate a process of consolidation may be taking place (McKay et al. 2002). Consolidation involves continued improvement in performance following the final training session (Karni et al. 1998) and has been documented in the visual (Karni and Sagi 1993) and the motor systems (Karni et al. 1995). This slow learning mechanism is an important feature for the possible application of the dual stimulation paradigm in a patient population. The persistent and prolonged changes may have therapeutic value and provide another method of improving motor control and function in people with brain injury such as stroke.

Another method of cortical stimulation used is transcranial direct current stimulation (tDCS). Weak anodal tDCS was shown to be capable of inducing long-lasting changes in cortical excitability in animal and human models (Islam et al. 1995; Nitsche and Paulus 2000; Nitsche and Paulus 2001; Priori 2003). The elevations in cortical

excitability were found to depend on the polarity, intensity (Nitsche and Paulus 2000) and duration (Nitsche and Paulus 2001) of stimulation. Although the exact mechanisms responsible for the changes observed with tDCS are still not fully understood, this technique is increasingly used to drive persistent neuroplastic changes in the motor cortex (Priori 2003).

The process of LTP is proposed to be the mechanism underlying learning and memory (Asanuma and Pavlides 1997). LTP in the motor cortex depends on the activation of NMDA receptors (Buonomano and Merzenich 1998; Castro-Alamancos et al. 1995). The increased motor cortex excitability demonstrated after synchronous pairing of TMS and peripheral nerve stimulation showed properties of associative LTP (Stefan et al. 2000) and was inhibited when subjects were administered the NMDA receptor antagonist dextromethorphan (DMO) (Stefan et al. 2002). Similar mechanisms have also been proposed for the excitability changes seen with tDCS. DMO also suppressed post-stimulation effects of anodal and cathodal DC stimulation. A significant reduction of the anodal stimulation effect was also seen following the administration of the sodium channel blocking agent carbamazepine (Liebetanz et al. 2002). This suggests that the mechanism behind the cortical excitability noted after tDCS is also dependent on the activation of NMDA receptors and a depolarisation of cortical cells. These findings provide evidence that the induced plasticity following dual stimulation or tDCS is linked to associative LTP.

It has been suggested that the increase in motor cortex excitability seen following a period of afferent (or dual) stimulation may bring about improvements in function (Conforto et al. 2002; Ridding et al. 2000; Traversa et al. 1997). This may have applications in the rehabilitation of people with compromised brain function. The

expansion of motor representation areas seen following afferent stimulation may prove useful in people with stroke for recruiting neighbouring intact cortical areas to take over the function of the lesioned areas. As the changes in cortical excitability can be made to persist in a normal sample group, the possible functional translation of using a combined dual stimulation protocol in a pathologic sample, more particularly a stroke population, needed to be explored. The experiments in Chapters 4 and 5 present preliminary results of the neurophysiological and functional outcomes in gait and hand function following the application of a dual stimulation protocol in a group with chronic hemiparesis. The pairing of tDCS with peripheral afferent stimulation is described in Chapter 6. This may offer yet another option in determining the optimal paradigm for inducing plastic changes in the motor cortex.

1.5 Transcranial Magnetic Stimulation (TMS)

1.5.1 Introduction

The introduction of TMS by Barker in the 1980s provided a safe, non-invasive and painless method of, *inter alia*, activating the motor cortex and testing the propagation of impulses from the central to the peripheral nervous system. It has been used to study the excitability of the central nervous system (Triggs et al. 1994) and central conduction time (Brasil-Neto et al. 1992b), and is used to map the representational areas of the motor cortex in normal and pathologic populations (Levy et al. 1991; Liepert et al. 1995; Uy et al. 2001; Wassermann et al. 1992). The application of TMS has provided new insights into the physiology and pathophysiology of the nervous system and has supported its development into a clinically-useful diagnostic and prognostic tool (Kobayashi and Pascual-Leone 2003).

The principles of electromagnetic induction apply with the use of TMS. A high-current pulse passed through an insulated coil induces a magnetic field that passes painlessly through tissues. This magnetic field runs perpendicular to the plane of the coil (Cohen et al. 1998). When the coil is held over the scalp, the skull offers very little impedance to the magnetic field produced. As the magnetic field passes through, it induces electric currents or eddy currents that flow at right angles to the magnetic field (Cohen et al. 1998; Rothwell 1991). With the appropriate current direction, duration and amplitude, depolarisation of cortical motor output cells (corticospinal neurons) can be induced. Activation of these cells results in the propagation of a descending volley in the corticospinal tract. This descending volley depolarises spinal motoneurons, which in turn results in a propagated peripheral nerve volley and muscle contraction. This muscle contraction can be recorded using EMG electrodes and is known as a motor evoked potential (MEP).

The shape of magnetic coil used affects the magnetic field produced by TMS and determines its focus. The circular coil and the figure-of-eight coil are commonly used. The circular coil induces a more distributed electric field. When held flat over the scalp, it produces a non-focal stimulation that can activate a larger area of neural tissue around the borders of the coil (Rothwell 1997). This coil can be used for bi-hemispheric stimulation (Kobayashi and Pascual-Leone 2003) and is widely employed in studying central motor conduction times (Rossini and Rossi 1998) as well as detecting the amplitude, latency and morphology of MEPs (Cramer and Bastings 2000). For more focal stimulation, a figure-of-eight coil is used. The electric fields produced with these coils are concentrated on the junction of the "8" (Rothwell 1997) with the current induced in this region twice as much as that under the two wings (Barker 1999). Stimulation using the figure-of-eight coil permits careful stimulation of one hemisphere

and is commonly used in the mapping of cortical representations (Levy et al. 1991; Liepert et al. 1995; Uy et al. 2001; Wassermann et al. 1992).

1.5.2 Neural Activation with TMS

Direct electrical stimulation of the cortex produces a complex descending volley of waves that are 1 – 2 ms apart (Patton and Amassian 1954). The first part of the volley is brought about by direct stimulation at or near the first segment of the corticospinal neurons producing D–waves (direct). Subsequent waves are brought about by trans-synaptic excitation of the corticospinal neurons to produce I-waves (indirect). The resulting multiple descending excitatory volleys from direct cortical stimulation have been reported in both animal (Edgley et al. 1990) and human (Day et al. 1987; Katayama et al. 1988) models. Insight into the neural structures activated by focal TMS can be best described by comparing the distinct differences of the stimulation properties of TMS to transcranial electrical stimulation (TES). Both methods activate the same population of output cells in the cortex (Edgley et al. 1990); however the latency of responses with TMS has been shown to be 1 – 2 ms longer than those measured with TES (Amassian et al. 1989; Day et al. 1989; Hess et al. 1987). This is due primarily to the difference in time taken by the two techniques in activating pyramidal neurons in the cortex (Day et al. 1989). It has been shown that TES activates corticospinal axons directly producing D-waves in the descending volley. In contrast, TMS activates corticospinal neurons trans-synaptically, to produce I- waves (Day et al. 1989).

Direct waves can also be induced by TMS. With increasing TMS intensity, D-waves similar to that produced by TES were shown to appear (Mills 1999). However, the latency of TMS induced D-waves is not affected by further increases in TMS intensity. This implies that TMS excitation occurs within the cortex and does not spread along corticospinal axons. TMS can also evoke D-waves by changing the direction of the

induced current. Responses obtained from actively contracting hand muscles using a figure-of-eight coil show that with a posterior-anterior induced current, I-waves were produced, while current flowing in a medio-lateral direction produced both D and I waves (Di Lazzaro et al. 1998). Neural activation by TMS can also be influenced by the site of stimulation. Stimulation of the leg area using both TES and TMS has been shown to generate responses of identical latencies (Nielsen et al. 1995; Priori et al. 1993), suggesting that the behaviour of responses from TMS of cortical sites is distinct for different muscle groups.

As TMS predominantly excites cortical cells transynaptically, the responses evoked by TMS are highly dependent on the level of cortical excitability. This is a positive consequence of TMS as it allows magnetic stimulation to be used as a measure of changes in cortical excitability brought about by normal or pathological conditions (Day et al. 1991). Furthermore, the difference in site activation between TMS and TES has been considered a major factor when evaluating the level at which changes in excitability take place.

1.5.3 TMS and Neuroplasticity

The introduction of TMS has provided a powerful tool to investigate the cortical reorganisations that take place following brain injury, repair and motor learning. It is used to map the functional representational areas of the brain, to assess cortical excitability, test the functional connectivity of neural structures, or evaluate the integrity of motor pathways (Siebner and Rothwell 2003).

Using TMS, cortical reorganisation has been demonstrated following congenital, surgical or traumatic amputations (Cohen et al. 1991) with motor maps of muscles in

the amputation stump showing a larger muscle representation. This finding was taken to indicate that the stump muscles representation had expanded into the representation of the missing muscles. In addition, these maps were bigger than the maps produced from the same muscles in the intact hemisphere (Ridding and Rothwell 1995). Similar results were seen in reversible deafferentation studies using regional anaesthesia. The amplitudes of the MEPs evoked by TMS were larger in the muscles immediately proximal to the temporarily anaesthetised forearm (Brasil-Neto et al. 1992a; Brasil-Neto et al. 1993). These changes were reversible when the anaesthesia wore off.

There is a growing use of TMS in studies of motor learning. A significant increase in the size of the hand representation area was revealed after subjects were trained in a five- finger exercise on the piano over a five-day period (Pascual-Leone et al. 1995). In addition to expansion of the motor maps, there was concurrent improvement in performance as well as a steady decrease of the motor thresholds for the target muscles. Expansion of motor maps was also seen in subjects during a serial reaction-time test (Pascual-Leone et al. 1994). This study provides good support for the ability of the cortex for rapid functional plasticity associated with learning and the transfer of implicit (e.g., learning to ride a bike) to explicit (e.g., reading the manual on how to ride a bike) knowledge. The progressive improvement in reaction time seen in the study was associated with improved implicit knowledge and was correlated with the enlargement of the maps of the target muscle. The motor maps returned to baseline levels when explicit knowledge was achieved.

The plasticity of the cortex is often associated with changes in the pattern of motor behaviour (Hallett 2001). Using TMS, the cortical topography of blind Braille readers was compared with non-Braille reading blind controls. The representation maps of the

first dorsal interosseous (FDI) muscle, which controls the reading finger, were significantly larger compared with blind non-Braille reading controls (Pascual-Leone et al. 1993). In contrast, the motor map of the abductor digiti minimi (ADM) muscle of the reading hand was smaller compared with the non-reading hand or blind controls, suggesting that cortical expansion of one muscle occurs at the expense of another. This enlargement of the FDI motor map was also shown to be highly dependent on use. In a Braille reader who took a 10-day break from Braille reading, the motor representation was dramatically reduced until the subject went back to reading (Pascual-Leone et al. 1993). Similar results were seen in subjects whose tibialis anterior (TA) muscle was immobilised without any nerve lesion (Liepert et al. 1995). The unilateral immobilization of the ankle joint diminished the representational area of the TA muscle without changing spinal excitability or motor threshold.

1.6 TMS Parameters

The diagnostic and therapeutic applications of TMS are constantly evolving. These parameters are often used in reporting change brought about by injury or intervention. The three frequently used parameters will be briefly discussed.

1.6.1 Motor Threshold

Motor Threshold (MT) is defined as the lowest TMS intensity needed to elicit an MEP in the target muscle (Rossini et al. 1994). It is influenced by neuronal excitability in the cortex, spinal cord, neuromuscular junction and muscle (Ziemann et al. 1996) and thus may also affect the tonic inhibitory and excitatory drives onto the cortical output neurons (Kobayashi and Pascual-Leone 2003).

Hemispheric differences have been reported to affect MT, with the threshold for activating the right hand lower than the left in a group of right-handed subjects aged 28-47 (Macdonell et al. 1991). The lower threshold seen in this study was attributed to the asymmetry of the neuronal pools between the two hemispheres, with more projections available to the right-hand muscles. This was also seen in the biceps and APB muscles with the dominant side having a lower threshold than the non-dominant side (Triggs et al. 1994). It was further suggested that the asymmetries seen may be related to the differences in corticospinal efferents or cortical motor afferent functions as well as differences in motor performance.

Other studies have failed to detect significant hemispheric differences in MT (Cicinelli et al. 1997a; Mills and Nithi 1997). This may be due to the differing age groups tested in the studies. Age has been shown to have an effect on the hemispheric difference in MT (Matsunaga et al. 1998). Young and middle-aged groups had threshold asymmetries but the old-age (61-82 years) group was found to have no difference in thresholds between the two hemispheres. In addition, MT was significantly higher in older subjects (51-86 years old) compared with younger (18-35 years old) subjects (Rossini et al. 1992). It was proposed that the required higher MT in older subjects may be due to a decrease in cortical thickness associated with ageing (Kozel et al. 2000).

Motor threshold is also affected by neurological disorders and is increased in conditions such as stroke, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), brain or spinal cord injury (Berardelli 1999; Boniface et al. 1991; Boniface et al. 1994; Eisen et al. 1990). A reduction in MT has also been shown in conditions such as general epilepsy (Reutens and Berkovic 1992), progressive myoclonic epilepsy (Reutens et al. 1993) and in some forms of ALS (Mills 1995). Pharmacological studies have revealed

that MT is increased when sodium channel blockers are administered but remains the same in the presence of GABAergic drugs (Chen et al. 1997; Inghilleri et al. 1996; Ziemann et al. 1996). This suggests that changes to MT are dependent on ion channel conductivity and reflect neuronal membrane excitability (Cohen et al. 1998). Considering the various factors mentioned, the MT in TMS can be potentially useful in showing changes in neuronal excitability induced by interventions and in the diagnosis and prediction of prognosis of neurological conditions.

1.6.2 Motor Evoked Potentials

Suprathreshold TMS applied to the motor cortex will excite corticospinal cells and can evoke a contraction of contralateral muscles which are recorded as MEPs. The presence of an MEP indicates that the corticospinal tract and peripheral nerves are functioning. Additionally, the amplitude of an MEP gives an indication of both the size and excitability of a corticospinal projection. The size and latency of MEPs produced exhibit great inter-individual and intra-individual variability (Kobayashi and Pascual-Leone 2003). The variability in MEP responses was shown to be influenced by changes in the level of activity and excitability of the corticoneuronal pool (Funase et al. 1999). Although MEP amplitude can vary significantly under stringent experimental conditions, it has been shown that reliable and accurate TMS maps could still be generated with the observed fluctuations in MEP amplitude (Thickbroom et al. 1999). The overall accuracy of MEPs in evaluating corticospinal function is high. However, its clinical usefulness is still under debate as there is great variability in the MEPs in pathological conditions (Di Lazzaro et al. 1999).

Despite this, there is a large, and growing literature describing the use of MEPs for the diagnosis and prognosis of neurological dysfunction (Chollet et al. 1991; Cicinelli et al. 1997b; Curt et al. 1998; Heald et al. 1993). As MEPs reflect cortical excitability, they

serve as a useful index in studies of neuroplasticity and reorganisation. However, with the inherent variability of MEP measures, stricter methodological parameters are warranted and the interpretation of results may need to be correlated with other neurophysiological and clinical measures (Di Lazzaro et al. 1999).

1.6.3 TMS Map Parameters

Mapping using TMS is now a widely used technique to investigate physiologic and pathologic changes in the human motor cortex. A focal figure-of-eight coil is used to stimulate specific points on a scalp-referenced grid. The resulting MEPs are used to generate a topographic representation of the area stimulated (Cohen et al. 1991; Wassermann et al. 1992; Wilson et al. 1993). In addition to providing information on topography, TMS maps provide a method of examining easily and non-invasively the excitability of cortico-motor projections of specific muscles (Rothwell 1997) and are also used to complement other neuro-imaging techniques (Pascual-Leone et al. 1999).

The maps provide quantitative parameters such as amplitude, area, volume, CoG, number of excitable scalp points and optimal site for stimulation. These are widely used to demonstrate re-organisation of the motor cortex in both experimental and clinical conditions. One important factor to consider is the reliability of the map parameters generated and how these parameters can accurately monitor changes that occur over time.

Several authors have addressed the reliability of these parameters. These studies have demonstrated that with a strict adherence to experimental protocol, the changes in subsequent TMS maps were not significant. Mortifee et al. (1994) found that the size, area and volume of the APB and ADM maps were very reproducible over a period of 23-84 days. In a study on MEP variability, map position was also determined to be very

stable (Thickbroom et al. 1999). Other studies have also briefly discussed the stability of TMS maps (Brasil-Neto et al. 1992b; Levy et al. 1991). However, most studies have not discussed specifically the sensitivity of the maps after repetitive measures of these parameters over time. This is an important point as changes associated with re-organisation are subtle and may be short-term (Classen et al. 1999; Sanes et al. 1992). The accuracy of these measurements is also a factor that needs to be resolved. Most intervention studies use map area, volume and CoG as a detector of change. It is thought that an increase in map area or volume indicates enhanced cortical excitability and that a shift in the CoG position indicates expansion of cortical representation. However, establishing the reasons for map area and volume changes can be complicated by factors relating to spread of currents, stimulating coil position and scalp stimulation points (Rothwell 1997; Thickbroom et al. 1998). Thus, interpretation of results from these parameters may be difficult. There is at present very little literature published that directly addresses the reproducibility of CoG measures.

Centre of gravity measures provide a weighted, spatial average of the centre of the corticomotor representation (Thickbroom et al. 1999). It is often used to define the position of TMS maps and identify shifts of the cortical representation of a muscle. It corresponds to an area of heightened excitability of motor neurons and is closely associated with the optimal stimulus site of a muscle (Wilson et al. 1993). Thus, CoG can be linked to the centre of motor output region of the cortex and changes in the location or size of this region will manifest as a shift in the CoG.

Previous studies have reported only small and non-significant shifts in the CoG under normal conditions. The CoG coordinates were reproducible within ± 3 mm in three mapping sessions of the left ADM (Miranda et al. 1997). Standard deviation of CoG

differences was reported to be 1.1 mm in latitude and 1.3 mm in longitude (Thickbroom et al. 1999). However, these studies did not evaluate the reliability of CoG measures over time. As CoG is often used as a parameter for the detection of change in motor area recruitment, it is important to address its capacity to reliably indicate that the shifts that occur are brought about by the intervention and not by time alone, and that these changes can persist when measured over time.

This question is addressed in Chapter 3, where an investigation on how time and repetitive CoG measures taken within 24 hours, one week and two weeks affects the CoG position in normal individuals not undergoing experimental intervention. It is hypothesised that under normal everyday functional demands, the subject's CoG will remain stable and that any detectable change in its position over time will not be significant.

1.7 TMS and Stroke

Neuroplastic changes are known to occur in stroke patients. After the lesion, the motor cortex is less excitable, resulting in a depressed or absent response to cortical stimulation (Berardelli et al. 1987; Byrnes et al. 1999; Cicinelli et al. 1997b). In addition, the cortical representation area of the hemiparetic muscles diminished in size compared with the non-affected hemisphere (Traversa et al. 1997).

In the acute stages of stroke, TMS can be used to determine the likely functional outcome of survivors. The absence of responses to TMS during the first 24 hours post-stroke has been correlated with poor functional recovery and a higher incidence of death (Heald et al. 1993). The amplitude of the MEP in the acute phase of stroke has greater

predictive value than latency (Rapisarda et al. 1996). The assessment of the presence of MEPs after acute ischemic stroke is a useful indicator of good motor and functional recovery (Catano et al. 1995; Delvaux et al. 2003; Escudero et al. 1998; Trompetto et al. 2000; Turton et al. 1996).

The recruitment of ipsilateral pathways after stroke has been extensively explored using TMS. The presence of ipsilateral activation has been suggested as a possible mechanism for functional recovery after a stroke (Chollet et al. 1991; Fisher 1992). Imaging studies from recovering stroke patients show enlarged activation volume in brain regions close and remote to the lesion extending to the contralateral hemisphere (Cramer and Bastings 2000; Weiller et al. 1992). Stroke modifies transcallosal inhibition and hyperexcitability of the undamaged hemisphere resulting in a state of disinhibition in the intact hemisphere (Boroojerdi et al. 1996; Cicinelli et al. 1997b; Liepert et al. 2000b). Although ipsilateral MEPs in stroke patients are larger, have a lower threshold and shorter latency than in normals, ipsilateral responses to TMS of the damaged hemisphere after stroke are linked with poorer functional outcomes (Caramia et al. 1996; Turton et al. 1996).

Mapping of the affected hemisphere has also been used to examine the effects of recovery and rehabilitation following ischemic stroke. The TMS maps in a group of subacute stroke patients undergoing neurorehabilitation had an enlarged motor representation area of the ADM in the affected hemisphere compared to the unaffected hemisphere (Traversa et al. 1997). Functional reorganisation as evidenced by shifts in cortical maps was also found in subcortical stroke patients of varying post-stroke history (Byrnes et al. 1999). These changes were also seen after even a single session of rehabilitative training of stroke patients (Liepert et al. 2000a) or after two weeks of

constraint-induced training (Liepert et al. 1998; Taub et al. 1999). In addition the preservation of cortical motor output in the stroke-affected hemisphere was shown to correlate with a positive motor recovery of hand function (Bastings et al. 2002). It was also suggested that the changes in motor maps associated with recovery in stroke may be due to changes in corticospinal excitability and that these changes occurred within the first three months post stroke (Delvaux et al. 2003).

Clearly, the use of TMS in studies investigating post-stroke reorganisation is increasing. The information that it provides on cortical excitability has been shown to be useful in predicting the prognosis of stroke survivors. However, there are a number of important issues that warrant caution in interpreting the parameters obtained from TMS. These will be discussed further in the following section and in Chapter 3.

Chapter 2. Stroke

2.1 Introduction

Stroke is a major issue in healthcare globally. The World Health Organisation defines stroke as "*rapidly developing clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin*" (Aho et al. 1980). The causes of stroke can be classified as either ischemic or haemorrhagic. Seventy-five to 80% of strokes are ischemic in origin. This is brought about by thrombotic, embolic or hemodynamic factors (Stewart 1999). Thrombosis can either be a result of a thrombus formation over an atherosclerotic plaque or from a hypercoagulable state. Embolism is usually caused by a travelling embolus occluding a pre-cerebral or cerebral artery. Infarction brought about by stenosis or occlusion in proximal circulation and uncompensated by collateral flow, leading to ischemia and eventual tissue necrosis is classified as a stroke of hemodynamic origin (Whisnant et al. 1990). Ischemia of the larger cerebral vessels has a poorer prognosis when compared to those affecting the small lacunar arteries.

Haemorrhagic strokes account for 20 – 25% of the annual incidence of stroke. Intracerebral haemorrhage is usually caused by long standing hypertension. This weakens the vessels and results in the rupture of an artery in the brain parenchyma. A ruptured aneurysm is the most common cause of subarachnoid haemorrhage, usually involving the bifurcation of a large superficial cerebral artery (Kaste et al. 1998). Mortality from haemorrhagic stroke is high and is associated with severe neurologic impairment when compared to other stroke types (Kelly et al. 2003).

2.2 Stroke Epidemiology

Stroke mortality differs from country to country. Globally, it is the second leading cause of death (Murray and Lopez 1997) and accounts for 10 – 12% of deaths in industrialized nations (Bonita 1992). Mortality rates are around 17 – 34% during the first 30 days post stroke and 25 – 40% in the first year (Terent 1989). Males have a higher stroke mortality compared to females (Bonita 1992) and 90% of stroke deaths occur in persons aged over 65 years. Overall global stroke mortality has dramatically declined with advances in medical science. Stroke mortality has decreased by as much as 50% in industrialised countries since the 1970s (Thom 1993).

Several risk factors have been identified to contribute to the incidence of stroke. The risk of stroke rises exponentially with age. There is a 25% risk of stroke in the 80 – 84 year old age group as compared to a 5% chance in the 55 – 59 age group. Gender has also been demonstrated to affect the risk of stroke with males having a 30% increased risk when compared to females. Racial differences have also been implicated. Studies show that people with an African racial background have a higher incidence and mortality when compared to a Caucasian population. Hispanics have similar ratios as Caucasians and Asians show a higher incidence than Caucasians (Frey et al. 1998; Thompson and Furlan 1996; Zweifler et al. 1995). Other factors that might affect stroke incidence include socio-economic factors, diet and access to health care (Engstrom et al. 2001; Kunst et al. 1998).

The medical management of stroke is limited once evidence of compromised cerebral circulation has been established. Although complete recovery is possible, 75% of stroke survivors present with some form of persistent impairment that might lead to a disability

or handicap (AIHW, 2001). This may lead to an enormous socio-economic burden. In the United States, the lifetime cost per stroke survivor varies between US$59,800 – 230,000, with annual costs reaching between US$6.5 to 11.2 billion nationally (Berk et al. 1978; Mills and Thompson 1978). Australian statistics show that approximately $1.3 billion is spent annually in healthcare for stroke victims and survivors (Dewey et al. 2001). Similar trends are seen internationally. Thus, there is a pressing need to improve stroke care and rehabilitation to lessen the economic impact on healthcare systems around the world.

2.3 Mechanisms of Stroke Recovery

Although the damage caused by stroke is permanent, several mechanisms are thought to be responsible for a person's recovery from stroke. However, there is still no direct, conclusive evidence with regards to a definite mechanism of recovery after a stroke and the theoretical framework is still evolving. The advances in medical imaging tools such as MRI, fMRI, PET and TMS have given new insights as to how the brain reacts in response to a stroke injury. Understanding the possible mechanisms for recovery allows the healthcare professional to maximise the potential for a positive outcome.

2.3.1 Recovery in the Acute Phase

During the acute phase of stroke, recovery is attributed to the resolution of oedema or inflammation brought about by the initial infarct. This event is related to the concept of the ischaemic penumbra; that is ischaemic tissue where the ischaemia is fundamentally reversible (Hakim 1987). Imaging techniques have provided evidence supporting the existence of the ischaemic penumbra in stroke patients. Positron Emission Topography studies in human stroke patients have demonstrated the presence of an area of ischaemic

tissue with substantial volumes that diminishes on scans performed several days later (Marchal et al. 1996). The use of Diffusion-weighted Imaging (DWI) and Perfusion-weighted Imaging (PWI) provides valuable volumetric data of cerebral blood flow in stroke patients. PWI volumes are generally greater than DWI volumes after an acute stroke episode (Neumann-Haefelin et al. 1999). It is estimated that this diffusion-perfusion volume discrepancy diminishes over six hours post-acute stroke (Schellinger et al. 2001). This region of the brain that exhibits a diffusion-perfusion discrepancy has been thought to represent the approximate area of the ischaemic penumbra (Schlaug et al. 1999). The early identification of this mismatch in patients will allow salvageable ischaemic tissue to receive appropriate therapeutic intervention.

Following a stroke, it is proposed that the function of intact cortical tissue is suppressed temporarily (Seitz et al. 1999). This process is known as diaschisis. The resolution of diaschisis is thought to coincide with recovery of function following a stroke (Seitz et al. 1999). In some instances, the absence of this process is related to improved function (Feeney and Baron 1986). Several studies of brain metabolism after cortical injury have confirmed the presence of diaschisis, with widespread metabolic changes seen in both the involved and unaffected cerebral hemispheres (Bowler et al. 1995; Infeld et al., 1995; Seitz et al. 1994). It has also been shown that diaschisis persists for a period of time after the injury (Infeld et al. 1995). Using a rodent stroke model, Carmichael et al. (2004) have shown substantial area of cortex adjacent to the stroke hypometabolic for up to eight days. In human stroke studies, PET scanning revealed an overlap between lesion-affected and recovery related neural networks and show motor function subserved by neural structures remote from the brain lesion at around six months post-infarct (Seitz et al. 1999).

The primary goal during the acute phase of stroke is the reduction of infarct size. Infarct size has been related to the amount of neurological and functional recovery post-stroke. It is presumed that the smaller the infarct size, the greater the preserved brain tissue present and thus would allow for a better outcome. The importance of acute medical management is imperative in order to keep the ischaemic brain tissue viable and prevent the progression to irreversible damage. At present, there is only one approved therapy for acute stroke - recombinant tissue plasminogen activator (rt-PA). When given within 3 hours post-stroke, rt-PA has been shown to improve the functional and neurological outcome in a group of stroke patients (Trouillas et al. 1998). However, this drug is rarely given in clinical practice with less than 6% of patients arriving in emergency rooms presenting signs of acute ischaemic stroke receiving this medication (Harvey 2003).

The concept of a single therapy may not provide the desired functional outcome after an acute stroke episode. The pathophysiology of brain ischaemia involves an array of events that can influence the survival of ischaemic brain tissue and associated outcomes. Variables such as extent and duration of ischaemia, atherosclerosis, extent and rapidity of perfusion, extent of damage and loss of neurons in conjunction with the aging process and the daunting metabolic requirements of the neurons in order to maintain function, have an interconnected impact on the potential for a favourable outcome after acute stroke (Fisher and Ratan 2003). Acute stroke management should therefore involve multiple, concurrent or sequential therapies that take into consideration the complex mechanisms involved in the acute stages of stroke.

2.4 Plasticity of the Brain After Stroke

The recovery of function following a stroke can also be attributed to other cortical or subcortical structures, which are either adjacent or remote, to take over the function of the lesioned area (Nudo et al. 2001). This vicariation of function has gained significant support from numerous studies suggesting this theory as a probable mechanism of stroke recovery. As plastic changes are seen in both hemispheres, the following review will cover studies that provide support for the contribution of the injured and uninjured cortices to the mechanism of stroke recovery.

2.4.1 Reorganisation of the Undamaged Hemisphere and Ipsilateral Pathways

Following stroke, hyperexcitability of the unaffected motor cortex occurs and results in a state of disinhibition during the early stages (Cicinelli et al. 1997; Liepert et al. 2000c; Traversa et al. 1997). This ipsilateral motor cortical disinhibition was shown to be accompanied by the disruption of transcallosal inhibition (TCI) following contralateral cortical damage (Shimizu et al. 2002). The disruption of TCI is suggested to trigger reorganisation in the undamaged cortex that results in down-regulation of GABA receptors and the enhancement of glutamatergic activity (Que et al. 1999; Reinecke et al. 1999) thus producing a state of hyperexcitability in the intact hemisphere. The benefit, if any, of the hyperexcitability of the unaffected hemisphere remains unclear. The disinhibition of the unaffected cortex shows a correlation with the course of stroke recovery up to four months after onset (Cicinelli et al. 1997; Traversa et al. 1998). The observed hyperexcitability of the intact cortex diminishes as recovery occurs and excitability of the damaged hemisphere increases (Traversa et al. 1998). This balancing phenomenon is mediated by transcallosal modulation and is observed to be absent in

stroke patients with poor functional recovery (Traversa et al. 1998). As such, the persistence of hyperexcitability in the undamaged cortex might indicate a poor functional prognosis.

However, other studies have shown the importance of the undamaged cerebral cortex in stroke recovery. In a PET study using six recovering stroke patients, Chollet and colleagues (1991) showed significantly elevated bilateral sensorimotor cortical activation while performing a skilled task of sequential opposition of thumb to fingers in the affected hand. This was also accompanied by elevated blood flow in the ipsilateral inferior parietal area and insula. This study highlights the involvement of the undamaged cortex in the recovery of function after a stroke. In a study of a group of hemiplegic patients undergoing passive elbow flexion, rCBF was also shown to be significantly increased in bilateral sensorimotor cortices and parietal lobes when compared to a normal group (Nelles et al. 1999).

Studies of people with aphasia after stroke also showed similar findings. During the stroke recovery process, the language area of the affected hemisphere appears to be capable of transferring function to homologous cortical areas in the unaffected hemisphere (Thulborn et al. 1999). Recovery from non-fluent aphasia (Belin et al., 1996) dense receptive aphasia (Thulborn et al., 1999) and Wernicke's Aphasia (Weiller et al., 1995) was found to produce an increased activation of the cortical circuitry of both the right hemisphere and left frontal lobe. Contrasting results were seen in a study of aphasia due to subcortical, frontal, or temporal lobe infarcts. Although increased cerebral blood flow was seen in the right superior temporal gyrus when performing a language task, it was concluded that language was more efficiently recovered with the preservation of the left temporal areas (Heiss et al. 1999). This conclusion holds merit

as despite the activation of the contralateral hemisphere, normal language function is represented bilaterally in the central nervous system and thus normal language function would require both hemispheres.

Studies using fMRI have led to similar conclusions. Increased activity was found in the motor network of the non-stroke hemisphere together with the supplementary motor area and the foci along the rim of the infarct in a group of recovered stroke patients who performed an index finger tapping task (Cramer et al. 1997). Using a more sensitive fMRI technique, Cao et al. (1998) studied a group of moderately recovered stroke patients while performing a sequential finger movement task. Results showed an enlarged volume of activation in the non-stroke sensorimotor cortex and supramarginal gyrus. However, it would be difficult to draw functional significance from these studies as they did not provide any quantitative measures of function.

