HUMAN MOTOR CORTICAL PLASTICITY AND UPPER LIMB PERFORMANCE

A thesis submitted for the Degree of

DOCTOR OF PHILOSOPHY

by

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Abstract

The capacity of the adult human nervous system to alter the strength of connections between neurons and between networks of neurons is an exciting area of research providing novel insights into the mechanisms involved in learning, memory and recovery following brain damage. In recent years, it has become clear that both afferent input into the motor cortex and the learning of a new motor task can drive cortical reorganisation. This thesis is concerned with the functional significance of this plasticity, in both normal subjects and stroke patients, and with the question of whether stimulation-induced plasticity can lead to improved fine motor performance.

My initial experiments were conducted to determine the optimal method of analysing responses to transcranial magnetic stimulation (TMS), and to investigate aspects of motor performance as the hand performs a precision task to grasp and lift an object. Studies on normal subjects showed that there is little difference between the dominant and non-dominant hands performing this task, but the type of grip used influences grip-force control. An investigation of stroke patients performing this task demonstrated that certain parameters were sensitive to differences between the affected and unaffected hands and these parameters were highly correlated with stroke-specific functional outcome measures.

The induction of plastic change in the human motor cortex can be induced by repetition of movements, performing a complex motor task or stimulation of the peripheral afferents and/or the motor cortex itself. I observed that the application of so-called “associative stimulation” to two hand muscles in normal subjects increased the excitability of the corticospinal projection to those muscles, and improved performance times on a subsequent motor task to a greater extent than subjects receiving a control intervention. I then applied associative stimulation to

the affected hand of stroke patients in conjunction with rehabilitation, which improved their ability to perform the dextrous grip-lift task. This is the first study to show that this method of inducing motor cortical plasticity can also lead to functional improvements in stroke patients.

These studies confirm that using afferent stimulation to drive cortical reorganisation is associated with improved function and fine motor performance in both normal subjects and stroke patients.

Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or 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.

SIGNED…… DATE……..……..

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Aims and general introduction

Reorganisation of the human motor cortex can be induced by manipulation of afferent inputs reaching the cortex. This can be achieved with motor training, or stimulation of peripheral nerves and/or muscles to increase the excitability of corticospinal projections, which supports the hypothesis that afferent input can drive cortical reorganisation. While this short-term reorganisation of the motor cortex has been demonstrated using various experimental paradigms, evidence for an associated functional effect is lacking. This is particularly pertinent as we (McKay et al., 2002; Ridding et al., 2000) and subsequently others (Bütefisch et al., 2004) have proposed that techniques to induce cortical plasticity may enhance the effectiveness of rehabilitation following brain damage such as stroke.

Cortical reorganisation can be demonstrated using transcranial magnetic stimulation (TMS). Stimulation of the motor cortex can induce descending volleys in the corticospinal tract and, in turn, muscle responses which are termed motor evoked potentials (MEPs). Changes in the amplitude of MEPs indicate changes in the strength of the corticospinal projection to the target muscles. Alternate methods of analysing MEPs had been reported in the literature and my first series of experiments was designed to determine the optimal method of analysing these potentials. The results of this study, detailed in Chapter 2, confirmed that measuring the individual peak-to-peak amplitude for each response, and then taking the mean over a number of trials, was the most appropriate method for analysing MEPs from small hand muscles and this method was thus used for the remainder of the studies detailed in this thesis.

The potential for afferent stimulation to improve motor performance was investigated in Chapter 3. I used a period of stimulation of the motor points of two hand muscles to increase the excitability of the corticospinal projection, in accordance with previous reports, and I

contrasted the effect of this type of stimulation with a control group who received no intervention, and another group of subjects who received a period of non-associative stimulation that does not increase excitability. Following this, all subjects performed a complex motor task a number of times. All subjects improved their performance times, but only subjects in the associative stimulation group also demonstrated an increase in MEP amplitude. This was not associated with an increased level of performance at the commencement of task, but during the task their performance improved more rapidly than the other groups, suggesting that the preconditioning stimulation which increased excitability also conferred a functional benefit.

A possible limitation of previous studies that describe changes in excitability but lack evidence of functional effect is the difficulty in detecting subtle changes in performance of the hand in healthy subjects. Common tools to assess manual dexterity, such as the Purdue Pegboard Test, may not be sensitive enough to detect improved performance in normal subjects who are already performing at a high level. In order to investigate aspects of a precision task in more detail, I used a grip-lift apparatus for the assessment of fine motor performance of the hand. This enabled quantitative assessment of differences between the dominant and non-dominant hands of normal subjects, as well as the effect of alternate postures of the hand when performing the precision grip-lift task. These studies are described in Chapter 4.

Few researchers have examined the precision grip-lift task in stroke patients, and none have included poorly-recovered patients, or have compared the affected hand with the non-hemiplegic, supposedly unaffected upper limb. I addressed these issues in experiments outlined in