Using transcranial Doppler ultrasonography (TCD), Silvestrini et al. (1998) found areas of the healthy hemisphere activated soon after focal injury. Bilateral TCD assessment of changes in the flow velocity of both hemispheres revealed increased middle cerebral artery (MCA) flow velocity during movements of the recovered hand in a group of nine patients with acute onset hemiparesis. They proposed that recovery from hemiparesis might be in part due to the activity of homolateral structures, suggesting that this contributes to the positive functional outcome in some patients. Furthermore, this phenomenon was not transient as it was still evident months after the initial stroke onset.

Conflicting results also exist in studies concerning the contribution of ipsilateral pathways to motor recovery after a stroke using TMS. In healthy, undamaged cortices,

ipsilateral responses are rarely found in distal muscles and are more predominant in the proximal ones when using intensities that are almost twice that needed to evoke a contralateral response (Basu et al. 1994; Wassermann et al. 1994). Ipsilateral response latencies in proximal muscles were found to be eight – 12 ms longer than the contralateral side in healthy individuals (Wassermann et al. 1994). However, using high intensity stimulation and a large coil makes it difficult to be sure that such ipsilateral responses are not due to current spread which activates the contralateral hemisphere (Basu et al. 1994; Meyer et al. 1990).

Ipsilateral responses in a stroke population show poor correlations to functional recovery. In a study of nine recovered stroke patients, no direct contribution of the ipsilateral corticospinal tract to functional recovery was found (Palmer et al. 1992). Netz et al. (1997) and Turton et al. (1996) also observed ipsilateral responses in patients with poor functional recovery. Ipsilateral and contralateral thresholds were similar, and in some instances, contralateral and ipsilateral responses had similar latencies (Turton et al. 1996). Additionally, lower stimulation intensities are needed to evoke an ipsilateral response in stroke patients when compared to normals (Netz et al. 1997). In contrast to the abovementioned studies, ipsilateral MEPs were found to be present in stroke patients who have had good functional recovery (Caramia et al. 1996). The resulting responses were found to be of lower amplitude but of shorter latencies when compared to contralateral responses. However, this study recorded ipsilateral MEPs during muscle activation and used a large circular coil and higher intensities compared to the study of Turton et al. (1996), which again carries the risk of contralateral hemisphere activation. Therefore, the significance of ipsilateral motor responses from the unaffected hemisphere and ipsilateral pathways requires further examination, but as the majority of corticospinal fibres from the motor cortex ultimately decussate (Porter and

Lemon 1993), it is highly unlikely that this is a major contribution to the functional recovery seen in stroke.

2.4.2 Reorganisation of the Affected Hemisphere

Recovery in the affected hemisphere may be mediated by the reorganisation of intracortical connections and the activation of other adjacent regions of the cortex. Changes in the neighbouring and connected cortical regions have been demonstrated following lesions. In animal studies, the topography of the sensory cortex of owl monkeys was shown to change following a small infarct, with the skin surface corresponding to the area of the lesion becoming topographically represented by the surrounding cortical region secondary to an enlargement of the cutaneous receptive fields (Jenkins and Merzenich 1987). In the motor cortex, a use-dependent plasticity seems to occur. Following a small infarct in the digit representation in monkeys, rehabilitative training preserved hand territory areas in the affected hemisphere and showed an expansion to the elbow and shoulder area (Nudo et al. 1996b). This preservation and expansion of cortical representation areas were not seen in animals not receiving training, and in some cases the area was reduced (Nudo and Milliken 1996). Further evidence of an intracortical reorganisation was provided by studies reported by Castro-Almancos and Borrel (1995). These authors demonstrated that a novel forelimb representation was present in an area caudal and lateral to the area of lesion following bilateral ablation of the forelimb area in rat motor cortex. The size of this new representation correlated directly with the performance levels of the recovered animals.

Another possible model of recovery is the change in balance between excitatory and inhibitory connections. Afferent stimulation of cortical slices prepared from animal stroke models demonstrates diminished inhibitory post-synaptic potentials as well as

prolonged excitatory post-synaptic potentials (Neumann-Haefelin et al. 1995). Inhibitory connections have also been shown to weaken following a focal cortical stroke in rats (Domann et al. 1993). Bilateral hemispheric reductions of GABA receptors and concurrent bilateral increases in excitatory glutamate receptors have been demonstrated in mice with middle cerebral artery occlusion (Qu et al. 1998). These changes have been shown to persist for up to four weeks. However, the increase in glutamatergic aminomethylisoxasole propionate receptors (AMPA) and kainate receptors is not significant (Qu et al. 1998). These results may imply that adaptive changes following a cortical injury involved primarily the down regulation of GABA receptors (Nudo et al. 2001). Neural pathways encompass a larger region of anatomical connectivity than their usual area of functional influence and thus produces a large area of redundant cortical connections (Hallett 2001; Lee and van Donkelaar 1995). Normally, these regions are kept in check by tonic inhibition (Hallett 2001). Following a stroke, the reduced inhibition allows the normally minor redundant connections to assume a major role in the cortical network through a process termed as "unmasking" (Rijntjes and Weiller 2002).

Another physiological process that may occur following a focal lesion is the strengthening or weakening of existing synapses through LTP or LTD. As discussed earlier, slices of rat motor cortex have shown LTP and LTD to occur in Layer II/III horizontal connections (Hess and Donoghue 1996; Hess et al. 1996). Induction of both LTP and LTD was also shown to take place in the rat neocortex following multiple, spaced stimulation sessions (Froc et al. 2000). Following an ischaemic lesion in the rat primary motor cortex, the down regulation of GABA receptors (Qu et al. 1998) was accompanied by an upregulation of NMDA receptors (Mittmann et al. 1998) and the facilitation of LTP in the cortex adjacent to the site of infarct (Hagemann et al. 1998).

Changes in the inhibitory/excitatory synaptic balance may be responsible for some of the post stroke TMS mapping changes reported in human subjects. Studies have tracked the expansion of cortical maps following rehabilitative interventions. After eight to ten weeks of neurorehabilitation, TMS maps of the affected hemisphere were shown to be larger when compared to pre-intervention maps (Traversa et al. 1997). Using constraint-induced therapy, cortical representation was also shown to demonstrate significant enlargement relative to the pre-therapy maps (Liepert et al. 1998; Liepert et al. 2000a). Following two weeks of constraining the unimpaired hand to induce goal directed movement in the involved hand, the motor output area size and MEP amplitudes of APB increased significantly, indicating enhanced neuronal excitability in the damaged hemisphere for the said muscles. Also, the mean CoG of the motor output maps was shifted considerably after the rehabilitation, likely indicating the recruitment of motor cortical areas adjacent to the original location (Liepert et al. 1998). However, it is obviously difficult to obtain direct evidence regarding the mechanism for this cortical expansion and reorganization in human stroke subjects.

There is also growing evidence that functional alterations in adjacent structures in the affected and intact hemispheres may contribute to functional recovery after a stroke (Cao et al. 1998; Cramer et al. 1997; Nelles et al. 1999). Enlargement of the hand representation area into the ventral PMC was seen in a study of adult squirrel monkeys with infarcts of the M1 (Frost et al. 2003). This study also found that the enlargement was proportional to the amount of hand representation area injured in M1. Following recovery of upper extremity function in macaque monkeys with M1 lesion, pharmacological inhibition of the ventral and dorsal pre-motor area with a GABA agonist, muscimol, resulted in the rapid reinstatement of initial pre-lesion behavioural deficits (Liu and Rouiller 1999). Changes in the SMA were also found following

lesioning of the primary cortex in monkeys. Activity in the SMA is usually present before the initiation of limb movement, however after extensive training, this pre-movement SMA activity is no longer observed (Aizawa et al. 1991). SMA activity reappeared following a lesion in the primary cortex, suggesting that as the lesion made the movement more difficult, there was a need for SMA contribution. These studies suggest that after damage to the primary motor cortex, reorganisation of other motor areas may contribute to the post-injury recovery.

Neuro-imaging studies in human subjects have also revealed the contribution of non-primary motor structures to stroke recovery. Using TMS, MRI and PET, Seitz et al. (1998) found motor recovery relied on the activation of the pre-motor cortical areas of both hemispheres. Activation of the stroke-side SMA and parietotemporal areas together with the intact parietal, temporal and occipital areas was evident when stroke subjects performed a slow squeezing task (Brion et al. 1989). Similar findings were shown in a PET study wherein stroke subjects performed a sequential thumb to finger opposition and produced bilateral activation of the sensorimotor cortex (Chollet et al. 1991). A comparison of TMS maps before and after motor recovery in stroke subjects showed a significant increase in hand movement areas within the affected motor cortex and the adjacent frontal lobe (Traversa et al. 1998). A significant increase in activity in the lateral PMC and SMA during the performance of motor tasks in stroke patients when compared to normal controls suggests that these non-primary motor areas are involved in the recovery process (Weiller et al. 1992). A stroke group MCA occlusion showed better outcomes if the PMC remained intact (Miyai et al. 1999). This was again highlighted in a TMS study that showed pre-motor cortex contributing to functional recovery following stroke (Fridman et al. 2002).

Although the different motor cortical regions are thought to have different roles in the control of movement (Lawrence and Kuypers 1968), these areas are interconnected and damage to one area may affect the function of other areas (Frost et al. 2003). Descending pathways from the SMA and limbic motor fields have been found in the anterior limb of the internal capsule, the pre-motor fibres running through the ventral posterior limb and the primary motor fibres in the middle third of the posterior limb (Fries et al. 1993). Depending on the site of the lesion, the link between different cortical areas may be important for facilitating recovery with the intact parallel motor systems compensating or substituting for the damaged motor areas. However, a fMRI study in stroke patients who were performing an index finger tapping task showed significant activation of the SMA and unaffected hemisphere for both the stroke and control group (Cramer et al. 1997). The similarity between the stroke group and the control group may be attributed to the fact that the patients had exhibited good recovery and may show almost normal patterns of cortical activation during movement. Still, this emphasises the contribution of non-primary motor regions to the execution of movement and suggests that plasticity of the damaged cortex may be influenced by intracortical connections.

2.4.3 Axonal Sprouting

The reparative process after stroke may also involve the formation of new local and more distant connections within the brain by the process of axonal sprouting. Growth of fibres from outside the immediate region of damage may produce invasion of the denervated or lesioned cortex and potentially induce functional changes during the stages of recovery (Kidd et al. 1992; Lee and van Donkelaar 1995; Ruocco et al. 2000). Axonal sprouting is considered a restorative process after an injury to the central

nervous system. This branching or sprouting can take place in the axons, nodes of Ranvier or by the extension of already pre-existing neurons (Hafidi et al. 1999).

In animal models, axonal sprouting has been demonstrated following a stroke lesion. Following a thermocoagulatory lesion to subcortical motor areas, labelled fibres from injected anterograde tracers in the uninjured hemisphere were located in the striatum of the injured side (Cheng et al. 1998; Napieralski et al. 1996). Newly formed synapses were observed following the lesion (Cheng et al. 1998) and could be attributed to changes in ultra-structural details such as gene expression and growth promoting factors (Szele et al. 1995).

Focal ischaemic injury in the rat brain shows increased growth cone markers (Stroemer et al., 1993). Growth-associated protein 43 (GAP-43) immunoreactivity increased in the peri-lesional area suggesting axonal sprouting (Stroemer et al. 1993). It is an important protein involved in linking membrane-signalling events to actin cytoskeleton modification (Benowitz and Routtenberg 1997) and is highly concentrated around the growth cone (De la Monte et al. 1989). The observed elevation of GAP-43 was also seen in human tissue using in-situ hybridisation with its neuronal expression up-regulated adjacent to the core of the lesion at 10 – 14 days post stroke (Ng et al. 1998). This finding is in agreement with Stroemer et al. (1995) who showed similar elevations of GAP-43 up to 14 days post infarct in a rat model.

Although there is an emerging body of correlative data linking axonal sprouting after a stroke, a number of points need to be considered. Although growth markers have been observed around the infarcted region, the method of detecting them is not a direct one. This casts doubt on the merit of using growth markers to demonstrate axonal sprouting

(Carmichael 2003). The levels of GAP-43 are not an exclusive indicator of growth cone formation. It is also implicated in other forms of cellular change, more specifically in the process of LTP (Benowitz and Routtenberg 1997). The process of LTP is also enhanced around the peri-lesional site, the same site where GAP-43 elevations are observed (Hagemann et al. 1998).

Our present understanding of the mechanisms that govern recovery from stroke has improved considerably. There is mounting evidence that demonstrates reorganisation of the brain following stroke and how this reorganisation may be important for functional improvements. With the advent of more sensitive imaging techniques, further studies will be able to elucidate more clearly on the contribution of the ipsilateral cortex and the ipsilateral pathways, and on how activation of the areas surrounding the lesion and distant non-primary motor areas affect the improvement of function. This will provide important insights on how these physiological changes can be used to mediate efficient recovery.

2.5 Functional Recovery After A Stroke

The functional recovery after stroke often parallels neurophysiological recovery (Duncan et al. 1992; Wade et al. 1985). Spontaneous recovery brought about by the resolution of oedema and cortical plastic changes is thought to occur within the first three months following stroke (Bonita and Beaglehole 1988; Skilbeck et al. 1983). Although recovery has been reported to continue for between six and twelve months after the initial onset of stroke, the observable changes are highly variable and may be of little clinical significance (Ahlsio et al. 1984; Dombovy and Bach-y-Rita 1988). Functional motor recovery and improvements in activities of daily living (ADL) have been reported to occur within the first three months after a stroke and eventually plateau

(Gresham et al. 1979) with as much as 60% of stroke survivors dependent on others in performing some activities of daily living after this time (Duncan et al. 1992). The functional recovery after a stroke is influenced by patient related variables such as stroke type and severity, age and co-morbid status (Duncan 1994). The factors that predict poor functional outcome in stroke survivors are listed in Table 2.1.

Prognostic factors for poor functional outcomes in stroke	
Coma at onset	Older age
Incontinence 2 weeks post-stroke	Inability to sit unsupported
Severe hemiparesis	Motor, sensory and visual deficits
Poor cognitive function	Depression
No motor return within 1 month	Lack of social support
Previous stroke	Significant cardiovascular disease
Perceptual and spatial disorders	

Table 2.1 Factors associated with a poor functional outcome in stroke survivors (Dombovy et al. 1986; Glass et al. 1993; Jongbloed 1986; Parikh et al. 1990; Sandin and Smith 1990; Schubert et al. 1992).

The most common problem facing stroke survivors is the inability to use the affected limbs in activities of daily living (Hartman-Maeir et al. 2002). The residual motor weakness, abnormal movement synergies, spasticity, sensory and perceptual deficits all contribute to an alteration of the use of the lower limb for gait and the upper limb for everyday functional tasks (activity restriction). This may predispose the stroke patient to a sedentary lifestyle (participation restriction), which will further affect cardiovascular condition and eventually result in a poor functional outcome (da Cunha et al. 2002). A discussion of the effects of stroke on upper and lower limb function and the strategies to improve their function follows.

2.5.1 Gait After Stroke

The inability to walk is one of the most common problems after a stroke (Duncan 1994) and is responsible for the prevalence of long-term disability and handicap (Hesse and Werner 2003). The improvement of gait is of paramount importance in stroke recovery as it is a major factor for the reintegration of the patient into vocational and social pursuits. In a study of 800 stroke patients, 75% of subjects were able to regain limited walking ability after 12 weeks of rehabilitation (Jorgensen et al. 1995). Similar results were shown by an earlier study where 85% of stroke survivors regained independent ambulation; however only 25% of the subjects had regained normal speed (Wade et al. 1987).

The hemiparetic gait is characterised by slow and short steps, a reduced cadence and a marked reduction in velocity (Brandstater et al. 1983; Goldie et al. 2001). The single limb support (SLS) phase of the unaffected leg may be prolonged secondary to the difficulty of the affected leg advancing forward. In addition, decreased time during the SLS phase for the affected leg can also be seen, most likely due to difficulty in balancing the full body weight on the affected leg or a hyper-extended knee which the stroke patient uses to lock the knee in place for additional support (Goldie et al. 2001). The double limb support (DLS) phase of the affected leg may be prolonged which may indicate the inability to transfer weight secondary to a balance problem (Goldie et al. 2001) as well as the inability of the affected leg to execute a short, sharp thrust on push-off (Olney et al. 1991).

2.5.2 The Upper Limb After A Stroke

After a stroke the affected upper extremity goes through a period of flaccidity and a period of increased tone often accompanied by impaired sensory perception that leads to a poor quality of gross and fine movement (Kraft et al. 1992). The recovery of upper limb function following a stroke is generally thought to be not as favourable as the lower limb (Katrak et al. 1998). Studies indicate that 85% of stroke patients initially will show a deficit in function of the affected arm, while 25 to 45% are expected to show functional recovery. Approximately 50% of stroke survivors will present with a non-functioning arm (Heller et al. 1987; Olsen 1990; Parker et al. 1986; Wade et al. 1983). Most recovery of the affected arm takes place within the first few weeks post-stroke, with the fastest rate of recovery happening in the first two months and plateauing after a year (Heller et al. 1987; Nakayama et al. 1994b; Olsen 1990; Wade et al. 1983). Several factors have been identified as positive prognosticating factors for arm recovery. The degree of initial upper limb deficit was found to be the most important determinant of motor and functional recovery in the stroke affected arm (Feys et al. 2000). The return of upper limb movement within the first month after a stroke has been associated with good recovery (Bard and Hirschberg 1965). Recovery of grip strength within the first three weeks followed by an improvement in the Frenchay Arm Test was related to a good prognosis for the affected upper limb, while patients who were unable to produce observable movement or recordable finger grip within 28 days were unlikely to recovery useful arm function (Heller et al. 1987). The return of proprioception and proximal traction response within the first two weeks were also shown to be good signs for recovery of voluntary movements (Twitchell 1951). Katrak et al. (1998) found early shoulder shrug and ability to perform synergistic hand movements predicted good hand movement and function. Intact sensory function has also been correlated with good motor recovery of the affected arm (Broeks et al. 1999).

Recovery of the affected upper limb is often viewed pessimistically. Unlike the lower limbs, where both extremities are needed to perform the function of gait; upper limb function encompasses a wide range of unilateral and bilateral activities. These may be achieved by having the unaffected limb compensate for the loss function of the affected limb. Thus, the recovery of function on the affected side may prove to be difficult as most stroke patients would find it easier to perform activities by compensating with the intact arm. Rehabilitation procedures should address this issue of non-use and focus on facilitating function of the stroke affected arm.

2.6 Neurophysiological Measures and Functional Recovery Following Stroke

Neurophysiological measures taken during the acute and subacute stages of stroke have been shown to correlate with functional outcomes. Absent or asymmetric somatosensory evoked potentials (SEP) have been correlated with poor upper limb function in stroke (Kusoffsky et al. 1982). Evidence from TMS studies also reveal a correlation between early EMG activity and MEP responses to the recovery of hand function. It is generally observed that a response to TMS in the acute stages of stroke is a good indicator of motor outcome (Catano et al. 1995; Pennisi et al. 1999; Rapisarda et al. 1996). Turton et al. (1996) found TMS responses to be present in stroke patients who recover voluntary contraction of the extensor digitorum communis and first dorsal interosseous muscles. In patients tested during the acute and subacute phase of stroke, recordable MEP from the affected FDI were present in the subjects that exhibited improvements in hand motor scores (Bastings et al. 1997). In a longitudinal study of 118 first time stroke patients, subjects who initially had normal or delayed TMS responses showed significantly better functional outcomes at 12 months when compared

to the group who had no responses at all (Heald et al. 1993). Alternatively, the absence of TMS responses is associated with poor motor outcome (Binkofski et al. 1996; Heald et al. 1993).

Preserved MEPs early in stroke were shown to be correlated with positive Medical Research Council and Barthel Index (BI) scores (Rapisarda et al. 1996). A better clinical outcome, as measured by the BI and Modified Canadian Neurological Scale, was seen at day 14 in patients with a recordable MEP at day one (Vang et al. 1999). Persistence of MEPs in the FDI of the affected side on day 1 post-stroke was again shown to be positively correlated with improved BI, Rankin and National Institutes of Health (NIH) scores when tested 1 year later (Delvaux et al. 2003).

Results also show that MEPs obtained from the lower limbs were of predictive value to the walking ability and walking impairment of stroke patients during the post-acute phase (D'Olhaberriague et al. 1997; Hendricks et al. 2003; Steube et al. 2001). Although a correlation was found between the preservation of MEPs and walking ability, no statistical significance was reached with the difference in the baseline and outcome measures (Steube et al. 2001). The authors also suggested that MEP data should be taken into consideration with variables such as patient's cognitive, emotional and social states as well as other clinical and diagnostic findings in predicting walking ability after stroke. It was also shown that MEPs together with the topography of lesions, infarct size on second CT, age and first day central motor conduction time measures had good correlations to functional outcome at one year post stroke (D'Olhaberriague et al. 1997). Hendricks et al. (2003) also showed the prognostic value of Tibialis Anterior (TA) muscle MEPs on the outcome for motor recovery and independent transfers in stroke patients with initial complete paralysis of the lower

extremity. Paralysis of the lower limb is an important prognostic indicator in stroke and reflects the extent of the lesion (Allen 1984; Schneider and Gautier 1994).

The predictive value of MEPs in stroke is more thoroughly documented in studies on the upper extremity than the lower limbs in stroke. However, the value of MEPs alone as a prognostic indicator is not supported and it is suggested that this measure should be used in conjunction with other diagnostic and clinical tools. Even so, the use of MEP measurements early in stroke has given valuable insights to possible functional outcomes in the post-acute stage of stroke. These would be important in helping to establish realistic rehabilitation goals and set the direction for therapy.

2.7 Functional Assessment Following Stroke

Functional assessment tools should focus on examining the factors associated with the functional recovery following a stroke. The instruments should exhibit sensitivity as well as ease of use in order to provide important measures that will guide the appropriate intervention and improve efficiency of rehabilitation services. The following section will provide a brief discussion of the common tools used in assessing gait and upper limb function following a stroke.

2.7.1 Gait Analysis

Analysis of hemiparetic gait is usually done in conjunction with outcome measurement instruments to give a general indication of mobility. Measures such as the Functional Independence Measures (FIM) (Rupright et al. 1997), the BI (Gresham et al. 1980) and the Rivermead Mobility Index (RMI) (Collen et al. 1990) are commonly used. These instruments have been found to be reliable and valid measures of ambulation (Dodds et

al. 1993); (Hsieh et al. 2000); (Kidd et al. 1995). Although a single desirable instrument has yet to be developed, the key factor in choosing an instrument is its simplicity, reliability, sensitivity and clinical relevance. In addition to the use of these instruments, temporal and spatial characteristics of gait can be measured through observation and by video recording. Assessment of velocity, cadence, step and stride length are simple and easily quantifiable measures that can quickly detect change. These mobility milestones are usually tested using a 10 metre walk test and have been shown to have favourable reliability (Baer et al. 2003).

More sophisticated gait analysis methods are available but are most predominantly used in research laboratories. Kinetic analysis using force plates provide ground reaction force measures and their associated torques. Alternatively, pressure sensitive in-soles are commonly used in the clinical environment to provide force and pressure readings during gait. The in-soles are slipped into the patient's footwear and gait analysis is usually performed without the need for laboratory space. This method is more cost and space efficient than the force plates.

Information regarding the pattern of muscle activation within the gait cycle can be assessed using dynamic EMG. The EMG readings obtained can be referenced against normative values to determine whether the onset of muscle activity occurs at the proper timing. Measures of energy expenditure during walking can also be obtained. Spiroergometry is used to provide data on the walking energy cost and cardiac walking cost during gait. These measures have been shown to be significantly different between hemiparetic patients and aged-matched healthy individuals (Bailey and Ratcliffe 1995). Instrumented gait analysis provides a vast amount of objective quantifiable data, however care should be taken in interpreting their clinical significance (Hesse 2003).

2.7.2 Functional Assessment of the Affected Upper Limb

The challenge for the assessment of function of the upper extremity after a stroke is greater when compared to gait analysis. Unlike the lower limbs, the upper extremity is involved with fine motor skills requiring sophisticated motor control and sensory perception. There are several functional assessment tools available in evaluating the affected upper extremity, however there is no agreement as to which tool or scale is the most appropriate. The assessment tool selected should be sensitive and reliable and representative of the status of the upper extremity in everyday activities.

The Brunnstrom-Fugl-Meyer (FMA) test is one of the most common tests used in measuring arm-hand function in stroke. This test is based on the different stages of recovery following a stroke and is considered not to suffer from a ceiling effect (De Weerdt and Harrison 1985). The FMA has demonstrated reliability (Duncan et al. 1983) and validity (Berglund and Fugl-Meyer 1986); (Kraft et al. 1992). However, the FMA has been suggested as a measure of motor recovery rather than arm function. Several studies have shown that the FMA has good correlation with other arm function tests (Dettman et al. 1987); (De Weerdt and Harrison 1985); (Wood-Dauphinee et al. 1990).

Another commonly used measure is the Motor Assessment Scale (MAS). This tool combines elements of impairment and disability in assessing functional capabilities (Carr et al. 1985). The MAS has been shown to be reliable (Carr et al. 1985; Poole and Whitney 1988; Poole and Whitney 2001) and valid (Poole and Whitney 2001). Though it is a popular assessment tool used in the clinical setting, very few systematic studies use it to measure recovery after stroke (Williams et al. 2001).

The Action Research Arm Test (ARAT) is another test specifically for the upper extremity. It is a shorter version of the Upper Extremity Function Test (Carroll 1965) and is designed in a hierarchical order of difficulty. It tests upper extremity function in four categories: grasp, grip, pinch and gross movement. The ARAT was also shown to be a reliable (Lyle 1981; van der Lee et al. 2001) and valid (Feys et al. 1998; Lyle 1981) assessment tool. A more detailed description of the ARAT will be presented in Chapter 5.

Several other tools such as the FMI, RMI, Motricity Index, Frenchray Arm Test and Stroke Rehabilitation Assessment of Movement are also available and have been proven to be valid and reliable measures (Poole and Whitney 2001). All these tests have their advantages and disadvantages. The choice of an assessment tool will depend on variables such as the level of motor impairment and disability, the available time and resources and the general purpose of administering the test. As each stroke patient presents with their own unique characteristics, it may be desirable that a series of different assessment tests be performed to ascertain their true functional levels and provide valuable information for planning their rehabilitation.

2.8. Rehabilitation After Stroke

Stroke rehabilitation is not a homogenous activity. The interventions and methods used to rehabilitate a stroke patient vary considerably. The factors that influence the choice of treatment include therapist preference and expertise, the rehabilitation unit providing the service, patient goals and motivational status and the constraints present on the healthcare system (Woldag and Hummelsheim 2002).

2.8.1 Conventional Therapeutic Approaches

The rehabilitation of stroke patients can be carried out by numerous approaches. Traditional physiotherapeutic approaches include: the Brunnstrom approach based on movement synergies; Proprioceptive Neuromuscular Facilitation (PNF) which advocates spiral and diagonal movement patterns; and Neurodevelopmental Techniques (NDT) using facilitation / inhibition strategies based on the theories of Rood and the Bobaths (Hummelsheim and Mauritz 1993). Although these rehabilitation approaches are used extensively in practice, the available scientific evidence is still equivocal with regard to efficacy and the superiority of one technique over the other as most studies present with low levels and low quality of evidence (Ernst 1990; Langhorne and Legg 2003). A summary of different studies that evaluated the effectiveness of these approaches in the affected upper limb and gait in stroke is presented in Tables 2.2 and 2.3 respectively.

Source	Design and Sample	Intervention	Conclusion
(Basmajian et al. 1987)	Randomised assignment; no control; n = 29	Five weeks training: • ADL training w/ biofeedback • Bobath approach	Both approaches showed clinical and statistical improvement for hand function at five weeks and nine months follow-up. No statistical difference found between the two approaches.
(Dickstein et al. 1986)	Randomised assignment; no control; n = 131	Six weeks training: • Conventional physiotherapy • Bobath approach • PNF approach	No statistical difference was found in active and passive motility of the wrist activities of daily living measurements among the three approaches
(Kraft et al. 1992)	No randomisation, with control; n = 22	3 months treatment period: • EMG initialised electrical stimulation • Electrical stimulation + simultaneous voluntary contraction • PNF approach	Improvements in hand function seen in all three groups when compared to control. Improvements maintained at three and nine months follow-up. Highest percentage improvement seen in the EMG initialised electrical stimulation group
(Langhammer and Stanghelle 2000)	Randomised assignment, no control; n = 61	3 months training: • MRP approach • Bobath approach	MRP found preferable to the Bobath approach in the acute rehabilitation of stroke patients. MRP treated groupfaired better in ADL than group treated with Bobath.
(Langhammer and Stanghelle 2003))	Randomised assignment, no control; n = 61	3 months training • MRP approach • Bobath approach	Follow up at one and four years after the initial study showed no significant difference between the two approaches in terms of long-term function

Table 2.2 Studies comparing the effectiveness of conventional rehabilitation techniques on arm function. ADL = Activities of Daily Living; MRP = Motor Relearning Program; PNF = Proprioceptive Neuromuscular Facilitation; EMG = Electromyography

(Lewis 1986)	Retrospective chart audit; n = 71	Training period not reported: • Traditional nursing approach • Bobath approach	Barthel index measures showed a statistically significant improvement in the Bobath group.
(Lincoln et al. 1999)	Randomised assignment, no control; n = 282	5 weeks training: • Bobath approach (standard) • Bobath approach (Bobath trained therapist)	No statistical difference was seen in arm function between the two groups at five weeks, three and six months follow-up
(Logigian et al. 1983)	Randomised assignment, no control; n = 42	Training period not reported: • Conventional physiotherapy • Bobath approach	No statistical significance was seen in the Barthel Index between the two groups.
(Nakayama et al. 1994a)	Prospective, no control; n = 115	71 daily treatment using the Bobath approach	No improvements seen in arm function on discharge. Subjects with initial severe arm paralysis recovered by compensating with the unaffected limb.
(Salter et al. 1991)	Retrospective non-equivalent control group design; n = 80	Chart audits of patients who received: • Traditional rehabilitation • Bobath approach	Bobath group showed statistical significant improvements in toileting; no statistical significance found between the two groups.
(Stern et al. 1970)	Randomised assignment, no control; n = 62	Training period not reported: • Conventional physiotherapy • Bobath + Brunnstrom approach	No statistical difference found between the two groups in the Kenny Self-Care Evaluation and Motricity Index
(Wagenaar et al. 1990)	Alternating treatment design, no control; n = 7	20 weeks training: • Bobath approach • Brunnstrom approach	No statistical difference found between the two groups in Barthel Index and Action Research Arm Test scores

Table 2.2 Studies comparing the effectiveness of conventional rehabilitation techniques on arm function. ADL = Activities of Daily Living; MRP = Motor Relearning Program; PNF = Proprioceptive Neuromuscular Facilitation; EMG = Electromyography

Source	Design and Sample	Intervention	Conclusion
(Dickstein et al. 1986)	Randomised assignment; no control; n = 131	Six weeks training: • Conventional therapy • Bobath approach • PNF approach	No statistical difference found in active and passive motility of the ankle and walking ability among the three approaches
(Hesse et al. 1993)	No randomisation, no control; n = 40	Four weeks inpatient rehabilitation using the Bobath approach	Significant improvements in maximal gait speed, stair climbing and velocity. None seen in gait symmetry and endurance.
(Hesse et al. 1994b)	No randomisation, no control; n = 148	Four weeks inpatient rehabilitation using the Bobath approach	Significant improvements in weight acceptance and push-off in gait. No follow-up
(Lennon 2001)	Case report, n = 2	28 – 30 individualised Bobath sessions over a 19 week period	Improvements in the pelvis, knee and ankle movement patterns of gait
(Trueblood et al. 1989)	No randomisation, no control; n = 20	Four sets of five repetitions each of manually resisted pelvic anterior-elevation and posterior-depression movements on the involved side (PNF)	Immediate effects were seen in the stance stability and limb advancement. Improvements were not seen when tested 30 minutes after treatment.
(Wagenaar et al. 1990)	Alternating treatment design, no control; n = 7	20 weeks training: • Bobath approach • Brunnstrom approach	No statistical difference between the two treatments on gait measures. One patient improved walking speed during the Brunnstrom treatment phase
(Wang 1994)	No randomisation, no control; n = 20	12 sessions of PNF (three times per week, 30 minutes duration)	Gait speed and cadence improved significantly at end of 12 sessions.

Table 2.3 Studies comparing the effectiveness of various rehabilitation techniques on gait.

2.8.2 Task-Oriented Training

Neurophysiological studies on animals have shown how specific and repetitive training can facilitate motor learning and recovery of function (Biernaskie and Corbett 2001; Liu and Rouiller 1999; Nudo et al. 1996a). Similar findings have also been demonstrated in human studies involving simple, repetitive movements (Classen et al. 1998; Liepert et al. 1999). The findings from these studies have been adapted to develop rehabilitative approaches such as the Motor Relearning Program (MRP), Treadmill Training and Constraint-Induced (CI) Therapy which are discussed below.

2.8.2.1 The Motor Relearning Program

The MRP approach is based on task-oriented motor learning ((Carr and Shepherd 1987). In a group of acute stroke patients given either a Bobath treatment or a MRP for three months, patients who underwent MRP showed significantly better scores in the MAS and the Sodring Motor Evaluation Scale (SMES) and had shorter duration of in-hospital treatment (Langhammer and Stanghelle 2000). In another study, 10 stroke patients were randomised into a control group and a group receiving task-oriented motor learning based on the MRP approach. Following the task training, the MRP treated group demonstrated bilateral activation of the inferior parietal cortex (IPC) and PMC, as well as the contralateral sensory cortex. The control group only showed weak activation of the ipsilateral IPC. This would suggest that a task-oriented training is likely to be associated with neuronal plasticity and incorporates networks from both hemispheres that will help optimise recovery of motor skills and behaviour (Nelles et al. 2001).

2.8.2.2 Treadmill Training

The type of training approach used to facilitate ambulation in neurologically injured patients has been shown to influence the degree of recovery (Fung and Barbeau 1994; Richards et al. 1993). Animal studies have shown that interactive locomotor training in spinal cats facilitated near normal walking patterns (Barbeau and Rossignol 1994; Smith et al. 1982). The locomotor training involved support for the weight of the hindquarters while stepping on a treadmill. This technique was also shown to be effective in spinal cord injured patients with different levels of spastic paresis (Wernig and Muller 1992). The use of treadmill training with body weight support has been expanded to the rehabilitation of gait in stroke (Moseley et al. 2003). The patient is suspended on a parachute harness, which provides the partial body weight support. Treadmill training was shown to improve gait following stroke in the acute stages (da Cunha et al. 2002). Significant improvements were also seen when treadmill training was combined with functional electrical stimulation of the paretic lower limb (Hesse et al. 1995) and training with body weight support (Visintin et al. 1998). Speed training on the treadmill has been shown to have better outcomes compared to conventional gait training and training at slow velocities (Pohl et al. 2002). Treadmill training provides for gait rehabilitation without the need of equilibrium reactions or stabilisation of the trunk and allows complex stepping movements to be performed by non-ambulatory patients (Hesse et al. 1994a). The task-specific nature of this technique shows great promise, however there is limited evidence available regrading it's effectiveness over other conventional gait training regimens (Moseley et al. 2003).

2.8.2.3. Constraint-Induced Movement Therapy

Constraint-Induced Movement Therapy refers to a novel rehabilitation technique developed to substantially reduce deficits and improve motor function of the affected upper limb after stroke. This technique was derived from behavioural studies in primates (Knapp et al. 1963). In experiments with monkeys after deafferentation of one forelimb through dorsal rhizotomy, a theory of learned non-use was developed (Taub et al. 1977). This non-use of the single deafferented limb is thought to be a learning phenomenon involving a conditioned suppression of movement (Taub et al. 1999). The learned non-use of the affected limb reinforces the use of the intact limb in performing daily activities. If this situation persists the animals will never learn to use the affected limb (Taub et al. 1999).

This period of learned non-use develops during the period of central nervous system shock (Taub et al. 1977). Consequently, it has been shown that the cortical representation of a limb contracts markedly when it is not used, resulting in a further depression of function (Jenkins et al. 1990; Recanzone et al. 1992). This use-dependent cortical organisation is suggested as occurring after lesions to the central nervous system and may be an important factor associated with recovery (Nudo et al. 1996a). However, movement in the deafferented limb can be induced by restricting the movement of the unaffected limb and forcing the animals to use the affected limb over several days (Knapp et al. 1963). This restriction of the intact limb in the monkeys instigates a change in motivation and overcomes the learned non-use of the affected upper limb (Taub and Uswatte 2003).

This concept has been expanded for use in humans, more particularly stroke patients. CI therapy involves intensive training of the stroke-affected limb together with the

restricted use of the intact limb. Numerous studies have been conducted to determine the effects of CI therapy in human stroke subjects and most have shown promising results. Improvements in speed or force of movement were seen in a group of stroke and brain injured patients using just restriction of the unaffected limb and no actual CI training (Wolf et al. 1989). Using a sling to restrict the unaffected arm and six hours of supervised task practice, Taub et al. (1993) were able to show significant improvements in motor function after 14 days. Subsequent studies also reveal similar results with improvements in arm function accompanied by TMS map expansion (Liepert et al. 1998; Liepert et al. 2000b; Liepert et al. 2001; Wittenberg et al. 2003) and increased fMRI activations of the pre-motor and somatosensory areas (Johansen-Berg et al. 2002) or ipsilateral motor cortices (Schaechter et al. 2002).

There is still great debate on the actual clinical implications of CI therapy. Although the learned non-use theory has been shown in animal models, the mechanism of this phenomenon is still poorly understood in humans. Initial studies that led to the development of CI were based on monkeys who had dorsal rhizotomy. The resulting neurological lesions would have different consequences and are not comparable to those seen in stroke. In addition, there is no known objective measure of the learned non-use in human stroke patients and can be poorly differentiated from sensory disorders or hemineglect (van der Lee 2003). Furthermore, CI therapy requires as much as 6 hours of continuos treatment time and is mostly applied to stroke patients who already possess some wrist extension and finger mobility. With very limited randomised controlled studies in CI therapy available, the functional changes observed can not be seen as unique to this technique. However, there is considerable promise in the use of CI therapy in facilitating upper limb recovery after stroke.

2.8.3 Peripheral Afferent Stimulation in Stroke

Somatosensory inputs driven by electrical stimulation (ES) of peripheral nerves or muscle motor points has been suggested to enhance recovery of motor function following stroke (Kralj et al. 1993; Ridding et al. 2000). Possible clinical applications of ES include the reduction of spasticity, muscle strengthening, increasing joint range of motion, the prevention of shoulder subluxation and contractures, improved muscle power and ability to elicit the desired movements required for performing daily activities such as walking (Alferi 1982; Chae et al. 1998; Linn et al. 1999; Merletti et al. 1978; Pandyan et al. 1997).

Functional Electrical Stimulation (FES) has been used in managing hemiparetic gait for a long time (Liberson et al. 1961). Stimulation of the peroneal nerve is the most common FES application and has been shown to improve ankle dorsiflexion (Bogataj et al. 1989). Using epimysial electrodes placed to the deep muscles of the hip and thigh, Waters et al. (1988) showed improved and controlled gait pattern in stroke patients. Multi-channel electrical stimulators have also been used to rehabilitate gait after stroke, however the technical requirements have proven difficult for daily application (Hesse et al. 1995). A randomised control trial on the use of FES on ambulatory stroke patients exhibiting footdrop showed the FES treated group walked significantly faster and more efficiently with the stimulator. These findings, however, did not carry over when the stimulator was not turned on (Burridge et al. 1997; Taylor et al. 1999). Larger clinical trials are needed to support the continued use of FES in facilitating gait after stroke.

Neuromuscular ES has been shown to enhance upper limb motor recovery in a group of acute stroke survivors (Chae et al. 1998). Scores in the upper limb component of the Fugl-Meyer Motor Assessment were significantly improved in the ES group compared

to controls tested at four and 12 weeks after treatment. No changes, however, were seen in the self-care function scores between the two groups. When compared to a standard treatment protocol, a cyclic neuromuscular ES plus standard treatment was shown to increase isometric wrist extensor strength and reduce upper limb disability (Powell et al. 1999).

In chronic stroke patients, EMG-initiated ES and low frequency transcutaneous ES demonstrated similar gains in motor function after treatment. EMG triggered ES to the wrist and finger extension showed improved block transfer and isometric force generation in the block and box test and force generation tasks (Cauraugh et al. 2000). In comparing four different conditions of treatment that included EMG triggered ES and ES with voluntary contraction, Kraft et al. (1992) showed significant changes in the Fugl-Meyer upper limb scores in the ES treated groups when compared to the group that received no treatment. This study also demonstrated that the functional gains were maintained at follow-up nine months post-treatment and suggests that voluntary ES is more effective in improving arm and hand function.

Median nerve stimulation for two hours elicited improved pinch strength in a group of chronic stroke patients (Conforto et al. 2002). Improvement in muscle strength was correlated with the intensity of the stimulus and occurred even in the absence of training. However, this study stimulated the median nerve, which subserves the flexors of the upper limb. Clinical observation reveals that flexor dominance is common in hemiparetic patients, which would put doubt into the actual strength gains reported in this study. Sonde et al. (1998) showed significantly improved motor function, as revealed by the Fugl-Meyer motor performance scale using low-frequency transcutaneous ES combined with a conventional physical therapy program.

Improvements were more pronounced in the less severely affected arms than in the patients with little or no voluntary movement.

Randomised trials looking into the effect of electrical stimulation and functional improvements in stroke show that improvements are most evident in mild to moderately impaired patients (Chae and Yu 2002). However, most of these studies prevent generalisation to the greater stroke population because of small sample sizes and the lack of control. Furthermore, the studies show outcomes based on behavioural observations and lack correlation with neurphysiological parameters. Afferent stimulation using electrical stimulation (ES) can induce cortical reorganisation in healthy subjects (Hamdy et al. 1998; Khaslavskaia et al. 2002; Ridding and Taylor 2001; Spiegel et al. 1999). The induced cortical changes have been documented using fMRI or TMS. However, no conclusive evidence is available whether this also occurs in a stroke population. Kimberley et al. (2004), using fMRI, found that repetitive movements coupled with electrical stimulation improved hand function and increased the intensity of activation of the ipsilateral cortex but did not increase voxel count measures. As motor control studies advocate the importance of use-dependent, active repetitive movement in recovery of function after stroke (Butefisch et al. 1995; Nelles et al. 2001), movement training mediated by ES may be a useful tool to facilitate post-stroke motor learning (Chae and Yu 2002; Kimberley et al. 2004). The repetitive, cyclical nature of this technique makes it appealing in facilitating post-lesion functional reorganisation of the motor cortex. Although methodological limitations in most studies on ES with stroke patients prevent generalisation to the general stroke population, the results still verify the capacity of afferent stimulation in decreasing motor dysfunction and improving functional capabilities of stroke patients with chronic hemiparesis.

2.8.4 Other Rehabilitation Strategies

The resulting hemiparesis presents as the most debilitating consequence of stroke. The ensuing impairment and functional disability poses a major challenge for healthcare professionals to develop effective clinical interventions. The rehabilitation team has several strategies that can be employed to lessen the negative impact of hemiparesis on the quality of life. However, interventions should provide measurable physiological changes that would justify its use for the recovery of function after stroke. A summary of other available strategies is presented in Table 2.4.

Approach	Source	Design, Sample	Intervention	Conclusion
Biofeedback (BF)	• (Bradley et al. 1998)	• Randomised controlled trial; n = 21	• Conventional therapy + EMG – BF or sham EMG-BF	• No statistical difference in gait ability outcome
	• (Intiso et al. 1994)	• No randomisation, with control; n = 16	• Biofeedback + physiotherapy vs. physiotherapy only	• EMG-BF training + physiotherapy improved functional quality of stroke patients with footdrop
	• (Prevo et al. 1982)	• Randomised controlled trial; n = 18	• EMG – BF on arm; 28 sessions; 11 weeks	• No significant improvement found
	• (Smith 1979)	• Randomised controlled trial; n = 11	• EMG – BF on arm; 12 sessions; 6 weeks	• Clinical improvement seen in arm function, no statistical significance found
Rhythmic Auditory Stimulus (RAS)	• (Thaut et al. 1997)	• No randomisation; with control; n = 10	• Gait training + RAS vs. gait training only	• RAS group showed significant improvements in stride length, velocity and reduced EMG variability in the gastrocnemius muscle

Table 2.4. Summary of different approaches available for the rehabilitation of function in stroke

Botolinum Toxin (BTX)	• (Bakheit et al. 2001)	• Randomised controlled trial; n = 59	• BTX-A administered to five arm muscles	• BTX-A reduces muscle tone ; sustained for 16 weeks
	• (Bhakta et al. 1996)	• No randomisation, with control; n = 17	• BTX administered to three arm muscles	• BTX safe and effective in reducing disability in patients with upper limb spasticity
	• (Hesse et al. 1996)	• No randomisation, no control; n = 12	• BTX-A administered to three leg muscles	• Improved gait in 9 out of the 12 subjects
	• (Reiter et al. 1998)	• Randomised controlled trial; n = 18	• Low dose BTX + ankle strapping vs. BTX only	• No difference between two groups, as both showed improved gait
Robot Assisted Therapy	• (Aisen et al. 1997)	• No randomisation, with control; n = 20	• Robot aided therapy using MIT-MANUS	• Robotic manipulation showed improvements in 3 measures of motor recovery
	• (Burgar et al. 2000)	• No randomisation, with control; n = 21	• Mirror Image Motion Enabler (MIME)	• Significant improvement in robot group in FM scores

Table 2.4. Summary of different approaches available for the rehabilitation of function in stroke

Assistive device • Ankle Foot Orthosis (AFO)	• (Gok et al. 2003)	• No randomisation, no control; n = 12	• Metallic and Plastic AFO used in gait analysis	• Both improved gait. Metallic AFO provided better stabilisation
	• (Zachazewski et al. 1982)	• Case report, n = 1	• Inhibitory cast and AFO	• Decreased positive supporting reaction
• Cane / Walking Stick	• (Chen et al. 2001)	• No randomisation, no control; n = 20	• Hemiparetic gait analysed while using cane	• Cane provided support and braking function
• Support aids	• (Ancliffe 1992)	• No randomisation, with control; n = 8	• Strapping hemiplegic shoulder to prevent shoulder pain	• Strapping delayed onset of shoulder pain
	• (Moodie et al. 1986)	• No randomisation, no control; n = 10	• Compared five support aids in managing subluxed shoulder	• Conventional sling, arm trough and lap tray effectively reduced subluxation
	• (Morin and Bravo 1997)	• No randomisation, no control; n = 15	• Radiographic evaluation of shoulder subluxation with sling and strapping	• Strapping combined with sling significantly reduces subluxation

Table 2.4 Summary of different approaches available for the rehabilitation of function in stroke.

Deafferentation	• (Muellbacher et al. 2002)	• Case report; n = 7	• Regional anaesthesia of the upper arm	• Increased flexor pollicis brevis MEP amplitude and improvements in pinch force and acceleration
Amphetamine	• (Sonde et al. 2001)	• Randomised controlled trial; n = 39	• 10 mg amphetamine combined with 10 sessions of stroke rehabilitation	• No significant difference found between the two groups.
	• (Walker-Batson et al. 1995)	• Randomised controlled trial; n = 10	• 10 mg amphetamine combined with 10 sessions stroke rehabilitation	• Increased rate and extent of motor recovery seen
Motor Imagery	• (Page et al. 2001)	• No randomisation, no control; n = 13	• Physical therapy three times a week for 6 weeks + 10 minute imagery exercises	• Imagery improved FM and ARAT scores
	• (Stevens and Stoykov 2003)	• Case report, n = 2	• 12 one hour imagery sessions, three times a week for four weeks	• Improved performance of paretic limb, sustained for three months

Table 2.4. Summary of different approaches available for the rehabilitation of function in stroke.

2.9. General Principles to Enhance Neuroplasticity in Stroke Rehabilitation

Animal and human models of brain injury have revealed important information that could directly or indirectly be utilised in stroke rehabilitation. The malleability of the central nervous system has made it possible for rehabilitation paradigms to shift its focus from compensation or adaptation to a reduction of impairments (Pomeroy and Tallis 2002). Evidence of structural and functional plasticity has been shown to occur following neural injury in animals and humans. Neurological rehabilitation is moving towards an approach based on reorganisation of the structure and function of the brain after the neural injury. Neuroplasticity can be induced through training and behavioural manipulations. Although numerous treatment approaches are available, there is still a gap in the evidence as to which technique is appropriate and which inputs are adequate to promote plasticity in the stroke-injured brain.

Environmental factors post-injury can influence the functional outcomes in animal models. An enriched environment allowing performance of a variety of activities and social interaction have been shown to drive purposeful neuroplastic change following infarcts in rodents (Biernaskie and Corbett 2001; Johansson and Ohlsson 1996; Ohlsson and Johansson 1995). However, the impact of environmental factors in human stroke factors is poorly understood.

It is observed that stroke patients who are in hospital have a low level of initiative (Ada et al. 1999; Lincoln et al. 1996) and feel disempowered by their roles as patients (Cant 1997). Motivation to actively participate in the rehabilitation process is an important factor in the success of stroke management. Personal and environmental factors,

however, can affect motivation (Maclean and Pound 2000). Active participation is more likely if rehabilitation takes place in the patients' own home (Widen Holmqvist et al. 1998). The home setting allows the stroke patient the opportunity to assume a greater responsibility and influence over the rehabilitation process (von Koch et al. 2000). Development of rehabilitation settings should take into account how patients can adopt this autonomy and control into other settings. Dedicated stroke units can be one option. Stroke patients who are managed in an organised stroke unit have been shown to have less mortality, physical dependence or requirement for long-term care (Collaboration 1997). With more appropriate individualised patient care and early active rehabilitation (Langhorne et al. 1995); stroke units could provide an enriched environment that promotes recovery when barriers to active patient involvement in their own rehabilitation are removed.

Variation between rehabilitation professionals and variation between stroke patients with the same diagnosis make it difficult to justify the use of one training technique as the gold standard. Cortical reorganisation is likely to be driven by the acquisition of new motor skills and not just by simple motor use of a limb (Nudo et al. 1997; Plautz et al. 1995). Skills training must then be considered imperative in managing stroke patients. It has been proposed from primate studies that the phenomenon of learned non-use of the affected limb can occur after an injury (Taub et al. 2002). When this is allowed to continue, functional recovery is compromised. CI therapy was developed from this theory and the high intensity nature of CI therapy have been shown to induce neuroplastic change with resulting improvement in hand function in chronic hemiparesis. Conventional rehabilitation can apply the intensive nature of CI therapy and devise programs that would allow the stroke patient to involve his/her affected limb in most activities. As therapist – patient contact time is limited, strategies that use a

detailed home program that can be facilitated by the caregiver would allow the stroke patient more practice time in using his or her affected limb (Gillot et al. 2003). Another option would be the use of circuit classes. The variety of the exercises and social interaction with other stroke patients would be of great value in facilitating the restoration of function.

The nature of the experience also influences the plastic changes after injury. Learning is related to the behavioural importance of the stimulus and rehabilitation success depends on the task and stimuli being important to the person (Kilgard and Merzenich 1998). This is evident in gait rehabilitation using treadmill training. As ambulation is of prime importance to a stroke patient, treadmill training allows the experience of near normal ambulation to be practiced and thus has shown promising results. Interventions should take this into consideration and make the training experience more meaningful to the stroke patient. This may provide a more positive outcome in functional recovery.

Another factor to be considered is the active performance of movement to induce functional cortical plasticity in stroke. A study comparing five physiotherapeutic treatment approaches was able to demonstrate active movement of the affected limb to be the most effective in generating MEPs (Hummelsheim et al. 1995). Active movement or an attempt to move the wrist and finger extensors was compared with tapping of wrist extensors, weight bearing through the affected upper limb, proximal activation of the shoulder and contralateral maximum isometric wrist extension in three stroke groups of varying severity. All the treatment approaches were able to enhance the frequency of occurrence of the muscular responses to TMS, however the most prominent effects were observed when active muscle contraction or the attempt of muscle contraction was performed.

2.9.1. Dual Stimulation and Stroke

Numerous studies in basic neuroscience provide a rich source of findings that can be used to effectively drive neuroplastic change. Repetitive training movements in string musicians have been shown to drive functional reorganisation of the cortex that is dependent on use and needs of the individual (Elbert et al. 1995). Skill acquisition and transfer was significantly improved when trained within a natural context (Ma et al. 1999). The use of peripheral afferent stimulation has been shown to increase the levels of cortical excitability (Charlton et al. 2003; Ridding et al. 2000). When afferent stimulation is paired with central cortical stimulation, plastic change was evident in the motor cortex. These changes were rapid, topographically specific, persistent and reversible (McKay et al. 2002; Stefan et al. 2000). The organisational changes brought about by the conjoint stimulation of somatosensory afferents and motor cortical circuits are thought to involve an LTP – like mechanism. As LTP is linked to the learning and memory, the application of using a paired dual stimulation paradigm in a patient population may prove useful.

The use of peripheral afferent stimulation paradigms in stroke has shown functional improvements with associated cortical changes (Conforto et al. 2002; Kimberley et al. 2004). However, there have been no reports to date on the use of a dual stimulation paradigm in a stroke population. Applying TMS as a therapeutic tool has numerous advantages. TMS is non-invasive, safe, painless and drug-free. The passive nature of TMS does not require active participation from the patient and thus would permit application to patients with impaired cognitive abilities and motor control. The therapeutic potential of this technique will be investigated in Chapters 4 and 5 of this thesis. The repetitive and associative nature of the paradigm is hypothesised to induce cortical reorganisation in a group with chronic hemiparesis. If the heightened

excitability seen in normal subjects is demonstrated in our stroke population, the results of these experiments will further demonstrate that the dynamic nature of the cortex is still evident following a stroke and during the chronic stages of the pathology. In addition, such cortical changes may be correlates of functional change. Most traditional rehabilitation methods only report behavioural changes following intervention. The use of the dual stimulation paradigm will enable me to correlate changes in gait and hand function with changes in neurophysiological parameters. Furthermore, as rehabilitation procedures are influenced by numerous subjective factors, the parameters used in this paradigm will allow for easy replication. It is also hypothesised that the increased state of cortical excitability will compel the stroke patient to use their affected extremities in natural, daily motor tasks. This will further enhance neuroplastic change, as subjects would be using their affected limbs in a context that is of relevance and importance to them. Although no detailed home rehabilitation program will be used, the concept of a stimulating and engaging environment with social interaction would be incorporated, as my target population would either be living independently at home or under managed care.

As evidence supporting neurological rehabilitation is constantly evolving, the use of a dual stimulation paradigm in a stroke population will allow me to translate current neuroscience research outcomes into a significant clinical application.

Chapter 3. Stability of maps of human motor cortex made with transcranial magnetic stimulation

3.1 Introduction.

Numerous studies have extensively reported the use of so-called representational maps of the human motor cortex in studying the plasticity of the brain. These maps are derived using TMS to determine the locations on the scalp from which a response in a given muscle can be evoked at a relatively low TMS intensity, and the amplitude of the response at each site. Various characteristics of these maps such as the optimal stimulation site and area of the scalp from which responses are evoked have been used to indicate changes in cortical reorganisation brought about by physiological interventions such as motor learning, pathological conditions such as limb amputation, and in studies of patterns of recovery from strokes. An emerging use for cortical mapping is the study of the topographical plasticity of the motor cortex (Classen et al. 1999; Cohen et al. 1998; Liepert et al. 1999), sometimes in conjunction with other neuro-imaging techniques (Hamdy et al. 1998; Pascual-Leone et al. 1999).

However, there is still debate over the stability of various parameters of such maps over time. These parameters include the surface area of the representation on the cortex of a given muscle, the volume or the CoG of the map. The map volume is often used to give a graphical indication of the total excitability of the cortical representation for a given muscle and consists of the sum of the average MEP amplitudes measured at all grid points that respond to stimulation. The CoG is a weighted, spatial average of the corticomotor representation (Thickbroom et al. 1999), which is often used to define the

position of TMS maps and identify shifts of the cortical representation of a muscle in response to an intervention. It corresponds with an area of high excitability of corticomotor neurons and is closely associated with the optimal stimulus site of the muscle being mapped (Wilson et al.1993). Thus, changes in the location or size of the motor map can be described in terms of a shift in the CoG.

This study addressed the issue of how time and repetitive measures within 24 hours, one week and two weeks affect the CoG position, map area and map volume in normal individuals not undergoing specific interventions.

3.2 Materials and Methods

3.2.1 Subjects

Eight right-handed subjects (ages 19 – 43) volunteered to participate in this study. Each gave written informed consent. The Human Research Ethics Committee of the University of Adelaide approved the experimental protocol. Prior to commencing the protocol, all subjects completed the Adult Safety Screening Questionnaire to determine suitability for TMS (Keel et al. 2001). Subjects were excluded from the study if they stated a history of neurological disorders and are contraindicated to TMS as revealed by the Safety Screening Questionnaire.

3.2.2 Subject Preparation

Subject's hands were cleaned with alcohol in preparation for electrode placement. Each subjects' right FDI, APB and ADM was palpated. A reference point on the muscle belly was measured from the corresponding interphalangeal (IP) joint. The distance between the corresponding IP joint and muscle belly was measured and recorded for use

in successive experiments. Bipolar silver/silver chloride electrodes were placed on the muscle belly of the abovementioned muscles and on the adjacent IP joint. The signals were amplified in the bandwidth of 20 Hz to 1 kHz and sampled at 5 kHz. EMG signals were then converted to digital signals using the Cambridge Electronic Device (CED). These signals were then fed into the compute and analysed using the Signal Software. Subjects were seated in a comfortable chair and wore a tight-fitting elastic scalp cap marked with a 1 cm x 1 cm grid. The centre of the cap was positioned on the vertex of the subject's head and measurements were referenced to the intra-aural line and the nasion-inion line. When the centre of the cap was properly referenced, additional measurements were also taken from the point on centre of the cap to the right and left tragus, the nasion and the occipital protuberance. This enabled us to fit the cap in the same position in subsequent mapping sessions. .

3.2.3 Protocol

The responses evoked in FDI, APB and ADM were recorded with surface electromyography. The resting threshold (RT) for evoking a motor evoked potential (MEP) in each muscle was determined using a Magstim 200 stimulator (The Magstim Co., Dyfed, UK) with a focal figure-of-eight coil, while the muscle was at rest. The scalp was then mapped systematically for each muscle with a stimulus intensity of 115% RT using a standard protocol (Wilson et al. 1993). The coil was oriented 45° oblique to the sagittal mid-line with the handle held posteriorly so that the induced current flowed in a plane perpendicular to the estimated alignment of the central sulcus. The RT was determined at the point on the scalp at which the highest amplitude MEPs were evoked in the three muscles, and was defined as the intensity at which five out of 10 successive stimuli evoked an MEP with an amplitude of at least 50 μV in all three muscles tested. The responses evoked by three stimuli at each scalp site in the resting

muscles were averaged. The scalp sites were stimulated in random sequence, and all points on the scalp that elicited a response in the target muscles were mapped. These stimulation sites on the cap grids were recorded manually using a mapping sheet and later transferred into the computer to generate the necessary data required to compute the CoG. The same investigator repeated the mapping procedure after 24 hours, one week and two weeks.

The area of each map was taken as the number of scalp points at which a response was evoked, and the volume of each map was taken as the sum of the averaged MEP amplitudes recorded at all scalp sites at which a response was evoked. These parameters together with the CoG were determined for each map on every occasion.

The CoG was calculated with the following formula (Wassermann et al. 1992):

$$CoG = \sum v_i x_i / \sum v_i , \sum v_i y_i / \sum v_i \text{ (for scalp sites } x_i, y_i \text{ and amplitudes } v_i)$$

The latitude and longitude of the calculated CoG measures were plotted into a vector for analysis of shifts over time. This allowed the relative location of the CoG from one mapping occasion to the next to be determined. The total area enclosed by a map is subject to variability arising from the small size of the MEPs at the boundaries. In an attempt to reduce this variability, we measured the number of scalp points (i.e. scalp area) at which the amplitudes of responses were greater than 10% of the maximal MEP recorded in the first mapping session in a given muscle. We also measured the number of points at which the response amplitude exceeded 25%, 50% and 75% of the maximum. This concept is depicted in Fig. 3.1, which shows a 3-dimensional representation of the map recorded for the FDI muscle on one occasion, and the series

of horizontal "slices" at these amplitudes through the map. These measurements were repeated for all maps in all sessions.

3.2.4 Statistical Analysis

The Statistical Package for Social Sciences (V11, SPSS Inc, USA) software package was used for all statistical analyses in this experiment. A value of $p < 0.05$ was set to describe significance for all analyses. Descriptive statistics (mean and standard deviation) were calculated for the subject's age and motor threshold. A repeated measures analysis of variance (ANOVA) design was employed to test for significant effects on map CoG, area and volume for the three tested muscles across the four experimental sessions. The factors were MUSCLE, TIME, CoG, Volume and AREA.

3.3 Results

There was no significant change in any of the parameters measured across all of the recording sessions. Mean RT was 42.3 % ± 0.13. and was constant across the four testing periods ($p = 0.99$; $F = 0.002$).

3.3.1 Centre of Gravity

CoG latitude and longitude measurements were plotted as vectors for analysis of positional shifts over time. The differences between the latitude and longitude coordinates of the CoG for each muscle were calculated for each individual subject. These measures were used to establish a displacement vector and the average vector displacement magnitude was calculated for all subjects and all muscles. The mean vector shift for all three muscles on the right hand over the three testing periods from baseline was shown to be 0.4 cm. A summary of the means and standard errors of these is shown in Table 3.1. The ANOVA showed the difference between baseline and

subsequent measurements did not differ significantly (p=0.882; F=.126 for FDI; p=0.139; F=2.171 for APB and p=0.675; F=.401 for ADM). The interaction between the three muscles and four measurement sessions was not statistically significant (p=0.879; F=.084).

Muscle	24 hours	1 week	2 weeks	Mean
FDI	4.0 (0.4)	4.0 (0.8)	4.0 (0.4)	4.0 (0.3)
APB	3.8 (0.5)	3.6 (0.6)	5.0 (0.8)	4.1 (0.4)
ADM	4.6 (0.8)	3.4 (0.6)	4.1 (0.9)	4.0 (0.4)

Table 3.1 Centre of Gravity shift for FDI, APB and ADM. The group mean (± sem) distance shown in mm. The column entitled Mean is the mean distance moved for each muscle across the three intervals.

3.3.2 Map Area

Area is expressed as the mean number of sites on the 1 cm x 1 cm grid on the scalp from which MEPs were evoked. The area is calculated for MEPs of various amplitudes relative to the maximal MEP amplitude recorded in that subject. The areas of the maps were also calculated as slices made at amplitudes of 75%, 50%, 25% and 10% of maximum MEP (Fig. 3.1). The map was constructed using linear interpolation. Each slice shows the area of the map that results from accepting only the amplitude values greater than a specified minimum. e.g., the uppermost "slice" shows the area of the map made from MEPs that were $\geq$75% of the maximal amplitude of MEP evoked in that session. The 0% max shows the area of the scalp from which responses of all amplitudes were evoked. The map slices were used to determine the most stable of the different map slices, i.e., the slice of the TMS map showing the least variability. There was no significant interaction between the three muscles, testing sessions and map slices

(F=1.4, p=0.14). However, the areas of the map slices were significantly different from each other (F=197,p=0.013). The map area based on all scalp sites at which MEPs were evoked had the least variability (means 64.84 ±1.88) among the five "slices" shown in Fig. 3.1 and summarised in Table 3.2.

3.3.3 Map Volume

Analysis of variance also revealed that there were no significant changes in the volumes of the maps for any of the three muscles over time (F=1.3, p=0.3 for FDI; F=0.52 p=0.67 for APB; and F=0.52, p=0.67 for ADM). The volume measures for the three muscles mapped are summarised in Table 3.3.

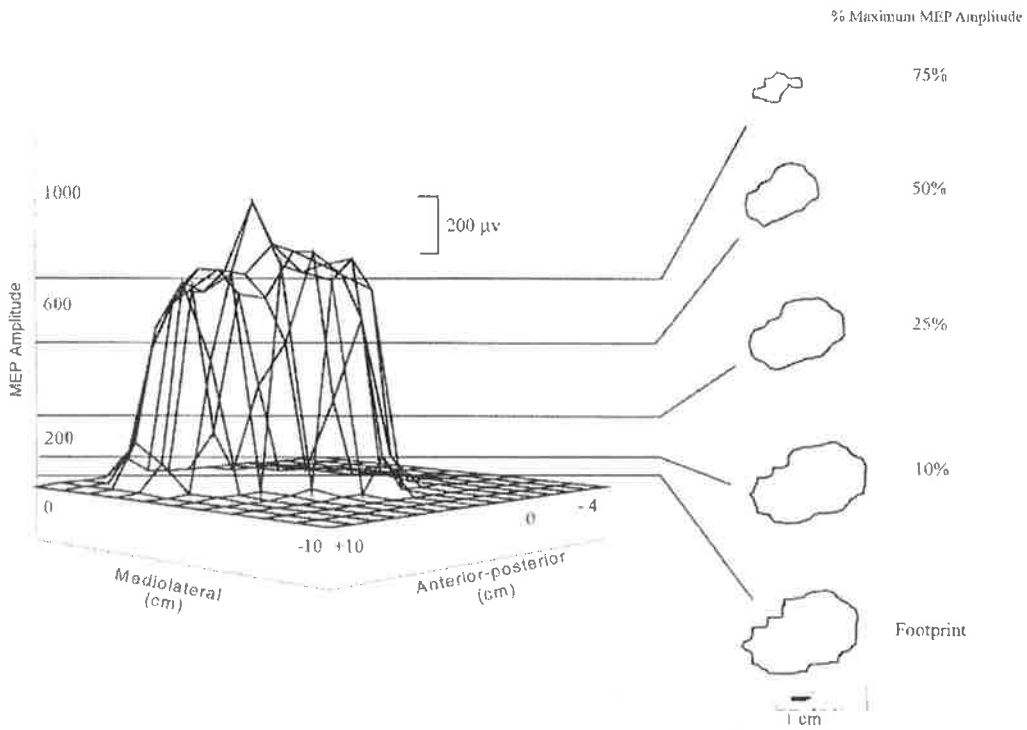

Figure 3.1. Volume map and area slices of FDI from one subject. The areas of the maps constructed from MEPs that exceeded 0, 10%, 25%, 50% and 75% of maximum amplitude.

Map Slice	*Mean number of points*	*Standard error*	*coefficient of variation*
≥ 75% max	6.9	1.6	0.23
≥ 50% max	11.9	2.1	0.17
≥ 25% max	18.1	2.1	0.11
≥ 10% max	25.1	1.6	0.06
≥ 0% max	64.8	1.9	0.03

Table 3.2 Analysis of the areas of the cortical representations of the maps of FDI, APB, ADM at various "slices" through the 3-dimensional map of each muscle (*cf* Fig. 3.1).

	Baseline (mV)	24 hours (mV)	1 Week (mV)	2 Weeks (mV)
FDI	21123 (±11226.1)	22940 (±15022.9)	23542 (±12323)	22059 (±9178.9)
APB	14058 (±9476.7)	18985 (±17279.1)	18509 (±16904)	15151 (±15743.2)
ADM	18176 (±22169.7)	22081 (±22658.9)	21299 (±25440.5)	27190 (±21531.8)

Table 3.3 Volume measurements of FDI, APB, ADM motor maps across the testing sessions. Volume data are the sum of the averaged MEP amplitudes recorded at all scalp sites at which a response was evoked and presented as mean ± sd.

3.4 Discussion

TMS map parameters are often used to quantify the capacity of the motor cortex for plastic change. Thus, reliability of these measurements is an important factor to consider. The areas of cortical maps of individual muscles are widely used as a measure of cortical topography. The area value computed with the TMS technique is always larger than the actual extent of the cortical representation of a muscle because of stimulus current spread (Mortifee et al. 1994; Pascual-Leone et al. 1999). However, it is difficult to establish an unambiguous criterion for the position of the boundary. Despite this, earlier studies have concluded that the maps are fairly stable over time. Wilson et al (1993) found no significant difference in mean location, area and elongation of the left APB and ADM mapped 21 – 181 days apart in five right-handed subjects, although the maps were made at variable intervals. Using a digital positioning system to plot scalp points, Mortifee et al (1994) showed that map area, size and volume were reproducible when plotted twice over a period of several weeks.

Thickbroom et al (1999) modelled the effect of randomly changing the amplitude of MEPs at each stimulus site on a coarser grid, and found that the map position and area were surprisingly insensitive to these. The variability induced in the modelled maps by the random changes of MEP amplitude in parameters such as the centre of the map was manifest in standard deviations of less than 2.3 mm.

However, several authors have commented on the variability of MEP amplitudes at the perimeter of the map (Brasil-Neto et al. 1992; Mortifee et al. 1994). Presumably for this reason, Thickbroom et al. (1999) based their map area calculations on MEPs greater than 12.5% of maximum amplitude. Accordingly, we investigated the variability in map sizes by examining the stability of the area of the maps determined at different

horizontal slices in relation to the maximum (e.g., Fig. 3.2). Our hypothesis was that map areas based on larger amplitude MEPs would be less variable than those based on all of the MEP data. This was found to be not true. Table 3.2 shows the mean number of points for all slices of all muscles. Both the standard error and the coefficient of variation of area diminished progressively as sites with smaller MEPs were included in the area measurement, and were least when all points at which responses were evoked were used. The same relationship held for each of the muscles in turn.

There is at present very limited literature that addresses the reproducibility of CoG measurements. Unlike parameters such as map volume used in a number of studies (Mortifee et al. 1994; Wassermann et al. 1992), the CoG is a measure of map position that does not require curve-fitting, and gives an amplitude-weighted indicator of map position. A shift in this position is often used to report reorganisation in the motor cortex. As changes associated with reorganisation are usually subtle and short term, it has been assumed (without supporting evidence) that CoG measures are reproducible and stable over a period of time. In the present study, the CoGs of three intrinsic hand muscles were found to move an average of 4 mm from the original position across 24 hours, one week and two weeks recording intervals. This is slightly less than the $\pm$ 3 mm reported by Miranda et al. (1997) who only mapped the ADM of six subjects on three occasions one or two weeks apart, using an accurate but complex method for localising scalp sites. The direction of the movement of the CoG was not consistent from one muscle to another during a given session, which indicates that the movements were not the result of cap displacement or variable coil positioning. It is possible that the shifts are the result of the continuous reorganisation of the motor cortex that occurs in response to the everyday functional demands of the hand. More probably, these small shifts are the result of noise in the measurement process, arising from the usual

variability of MEPs and the rather coarse spatial grain of the grid. Although the results show that TMS map parameters do not differ significantly when measured serially over time, the statistical measures employed are not indicative of reliability of the measures. Future studies should test for Intercalss Correlation Coefficients to truly show the reliability of the parameters measured.

3.5 Conclusion

It is concluded that the conventional method for mapping the cortical representational areas of three intrinsic hand muscles gives maps that are stable over times up to at least two weeks. The study also suggests that the conventional scalp grid used by the present and most other studies are equally as accurate in determining map coordinates. Another novel feature of the study is the comparison of map area using different horizontal slices of the volume map. It was shown that maps that include all scalp sites at which responses are evoked are less variable than those based on larger amplitude responses. The findings of the present study validates the use of map parameters as CoG and area for the investigation of both short-term and long-term effects of physiological interventions that change the cortical representation of hand muscles (Cracco et al. 1999; Levy et al. 1991; Ridding et al. 2001). As TMS map parameters are increasingly used in pathological studies (Byrnes et al. 1998; Cramer and Bastings 2000; Liepert et al. 1998), the results from this experiment can offer valuable insights into the mechanisms involved in the pattern of cortical reorganisation in the presence of brain injury.

Chapter 4. Induction of Plastic Change in Motor Cortex and Associated Improvements of Gait in Chronic Hemiparesis

4.1 Introduction

Stroke remains one of the leading causes of disability in adults. Disturbances in gait are common sequelae of strokes and often interfere with general mobility. Several characteristic patterns of hemiplegic gait are clearly recognisable. The most common pattern in the foot is ankle plantarflexion and inversion during loading and swing and an obvious lack of roll-off at toe-off (Nadeau et al. 2001). This limited lack of ankle dorsiflexion adds to the effective length of the limb, which perpetuates lower limb circumduction. The absence of normal ankle dorsi- and plantar- flexion patterns during gait often leads to initial landing on either the front or the medial side of the foot instead of the heel. This greatly reduces the capacity of the ankle to push off to propel the limb forward and prepare for the next initial contact phase (Murray 1967; Nadeau et al. 2001, Richards and Knutsson 1974).

Recovery of independent, functional gait determines the degree of quality of life post-stroke and is an important factor to consider in rehabilitation (Richards et al. 1993). Attempts to rehabilitate gait after a stroke have given very inconsistent results. Different approaches are currently in practice in gait rehabilitation. However, no one approach has been shown to exhibit better functional benefits over the other (Mauritz 1990).

The techniques of TMS and TES have been employed to investigate the motor system following stroke. The MEPs elicited by TMS have been shown to be delayed or absent (Berardelli et al. 1987; Macdonnel et al. 1989) and the intensity of stimulation needed to

evoke an MEP may be higher (Hummelsheim et al. 1995). Following stroke, the scalp representation of paretic muscles is reduced (Traversa et al. 1997). During recovery, improvements in motor performance are correlated with increases in the amplitude of MEPs, as well as with an expansion of the scalp representation of the paretic muscles (Arac et al. 1994; Caramia et al. 1991). Hence, there appears to be a close relationship between the size of the motor map of a muscle and the functional state of that muscle. These studies have led to a better understanding of the physiological mechanisms of recovery following a stroke and have led to the creation of innovative learning and training paradigms in stroke rehabilitation.

Sensorimotor stimulation has been shown to induce cortical plasticity and reorganisation in the undamaged brain. Stimulation of peripheral nerves (Ridding et al. 2000; Ridding et al. 2001), or combined peripheral nerve and low frequency brain stimulation using TMS (Stefan et al. 2000) can induce an increase in the area of the scalp representation of target muscles. Repeated sessions of peripheral and central stimulation (dual stimulation) can induce changes that persist for several days following the last stimulation session (McKay et al. 2002). The use of TMS as a therapeutic tool has never been previously reported in a stroke group. The efficacy of afferent stimulation techniques such as FES in stroke has been mixed (de Kroon et al. 2002). However, the possible mechanism underlying the cortical changes when combining central and peripheral stimulation (dual stimulation) in normal subjects show a similarity to that observed in motor learning (Stefan et al. 2000). The application of such a paradigm may prove an effective method of driving functional plastic changes following stroke. The present study aimed to determine the effects of combining central stimulation via TMS and peripheral electrical nerve stimulation to induce increased cortical excitability in chronic hemiparesis. A protocol of repeated periods of combined

peripheral and central stimulation (McKay et al. 2002) would be used to determine if increases in the excitability of the corticospinal projection to paretic ankle dorsiflexors and evertors occurred in a group of patients with hemiparesis after stroke. We also sought to determine whether induced neurophysiological changes were accompanied by functional improvements in gait.

4.2 Methods

4.2.1 Subjects

Thirteen subjects with chronic stable hemiparesis gave written informed consent to participate in the study, which was approved by the Royal Adelaide Hospital and University of Adelaide Human Research Ethics Committees. Three subjects pulled out and were unable to complete the entire protocol and were excluded from the study. Subjects were selected for inclusion in the study on the basis of weakness of the ankle dorsiflexors and evertors, ability to walk at least 10 metres with or without a mobility aid, and functional stability for the last two years. At the time of testing, all subjects had undertaken long-term physiotherapy and have been discharged from their rehabilitation programs. Subjects were excluded from the study if they had significant cognitive impairments, history of seizures, metal skull implants, or cardiac pacemakers. On initial assessment, the functional level of each subject was determined using the FIM and the RMI. Both these measures are valid and reliable measures of mobility function in stroke (Collen et al. 1991; Dodds et al. 1993).

The common functional deficit was one paretic lower limb with increased muscle tone, hyperactive stretch reflexes and weakness. All had weakness in the anterior tibial muscles (dorsiflexors) and hypertonicity in the posterior or calf muscles (plantar

flexors) and had a substantial disturbance in gait pattern often requiring the use of an ankle foot orthosis (AFO) to provide adequate primary heel contact and foot clearance in the stance and swing phase of gait. Patient details including lesion site obtained from scan reports and gait pattern are given in Table 4.1.

4.2.2 Testing Protocol

Before the intervention commenced, all subjects were evaluated with the functional and neurophysiological tests described below on two separate occasions two weeks apart. They were then given 30 minutes of dual stimulation on each day from Monday to Friday for four weeks. Neurophysiological measurements were made each day prior to the dual stimulation, and the functional measurements were made at the end of each week of stimulation. Follow-up neurophysiological and functional measurements were then repeated two weeks after the completion of the stimulation. The subjects received no additional therapy during the course of the dual stimulation.

4.2.3 Subjective Measures of Function

Each subject completed questionnaires in consultation with their partner to ascertain their mobility self-rating and mobility functioning scores. These questionnaires were developed specifically for this study by Dr Susan Hillier (University of South Australia) and included a daily reflection on the quality of walking, a weekly reflection on the impact of mobility on activities of daily living (disability) and on life roles (handicap). Scores were recorded using Likert scales and grades of competency (Domholdt 1993). An open question was also asked each subject/partner at each functional test session in order to capture unanticipated changes (positive or negative).

Subject	Age/ Gender	Years post stroke	Lesion Site	Impairment Side	FIM (max 126)	RMI (max 15)	Mobility:
1	47/M	2	R Putaminal Hemorrhage	L Hemiparesis	122	12	AFO
2	67/M	8	L Pontine Infarct	R Hemiparesis	123	14	AFO
3	59/M	5	R MCA Territory	L Hemiparesis	118	12	AFO Stick outside
4	61/M	3	R Thalamo-capsular Area	L Hemiparesis	119	12	AFO Stick outside
5	66/F	2	R MCA Territory	L Hemiparesis	108	8	AFO, Stick inside, Min walking Outside
6	43/F	4	Left Medulla secondary to VBA infarct	R Hemiparesis	123	14	No AFO Stick outside
7	65/M	3	R MCA Territory	L Hemiparesis	120	13	Stick at all times
8	60/M	4	R MCA Territory	L Hemiparesis	96	7	AFO, Quad stick inside No walking outside
9	78/F	2	R MCA Territory	L Hemiparesis	120	10	Ankle splint Quad stick in and outside
10	61/M	2	R Basal Ganglia	L Hemiparesis	120	13	Stick inside and outside
Ave	60.7 (± 9.9)	3.5 (± 1.9)			116.9 (± 8.5)	11.5 (± 2.4)	

Table 4.1 Background data for the 10 chronic stroke subjects tested. Mean ± sd; FIM = Functional Independent Measure, maximum score is 126; RMI = Rivermead Mobility Index, maximum score is 15; MCA = Middle Cerebral Artery, VBA = Vertebro Basilar Artery, AFO = ankle foot orthosis.

4.2.4 Objective Functional Tests

The functional tests were carried out by the same experienced, independent physiotherapist in all testing sessions.

4.2.4.1 Range of Movement

Passive dorsiflexion range of movement (ROM) of the ankle was assessed using the Lidcombe template (Moseley and Adams 1991). Active dorsiflexion ROM was tested in the seated position with knees at 90 degrees flexion. Markers were placed on the lateral and medial malleoli, on the base of the first and fifth metatarsals and on the head of the fibula. A digital image was taken with the ankle at rest and following the command to dorsiflex actively. Angle measurements were then computed using the Image Tool® software (UTHSC, 1996).

4.2.4.2 Gait Analysis

Spatial and temporal characteristics of gait such as step and stride length, cadence, and the level of independence were determined from a 10 metre timed walk. The gait measures were recorded using a video camera on a marked walkway (Robinson and Smidt 1981). The strike pattern of the foot was measured during gait using the FSCAN Plantar Pressure System (TekScan, Inc., USA). This technique employed insole sensors that allowed the subjects to walk in their normal shoes and with their normal pattern. The insoles are composed of multiple sensor cells that provide data regarding the pressure distribution around the foot (Luo et al. 1998). This system is relatively easy to use and can be conducted in a short time in a clinical setting (Luo et al. 1998; Randolph et al. 2000). There are qualitative reports on the accuracy of the insole sensor data obtained from the FSCAN (Sumiya et al. 1998); however, studies that support its

validity and reliability as a clinical gait analysis tool are limited (Luo et al. 1998; Randolph et al. 2000; Sumiya et al. 1998; Woodburn and Helliwell 1997). The FSCAN data has been shown to be adequate in determining the pressure distribution during gait provided the following factors were considered: contact surface, loading speeds and temperature (Luo et al. 1998). In order to address these variables, all subjects were tested on the same surface and with the same footwear to maintain similar contact surface for each test. The subjects were given two to three minutes of warm-up before testing to allow warming up of the insole sensor. The sensors were also calibrated before each test to maintain equal loading speeds. The time to heel-strike, peak pressures on medial and lateral zones of the plantar aspect of the foot and the total surface area contact were measured and analysed using the proprietary software. Foot slap (indicating reduced eccentric control of dorsiflexors after initial contact) was also captured with the FSCAN, and foot clearance during swing phase from the video footage. In addition, gait speed and cadence were also calculated.

4.2.4.3 Neurophysiological tests

Surface EMG was recorded from the TA and PL muscles bilaterally, using silver/silver chloride surface electrodes. The signals were amplified 1000x in the bandwidth 20 Hz to 1 kHz, digitised at 5 kHz with a laboratory interface (CED 1401, Cambridge, UK) and stored on a personal computer. EMG waveforms were analysed off-line with custom software.

The excitability of the cortical projection to TA and PL was investigated using TMS. Magnetic stimuli were delivered using a Magstim 200 stimulator (Magstim Co., Dyfed, UK) with an angled figure-of-eight coil (13 cm external wing diameter). The angle between the two wings was 90^0. The optimal stimulation site was revealed by moving

the coil over the scalp, in the region of the vertex, until the location at which maximal amplitude MEPs in TA and PL was determined. In all cases this site was in the midline, just anterior to the vertex. Both resting and active (5-10% of maximum voluntary contraction) motor thresholds were then determined. Resting motor threshold was measured at the optimal scalp site for eliciting MEPs in the target muscle, and defined as the stimulus intensity at which five out of 10 consecutive stimuli evoked a MEP with an amplitude of at least 50 μV in the relaxed muscle. Active motor threshold was determined during a minimal voluntary contraction and was operationally defined as the stimulus intensity at which five out of 10 consecutive stimuli evoked an MEP with an amplitude of at least 100 μV in the active muscle. MEPs evoked by stimulation at the optimal scalp site were recorded from TA and PL bilaterally in both resting and active conditions. In each condition, 10 stimuli were applied at an intensity of 15% of stimulator output above the respective resting or active motor threshold, and the MEPs were averaged. Subjects were given visual feedback to ensure they were either fully relaxed or maintaining the correct level of voluntary contraction. Mean maximal voluntary EMG activity was obtained by rectifying and averaging the EMG activity during a maximal isometric contraction of TA and PL.

4.2.4.4 Dual Stimulation Protocol

The dual stimulation paradigm was a modification of a protocol reported previously (Stefan et al. 2000) and employed combined TMS and peripheral nerve stimulation (see Figure 4.1; McKay et al. 2002). The peripheral nerve stimulation consisted of a 500 ms train of 10 Hz, 1 ms shocks repeated every 10 seconds applied to the common peroneal nerve in the weak limb through surface stimulating electrodes. The optimal position for stimulating the common peroneal nerve was determined by exploring the

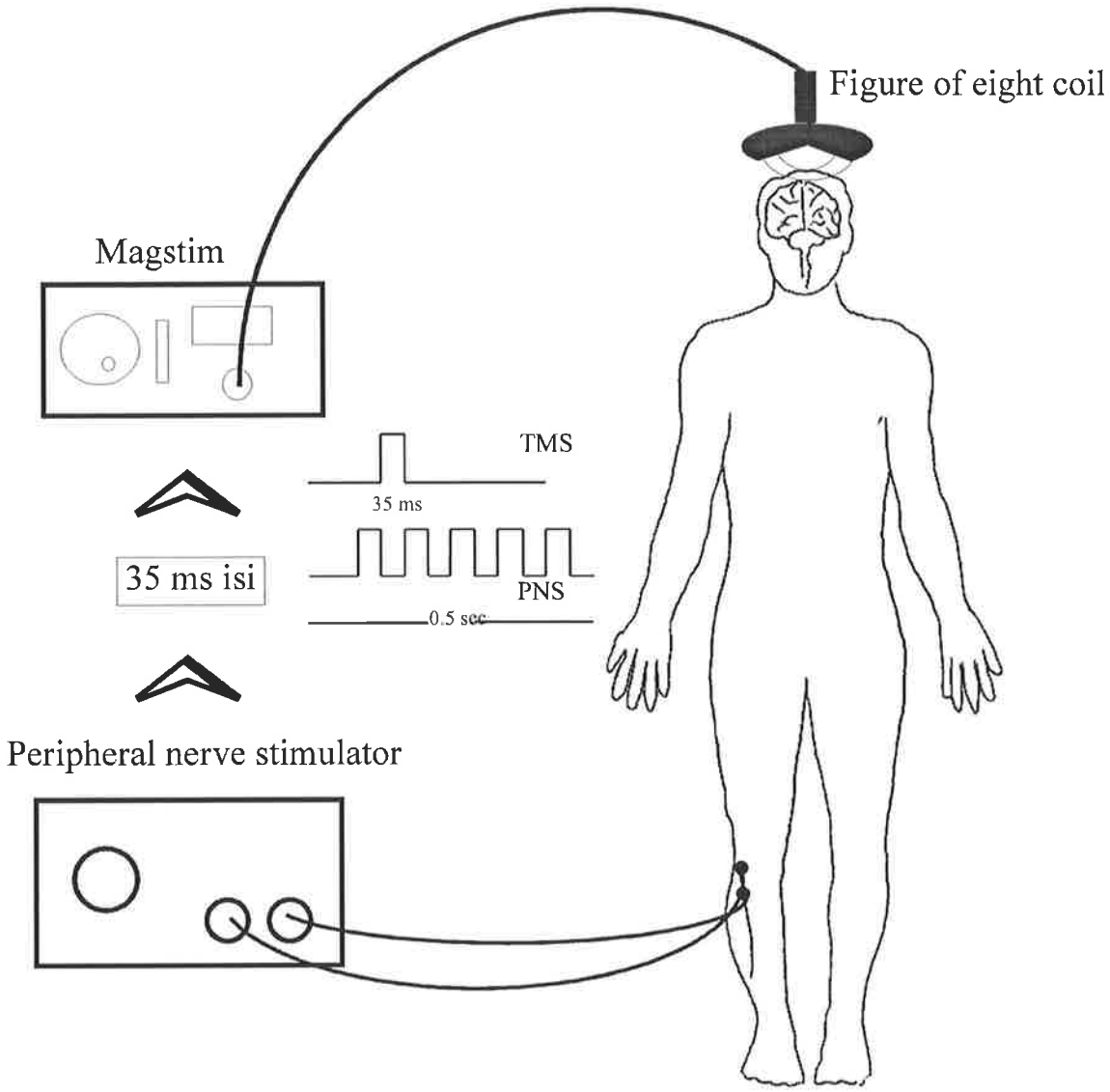

Figure 4.1. Graphical representation of the dual stimulation paradigm modified from Stefan et al., 2000. The coil was held over the scalp site at which maximal MEPs could be evoked from TA. TMS was delayed by 35 ms with respect to the onset of the peripheral stimulation train so that initial afferent volley evoked by nerve stimulation arrived at the cortex at approximately the same time as the magnetic stimulus

area around the neck of the fibula with a stimulating probe until the largest M-wave was evoked in TA. The intensity of the peripheral nerve stimulation was adjusted to evoke a minimal visible motor response in both TA and PL. TMS was applied using the same figure-of-eight coil as described above at an intensity that evoked a just-visible motor response in both the TA and PL muscles (approximately 15% above resting threshold intensity). The coil was held over the scalp site at which maximal MEPs could be

evoked in TA, as described previously. The TMS was delayed by 35 ms with respect to the onset of the peripheral stimulation train so that the initial afferent volley evoked by nerve stimulation arrived at the cortex at approximately the same time as the cortical magnetic stimulus was delivered.

4.2.5 Statistical Analysis

All statistical analyses in this study were performed using the Statistical Package for Social Sciences (SPSS) software package. A value of $p < 0.05$ was set to describe significance for all analyses. Descriptive statistics (mean and standard deviation) were calculated for the subject's age, time since stroke, FIM and Rivermead Index scores.

4.2.5.1 Motor evoked potential size and latency

The daily neurophysiological measures were averaged into a weekly score for comparison with the baseline and follow-up measures. The post intervention neurophysiological data were compared with baseline values using a two-way repeated measures ANOVA with main factors as muscle (2 levels) and time (5 levels) (Portney and Watkins 2000). The repeated measures ANOVA analysed the effect of the dual stimulation across the time periods, the main effect on the subjects and the interaction between these two factors. If the scores were significant, a multiple comparison test computing for Tukey's honestly significant difference was performed. As the data were highly variable between subjects, an ANOVA was used to test the significance of changes in neurophysiological measures on an individual subject basis.

4.2.5.2 Stimulation Thresholds

The motor thresholds for TMS for the affected and unaffected side were compared with a paired t-test. A repeated measures ANOVA was used to determine the effect of the dual stimulation on the thresholds across the intervention period and follow-up.

4.2.5.3 Functional Measures

A paired t-test was used to establish the stability of the scores taken from the succeeding baseline functional tests. A repeated measures ANOVA was used to determine the effect of the dual stimulation on the range of passive and active dorsiflexion of both ankles. A Friedman two-way analysis of variance by ranks was used to analyse the FSCAN scores, gait variables and the subjective questionnaire scores. Since these scores were non-parametric, the Friedman test is considered the appropriate alternative to the parametric repeated measures ANOVA. When there was statistical significance, further analysis of pair-wise contrasts were performed by computing for the minimum significant difference (Portney and Watkins 2000).

4.3 Results

4.3.1 Neurophysiological Parameters

4.3.1.1 Thresholds of MEPs

The thresholds for evoking MEPs in both resting and active muscles were significantly higher for PL and TA muscles in the paretic limb than in the unaffected limb (Repeated Measures ANOVA $p<0.05$, $F=7.6$). The thresholds for both the weak and the normal muscles did not change throughout the testing period (for all comparisons $p=0.99$; $F=0.015$, ANOVA).

	TA (%)		PL (%)	
	Resting	Active	Resting	Active
Affected	70.4± 2.1	48.8± 1.6	70.3 ± 2.7	48.8± 1.6
Unaffected	46.9± 1.9	32.6± 0.8	46.9± 1.9	32.7± 0.8

Figure 4.2 Motor Threshold for tibialis anterior (TA) and peroneus longus (PL) for the affected and unaffected side. Data recorded from both resting and active states (mean ± se, n=10).

4.3.1.2 Maximal voluntary EMG

Figure 4.2 shows that, when averaged within each testing week, the EMG activity recorded during a maximal voluntary contraction increased by 282% ± 91 in PL (baseline value = 0.05 mV) and 174% ± 52 (baseline value = 0.04 mV) in TA by the end of the fourth week. However, the degree of change was extremely variable between subjects (range 5-2125% in PL, 5-1075% in TA), and as a consequence, the overall increase in EMG did not reach significance (Repeated Measures ANOVA, $p=0.75$;

F=0.53). Within-subject analysis revealed a significant increase in EMG activity during a maximal voluntary contraction of the PL and TA muscles of the affected side in four subjects by the end of the fourth week (for all cases p=0.0002; F=4.3) (Table 4.3).

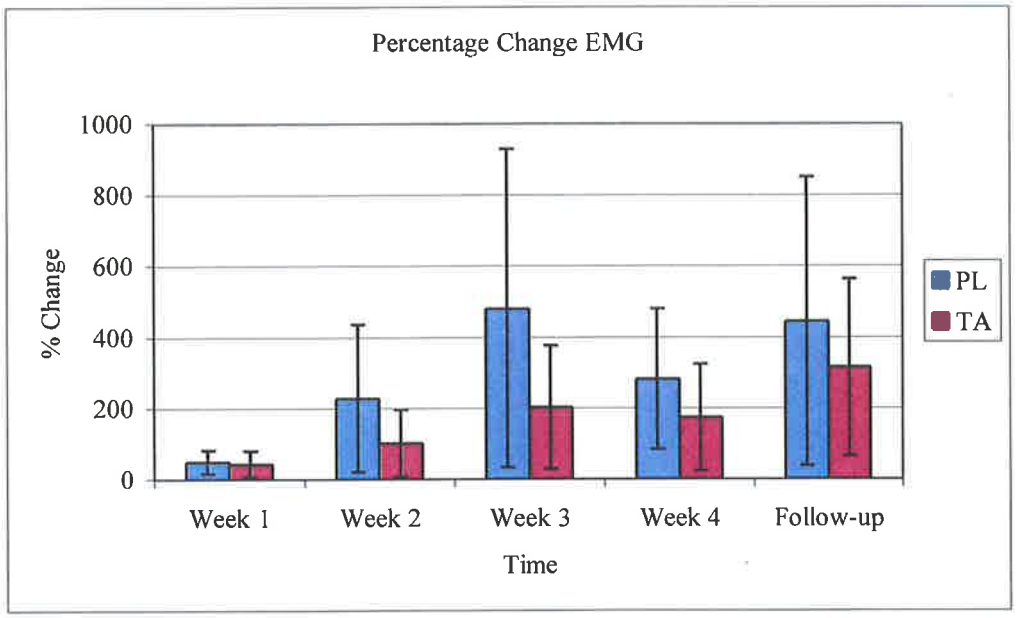

Figure 4.2 Percentage change from baseline of the integrated EMG in both the tibialis anterior (TA) and peroneus longus (PL) on affected side throughout the testing period. Data recorded during a maximum voluntary contraction (MVC) (mean ± se, n=10).

	TA		PL	
Subject	**Baseline**	**Week 4**	**Baseline**	**Week 4**
1	0.01	0.08*	0.001	0.02*
2	0.08	0.05	0.01	0.03*
3	0.07	0.10	0.03	0.04
4	0.08	0.13*	0.03	0.02
5	0.02	0.02	0.01	0.01
6	0.03	0.03	0.01	0.01
7	0.06	0.07	0.02	0.03
8	0.04	0.01	0.02	0.03
9	0.002	0.01*	0.001	0.01*
10	0.05	0.05	0.01	0.01
Mean	***0.04***	***0.05***	***0.01***	***0.02***

Table 4.3 Baseline and Week 4 EMG – MVC data of all 10 subjects for both the affected tibialis anterior (TA) and peroneus longus (PL). *indicates a significant difference from baseline (repeated measures ANOVA $p<0.05$).

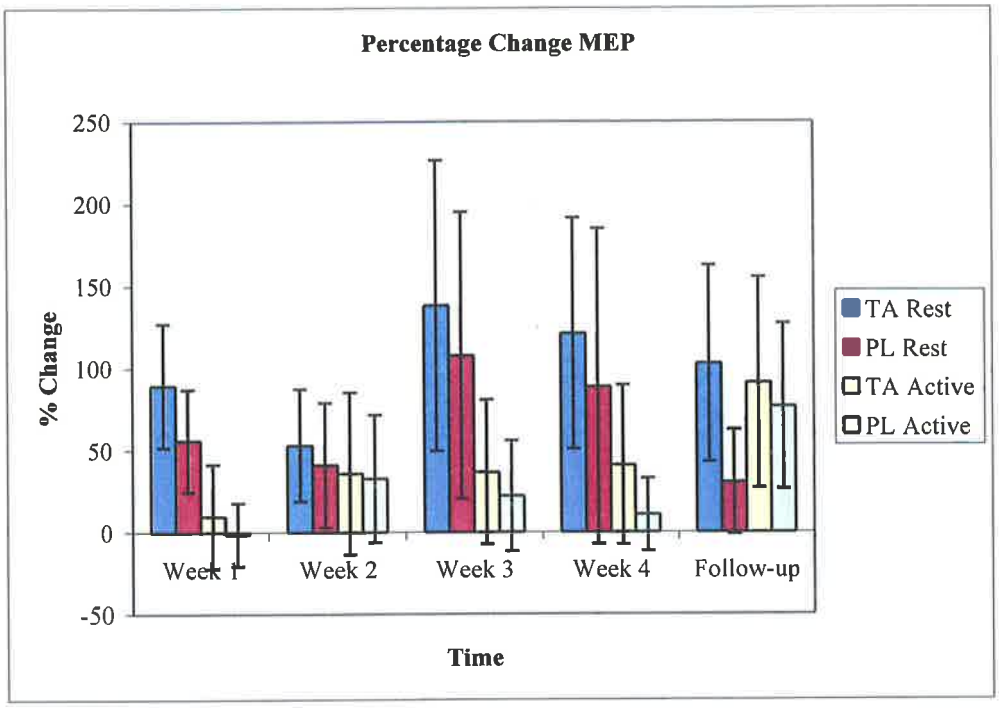

Figure 4.3 Percentage change of the MEP in both the affected tibialis anterior (TA) and peroneus longus (PL). Data recorded during a relaxed state and active contraction on affected side (mean ± SE, n=10) compared from baseline throughout the testing period.

4.3.1.3 MEP Amplitude

MEP amplitudes in both relaxed and voluntarily active PL and TA muscles were also highly variable both between subjects and within subjects across the testing period. At the end of the four-week dual stimulation period, MEPs in the stroke-weakened relaxed PL increased by an average of 89 ±56.8% at week four (range of 63 - 850%; mean baseline value = 0.07 mV). The MEPs in the voluntarily activated PL were increased by an average of 11 ± 32.8% by the fourth week (range of 90 -160%; mean baseline value = 0.28 mV). By the end of the fourth week of stimulation, MEP amplitudes in the relaxed TA increased 121 ±58% (range 4-655%; mean baseline value = 0.11 mV) and in the active TA 146 ±47.6% (range 2-4850%; mean baseline value = 0.73 mV). The data for both TA and PL are shown in Figure 4.3 and Table 4.3.

	Neurophysiological Measures							
	MEP Relaxed (mV)				MEP Active (mV)			
	TA		PL		TA		PL	
Subject	*Pre*	*Wk4*	*Pre*	*Wk4*	*Pre*	*Wk4*	*Pre*	*Wk4*
1	0.12	0.36*	0.06	0.11*	0.36	1.57*	0.18	0.47*
2	0.05	0.38*	0.01	0.10*	1.12	0.75	0.09	0.17*
3	0.06	0.09*	0.04	0.04	0.71	0.69	0.25	0.30*
4	0.14	0.19*	0.06	0.08*	0.49	1.60*	0.25	0.23
5	0.09	0.07	0.05	0.03	0.46	0.40	0.16	0.16
6	0.31	0.21	0.17	0.15	0.82	0.69	0.31	0.40*
7	0.05	0.18*	0.12	0.06	1.81	1.35	0.69	0.56
8	0.18	0.16	0.16	0.06	0.25	0.31*	0.39	0.33
9	0.08	0.08	0.09	0.10	0.60	0.47	0.38	0.46*
10	0.03	0.05	0.01	0.01	0.70	0.76	0.10	0.10
Mean	0.11	0.20	0.07	0.07	0.73	0.85	*0.28*	*0.32*

Table 4.4. Baseline and Week 4 MEP data of all 10 subjects for both affected Tibialias Anterior (TA) and Peroneus Longus (PL). *indicates a significant difference from baseline (Repeated Measures ANOVA $p<0.05$).

The patterns of change in MEP amplitude in two subjects who responded in different ways are shown in Figure 4.4. The upper record shows the data from a subject in whom the intervention was associated with a progressive increase in the MEP amplitude from the first treatment. The response reached a plateau on day six, and was maintained into the follow-up examination two weeks after the cessation of the dual stimulation. At the other end of the spectrum, the MEPs of the subject whose responses are charted in the lower graph did not change consistently throughout the course of the intervention.

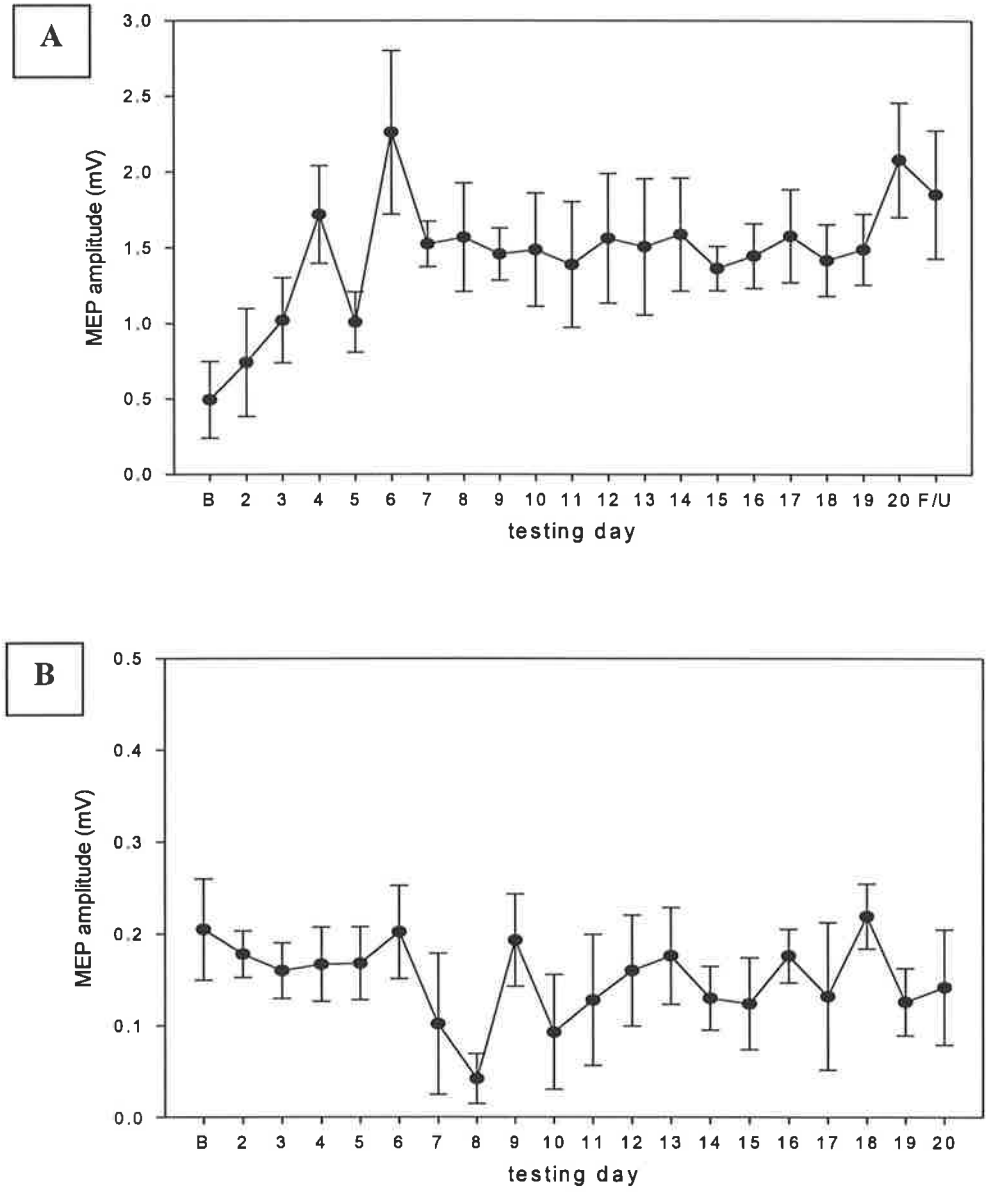

Figure 4.4 Data from two subjects' lower limb MEP responses to the dual stimulation.

This variability in the small sample tested no doubt contributed to the resultant non-significant change in MEP amplitude across testing sessions in the grouped data (Repeated Measures ANOVA p=0.84; F=0.042). Given this variable pattern of response, we analysed all of the variables within each individual across the course of the

study. This demonstrated significant improvements in both neurophysiological and functional measures in a number of subjects (Table 4.2, 4.3 and 4.4). However, even within individual subjects, the results were variable between testing sessions.

Lesser changes were also seen in the responses of the leg that was not affected by stroke. By week four, the MEP amplitude in the unaffected leg had increased 4% (range -28-85%; mean baseline value = 0.39 mV) in the relaxed PL, and changed -8% (range – 52 to +30%; mean baseline value = 0.88 mV) in the voluntarily active PL. MEP amplitudes in the relaxed TA increased 9.3% (range -30 to +335%; mean baseline value = 0.67 mV) and MEPs in the active TA changed -2% (range -36 to +38%; mean baseline value = 2.47 mV).

Analysis of individual data revealed that, for the affected limb, MEP and MVC amplitudes were consistently elevated in five of the ten subjects (for all cases $p<0.05$, Repeated Measures ANOVA). Improvements in neurophysiological measures were evident as early as the first week of dual stimulation (Figure 4.5). However, in other subjects, no facilitation or even depression was found.

4.3.1.4 MEP Latency

MEP latencies for TA and PL were significantly longer on the affected hemiparetic side than on the unaffected side under both resting conditions ($p=0.0002$; $F=4.43$) and during weak contractions ($p=0.001$, $F=26.9$). On the affected side, the latency shortened from a mean of 50 ± 13 ms for TA and PL at rest, to 37 ± 5 ms for TA, and 36 ± 5 ms for PL during weak muscle contraction. The shortening of latency was significant for both muscles ($p=0.007$; $F=12.04$). On the unaffected side, there was no significant difference

in the latency of MEPs between the relaxed and contracting muscles. The latencies of MEPs in PL and TA did not change significantly throughout the course of this study.

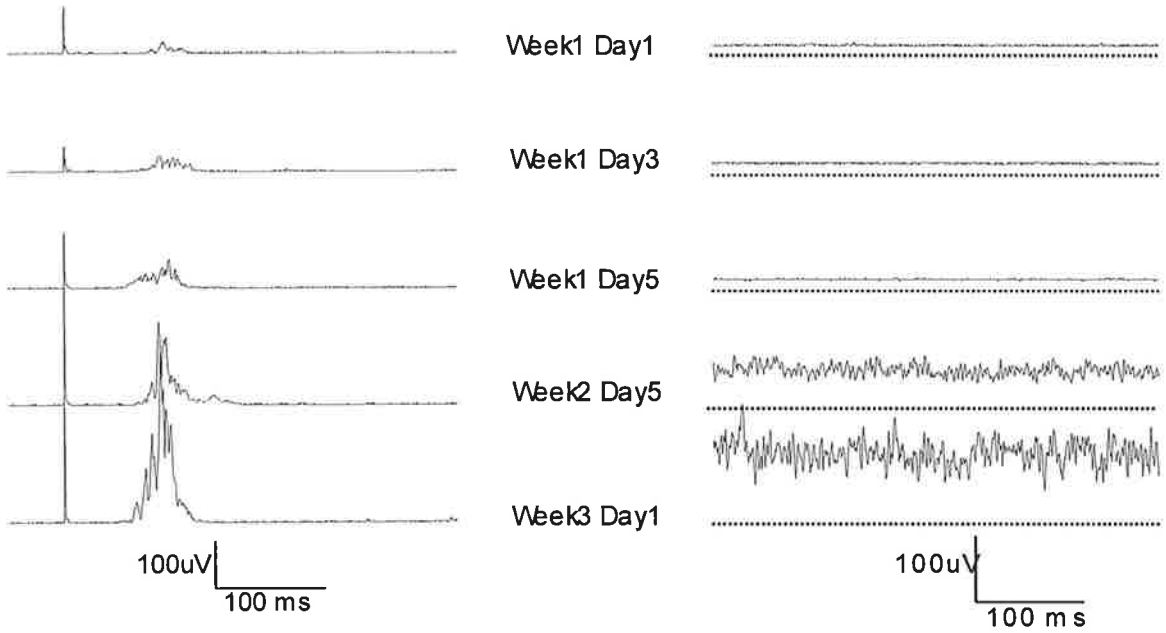

Figure 4.5. An example of raw data traces from a subject (S2) who responded positively to the dual stimulation intervention. Left panel: Average rectified motor evoked potentials (MEPs) in the weak peroneus longus muscle. The top trace shows that on day 1 before any dual stimulation the MEP was very small. The MEPs evoked at the same stimulus intensity increased dramatically in amplitude over successive days during the course of this intervention. Right panel: Mean rectified EMG recorded during maximal voluntary contractions of the peroneus longus on the same days. The dotted lines are at 0 V.

4.3.2 *Functional Tests*

4.3.2.1 Group analysis

A paired t-test was used to test the two baseline functional scores. No significant change was noted on the functional measures across the two periods (t=0.89) indicating that functional scores were stable before the intervention. A Friedman Two-Way Analysis of Variance was used to test all the functional scores. Cadence, stride length and time to heel strike (FSCAN) scores significantly improved by the fourth week of stimulation when compared to the two baseline scores (p=0.031; F=4.26). Though no significant change was found in the other gait measures, it should be noted that individual subjects showed remarkable improvements on some scores by the end of the stimulation period (Table 4.5).

4.3.2.2 Analysis of individual responses

Changes in functional measures for the ten individual subjects are summarised in Table 4.5. Note that two of the early subjects were not tested on some outcomes.

4.3.2.3 Plantar Pressure

FSCAN analysis of the pattern of plantar contact on landing while walking showed that the timing of heel-strike improved significantly (Friedman Test-0.001) in seven out of the nine subjects tested by week four (Baseline score (Mean ± SE) = -3.4 ±0.8; score at week 4 = 10.6 ±2.6). Significant improvements began as early as the second week of dual stimulation and were still evident on follow-up.

Subject	Functional Scores																							
	Cadence (steps/10 m)			Stride (cm)			Heel strike timing (ms)			Speed (secs/10m)			Step Ipsi (cm)			Step Contra (cm)			Passive DF (degrees)			Active DF (degrees)		
	BL1	BL2	WK4	BL1	BL2	WK4	BL1	BL2	WK4	BL1	BL2	WK4	BL1	BL2	WK4	BL1	BL2	WK4	BL1	BL2	WK4	BL1	BL2	WK4
1	*	*	*	*	*	*	-15	-15	-12	*	*	*	*	*	*	*	*	*	80	*	82	120	*	90
2	*	*	*	*	*	*	-11	-5.8	***4.29***	*	*	*	*	*	*	*	*	*	85	*	70	90	*	85
3	50	50	***40***	41.25	40	***51.25***	-5	-5	***0***	39	41	31	24	24	34	19	18	19	118	122	118	120	120	122
4	41	42	***27***	48	47	***75***	-5	0	***68***	40	42	100	38	38	38	10	10	37	138	140	134	135	136	129
5	41	40	***29***	45	45	50	-3	-3	***10***	54	53	43	27	28	34	20	29	18	125	125	125	129	130	127
6	22	22	20	78	85	***110***	7	5	***12***	15	14	15	36	38	54	49	50	54	104	109	117	107	108	115
7	48	51	46	45	42	43	-10	-10	-9	38	39	36	23	25	23	20	20	22	121	121	121	134	134	124
8	52	50	***40***	44	43	***54***	3	6	***12***	66	74	58	33	34	35	11	7.5	18	127	129	121	139	140	133
9	92	92	***50***	16	16	***41***	*	*	*	100	100	33	28	28	23	12	12	18	137	133	138	144	145	147
10	62	60	***50***	42	42	***64***	3	3	***10***	42	40	30	32	30	38	11	10	14	125	122	130	130	132	135
Mean	51	50.8	37.8	44.9	45	61	-4	-2.75	10.6	49.3	50.4	43.3	30.1	30.6	34.9	19	19.6	25	116	116.6	115.6	124.8	125.5	120.7

Table 4.5 Summary of the functional measures data of all subjects across the two baselines (BL1 & BL2) and at the end of week 4 (Wk4). Significant differences (Friedman Two-Way ANOVA, $p<0.05$) are highlighted in bold and italics. Step Ipsi = Ipsilateral step length (weak side); Step Contra = Contralateral step length (unaffected side); DF= Dorsiflexion; * indicates not tested.

4.3.2.4 Cadence

By the end of the fourth week of stimulation, six subjects showed significant improvements (Friedman Test=0.003) in cadence (Baseline scores (Mean ± SE) = 50.9 ± 2.5 steps/ 10 m; Week 4 scores = 37.8 ± 1.4 steps / 10 m). Further analysis showed that significant improvements occurred after three weeks of stimulation.

4.3.2.5 Stride Length

Stride length significantly improved in six subjects by the end of the third week of intervention (Friedman Test=0.008). The stride length increased accordingly as the subjects' improved cadence translated to fewer steps taken to cover 10 metres. Baseline measures (Mean ± SE) = 44.95 cm ± 2.2 and measures taken at week four = 61 cm ± 2.83.

No statistically significant improvements were noted in the other gait variables measured.

4.3.3 Subjective Scores

The subjective scores were derived from a Mobility Self-Rating Scale (MSRS) and from a Mobility Functioning Scale (MFS). The MSRS allows the subject to report his /her daily mobility using a Likert Scale during the intervention. Analysis of the MSRS scores did not reveal any statistical significance (Friedman Test=0.03). The MFS allows the subject to report his/her perception of mobility in seven functional categories. Statistical analysis of MFS scores revealed scores to be significantly different at week four when compared to baseline (Friedman Test=0.002). Further analysis showed that subjects reported marked improvements in their ability to walk inside their homes

without a splint or aid (MFS Category 2) and walking outdoors without the need for a splint of walking aid (MFS Category 4). These improvements occurred as early as the second week of intervention and continued to be reported at follow-up.

4.4 Discussion

There are difficulties with the interpretation and presentation of the data in this preliminary study on the use of a dual stimulation paradigm on a group with chronic hemiparesis. Although considerable effort was made to recruit as many subjects possible within the expected time frame, the number of subjects who agreed to participate and completed the experiment was still insufficiently small. As such, the presentation of lesions responsible and resultant impairments of the subjects were heterogeneous. This contributed to the variability of the responses of individuals. However, improvements were clearly seen in some patients and suggest the therapeutic potential of the dual stimulation paradigm.

4.4.1 Neurophysiological parameters

The baseline voluntary EMG and MEP measurements in the present study confirm previous results that these parameters are depressed or absent after a stroke. In the acute stages of stroke, large MEPs indicate a good prognosis for recovery, and small or absent MEPs indicate a poor prognosis for functional recovery (Macdonnel et al. 1989). The subjects entering the present study had chronic stable hemiparesis, and small, delayed MEPs and low-amplitude EMG during maximal voluntary contractions, which would be considered unlikely to improve with conventional therapy. Despite this, improvements

were seen in function as well as objective measurements during the course of the intervention in some subjects.

The mechanism underlying the change in excitability of the corticospinal projection is not known. However, a number of possibilities exist. Firstly, while the evidence for neuronal regeneration in the adult human is limited, it has been reported in some other species, especially in the presence of behavioural demand (Bury et al. 2000). However, it is very unlikely that the increases in MEP amplitude, voluntary EMG and improvements in function reported in the present study are due to regeneration, given the time-scale of change. For example, clear improvements in the above measures were apparent in some subjects as early as the first week of dual stimulation (Figure 4.5).

The second, and more likely, explanation for the improved corticospinal excitability is the unmasking of previously silent cortico-cortical or cortico-subcortical connections. The mechanisms by which this unmasking is brought about may include both a reduction of local inhibition or changes in synaptic efficacy (Ridding et al. 2001). Periods of prolonged peripheral nerve stimulation produce similar changes to those seen with the dual stimulation paradigm described here (Ridding et al. 2000), and it has been proposed that the mechanisms behind these changes may depend on GABAergic synapses (Ziemann 1998). The nature of the changes induced by dual peripheral and central stimulation (i.e. persistent but reversible, and topographically specific) also suggest a role for long-term potentiation (Stefan et al. 2000). The opening up and strengthening of previously silent synapses would provide the mechanism by which cortical map expansion and displacement could occur.

It has been shown using TMS that, following stroke, there is a displacement of a muscle's scalp representational map (Byrnes et al. 2001). In addition, functional imaging techniques have demonstrated that use of a stroke-weakened hand results in an activation of the sensorimotor cortex that is posterior to that seen in control subjects (Pineiro et al. 2001). This reorganisation of motor output has been suggested as a substrate of functional recovery and may indicate a shift in a muscle's cortical representation into adjacent non-damaged cortex (Chen et al. 2002; Nudo et al. 1996). The factors responsible for triggering shifts in a muscle's representation are not fully understood. However, changes in afferent input are likely to play a role. It has previously been shown that periods of afferent stimulation can lead to representational map expansion and displacement (McKay et al. 2002; Ridding et al. 2001). Changes in afferent input can be brought about by both passive or voluntary use of a muscle or by peripheral nerve or muscle stimulation. Therefore, it is possible that either use (passive or voluntary) of a muscle or peripheral stimulation of a muscle could induce a shift of that muscle's representation into adjacent undamaged cortex with an associated functional improvement.

4.4.2 Functional Changes in Gait

Up to 80% of stroke survivors achieve independent gait (Wade et al. 1987). However, independent gait does not imply normalised gait. In order to manage walking independently, most stroke survivors need the assistance of a walking aid or an ankle foot orthosis to counteract the effect of their diminished motor control. In the present study, we targeted our dual stimulation on the TA and PL muscles that are the primary dorsiflexors and evertor muscles respectively in the normal gait cycle. Improved function in these muscles was therefore considered most likely to reverse gait

disturbances. In particular the earlier heel-strike exhibited by seven subjects indicated a more normalised pattern using appropriate timing and recruitment of TA and PL.

The hemiparetic gait is characterised by a reduced walking speed, decreased stride length and cycle duration (Knutsson 1981; Knutsson and Richards 1979; Wall and Ashburn 1979). Two of the subjects in the present study showed marked improvements in gait speed, cadence, stride and step length. However, the walking speed decreased significantly in a third subject (S4): while the timing of his heel-strike improved markedly. It was observed during testing that recruitment of TA during initial contact required extra time. The improvements in step length in four subjects may be due to an increased swing phase brought about by increased activity of TA resulting in a better foot clearance and greater ankle stability. This provided for an effective propulsion in terminal stance.

4.4.3 Subjective questionnaire data

Most subjects reported subjective improvements as a result of the protocol, although it must be remembered that they were not blinded to treatment. Four subjects reported an increased level of confidence in walking without the aid of their ankle foot orthosis inside their homes. This lends further support to the presence of improved control of the PL and TA muscles.

4.4.4 Pattern of response to dual stimulation

Some subjects showed dramatic and unambiguous changes in objective measures such as corticospinal excitability, maximal voluntary EMG and earlier heel strike, while there was little or no change in others. In those subjects in whom the neurophysiological measures improved, similar changes were often seen in the *non-affected* limb muscles. There are several possible explanations for this observation. Although subjects were instructed not to carry out any special or additional exercises at home during the period of the study, the positive results experienced by some subjects may have led to changes in the pattern of their daily activities and consequent changes in the variables and parameters that we measured. For example, if a subject's ability to walk improved during the course of the intervention, it is likely this led to greater time spent walking. However. conversely it has been noted clinically that when the motor performance of the hemiparetic side improves, the non-affected side would be expected to be less dominant. It is also possible that changes may have been induced in the unaffected leg by the repeated low-frequency brain stimulation applied during the dual stimulation paradigm. The low-threshold scalp site for the TMS of the leg is near the midline, and TMS usually activates the leg areas of motor cortex bilaterally. Although TMS at these low frequencies has not been shown to affect cortical excitability measures in normal subjects (Chen et al. 1997), it is possible that repeated application to stroke subjects over a number of weeks might have induced some effect.

It could be argued that the improvements seen in function were a non-specific placebo effect. There are a number of reasons why this is unlikely to be the case. Firstly, subjects were included in this trial only if they have had regular physiotherapy previously and were discharged from active rehabilitation as they were considered to

have been functionally stable (for at least six months and, in some cases, for several years). Secondly, many of the parameters that improved in some subjects, such as maximal MEP amplitude and maximal voluntary EMG, are objective and are most unlikely to be subject to modulation as the result of placebo effect. Thirdly, the functional measures improved more in those subjects in whom the neurophysiological measures improvements were larger (Figure 4.6). Finally, by the end of the period of intervention, several subjects reached a level of function never attained during their course of conventional rehabilitation. I therefore contend that the improvements documented are unlikely to be the result of a placebo effect.

4.4.5 Factors contributing to the variable pattern of responses

Several factors may have contributed to the variable responses to the dual stimulation. Firstly, while we attempted to achieve a reasonable consistency of functional disability in our subject selection, subjects varied considerably in age, the size and site of the lesion, and in the time post-stroke. These factors may be critical in determining the nature of the response to the dual stimulation intervention (Duncan et al. 1992). For example, sparing of the cortical mantle may be an important factor in determining neurophysiological/functional outcome following dual stimulation. Subjects 1 and 6 almost certainly had no direct cortical infarction whiles the other subjects most likely did. Subjects 4, 6 and 7 responded most positively to the dual stimulation. Therefore no clear conclusions can be drawn as to the importance of direct cortical infarction.

Secondly, attentional and cognitive issues may be important. Attention is known to have a major influence on motor learning and cortical reorganization (Byl et al. 1997). While the subjects selected for this study were judged to have no significant cognitive deficit,

it is possible that some paid more attention to the stimulus. It is also possible that the subjects with the more positive outlooks were prepared to try harder to achieve their optimal performance during testing. Rehabilitation professionals have used patient motivation alongside other objective measures as clinical predictors of outcomes (Maclean and Pound 2000).

The nature and determinants of motivation in rehabilitation is poorly understood. Most reports are based on anecdotal evidence and do not provide a clear theoretical concept. Clark and Smith (1998) defined a set of characteristics in stroke patients as abnormal illness behaviour (AIB) and have shown how it can affect recovery following rehabilitation. The AIB typically involve traits such as apathy, dependency and refusal to accept responsibility for recovery. The AIB state can persist in the chronic stage of illness and involves an excessive adoption of the sick role (Pilowsky 1989). Although we did not formally test for AIB in our patient group, it was observed that subjects who manifested AIB characteristics did not show any improvements in the neurophysiological and functional scores. Future studies should employ social and psychological indicators to determine the presence of AIB and correlate it to any changes observed after intervention.

Medical and surgical management after stroke is very limited. Rehabilitation is the major option to improve long-term function for chronic stroke survivors. There is inadequate evidence for the efficacy of conventional physical therapy techniques to improve gait after stroke. Functional electrical stimulation was shown to enhance balance and gait quality in hemiparetic patients (Isakov and Bowker 2002).

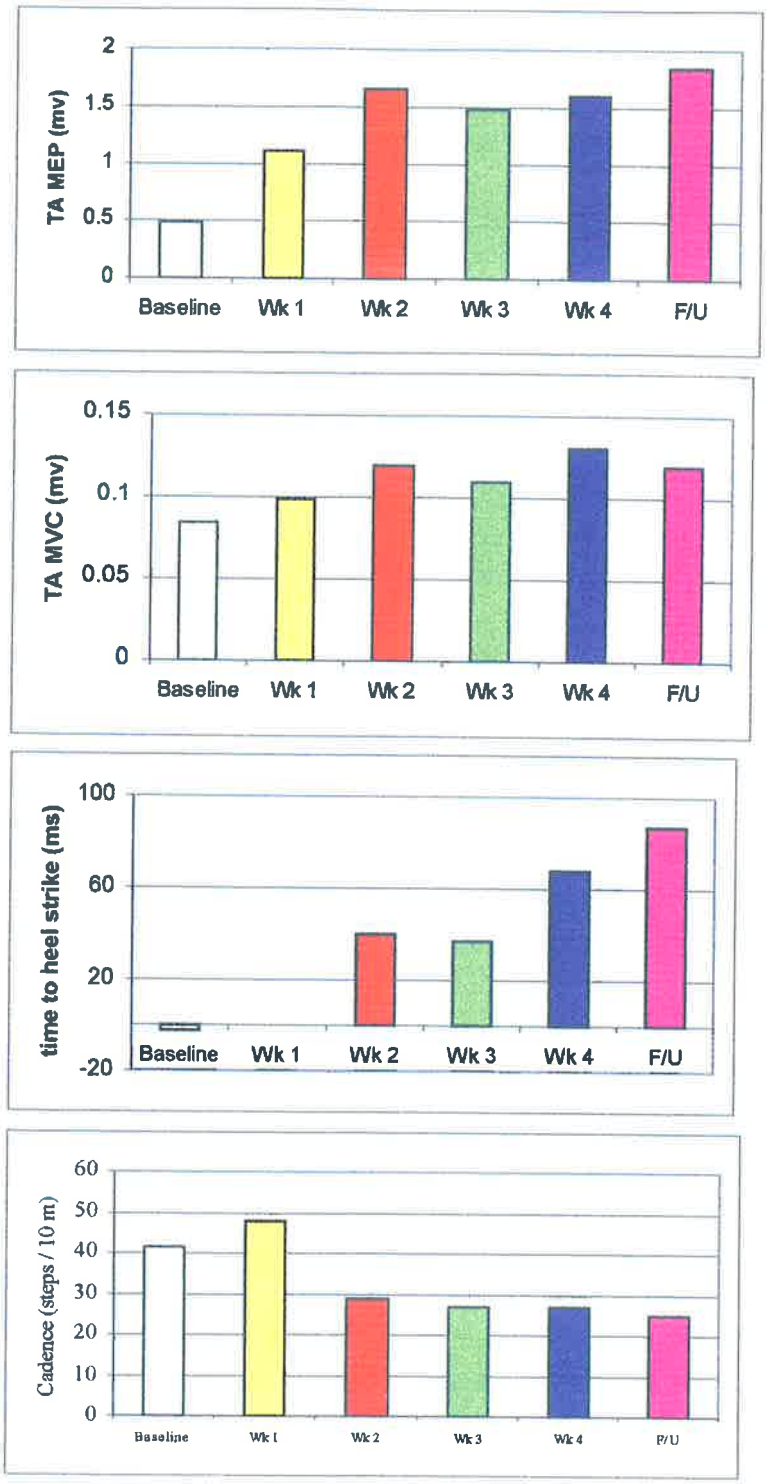

Figure 4.6 Comparison of TA MVC and MEP during weak active contraction, FSCAN scores and gait speed of one subject (S4) from baseline through to the 4 weeks of stimulation.

Improvements in gait outcomes were also seen after a 3-week supported treadmill ambulation program (da Cunha et al. 2002). Though these approaches show promise for therapeutic use, the improvements reported were mostly observed in the acute stages of stroke where recovery has been shown to be most evident (Traversa et al. 2000). Furthermore, objective measurements used in most gait studies include only outcome measures and do not present direct evidence of changes in functional plasticity.

4.5 Conclusion

In this study, I sought to establish whether a stimulation paradigm that induces prolonged increases in cortical excitability in normal subjects leads to improved motor function in chronic stroke patients. While the sample size is a limitation of the study, the dual stimulation paradigm used had quite profound effects on neurophysiological, functional and subjective parameters in some subjects. These findings lend further support to previous studies that demonstrated chronic stroke patients are still capable of undergoing improvements in neurophysiological parameters and function (Cicinelli et al. 1997; Steube et al. 2001; Traversa et al. 1997; Traversa et al. 2000). Even though the present results did not reach statistical significance across the whole group, most of the subjects showed an improving trend for their scores, which may indicate clinical if not statistical significance. Thus it is sufficiently encouraging to suggest that this approach be extended to a larger group of chronic stroke subjects with a view to determining what subject characteristics are associated with positive outcomes.

Chapter 5. Cortical Excitability and Hand Function Following Dual Stimulation in Chronically Hemiparetic Patients

5.1. Introduction

The loss of upper limb function following a stroke is one of the leading causes of long-term disability. Loss of function of the affected arm is very common, affecting up to 85% of stroke survivors (Nakayama et al. 1994). Recovery generally occurs within 6 months and plateaus in about 1 year, leaving up to 50% of chronic stroke survivors with some form of functional limitation beyond this period (Olsen 1990; Parker et al. 1986). Although the medical or surgical treatment of stroke is limited once the infarct is stable, there is a diverse range of therapeutic options available. The evidence supporting the specific effects of the rehabilitation interventions is not conclusive. Comparative studies on their efficacy are difficult as most strategies are based on the patient's needs, the skill and philosophy of the therapist and existing resources (Wittenberg et al. 2003). There is a need to provide an objective foundation for stroke rehabilitation based on available neuroscience research in order to improve its therapeutic value.

Cortical reorganisation has been demonstrated in the brain after a stroke. The capacity of rehabilitative training in inducing plastic change has been demonstrated in animal and human studies. Nudo et al. (1996) have shown changes in the movement representational maps in the primary cortex of primates after an ischaemic lesion following rehabilitative training of hand movements. Studies on human stroke patients undergoing constraint-induced therapy report similar results, with increased cortical

excitability accompanied by TMS map changes (Liepert et al. 2000b; Liepert et al. 2001). Different forms of afferent stimulation have been reported to induce reorganisation of the motor cortex in humans. An increase in cortical excitability has been shown with peripheral nerve stimulation (Ridding et al. 2001), combining peripheral nerve and central cortical stimulation (Stefan et al. 2000) and stimulation of motor points and motor cortex (McKay et al. 2002). The changes have also been shown to persist over time and increase the cortical map representation of the stimulated muscles (McKay et al. 2002). The nature of the reorganisation observed in these studies is akin to those in learning a motor task and thus show potential for possible use as a therapeutic intervention. To date, there are no reports on the effects of a dual stimulation paradigm on cortical excitability and hand function in brain injury, more specifically a stroke population. This study presents findings on the effects of using a combined motor point stimulation of the wrist extensors and central cortical stimulation on the neurophysiological and functional scores on a group with chronic hemiparesis.

5.2 Methods

5.2.1 Subject Selection:

Ten subjects were recruited from stroke groups and private physiotherapy practices in Adelaide. All gave written informed consent to participate in the study. The study was approved by the Ethics Committee of the University of Adelaide and Royal Adelaide Hospital. The diagnosis, age, sex, and time since the onset of hemiplegia were obtained from patient interviews and CT scan reports. Prior to commencing, each subject completed the Adult Safety Screening Questionnaire to determine suitability for TMS (Keel et al. 2001). Subjects were excluded from the study if they had significant cognitive impairments, history of seizures, metal skull implants, or cardiac pacemakers.

All subjects exhibited functional deficits of the affected hand brought about by increased muscle tone, hyperactive stretch reflexes and muscle weakness. The common muscle weakness pattern was inability to dorsiflex the affected wrist. At the time of study, all subjects were not participating in an active rehabilitation program. Of the ten subjects who volunteered, eight were able to complete the protocol and return for follow-up measures. The case profiles of each subject are presented in Table 5.1.

Subject No.	Age, y/gender	Years since stroke	Impairment side	Lesion	Modified Ashworth Scale Score (Affected wrist)	ARAT Score
1	67 / M	9	R hemiparesis	L MCA Territory	3	3
2	59 / M	5	R hemiparesis	L pontine infarct	3	3
3	60 / M	5	L hemiparesis	R MCA Territory	3	3
4	78 / F	3	L hemiparesis	R MCA Territory	4	3
5	44/ M	11	L hemiparesis	R Putaminal haemorrhage	1	54
6	60/ M	3	L hemiparesis	R basal ganglia	4	3
7	65 / M	4	L hemiparesis	R MCA Territory	3	3
8	72 / M	5	R hemiparesis	L MCA Territory	4	3
Mean ± SD	63.1 ± 10.1	5.6 ± 2.9			Median = 3	9.4 ± 18

Table 5.1 Background data for the eight upper limb stroke patients tested. Action Research Arm Test (ARAT) maximum score = 57, MAS maximum score =5. AFO = ankle foot orthosis

5.2.2 Testing Protocol

Each subject came on two occasions separated by one week for baseline tests of hand function, baseline neurophysiological testing and motor cortex mapping to establish stability of measurements as well as a point of comparison after the stimulation sessions. Dual stimulation was conducted every weekday for four weeks, for 30 minutes per session. Neurophysiological measures were taken each day prior to stimulation. At the end of each week, hand function was assessed using the tests described below. At the end of the four -week period, motor cortex mapping was repeated. Follow up assessment of neurophysiological measures, hand function and motor cortex mapping was conducted two weeks after the last stimulation session.

5.2.3 Functional Tests

5.2.3.1 Range of Movement

The passive and active range of movement (ROM) of the wrist was measured to determine the effects of dual stimulation on the contractile and non-contractile properties of the affected wrist. Landmarks on the base of the metacarpal for the index and fifth fingers, the radial and ulnar tuberosity on the wrist and the medial epicondyle on the elbow were marked and used as reference points for measuring wrist ROM. Active movement was measured by asking the subject to extend the wrist maximally. This was done for both upper limbs. The point from the base of the fifth finger to the medial epicondyle of the elbow was measured and taken as active wrist range. Passive wrist range was measured using a strain gauge device to ensure that the amount of force used was uniform for all sessions. The subject held on to a bar attached to a strain gauge. The examiner then pulled on the strain gauge with 60 N force and recorded the

point from the base of the fifth finger and the medial epicondyle of the elbow as the passive ROM.

The modified Ashworth scale (MAS) was used to assess the amount of resistance encountered during passive movement. The MAS is a common method used in the assessment of muscle spasticity in clinical practice and research (Bakheit et al. 2003; Katz and Rymer 1989) and has shown good intra and inter-rater reliability when performed by trained health professionals (Brashear et al. 2002). In the study, the affected wrist was assessed for spasticity using the simple five-point scale of the MAS. The subject's elbow was positioned as straight as possible with the forearm supinated. The wrist was then moved three consecutive times from a maximum flexion to maximum extension. The amount of muscle tone encountered was assessed accordingly to the MAS scale.

5.2.3.2 Action Research Arm Test (ARAT)

Hand disability was assessed using the ARAT. This is a valid and reproducible measure of upper limb function in hemiplegia (De Weerdt and Harrison 1985); (Hsieh et al. 1998); (Lyle 1981); (van der Lee et al. 2001). It provides information on the functional recovery of the upper extremity of stroke patients. It is an easily administered evaluation tool that examines both proximal control and dexterity, and assesses upper limb function in four categories: grasp, grip, pinch and gross movements.

In the present study, we used an 83 cm-high table with a 37 cm wooden shelf on top of it. The other items used were similar to the ones proposed by Lyle (1981). The ARAT was performed with both the affected and unaffected upper extremity. While

performing the ARAT, the subjects were videotaped to allow visual monitoring of the possible changes in hand function.

5.2.4 Subjective Questionnaire

To test the level of handicap of the affected upper limb, a motor activity log and a general functioning questionnaire were used. The motor activity log (MAL) gauged the amount as well as the quality of movement of the affected extremity in comparison to the unaffected one. The MAL used consisted of 13 categories that represented common everyday activities. The subjects responded using a five-point scale. This enabled the subject to report any changes affecting the activities of daily living that may be brought about by the intervention. In addition, a general functioning questionnaire was used. This presented open-ended questions that would allow the subjects to report whatever changes they have observed from an individual point of view, whether it be positive or negative. The aid of the primary carer was needed in some instances when the subject was incapable of writing independently.

5.2.5 Motor Cortex Mapping and Neurophysiological Measures

Mapping of the motor cortex of both hemispheres was performed with a Magstim 200 stimulator (Magstim Co., Dyfed, UK). Recording electrodes were placed over four upper limb muscles: extensor carpi ulnaris (ECU), extensor digitorum (ED), FDI and biceps brachii (BB). Electromyograph signals were amplified and filtered (bandwidth 20 Hz to 1 kHz), sampled at a frequency of 5 KHz and stored on a computer for off line analysis. A snugly - fitting cap marked with a 1 x 1 cm grid was placed on the head of the subject and stimulation done over each grid point. The coil was oriented 45° oblique to the sagittal mid-line with the handle held posteriorly so that the induced current

flowed in a plane perpendicular to the estimated alignment of the central sulcus. The optimal stimulation site for eliciting a MEP from the ECU and ED was established with the TMS using a standard figure of eight coil. Mapping was performed at 15% above resting threshold. Three MEPs were recorded at each scalp point. The boundary of the map was determined by ensuring at least one unresponsive site for ECU was recorded along each outer edge of the map. Both hemispheres were mapped during two sessions prior to the 4-week stimulation sessions, on the fourth week of stimulation and two weeks post stimulation. To measure the excitability of the cortical projection to the muscles, TMS was also applied over the optimal stimulation site on the scalp as previously determined by the mapping session. In addition to resting threshold, active threshold was also determined with the subject attempting a minimal voluntary (5-10% of MVC) wrist extension movement. A series of 10 stimuli were given during both the resting and active states. The average of these 10 stimuli were assigned as the resting and active MEP amplitudes. The EMG during a maximal isometric wrist extension for 20 seconds were also recorded

5.2.6 Dual Stimulation Protocol

The dual stimulation protocol was based on the paradigm described by Stefan et al., (2000) and McKay et al., 2002. It consisted of combined TMS and muscle motor point electrical stimulation (ES) delivered at an inter-stimulus interval of 25 ms. This timing is selected to ensure that the afferent volley from the ES arrives in the motor cortex at approximately the same time as the magnetic stimulus is applied (Stefan et al. 2000). The intensity of stimulation was set at 15% above resting motor threshold. The ES consisted of a 10 Hz, 500 ms train of pulses (1 ms duration) repeated every 10 seconds (McKay et al. 2002). The intensity was set at a level that evoked small visible twitches in the wrist and finger extensors.

5.3 Data Analysis

All statistical analyses in this study were performed using the Statistical Package for Social Sciences (SPSS) software. A value of $p < 0.05$ was set to describe significance for all analyses.

5.3.1 Baseline Tests

Descriptive statistics (mean and standard deviation) were calculated for the subject's age and time since stroke. The baseline neurophysiological and functional measures were analysed using a paired t-test to assess its stability. After which the two sets of baseline measurements were then averaged to form the baseline measure. This baseline measure was used as a point of comparison for the subsequent test measures.

5.3.2 Motor Evoked Potential Size and Latency

The daily neurophysiological measures were averaged into a weekly score for comparison with the baseline and follow-up measures. A two-way repeated measures ANOVA was used to analyse the scores. The repeated measures ANOVA analysed the effect of the dual stimulation across the time periods, the main effect on the subjects and the interaction between these two factors. If the scores revealed significance, a multiple comparison test computing for Tukey's honestly significant difference was performed.

5.3.3 Transcranial Magnetic Stimulation Thresholds

The motor thresholds for TMS for the affected and unaffected side were compared using a paired t-test. A repeated measures ANOVA was used to determine the effect of the dual stimulation on the thresholds across the intervention period and follow-up.

5.3.4 Centre of Gravity Measures

The CoG measures taken from the TMS maps of the affected and unaffected hemisphere were also compared using a paired t-test. Further analysis using a repeated measures ANOVA with main factors as time (6 levels) and muscle (4 levels). This was used to determine the effect of the intervention on the movement of the CoG across the intervention period and on follow-up.

5.3.5 Functional Measures

A repeated measures ANOVA with main factors as movement (2 levels) and time (6 levels) was used to determine the effect of the dual stimulation on the range of passive and active wrist extension movements of both upper limbs. A Friedman two-way analysis of variance by ranks was used to analyse the ARAT scores and the subjective questionnaire scores. The main factors in the ARAT score analysis were time (6 levels) and function (4 levels). Factors analysed from the subjective scores included time (6 levels) and response items (8 levels). Since these scores are considered non-parametric, the Friedman test is considered the appropriate alternative to the parametric repeated measures ANOVA. When there was statistical significance, further analysis of pair-wise contrasts was performed by computing for the minimum significant difference (MSD) (Portney and Watkins, 2000). The computed score should be equal to or greater than the computed MSD to establish significant difference.

5.4 Results

5.4.1 Baseline measurements

There was no significant difference between baseline measures of CoG (t=2.75, p=0.72), MEP amplitude (t=2.48, p=0.87) and latency (t=3.07, p=0.91) and motor thresholds (t=3.14, p=0.98). Likewise, there were no significant differences between baseline measures of range of movement of wrist extension, Ashworth scale (t=2.79, p=0.83), ARAT scores (t=1.20, p=0.97) and MAL scores (t=3.41, p=0.98). This indicates that the scores were stable during the two weeks of baseline prior to the stimulation period. The two sets of baseline measures were then averaged and used as the baseline score for comparison with the weekly and follow-up measures.

5.4.2 Neurophysiological Measures

5.4.2.1 TMS Motor Threshold

Motor thresholds were significantly different for the affected and unaffected hemisphere (p=0.00003; F=11.7). The mean threshold for evoking TMS responses on the unaffected side was 47 ± 6% at rest and 37 ± 6% during active contraction. The average threshold for the affected side was 75 ± 19% at rest and 64 ± 21% during active contraction. Motor thresholds did not change significantly for either hemisphere during or following the intervention (p=0.99; F=0.001).

5.4.2.2 Maximal EMG

The EMG recorded during maximal voluntary contractions in the four muscles tested on the affected and the unaffected side were significantly different (p=0.000016; F=3624). These measures did not change significantly for side or any muscle across time (p=0.09, F=0.13). By the fourth week of stimulation, there was a 29% increase in the EMG of the affected wrist extensors (ECU) and 39% with the affected finger extensors (ED) (Figure 5.1). The FDI and BB muscles increased by 2.2% and 2.1% respectively by the end of the fourth week of stimulation.

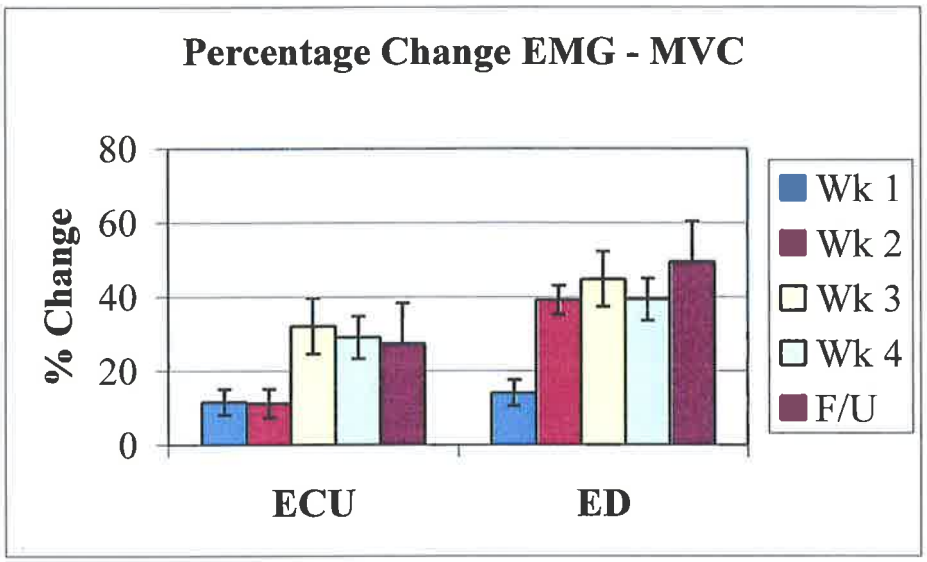

Figure 5.1 Percentage change of the integrated EMG recorded during a maximum voluntary contraction (MVC) in both the extensor carpi ulnaris (ECU) and extensor digitorum (ED). Data recorded from the affected side and compared to baseline against the testing periods (mean ± se, n=8).

5.4.2.3 Motor Evoked Potential Latency

The latency of MEPs for the four muscles tested were significantly different on the affected and the unaffected sides ($p=0.0007$; $F=31.7$). Latency did not change significantly across time for either side or any of the muscles ($p=0.99$; $F=0.01$).

5.4.2.4 Motor Evoked Potential Amplitude

The amplitude of the MEPs from all four muscles did not change significantly across the four weeks of intervention and on follow-up compared with baseline ($p=0.91$; $F=2.14$). There was great variability in the responses patterns of the subjects to the dual stimulation protocol. Figure 5.2A and B show examples of the data recorded in two subjects, one of whose MEPs increased and the other who did not. Although the change in MEP amplitudes across the group over the course of the intervention was not significant, subjects' MEP amplitude increased by an average of 40% at rest and 48% during background contraction in ECU, and 34% resting and 57% active in ED, compared with baseline. The FDI MEP increased in amplitude by 0.5% for both resting and active states by week four and the BB increased 2.1% at rest and 1.2% increase in the active state. The group data are shown as the percentage change from baseline of the stimulated muscles tested across the intervention period and on follow-up in Figure 5.3.

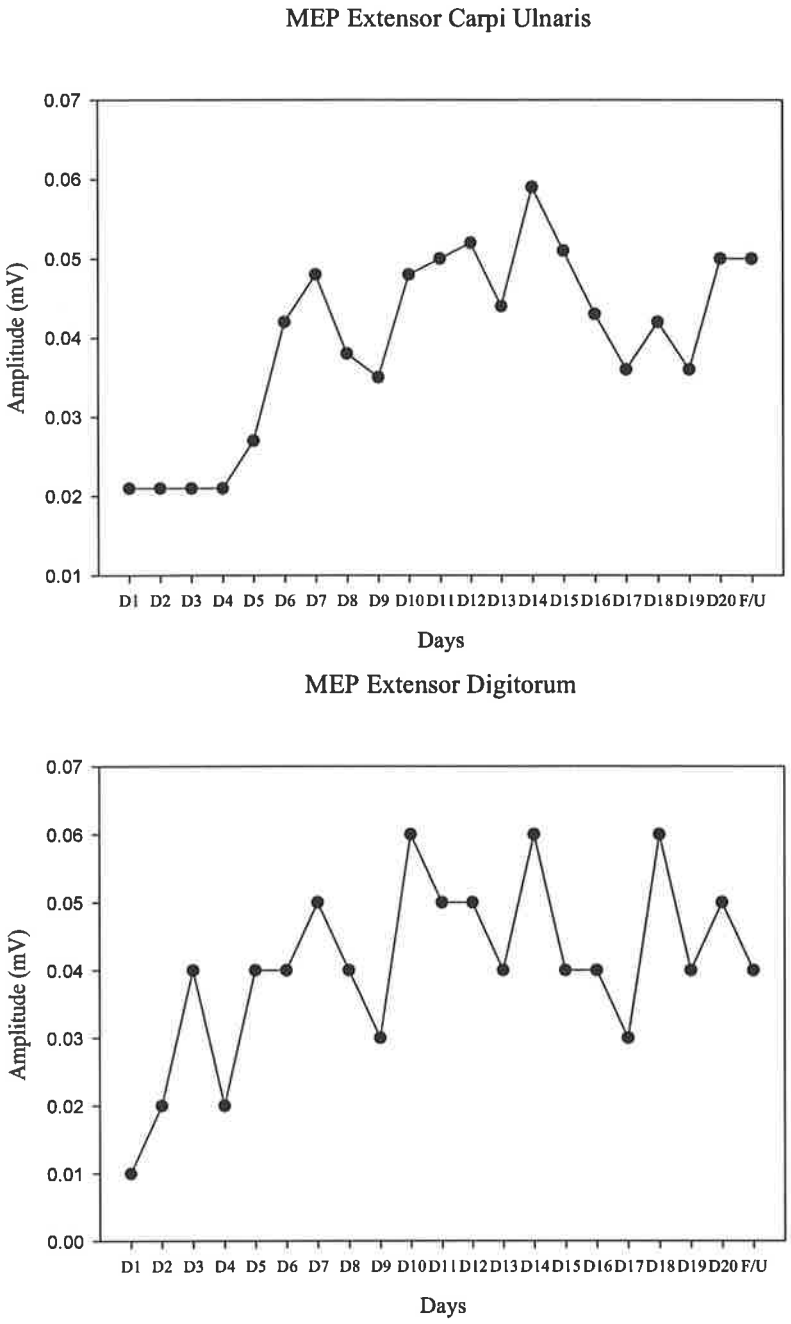

Figure 5.2A Day-by-day upper limb MEP amplitudes from a subject who showed facilitation.

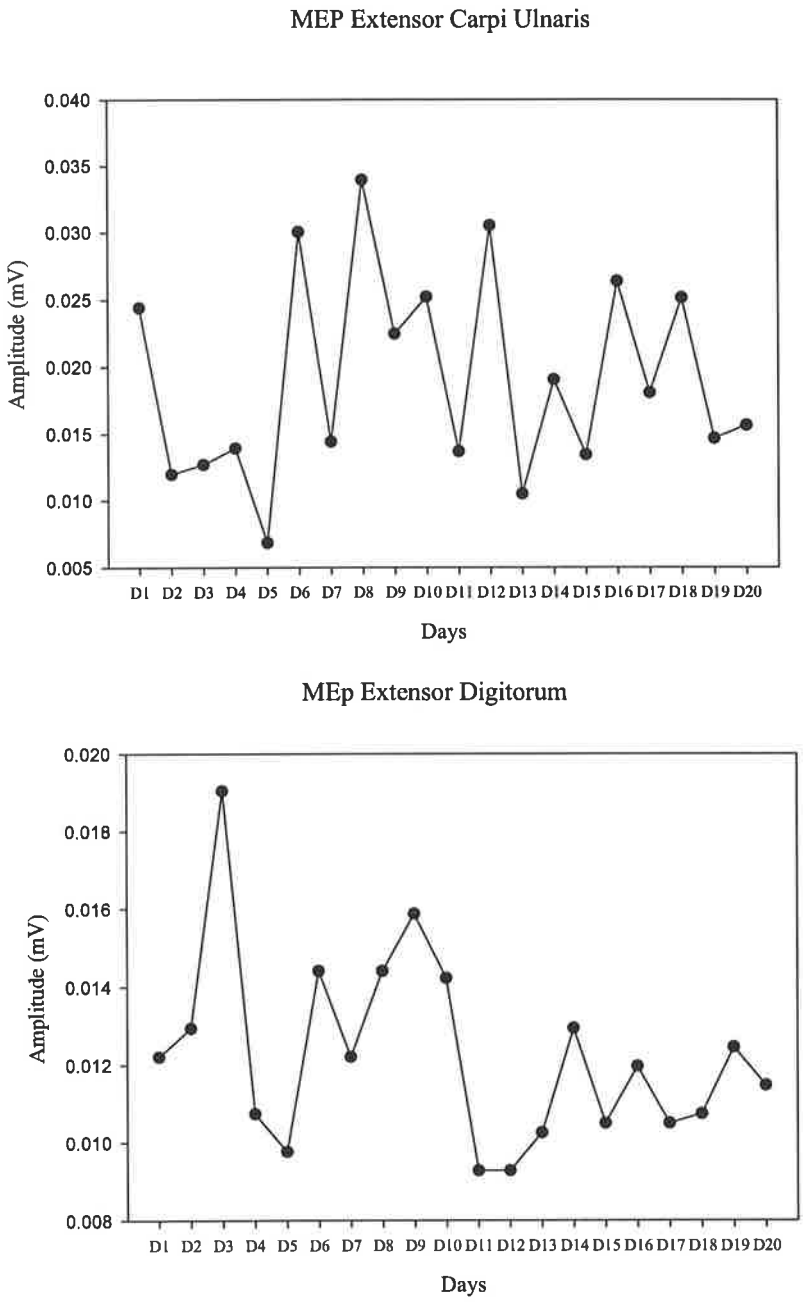

Figure 5.2B Day-by-day upper limb MEP amplitudes from a subject who did not show facilitation.

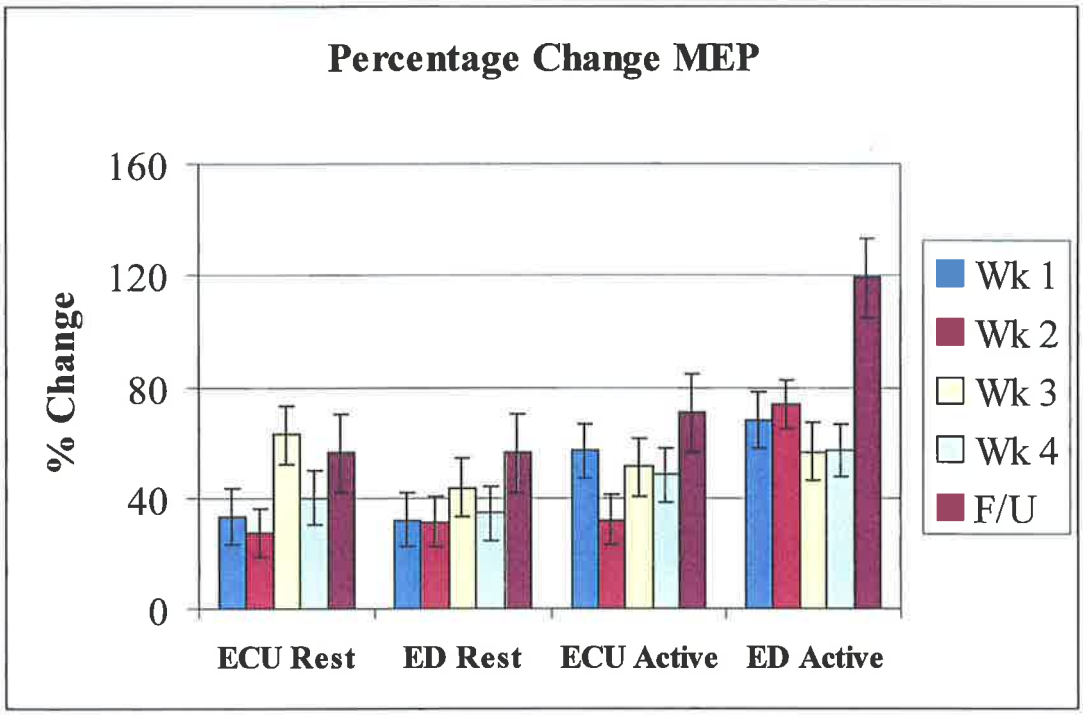

Figure 5.3. Percentage change of the relaxed and active MEP recorded from both the extensor carpi ulnaris (ECU) and extensor digitorum (ED). Data recorded from the affected side and compared from baseline against the testing periods (mean ± se, n=8).

5.4.2.5 CoG Measures

The CoG measures taken at the fourth week of intervention and on follow-up two weeks post intervention were not significantly different from baseline ($p=0.93$; $F=0.06$). Like the MEP measures, movement of the CoG was variable from one subject to the next. Tables 5.2 and 5.3 summarise the average CoG measures of the affected and unaffected hemispheres respectively. Figure 5.4 shows a comparison of the baseline and fourth week motor map of ECU on a subject who responded positively to the dual stimulation paradigm.

	BL – Week 4 Latitude	BL – Week 4 Longitude	BL – FU Latitude	BL – FU Longitude
ECU	6.5	4.2	4.9	3.2
ED	4.6	2.7	3.0	2.8
FDI	3.8	3.3	1.9	1.8
BB	3.6	2.6	1.4	1.4

Table 5.2 Average movement (mm) of the centre of gravity (CoG) of the motor maps of the affected hemisphere. Maps taken from the four muscles tested, comparing baseline (BL) to the fourth week and follow-up (FU).

	BL – Week 4 Latitude	BL – Week 4 Longitude	BL – FU Latitude	BL – FU Longitude
ECU	2.5	2.8	1.6	2.2
ED	2.6	2.8	2.1	2.5
FDI	3.1	2.8	2.0	1.6
BB	2.4	2.7	2.3	2.0

Table 5.3 Average movement (mm) of the centre of gravity (CoG) of the motor maps of the unaffected hemisphere. Maps taken from the four muscles tested, comparing baseline (BL) to the fourth week and follow-up (FU)

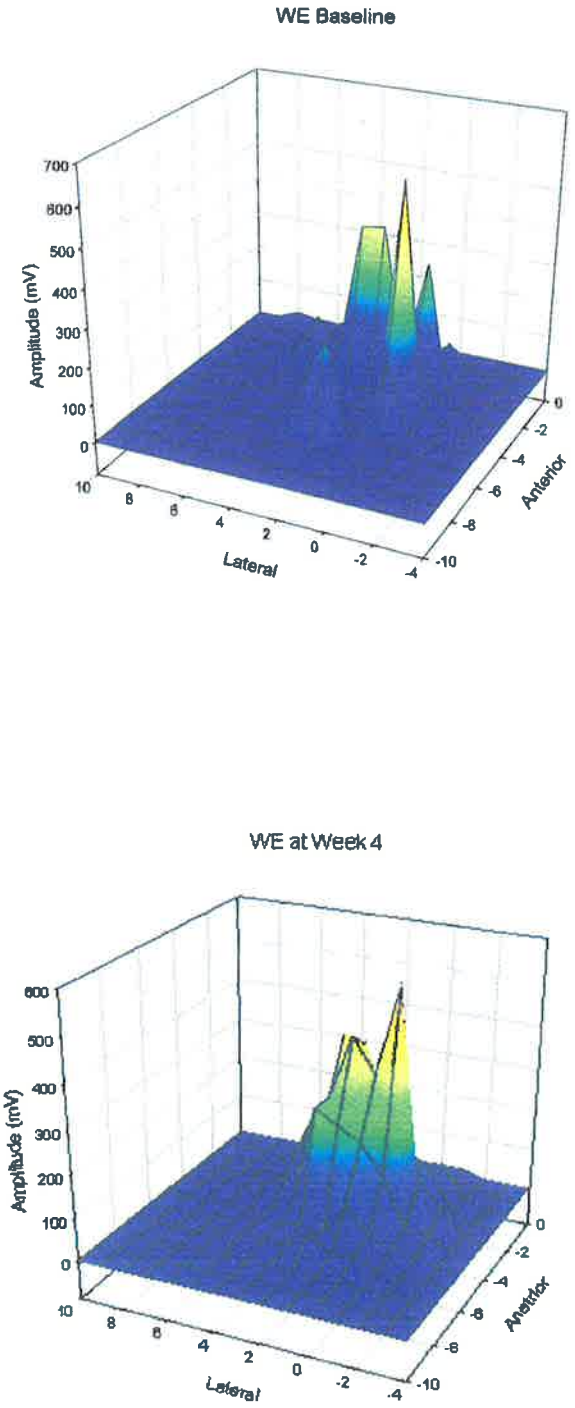

Figure 5.4. Motor map of the affected Extensor Carpi Ulnaris for a subject who responded positively to the dual stimulation.

5.4.3 Functional Measures

5.4.3.1. Modified Ashworth Scale Scores

There were no significant differences between the baseline Ashworth Scale scores and the weekly and follow-up scores (p=0.41; F=1.02).

5.4.3.2. ARAT Scores

The ARAT scores were significantly different between the baseline and across the four weeks of intervention and follow-up (Friedman Test=0.002). Further analysis revealed that the scores on the third and fourth week of intervention and on follow-up were significantly different from the baseline ARAT scores (MSD =/ >17.9, Week 3 = 20.5; Week 4 = 23.5, Follow-up = 25). Improvements were most evident in subjects who were able to perform gross upper limb movements during the baseline test. Table 5.4 shows a summary of the scores and Figure 5.5 illustrates this trend.

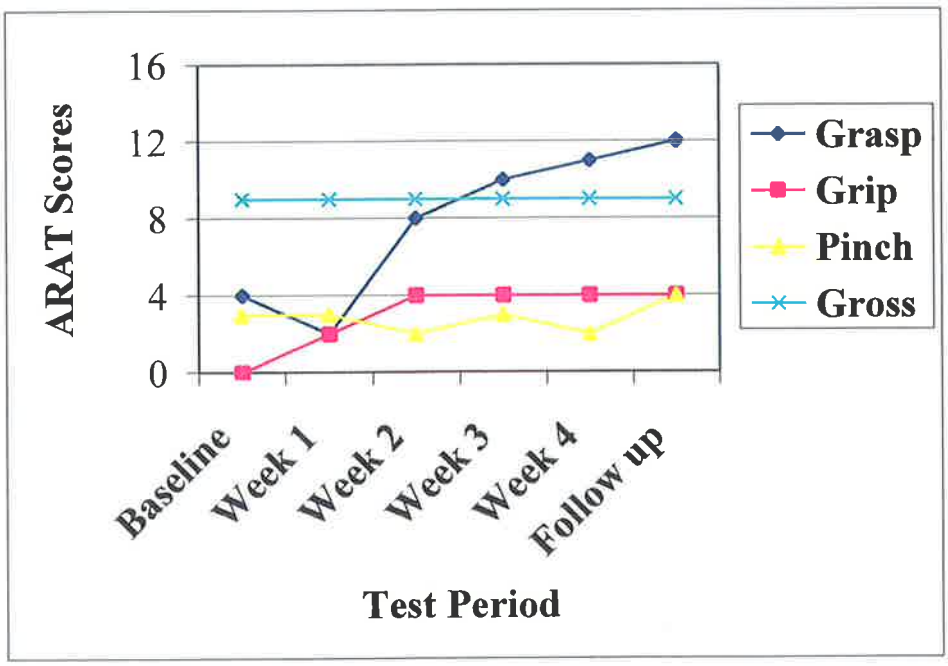

Figure 5.5 ARAT Scores of one upper limb stroke subject who responded positively to dual stimulation.

ARAT scores	B/L	Wk1	Wk2	Wk3	Wk4	F/U
S1	16	16	23	26	26	29
S2	7	9	16	19	17	19
S3	3	3	6	6	6	6
S4	3	6	6	10	10	8
S5	0	0	0	3	3	3
S6	51	51	51	51	51	51
S7	0	0	4	6	8	8
S8	0	0	0	3	3	3
Mean ± se	**10**	**10.625**	**13.25**	**15.5**	**15.5**	**15.875**

Table 5.4 Summary of the ARAT scores for all subjects across the testing protocol.

5.4.3.3 Motor Activity Log (MAL) Scores

The scores for the amount of use (AOU) and quality of movement (QOM) of the MAL revealed a significant effect of the intervention (Friedman Test=0.008). After the four weeks of intervention, all the subjects reported subjective improvements in the use of their affected upper limb and this was maintained on follow-up. Further analysis revealed that the improvements became significant at the end of the third week and were still present on follow-up (MSD = / > 17.9, AOU; Week 3 = 19, Week 4 = 21.5, Follow-

up = 22.5; QOM; Week 3 = 21, Week 4 = 23, Follow-up = 19). A summary is presented in Table 5.5.

MAL Scores	B/L	Wk1	Wk2	Wk3	Wk4	F/U
S1	18	29	33	35	36	36
S2	7	12	15	15	15	15
S3	4	4	7	11	13	13
S4	7	7	7	12	12	12
S5	7	7	7	7	7	7
S6	65	65	65	65	65	65
S7	7	10	12	15	15	15
S8	7	7	15	15	15	15
Mean ± se	**15.3±2.6**	**17.6±2.6**	**20.1±2.5**	**21.9±2.4**	**22.3±2.4**	**22.3±2.4**

Table 5.5 Summary of the Motor Activity Log (MAL) scores for all subjects across the testing protocol.

5.4.3.4 General Functioning Questionnaire

All subjects were given a general functioning questionnaire to complete at the end of each intervention week. The questionnaires posed an open question to the subjects on what they felt about their affected upper limb during the intervention. Subjects were encouraged to report any feedback, whether positive or negative. Six of the eight subjects reported a decreased in stiffness of their affected hand during the intervention. Although the changes in Ashworth Scale were not significant, a majority of the subjects

described a positive effect of the dual stimulation on the tone of their affected hand. Table 5.6 presents a summary of the MAS scores of all subjects.

MAS Scores	B/L	Wk1	Wk2	Wk3	Wk4	F/U
S1	3	3	2	2	2	2
S2	2	2	2	2	2	2
S3	3	3	3	3	2	2
S4	3	3	3	2	2	2
S5	5	5	5	3	3	3
S6	1	1	1	1	1	1
S7	2	2	2	2	2	2
S8	3	2	2	2	2	2
Mean ± se	**2.75±0.15**	**2.63±0.15**	**2.5±0.15**	**2.13±0.08**	**2±0.07**	**2±0.07**

Table 5.6 Summary of the Modified Ashworth Scale (MAS) scores for all subjects across the testing protocol.

Patients in whom the functional and subjective scores improved most were generally those in which neurophysiological measures also improved most. This finding is similar to that reported in the gait study described in Chapter 4. Therefore, there appears to be a relationship, albeit weak, between functional outcome and motor cortical excitability change. Figure 5.6 illustrates the complimenting neurophysiological and functional measures following dual stimulation in stroke.

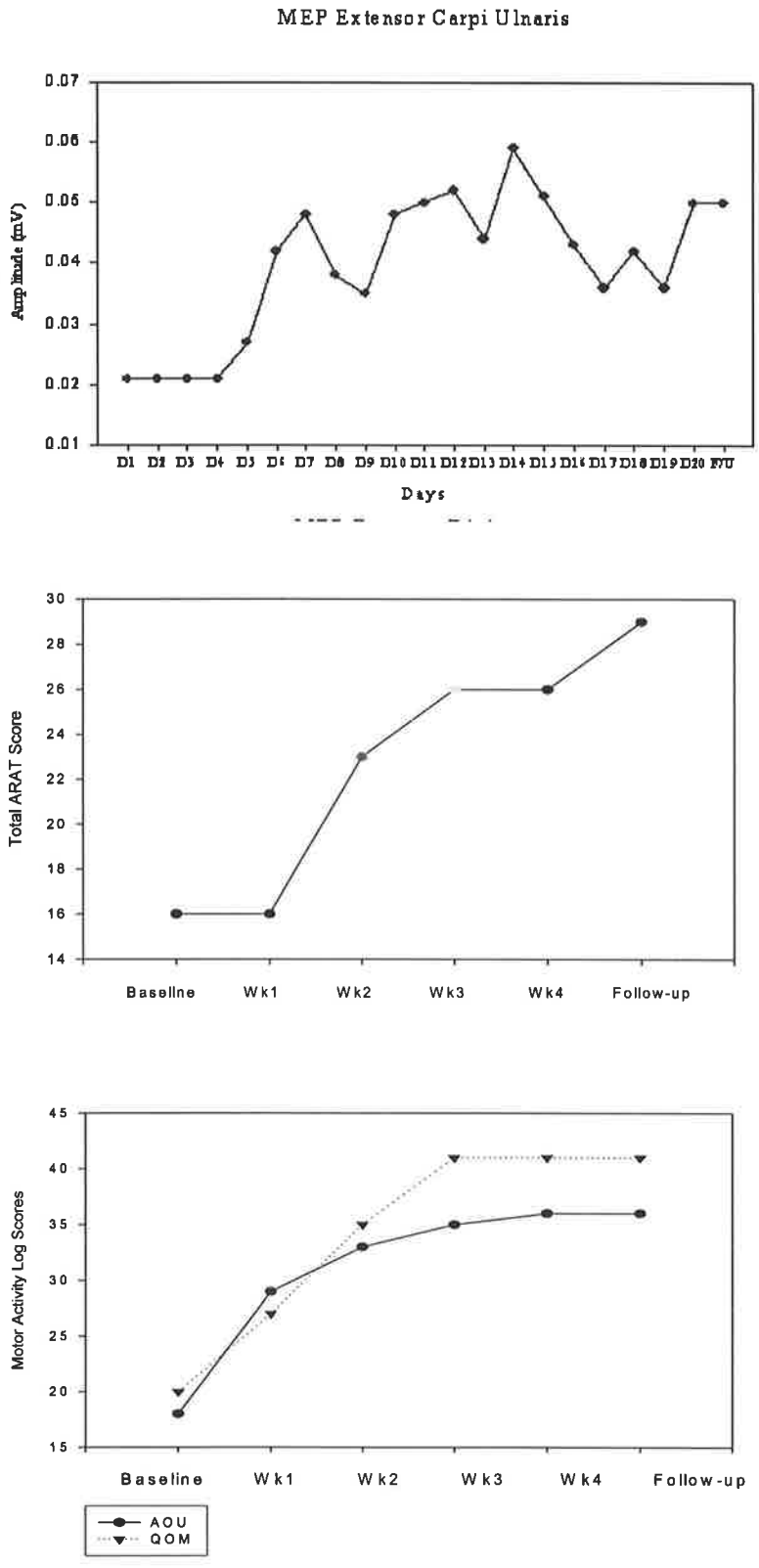

Figure 5.6 Complimenting neurophysiological scores and ARAT and Subjective Questionnaire Scores in one subject. AOM = Amount of use; QOM = Quality of Movement in one subject.

5.5 Discussion

The present study examined the effects of combined central and peripheral afferent stimulation on the neurophysiological and functional scores of a patient group with chronic hemiparesis. Although we actively recruited for subjects to participate in the study, only a small number agreed to participate. Most of the stroke patients contacted found the amount of time needed to complete the study a major commitment and thus declined to participate. As such, we were again unable to control other factors such as age, duration of stroke or lesion site. Owing to the limited sample size, the results demonstrated the response to the intervention was highly variable, especially in the neurophysiological measures. Although no significant changes were found in the group analysis of the neurophysiological measures, the behavioural changes were significant by the third week of intervention.

5.5.1 Motor Evoked Potential Changes

The baseline MEP recordings confirm previous reports that MEPs are depressed or absent after a stroke. All subjects had MEPs with significantly longer latencies and smaller amplitude on the affected side compared with the unaffected side. Long-latency and small amplitude signals usually suggest a poor prognosis for functional recovery (Macdonnel et al. 1989). However, following the intervention, MEP amplitudes increased in the stimulated muscles. Although this change did not reach a significant level, there was an overall trend to increased corticospinal excitability of the projection to stimulated muscles. Approximately half of the subjects demonstrated clear MEP facilitation following the intervention. The MEP amplitude increases were not limited to the resting state. Previous studies examining the effect of dual stimulation in normal subjects have shown that MEP facilitation is not evident when recorded during a

background contraction (Ridding et al. 1995; Ridding and Rothwell 1997; Ridding and Taylor 2001). In this study, the active MEP of the target muscles on the affected side increased following dual stimulation. Similar results were reported by Hummelsheim et al. (1995), who showed significant facilitation of MEP following voluntary contractions of the paretic hand in stroke patients. It was suggested that the MEP facilitation seen in stroke patients might be brought about by spreading effects derived from the neural circuits that had remained intact (Hummelsheim et al. 1995). The lack of MEP response to the dual stimulation from some of our subjects may indicate the severity of their lesion (Hendricks et al. 2002b). The integrity of the corticomotor pathways can be evaluated objectively using MEPs and their amplitudes predict the level of post-lesion recovery. This may provide an explanation for the variable responses we obtained from our sample. Furthermore, this may suggest that, even at the chronic stages of hemiparesis, absent or weak responses to TMS may indicate a poorly recovered state and may be a variable for a non-favourable response to dual stimulation or other therapeutic interventions.

5.5.2 Movement of the CoG

The CoG is the amplitude-weighted spatial average of the corticomotor representation of the different scalp sites from which MEPs from a target muscle are obtained. It is often used to define the position of TMS maps and provide an indication of shifts in the representation of muscles. It represents an area of high corticomotor excitability and is closely associated with the optimal stimulus site of the muscle being mapped (Thickbroom et al. 1998; Wilson et al. 1993). Thus, changes in the location of the motor map can be described in terms of movement of the CoG. In mapping sessions separated by 24 hours, one and two weeks, the CoG was reproducible within 4.0 mm (Uy et al.

2001: chapter 3). In an independent study of chronic stroke patients, CoG measures were found to shift on average 5.59 mm after 2 weeks of constraint-induced therapy (Liepert et al. 1998). Therefore, shifts in the CoG greater than approximately 4.0 mm are likely to indicate a true shift in the CoG. In the present study, The CoGs of the TMS maps moved compared with the baseline maps. However, the magnitude of the shifts was highly variable between the subjects and overall did not achieve statistical significance. There was, on average, a 6.5 mm mediolateral shift of the ECU. The shift observed in the TMS maps of our stroke group exceeds the variability seen in our control studies as described above and is likely to represent a true shift in the muscle representations.

Enlargement of the motor map area of the paretic hand in a group of stroke patients was seen following a comprehensive inpatient rehabilitation program (Bastings et al. 2002). This supports the idea that changes in the surface area of TMS-derived maps reflect alterations in cortical representation. However, TMS map area exceeds the likely cortical area that corresponds to the stimulated muscle area (Butler and Wolf 2003). Thickbroom et al. (1998) demonstrated that surface area of TMS maps are determined by current spread and the relationship of coil position and the depth of cortical output region. Hence, the use of the extent of the TMS map area as a measure of cortical reorganisation may prove to be unreliable. This supports the use of CoG measures as an indicator of plastic change in the cortex.

5.5.3 Mechanism of Change

The mechanism by which dual stimulation brings about changes in cortical excitability remain unknown. The rapid nature of the changes indicates that the mechanism involved may be functional rather than structural. Several possible mechanisms have been suggested to bring about changes following stroke and rehabilitation. The changes observed in TMS map parameters may be brought about by an increase in cortical excitability (Bastings et al. 2002). Enlargement of the map area can be brought about by the spread of stimulus across the cortex and adjacent areas. As cortical excitability increases and the threshold decreases, the TMS stimulus can depolarise previously silent cortical cells and lead to the generation of MEPs.

The changes observed are probably brought about by alterations in the balance of excitation and inhibition within the motor cortex. The mechanism behind this increased excitability is thought to involve the unmasking of silent cortical connections by a reduction of local inhibition owing to changes in GABAergic synapses (Liepert et al. 2000b; Werhahn et al. 2002) or by improved glutaminergic transmission (Garraghty and Muja 1996; Jablonska et al. 1995; Kano and Iino 1991). It is suggested that cortical excitability and reorganisation is dependent on the actions of inhibitory neurones (Jacobs and Donoghue 1991; Sanes and Donghue 2000). It has been proposed that cortical excitability may be brought about by the down-regulation of GABAergic activity (Jacobs and Donoghue 1991; Jones 1993; Schiene et al. 1999). Pharmacological studies have demonstrated that cortical excitability can be affected by manipulating GABA circuits (Ziemann et al. 1996; Ziemann et al. 1998a). However, using a similar dual stimulation paradigm in a normal population, Ridding and Taylor (2001) showed that the level of short interval intracortical inhibition was not affected

during periods of MEP facilitation, indicating that mechanisms other than GABA activity may be involved.

Displacement of the CoG following intervention involves recruitment of a larger neuronal network (Liepert et al. 2001). The shifts observed in our study persisted within the four-weeks of intervention and may involve mechanisms other than increased excitability. The duration of the changes suggest the involvement of an LTP -like phenomenon. Stefan et al. (2000) proposed that the changes observed following paired associative stimulation are brought about by improved synaptic efficiency *via* mechanisms similar to LTP. Although there is no available direct evidence, it is suggested that LTP is likely to be involved in stroke recovery and responsible for the treatment-induced changes seen following rehabilitation (Hagemann et al. 1998; Liepert et al. 2000a; Liepert et al. 2001).

5.5.4. Functional Improvements

Two separate baseline functional testing sessions were performed to establish the reliability of the functional scores. No significant difference was found between the two baseline ARAT and MAL scores indicating that these measures were stable and reliable. Following the intervention, the results of a number of functional tests changed significantly. Following the dual stimulation intervention there was a significant improvement in the both the ARAT (Friedman Test=0.002) and Motor Activity Log scores (Friedman Test=0.008). Changes in passive (Friedman Test=0.99) and active (Friedman Test=0.98) wrist extension range measures were not significant. Further analysis revealed that the ARAT scores were significantly higher than baseline at the third and fourth week, and maintained at follow-up. The average difference in ARAT scores at week three and week four was 5.875 and 6.25 on follow-up. The minimal

clinically significant difference between scores has been reported at 5.7 (van der Lee et al. 2001). Like the neurophysiological measures, the functional response to the dual stimulation in our patients was highly variable. However, the functional changes in a number of patients were striking. These results contrast with those reported in normal subjects where no functional correlate of dual stimulation-induced excitability change has been reported. For example, normal subjects' finger-tapping speeds did not change following a period of dual stimulation (McKay et al. 2002). It is possible that this is because normal subjects already function at an extremely high level and so it is difficult to improve further. Additionally, finger-tapping speed may not be a sensitive enough index of function in normal subjects. The results from the subjective questionnaires also revealed significantly improved scores by the end of the intervention. Scores obtained from the MAL on the third and fourth week and on follow-up revealed significant improvements compared with baseline. Both the amount of use and quality of movement categories of the MAL were improved. The general functioning questionnaire, which posed open-ended questions, revealed that seven subjects reported a reduction of stiffness in their affected hand. However, the MAS scores did not reveal any significant difference. Although the MAS is a commonly used tool to measure spasticity in the clinical setting, the reliability of the measure is often questioned. This is due to the highly subjective scoring system used, which is based largely on the impression of the examiner (Pandyan et al. 1999). Perhaps more sensitive measures of muscle tone should be used in future studies to ascertain the effects of dual stimulation on spasticity.

5.5.5 Factors Affecting Change

The results of this study indicate that the effect of dual stimulation on the neurophysiological and functional measures on a group with chronic hemiparesis was highly variable. Factors such as lesion type and location, age of patient and severity of deficits have been shown to influence outcome and recovery (Alexander 1994; Ween et al. 1996; Ween and Shutter 2002) and may also be important in determining individual response to dual stimulation. However, with the limited size of our sample, it is difficult to find significant relationships between these factors and outcome. One factor that may be important is the presence or absence of baseline MEPs. The TMS-evoked responses in the acute stages following stroke are correlated with good functional outcomes (Hendricks et al. 2002a; Hendricks et al. 2003; Steube et al. 2001). Our results indicate that absent or small MEPs during the baseline measures may be related to poor outcome following dual stimulation. Additionally, those subjects who had proximal arm control on initial ARAT assessment improved significantly throughout the four weeks of intervention and maintained this at follow-up (Figure 5.5). The majority of the ARAT categories involve proximal to distal upper limb interaction. The presence of proximal arm control might have allowed subjects to focus more on using their affected hand when performing grasp, grip and pinch movements. It might be argued that the improvements in performance and neurophysiological measures reported here were due to spontaneous recovery. However, this is unlikely. Recovery of arm function usually occurs during the first six – 12 months after a stroke incident (Jorgensen et al. 1999), and all subjects in the present study were investigated at least two years following their stroke. In addition, these subjects were not undergoing any other rehabilitation intervention. Therefore the improvements seen in function and neurophysiological measures are likely to be attributable to the dual stimulation intervention. The results of this experiment indicate that improvements are possible in

subjects exhibiting chronic hemiparesis. There appears to be a complimenting improvements between the neurophysiological and hand function measures in subjects following dual stimulation. However, the size of the population was too small to enable correlational analysis between the scores.

5.6.Conclusion

The neurophysiological and functional changes in the present study suggest that a larger-scale study examining the potential of dual stimulation for motor rehabilitation may prove useful. Hand dysfunction contributes greatly to disability following a stroke and this type of approach utilising afferent stimulation paradigms may offer therapeutic options to patients where conventional therapies have nothing further to offer.

Chapter 6 Increased Cortical Excitability Induced by Transcranial Direct Current (tDCS) and Peripheral Nerve Stimulation.

6.1 Introduction

Alterations in afferent inputs can induce plastic changes in the adult human motor cortex. Increased levels of cortical excitability have been shown following a period of peripheral nerve stimulation (Ridding et al. 2000) or after practising a task as simple as thumb movements (Classen et al. 1998). Combining either peripheral nerve stimulation with low-frequency cortical stimulation with TMS (Stefan et al. 2000) or muscle motor point with low-frequency cortical stimulation (McKay et al. 2002) also facilitates the induction of plastic change. When compared with afferent stimulation alone, combined peripheral and central stimulation resulted in changes that were induced in a shorter time and persisted for a longer period (McKay et al. 2002). Given the nature of the changes induced by combined peripheral and central stimulation, it has been proposed that the plasticity induced by these paired stimulation protocols may represent a signature of associative LTP of cortical synapses or closely related neuronal mechanisms in the human cortex (Stefan et al. 2000). These findings suggest that providing afferent input to the motor cortex while its excitability level is increased (i.e. by TMS) may be a highly effective means for inducing plasticity.

An emerging method of induction of cortical excitability transcranially is transcranial direct current stimulation (tDCS). This technique uses weak direct currents to modify the excitability of cortical cells. The application of tDCS results in the depolarisation of

cortical neurones and shows persisting cortical excitability in animal models and in human studies. In animals, anodal tDCS stimulation elevated the excitability levels of the cortex for hours (Bindman et al. 1964). In human subjects, tDCS also induces excitability changes in the motor cortex. The polarisation effects resulting in changes in MEP amplitude have been attributed to changes in cortical excitability (Nitsche et al. 2003a). A reduction in TMS-evoked MEP amplitude was seen following cathodal stimulation, however TES-evoked MEPs did not show any change. Similarly, no effect was found on H-reflex measurements of motoneuronal excitability. This clearly suggests that tDCS influences cortical neurons and has no significant effect on spinal excitability. The changes induced depend on the polarity, intensity and duration of the stimulation (Nitsche and Paulus 2000; Nitsche and Paulus 2001; Nitsche et al. 2003a).

The application of tDCS in humans is safe and without any side-effects. Nitsche et al. (2003a) used serum neurone specific enolase (NSE) measurements, which is a sensitive marker of neuronal damage (Steinhoff et al. 1999) to assess the safety of tDCS. Following nine minutes of polarisation, serum NSE concentrations were unchanged, suggesting that tDCS is a safe procedure to use in humans (Nitsche et al. 2003b).

The neuronal mechanism responsible for reorganisation induced by afferent inputs, such as peripheral nerve or tDCS, has characteristics similar to those seen during motor learning. The aim of the current experiment was to determine if afferent stimulation induced plasticity could be facilitated by increasing motor cortical excitability transiently by preceding it with a brief period of transcranial direct current stimulation.

6.2 Materials and Methods

Ten normal subjects (three females, seven males; age range 19-49 years) gave written informed consent to participate in the study. Prior to commencing the protocol, all subjects completed the Adult Safety Screening Questionnaire to determine suitability for TMS (Keel et al. 2001). All subjects were right handed. The experimental protocol was approved by the Human Research Ethics Committee of the University of Adelaide.

6.2.1 Electromyographic (EMG) Recording

Motor evoked potentials (MEPs) were recorded using Ag-AgCl disposable surfaces electrodes (3M Red Dot ^{TM}, Ontario Canada) placed over three test muscles on the right side, namely, FDI, ADM and flexor carpi ulnaris (FCU). One electrode for the FDI and ADM was placed over the metacarpophalangeal joint of the index and little finger and the other over the muscle bellies; for FCU one electrode was placed 3 cm proximal to the muscle belly on which the other electrode was positioned. The signals were amplified and filtered at a 20 Hz - 1 kHz bandwidth and sampled at 5 kHz. Data were recorded on a computer-based data acquisition system (CED 1401, CED Cambridge, UK) and stored in a computer for off-line analysis.

6.2.2 Transcranial Magnetic Stimulation (TMS)

A Magstim 200 magnetic stimulator (Magstim Co. Dyfed, UK) was used to evoke MEPs. The optimal scalp stimulation site for evoking MEPs from FDI was determined using a figure of eight coil and was marked and measured from the left tragus for future reference. This point was used to provide reliability for succeeding trials and also as the point for anodal DC stimulation. A 13 cm round coil was then used for the rest of

the experimental conditions. Motor threshold was determined in increments of 5% was defined as the minimal stimulus intensity that evoked five MEPs in a series of 10 with an amplitude of at least 50 μV amplitude. For all further MEP measurements the test TMS intensity was set at 115% of relaxed motor threshold. Two trials of 10 stimuli were given to assess cortical excitability at each time point. The average MEP amplitude at each time point was then calculated.

6.2.3 Direct Current Stimulation (DC)

Two saline soaked sponges (*ca* 5 cm x 5 cm) were used for the DC stimulation. The anode was placed over the FDI optimal stimulation site on the scalp and the cathode over the contralateral orbit. This orientation has been shown to be optimal for stimulation of the motor cortex if the stimulation duration lasts for five minutes, and has been used to induce an increase in motor cortical excitability that lasts for approximately five minutes (Nitsche and Paulus 2000). The stimulus was delivered using a constant current stimulator (Grass SD9) with the stimulus intensity set to 1 mA (Nitsche and Paulus 2000). This stimulus intensity was perceived as a mild itching under the electrodes, but was not considered painful. The use of this stimulation intensity has been shown to be optimal for inducing excitability changes and is considered safe and offer no adverse reactions (Nitsche and Paulus 2000).

6.2.4 Peripheral Ulnar Nerve Stimulation (ES)

Ulnar nerve stimulation was applied as a 500 ms train of 10 Hz, 1 ms shocks repeated every 10 s through surface Ag-AgCl electrodes placed over the course of the ulnar nerve at the wrist just proximal to the pisiform. A Digitimer SD7A (Digitimer Ltd, Welwyn

Garden City, UK) was used. Stimulus intensity was set at a level where a minimal visible contraction was seen in the FDI and ADM muscles.

6.2.5 Experimental Protocol

All subjects were studied during each of four experimental paradigms. For each experimental paradigm, MEPs were recorded from the three muscles at five different times: baseline (BL); immediately post first interventional period (PI-1); immediately post second interventional period (PI-2); 15 minutes post second interventional period (P15), and 30 minutes post second interventional period (P30). Two conditioning sessions were performed in order to verify whether a five-minute DC stimulation duration was capable of inducing excitability changes as previously reported (Nitsche and Paulus 2001) and when an increase in excitability was demonstrated, a second stimulation session was given to find out whether this would further potentiate the increase in excitability and increase its persistence. There was a period of at least one week between different paradigms testing sessions for each subject. The order in which subjects were tested with each paradigm was randomised. A diagrammatic representation of the experimental paradigms is shown in Figure 6.1.

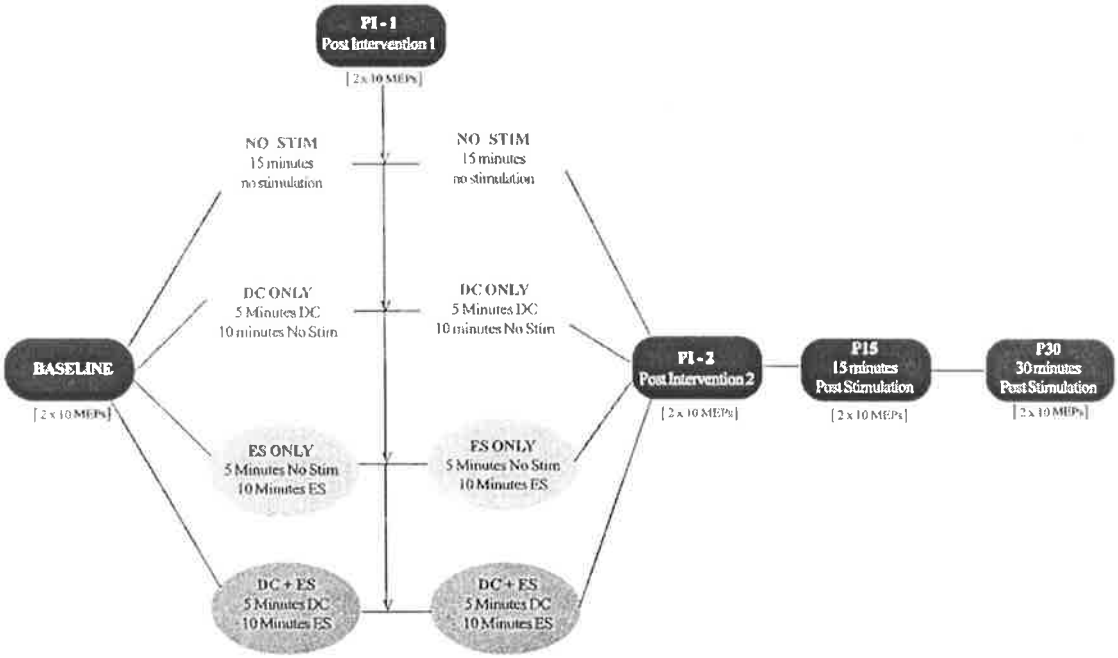

Figure 6.1 Summary of the four test protocol used. No Stim, no stimulation; DC only, direct current only; ES, peripheral ulnar nerve stimulation only; DC+ES, direct current followed immediately by peripheral ulnar nerve stimulation.

6.2.6 Statistical Analysis

MEP amplitudes were measured with custom software. A repeated measures analysis of variance (ANOVA) design was employed to test for significant effects on MEP amplitude for the three tested muscles under the four experimental paradigms using SPSS Software (V11, SPSS Inc, USA). The factors were muscle, time and paradigm. Further ANOVA were performed on data from each individual muscle to determine the effect of TIME on the MEP amplitudes across the testing intervals.

6.3 Results

There was a significant MUSCLE effect across all experiments ($p < 0.01$ and $F = 20.13$), indicating that the three muscles behaved differently. There was also a significant TEST and TIME effect ($p<0.05$ and $F = 2.10$) and a significant MUSCLE and TEST effect ($p<0.05$ and $F = 2.34$).

Therefore, further analysis (ANOVA) was performed for individual muscles under the four experimental paradigms. For both the NO STIM and ES ONLY paradigms there were no significant differences in MEP amplitude across the testing intervals for the three muscles tested (ANOVA; for each muscle TIME $p>0.05$).

In the DC ONLY protocol there was no significant change in MEP amplitude for ADM and FCU (ANOVA; $p>0.05$) across the five testing intervals. There was a significant TIME effect for FDI ($p=0.036$; $F=2.89$). The MEP amplitudes were significantly facilitated at the PI-2 interval ($p<0.05$).

There were significant TIME effects for FDI with the DC + ES paradigm (ANOVA, $F= 3.132$, $p=0.026$). The MEPs were significantly facilitated ($p<0.05$), compared with baseline, at the PI-2, P15 and P30 time points (baseline = 1.53 ± 0.33 mV, PI-2 = 2.29 ± 0.54 mV, P15 = 2.17 ± 0.53 mV, P30 = 2.13 ± 0.48 mV). The results of the four paradigms are shown in Figure 6.2. The effect of the different test conditions on the FDI muscle is shown in Figure 6.3.

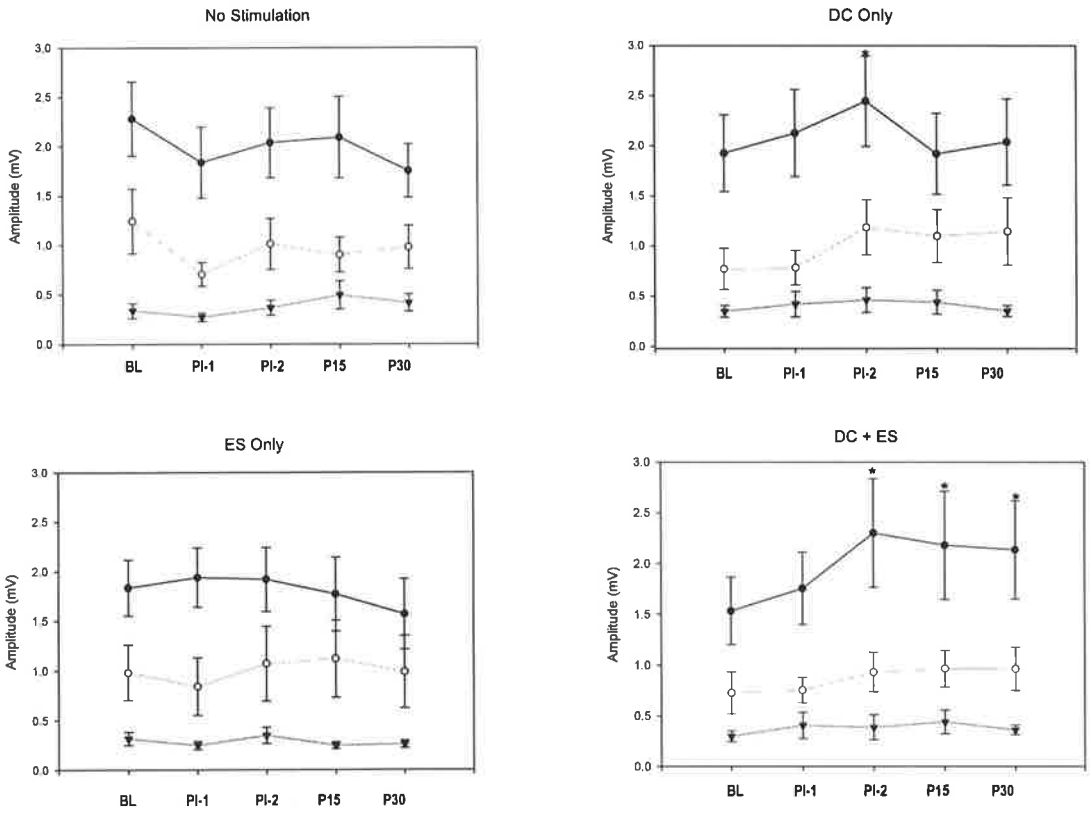

Figure 6.2. Comparison of MEP changes of the three muscles tested. Comparison of MEP amplitude changes across the three muscles (FDI filled circles; ADM open circles; FCU filled triangles), tested at 5 time periods for the 4 stimulation paradigms (Mean ± sem). The changes observed in FDI with both DC stimulation ($p=0.036$; $F=2.89$) and DC + ES stimulation ($p=0.026$; $F=3.132$) were significantly different across time. However, only the DC + ES stimulation paradigm induced changes in excitability that persisted for 30 minutes post stimulation (* $p<0.05$).

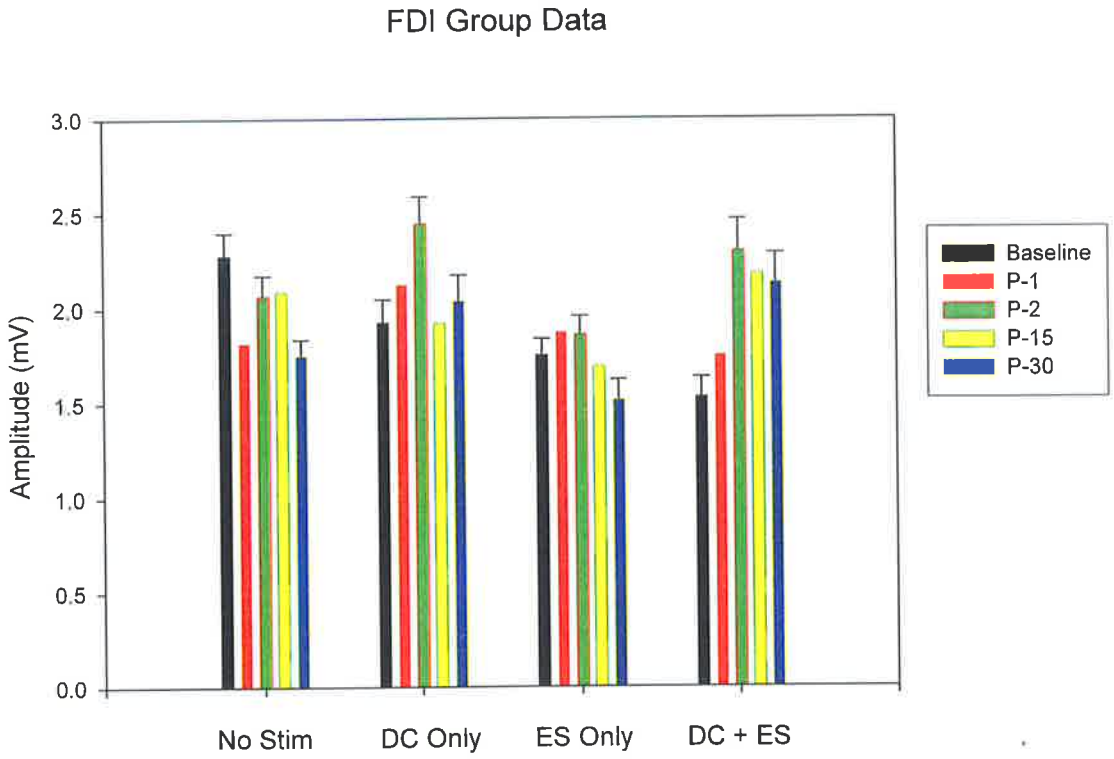

Figure 6.3 FDI Response to the four test protocols. Comparison of MEP Amplitude show that the DC + ES show significant changes following the second period of stimulation and the changes persisted when measured at 15 and 30 minutes post stimulation. P1 = post first intervention; P2 = post second intervention; P-15 = 15 minutes post stimulation; P-30 = 30 minutes post stimulation.

6.4 Discussion

The results of the present study show that a period of anodal DC stimulation preceding peripheral ulnar nerve stimulation resulted in a significant and persistent increase in motor cortical excitability. The effect was confined to the FDI muscle, with no significant changes in MEP amplitude observed in ADM and FCU. Similar MEP changes were seen in the DC-only protocol; however, the MEP amplitude elevations occurred only immediately after the second lot of stimulation and were not present when tested 15 and 30 minutes post-intervention. This finding is in agreement with Nitsche and Paulus (2001) who found that the effects of anodal DC stimulation were dependent on stimulus duration. Their data showed that the MEP elevations from a five

– seven minute DC stimulation session persisted only for five minutes post intervention. The ulnar nerve stimulation protocol used in this study did not show any significant effects on MEP amplitude for all three muscles tested. This is in contrast to previous studies that showed peripheral nerve stimulation to be capable of inducing change in cortical excitability (Charlton et al. 2003; Ridding et al. 2000). However, the stimulation duration in our study was shorter, 10 minutes compared to other studies that stimulated a peripheral nerve for at least 30 minutes and induced significant excitability changes. However, in the present study, when peripheral nerve stimulation was preceded by a period of five minutes transcranial anodal DC stimulation, the MEP changes were significant and persisted for at least 30 minutes post intervention. Therefore, a brief period of DC stimulation appears to potentiate the effect of a peripheral nerve stimulation period.

6.4.1 Specificity

The excitability change seen with the DC and ES paradigm is predominantly confined to FDI. This indicates that the effect is not simply a global change in excitability. Previously it has been demonstrated that excitability changes induced by peripheral nerve stimulation are confined to muscles innervated by the stimulated nerve (Ridding et al. 2000). The focal nature of the induced changes appears to be maintained when the peripheral nerve stimulation is preceded by a period of anodal DC stimulation. The reason that significant excitability changes were not seen in ADM, which is also innervated by the ulnar nerve, is not clear. However, optimisation of the position of the magnetic stimulation for evoking MEPs in FDI may have resulted in a more profound effect on the induced changes seen.

6.4.2 Mechanism of change

The mechanisms of action of anodal DC stimulation are still under debate. The mechanisms underlying the effects of tDCS have been proposed to involve changes in the behaviour of neuronal membranes. Paulus (2003) suggested that tDCS manipulates ion channels or shift electrical gradients to affect neuronal signalling and have an effect on the electrical balance of ions; involving primarily non-gated and voltage-gated channels.

Results from animal studies implicate a disturbance of calcium homeostasis or cAMP concentration in neurones. Calcium accumulation was detected for up to 72 hours in the cerebral cortex as well as the hippocampus and thalamus in rat brains after repeated anodal polarisation, and were accompanied by the appearance of dark neurons, which were associated with increased cortical excitability (Islam et al. 1995). Histological studies show that anodal stimulation induces bi-phasic effects on the adenosine-elicited accumulation of cyclic AMP in the rat cerebral cortex (Hattori et al. 1990).

In humans, DC stimulation affects membrane depolarisation. The depolarising effect of DC may activate voltage-sensitive events that involve presynaptic sodium channels increasing the release of excitatory neurotransmitters and postsynaptic elevation of Ca influx (Nitsche and Paulus 2001). The application of the Na+ channel blocking agent carbamazepine (CBZ) and an N-methyl-D-aspartate (NMDA)–receptor antagonist dextromethorphan (DMO) resulted in changes in DC stimulation induced neuroplasticity. CBZ binds to sodium channels and slows down the channels' recovery rate, which results in fewer available channels to open and cause depolarisation. This action was blocked after the application of CBZ, with resting MEP size significantly decreased after anodal DC stimulation compared with controls. This indicates that the

after-effects of anodal DC stimulation act on membrane potentials resulting in subsequent cortical cell depolarisation leading to increased excitability (Liebetanz et al. 2002).

The administration of DMO suppressed the induction of plastic change by anodal and cathodal DC stimulation in a group of healthy human subjects. Anodal stimulation increases excitability and cathodal stimulation results in the opposite (Nitsche and Paulus 2000). The suppression of these effects by DMO suggests the involvement of NMDA receptors in DC stimulation-induced synaptic plasticity (Liebetanz et al. 2002). NMDA receptors in the postsynaptic neuron act as Ca channels, thus their activation will lead to an increased influx of Ca. The entry of Ca in the post-synaptic neuron activates Ca dependent second messengers, which results in the increased availability of the glutamate receptor AMPA. This enables the postsynaptic neuron to be more sensitive to presynaptic release of glutamate, which is necessary for maintaining LTP.

The mechanism by which peripheral nerve stimulation induces increased motor cortical excitability is not known but it is thought to involve unmasking or long-term potentiation of cortical synapses (Ridding et al. 2000). When peripheral nerve stimulation is combined with low-frequency TMS, motor cortical excitability increases can be induced more quickly (Stefan et al. 2000). The changes induced by this paired paradigm can be blocked when performed under the influence of DMO, an NMDA receptor antagonist known to block LTP (Stefan et al. 2002).

6.5. Transcranial Direct Cortical Stimulation (tDCS) and Motor Learning

Motor learning is also influenced by tDCS. Early animal studies show that anodal DC stimulation of dorsolateral pre-frontal cortex of monkeys improved reaction-time performance, while cathodal stimulation impaired performance (Rosen and Stamm 1972). Prolonged anodal stimulation in the rabbit motor cortex resulted in the emergence of reflex-like reactions to sensory stimuli (Hori and Yamaguchi 1975; Lu et al. 1994; Rusinova 1988). These reactions were absent before the stimulation and were thought to be inhibited flight reflexes enhanced by the DC stimulation (Hori and Yamaguchi 1975). The induced reaction persisted, with the neural activity in the stimulated area behaving differently from other non-stimulated cortical areas. These studies imply that anodal tDCS can induce cortical plasticity.

There are limited human studies on tDCS and motor learning. Elbert et al. (1981) demonstrated improved performance in a reaction time task following low-level trans-cortical DC stimulation with the positive pole on the vertex. The application of anodal and cathodal tDCS resulted in an interference of rapid training-induced plasticity (Rosenkranz et al. 2000). The angular deviations of the subjects hand during the reaction time task following both tDCS conditions were significantly lower than baseline measures. However, more recent evidence showed that the application of tDCS on the motor cortex during the performance of a serial reaction time task resulted in significant improvements (Nitsche et al. 2003c). Stimulation of the pre-frontal and premotor cortices did not show improved reaction time. Although no direct evidence exists, the improved performance observed has been linked to excitability enhancement and a focusing of cortical activity on the neurons that are involved with the learning

process (Nitsche and Paulus 2000; Nitsche et al. 2003c). The results presented by Rosenkranz et al. (2000) and Nitsche et al. (2003c) also suggest that the functional effects of tDCS may be task-specific.

6.6 Conclusion

Anodal polarization increases the firing rate of cortical neurons and activates previously silent cortical cells in animals (Bindman et al. 1964). Pharmacological studies in humans suggest that the NMDA receptors in the glutamatergic system are responsible for the induction and maintenance of changes in cortical excitability (Liebetanz et al. 2002). Although we have no direct evidence to confirm it, we suggest that the changes induced in the present study where anodal DC stimulation and peripheral nerve stimulation are applied successively are most likely to be due to an LTP-like mechanism. The anodal DC and ulnar nerve stimulation paradigm conforms closely to Hebbian principles, and would be a promising tool to use to induce persisting changes in cortical excitability.

The results of these early studies of motor control and tDCS can be used to expand the applications of this technique in neuroplasticity research. As the functional implication of this induced plasticity is being developed, tDCS may offer an opportunity to facilitate afferent stimulation-induced plasticity and may have potentially useful therapeutic possibilities.

Chapter 7 General Discussion

My primary aim in this thesis was to determine whether the induction of increased cortical excitability in stroke patients would lead to improved function of their impaired leg and hand. Additional aims that arose from this study were to provide supportive evidence for the use of TMS maps in neuroplasticity research, and investigate an alternative method of transcranially inducing increases in cortical excitability.

The following discussion presents a synthesis of the major findings from the studies conducted and their contribution to the knowledge available in this area.

7.1 TMS Motor Maps

The application of TMS to produce representational maps in human subjects has been widely used in recent years. However, only limited studies have been performed to examine the reliability and reproducibility of these maps across time (Mortifee et al. 1994; Wilson et al. 1993). This is obviously crucial where the brain is being mapped serially, for example, before and after an intervention that may result in cortical reorganisation.

The first series of experiments performed in this thesis aimed to determine the stability of common map parameters when measured over time. The findings from this study indicated that map parameters such as CoG, area and volume were stable when measured over 24 hours, one week and two weeks after baseline. These findings support the use of TMS mapping as an indicator of reorganisation. The study also

confirmed that the conventional scalp grid, used in the present and most other studies, is an acceptable and accurate method for determining map coordinates. This method is easy to perform and economical, making it an attractive option for monitoring neuroplasticity. Furthermore, the results of this experiment substantiated the use of TMS maps in the subsequent intervention protocol performed in a population with chronic hemiparesis in Chapter Five.

This study was also the first to investigate the reliability of map areas, particularly at the margins of the maps. To do this, I measured the map characteristics at five different "levels" of a three-dimensional map, based on the maximum amplitude of the map. It was proposed that the area of the maps determined at higher MEP amplitudes would be less variable. However, this hypothesis was not supported by the results as both the standard error and the coefficient of variation of area were progressively reduced when measured at sites with smaller MEPs. The inherent variability encountered in MEP amplitudes makes map area less stable when measured using larger amplitude responses. This should be taken into consideration in future studies using TMS derived motor maps and calculate map area using smaller amplitude evoked measures as these points offer less variability.

7.2 Functional Plasticity of the Stroke-Injured Brain

Cortical reorganisation is a major contributing factor to the recovery of function following a stroke. The aim of normal therapeutic interventions is to alter neural activity patterns in a manner that improves function: however, unbeknown to most

therapists, these interventions probably also induce functionally relevant plastic changes in the motor cortex.

The process of rehabilitation varies considerably and depends on factors such as the therapist's skill, preferred approach, resources available, social support and the patient's motivational state. Even though physical rehabilitation in general has been shown to contribute to the recovery of function following stroke, these factors have made it very difficult to provide direct evidence as to which techniques are the most effective.

This thesis examined the possibility of inducing increases in motor cortical excitability and their potential functional significance in patients suffering chronic hemiparesis. A chronic and functionally stable patient group was selected because it was unlikely that any positive outcomes were due to spontaneous recovery. In addition, it was important to investigate whether induction of reorganisation and functional improvement was still possible in a group that had not been engaged in any form of active rehabilitation at that time and was considered by their therapists to have reached a plateau in their rehabilitation. The intervention applied to the subjects was based on a stimulation paradigm that was capable of inducing reorganisation of the motor cortex in normal subjects, likely through a mechanism similar to LTP. This stimulation paradigm is thought to induce changes in organisation that are very similar in nature to those seen during motor learning. The application of this dual stimulation paradigm, if shown to be effective, would provide a novel therapeutic option that is based on neurophysiological evidence, safe, and easily reproducible.

The improvements in function and neurophysiological measures did not reach significance in the group as a whole. This was probably the result of the high variability

between subjects. However, individual analysis showed that subjects who showed marked improvements in neurophysiological measures also had marked improvements in their functional test scores. Furthermore, these subjects also reported subjective improvements as stated in their questionnaire answers. In the subjects who showed significant increases in their scores, the improvements were seen as early as the second week of intervention. The trend also suggests that the scores reached their peak by the third week of the protocol.

These results suggest that this type of intervention may offer useful therapeutic options in selected patients. The factors that determine a patients' positive response to this kind of intervention need to be elucidated in a more comprehensive study.

7.2.1 Functional Changes Following Dual Stimulation

The ability to walk independently is one of the primary goals of patients following a stroke. As stroke limits mobility due to the resulting weakness or paralysis, survivors usually focus on achieving independent mobility in the early part of their rehabilitation. The recovery of independent walking function is rapid in the acute stages with approximately 70% of stroke survivors achieving limited independence in ambulation in the first 12 weeks (Jorgensen et al. 1995). There is an observed slowing down of the recovery process after this acute phase and it is generally thought that recovery might be complete after a period of 3 months (Jorgensen et al. 1995; Wade et al. 1987). However recent studies using body-weight support treadmill training in chronic non-ambulatory stroke patients have revealed significant improvements beyond this period (Hesse et al. 1995a; Hesse et al. 1995b).

The results of the reported gait study (Chapter 4) further support previous studies that found that improvements in gait are possible in chronic hemiparesis (Ada et al. 2003; Hesse et al. 1995a; Malezic et al. 1994). Although results were highly variable and no one functional parameter improved consistently across subjects, individual analysis showed that each subject improved in at least two of the functional test criteria. Additionally, all subjects reported improvements in at least one criterion in the function questionnaire. The gait parameters measured were common clinical tests, which can be easily applied in the rehabilitation setting. These clinical measures were supplemented by the FSCAN plantar pressure system used to determine the pressure pattern of the foot during walking. As the dorsiflexor of the foot was primarily targeted in our protocol, the FSCAN measures were employed to assess whether subjects were able to dorsiflex at the correct point of the gait cycle. The subjects who significantly improved with the functional scores also showed marked improvements in the neurophysiological measures.

Impairment of hand function is a common and devastating consequence of stroke. The recovery of upper extremity, and more specifically hand function, is an important rehabilitation goal in order to facilitate independence in activities of daily living. Similar to the recovery of ambulation, the restoration of hand function is mostly established during the acute stages of stroke, with further improvement beyond the initial few months highly uncertain. Clinical observations reveal that the level of hand function at one-year post stroke is the highest level achievable by the stroke survivor as recovery plateaus after this point. Therapeutic interventions available are numerous but there is little evidence of their efficacy. The results from Chapter 5 mirror those from the gait study (Chapter 4) in that although individuals demonstrated marked improvements in neurophysiological, functional and subjective scores or a combination

of the three; overall there were few significant group effects. As in the gait study, the subjects who showed marked improvements in neurophysiological measures also showed improvements in functional and subjective scores. Movements of the CoG of the stimulated hand muscles were also evident in these subjects. This finding supports the notion that the improvements were accompanied by reorganisation in the cortex.

Owing to the heterogeneous nature of our subject population and the relatively small numbers, it was difficult to identify factors that might predict a positive response to the dual stimulation paradigm. The duration post-stroke did not appear to be a factor as the subject with the longest history of stroke showed significant improvements. Likewise, the age of the subjects did not seem to be a factor as one of the older subjects in both our patient groups responded favourably to the treatment. However, no statistical correlation can be established to support this observation. The size and severity of the lesion can be another factor, as this would contribute greatly to the initial recovery process. Again, the small sample size did not permit us to make any correlation.

The subject's pre-intervention walking ability after their stroke may be a factor. Subjects who had at least limited independence in walking at the beginning of the study showed greater improvements than subjects who were partially or totally dependent for ambulation. In the upper extremity, too, the degree of deficit prior to intervention was a determinant of outcome. Subjects who were able to score in the functional test, more particularly in the gross movement category of the ARAT, showed significant improvements after the four weeks of intervention. In addition, the subjects who were capable of ambulation in the community likewise demonstrated significant improvements in upper extremity function. Six of the subjects in the hand study reported a weekly reduction of tone of their affected hand. The Ashworth Scores did

not reveal any significant improvements; however, this test is qualitative, but not quantitative. More sensitive objective measures should be utilised in future studies if these become available. Another qualitative observation was made with the subjects who improved most having a higher motivation. Subjects who improved were the ones who reported practising more walking or using their affected upper limb more often after the given intervention. Therefore, subjects with highest motivation levels may have positively reinforced any effects from the dual stimulation intervention. This issue needs to be examined more thoroughly in a controlled study.

The recovery of mobility and function, specifically independent ambulation and hand function, are vital to regaining independence in activities of daily living. The evidence available advocates treatment approaches in rehabilitation that follow a task-specific repetitive training program (Barbeau 2003; Butefisch et al. 1995; Taub et al. 1993). If a specific function is to be restored, that task has to be practised. The dual stimulation paradigm offers an approach in which cortical excitability is increased in chronic hemiparesis. This elevated state of cortical excitability might facilitate motor learning. The rationale for this lies in the observation that during motor learning motor cortical excitability is increased (Bonato et al. 2002; Pearce et al. 2000). Therefore, it may be that increased motor cortical excitability is critical for improvements in motor performance. Although the dual stimulation paradigm employed in the studies reported here failed to produce significant improvements in this patient population, there was a trend towards clinical significance in many of the functional outcome measures. The results highlight the need for further development of the dual stimulation paradigm in stroke, and larger sample sizes. Despite the lack of statistical significance, behavioural improvements were demonstrated and associated with changes in cortical excitability. This is analogous to current reports on the capacity for plastic change in the stroke-

injured brain even in the chronic stages. The cortical changes observed provide an excellent foundation for enhancing motor learning. Further studies should use this enhanced state and possibly combine it with some form of training. With further refinement of the protocol and careful selection of patients, the dual stimulation paradigm may offer a novel therapeutic option in some stroke patients. The challenge now is for scientists and clinicians to use the existing knowledge and bridge the gap between available evidence and clinical practice.

7.2.2 Possible Mechanisms of Reorganisation

The human motor cortex has the capacity for plastic change. Rapid and slow developing reorganisation may develop in response to injury and repair. The slow mechanisms may involve phenomena such as collateral or axonal sprouting leading to the formation of new synaptic connections. This is considered a restorative process following injury to the nervous system. In the experiments conducted in this thesis, it is more likely that the rapid plastic changes observed are based on modifications of the pre-existing neural circuitry.

The mechanisms proposed for the cortical changes observed in our stroke subjects are mediated at the synaptic level and involve the unmasking of latent connections, an increase in the responsivity of synapses or possible changes in synaptic morphology. A change in the balance of excitation and inhibition within the cortex is a likely explanation for the increased cortical excitability seen in the subjects. There is a capacity to increase cortical representation areas by reducing tonic inhibition. Dual stimulation appears to recruit additional cortical representational areas by reducing tonic inhibition. This increase in representational area is manifest as either an expansion or

change of location of the MEP map or an increase in MEP amplitude. It is thought that the change in excitability is brought about by down regulation of GABA-ergic activity and an alteration in glutamate transmission (Liepert et al. 2000). The cortical plasticity seen may also reflect changes in the efficacy of existing synapses (Rioult-Pedotti et al. 1998) by increased synaptic strength via long-term potentiation (Stefan et al. 2000) or through changes in neuronal membrane excitability (Aou et al. 1992; Woody and Engel 1972).

The nature of the changes seen in our results suggests the involvement of an LTP-like mechanism. The results also demonstrate that the dual stimulation paradigm that induced excitability changes in normal subjects can also produce similar responses in a population with brain injury. The dual stimulation parameters in normals and our stroke population may have not been optimal in inducing significant plastic changes. Further refinement of this technique is needed together with the identification of positive prognosticating factors in order to elicit a positive functional outcome in chronic hemiparesis.

7.3 Limitations of the Study

There are factors that need to be considered when attempting to generalise the findings obtained from the experiments conducted in Chapter 4 and 5. First, the subject selection process was based on a self-selected group who volunteered to be part of the study. It is possible that this group might have represented a more physically and mentally motivated sub-group of people with chronic hemiparesis. Second, the need for a substantial commitment of time reduced the number of people who could or would volunteer to participate. As a result, the small number of volunteers available was

insufficient for the assignment of a randomised control group and for conducting an a priori sample size calculation to establish power and determine the optimal number of subjects needed to determine an effect. Third, an investigator who was not blinded to the subjects' baseline and intervention status performed the neurophysiological and functional assessments in all the experiments. Lastly, all the subjects and their carers were provided with an information sheet detailing some basic points of the protocol. Even though it was not specified that they were being given any treatment, the subjects' could not be considered blind to the intervention process.

On the other hand, most of the experimental procedures conducted in the studies were quantitative measures. Variables such as MEPs, EMG, map CoG, map area and volume, FSCAN scores, gait speed, stride and step length, the ARAT and range of movement are all objective data. Furthermore, the ARAT is a performance test that has been shown to have a test-retest summative interclass correlation coefficient (ICC) of 0.99 (van der Lee et al. 2001). Hence, it is unlikely that the principal investigator was able to bias the subjects' test performance. The Self-Rating Mobility Scale and the General Functioning Questionnaire were subjective tests completed by the subject themselves or by their carers. All the subjects were assumed to have responded to the questionnaire honestly and accurately. It may also be argued that part of the improvement observed post-intervention may be attributed to an increase in the subjects' motivation and effort. Conversely, analysis of individual scores revealed that subjects who scored significantly with the objective tests were the ones who reported only significant, positive subjective responses. Although the subjective bias is a type of limitation that cannot be avoided, the complimenting objective and subjective scores strengthen the notion that the improvements observed were brought about by the intervention protocol.

It is clear, therefore, that this study has a number of limitations and must therefore be regarded as preliminary rather than definitive. The significant increases in neurophysiological measures following dual stimulation in normal population do not seem to translate to a population affected with brain damage as stroke. The specifics of the protocol such as inter-stimulus intervals or duration of stimulation should be investigated exclusively in a pathological population to determine optimal parameters. Despite this, I believe that the data justify the undertaking of a larger-scale randomised clinical trial to establish whether the positive outcomes that I have observed can be generalised to the larger stroke population.

7.4 Modulation of Cortical Excitability by Transcranial Direct Current Stimulation (tDCS)

Animal and human studies have verified how passing weak direct currents transcranially can alter and modulate neuronal membrane potentials. The use of tDCS has shown great promise in elevating cortical excitability and inducing plastic changes in the cortex. The effects of tDCS are dependent on the duration and direction of the current. A minimum duration of stimulation is needed if the effects of tDCS are to be seen (Bindman et al. 1964; Nitsche and Paulus 2001). Anodal and cathodal tDCS have also been shown to have different after-effects. Anodal stimulation produces current flow that increases excitability and cathodal stimulation lowers cortical excitability (Nitsche and Paulus 2000).

In the final series of experiments, it was demonstrated that anodal tDCS applied before a period of peripheral nerve stimulation induced a significant increase in motor cortical excitability reflected by an increase in MEP amplitude. The increases in motor cortical excitability persisted for at least 30 minutes post stimulation. Previous findings have shown that one hour of peripheral nerve stimulation was needed to induce cortical excitability changes (Ridding et al. 2000). The current findings demonstrated how a period of anodal tDCS prior to nerve stimulation could facilitate the induction of motor cortical excitability by shortening the period required for induction in a normal population. Further investigations should correlate the increased neurophysiological parameters with function by incorporating functional tests or tasks as outcome measures in order to determine the functional translation of tDCS induced cortical plasticity. The use of tDCS as an alternative method for affecting cortical plasticity should also be investigated in a population with neurological dysfunction such as stroke. The safe, painless, non-invasive nature of tDCS may show possibilities for therapeutic purposes and offer benefits for neurorehabilitation.

7.5 Areas for Future Research

The experiments described in this thesis have shown that functional plasticity is possible in a population with chronic hemiparesis. Numerous studies have already demonstrated the capacity for reorganisation of the stroke-injured brain. However, this is the first study to use a combined central and peripheral dual stimulation paradigm to induce cortical reorganisation in a stroke population. Although the group data were not statistically significant, analysis of individual subjects has shown a trend for improvements in neurophysiological and functional measures indicating a possible

clinical significance. The dual stimulation paradigm offers a promising method of inducing functionally-relevant cortical plasticity in stroke. Future areas of research may look into the following:

- Establishing a randomised controlled trial in a larger stroke population in order to draw definitive conclusions about the efficacy of the technique and identify factors that contribute to a positive or negative response.
- Incorporating a training program with the induction of cortical plasticity, and examining whether this improves the functional outcomes.
- Establishing the optimal inter-stimulus interval between the central and peripheral stimulation paradigm may for a stroke population. The dual stimulation parameter used in this study followed the paradigm that induced plasticity effectively in a normal population (Stefan et al. 2000; McKay et al. 2002). The optimal inter-stimulus interval may be different in a population with central nervous system damage, for example, due to altered afferent conduction times. .
- Develop a more objective test of spasticity. One common subjective remark made by our subjects was that their hand did not feel as "tight" as before the start of the protocol. This may suggest that the dual stimulation affects spasticity and tone. However, the clinical Ashworth Scale failed to reveal any significant improvement. It is possible that the scale is not sensitive enough to detect the changes in our subjects.
- Test hand function more precisely. It is possible that discrete changes in hand function from our stroke population were not identified with the functional tests used. The ARAT, although reliable and valid, may be insufficiently sensitive to

pick up the improvements in hand function, most specifically in the subjects who had severe limitations or the ones with a high level of hand function. Future studies may need to develop a more sensitive test or use the ARAT in conjunction with other functional measures. This will allow changes in any form to be easily recognized.

- Determine whether other methods of inducing cortical plasticity are more effective in stroke patients. The studies outlined in this thesis examining the use of peripheral nerve stimulation and tDCS raise the possibility of increasing the efficacy of afferent stimulation by the use of other techniques. Application of these techniques to a patient population will enable an assessment of their therapeutic capabilities.

7.6 Conclusion

The concept of plasticity in the intact human motor cortex has been extensively documented in numerous studies. However, reports on the functional relevance of the neural plasticity are still limited, particularly in brain injuries. Two studies in this thesis have provided initial complimenting results of increased cortical excitability and functional outcomes in a population with chronic hemiparesis. These studies demonstrate the possible therapeutic applications of a combined central and peripheral stimulation in the chronic stages of stroke. Although the results were highly variable there was a trend for increases in neurophysiological measures to be accompanied by improvements in functional outcomes.

The reliability of TMS-derived cortical maps was also examined in this thesis. As there is a growing interest in the use of TMS maps in reporting cortical reorganisation, there was an obvious question as to whether these maps were stable when measured serially. The findings of these studies confirmed that under certain conditions TMS motor maps are stable over time. This finding confirmed the suitability of employing this technique to examine changes in motor cortical organisation in the stroke studies.

An alternate means of inducing cortical plasticity was presented in the final experimental series of this thesis. Anodal tDCS has been shown to induce significant, transient elevations in cortical excitability (Nitsche and Paulus 2000). Here, I have shown that motor cortical excitability could be modulated more effectively with combined tDCS and peripheral stimulation compared with peripheral stimulation alone (Chapter Six). This raises the possibility that it may be possible to optimise stimulation paradigms to result in more functionally beneficial outcomes in reorganising the injured brain.

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APPENDICES

PUBLICATIONS ARISING FROM THIS THESIS

Uy, J., Ridding, M.C. and Miles, T.S. (2002): Stability of maps of human motor cortex made with transcranial magnetic stimulation. *Brain Topography 14: 293-297.*

Uy, J. and Ridding, M.C.: (2003): Increased cortical excitability induced by transcranial DC and peripheral nerve stimulation. *Journal of Neuroscience Methods 127: 193-197.*

Uy, J., Ridding, M.C., Hillier, S., Thompson, P.D. and Miles, T.S. (2003): Does induction of plastic change in motor cortex of stroke patients improve leg function? *Neurology 61: 982-984.*

Ridding, M.C. and **Uy, J.** (2003): Induction of motor cortex plasticity by paired associative motor point stimulation. *Clinical Neurophysiology 114: 1437-1444.*

PRESENTATIONS AND ABSTRACTS ARISING FROM THIS THESIS

Uy, J., Ridding, M.C., Hillier, S and Miles, T.S. (2003): Cortical excitability and hand function following central and peripheral stimulation in chronic hemiparesis. *Oral presentation at the 1st Neurological Physiotherapy Conference – Australian Physiotherapy Association. Sydney, Australia.*

Uy, J., and Ridding, M.C. (2003): Increased cortical excitability induced by transcranial DC and peripheral nerve stimulation. *A poster presented at the 23rd Annual Meeting of the Australian Neuroscience Society. Adelaide, Australia.*

Uy, J., Ridding, M.C., Hillier, S, Miles, T.S. and Thompson, P.D. (2002): Cortical reorganisation and associated functional changes in chronic stroke patients. *A poster presented at the 3rd Federation of Asian and Oceanian Neuroscience Congress, Seoul, South Korea.*

Ridding, M.C., **Uy, J.**, Hillier, S., Miles, T.S. (2002): Repeated afferent stimulation induces persistent changes in the organization of human motor cortex. *A poster presented at the International Stroke Symposium. The University of Kansas Medical Centre. Kansas City, USA.*

Ridding, M.C., **Uy, J.**, McKay, D.R., and Miles, T.S. (2001): Repeated afferent stimulation induces persistent changes in the organisation of human motor cortex. *A poster presented at the Proceedings of the Sensation and Movement Satellite to the International Union of Physiological Sciences, Cairns, Australia.*

MOTOR ACTIVITY LOG QUESTIONNAIRE

Subject: .....Date:.....

Instructions

Listed below is a series of everyday activities. After each activity, please answer whether **Yes** (you can perform activity) **No** (you can not perform activity) or **Not Applicable** (activity is not relevant to me). In addition, please use the scales listed below to give us more information about the use of your involved arm. Please go over the scales and think about the amount of use and quality of movement of your involved arm.

Amount of Use (AOU) Scale

0. Did (does) not use the involved arm.
1. Occasionally tried (tries) to use the involved arm.
2. Used (uses) the involved arm but did (does) most of the activity with the uninvolved arm.
3. Used (uses) the involved arm about half as much as often as the uninvolved arm.
4. Used (uses) the involved arm almost as much as normal.
5. Used (uses) the involved arm as much as normal.

Quality of Movement (QOM) Scale

0. The involved arm was (is) never used for this activity.
1. The involved arm moved (moves) during the activity but was (is) of little use (poor quality).
2. The involved arm was (is) of some use during that (this) activity but needed (needs) some help from the stronger arm. It moved (moves) very slowly or with difficulty (poor).
3. The involved arm was (is) used for the purpose indicated, but movements were (are) slow or were (are) made with some effort (fair).
4. The movements made by the involved arm were (are) almost normal but not quite as fast and accurate as normal.
5. The ability to use the involved arm for that (this) activity was equal to the ability of the uninvolved arm (normal).

Sample Activity:	**YES/NO/NOT APPLICABLE**	**AOU**	**QOM**
Holding a paper for reading with two hands			
Push open door with affected arm			
Hold a cup with affected arm			
Bring cup to mouth as in drinking			
Turn on/off a light switch			
Use both hands to dry self			
Carry an object in affected arm (eg shopping bag)			
Use both hands for dressing (eg holding clothing)			
Eat finger foods with affected arm (eg potato chips, candy)			
Turn handle of door			
Turn pages of book			
Use fork to pick up food			
Turn on a tap			

GENERAL FUNCTIONING QUESTIONNAIRE

Please fill out this form at the end of each week

Please tick the appropriate response to each question regarding the level of functioning of your affected arm.

1. In the last week did your disability limit you undertaking activities of personal care (such as showering, dressing, etc)?

Not at all	☐
A little bit	☐
Moderately	☐
Quite a bit	☐
Extremely	☐

2. In the last week how much did your disability affect your normal activities including work at and away from home?

Not at all	☐
A little bit	☐
Moderately	☐
Quite a bit	☐
Extremely	☐

3. In the last week did your disability interfere with your social activities for example visiting friends, going out?

Not at all	☐
A little bit	☐
Moderately	☐
Quite a bit	☐
Extremely	☐

4. Has anything out of the ordinary happened to you in the past week affected your level of functioning?

Yes	☐
No	☐

If Yes – please give details of what and how _____

_____

_____

_____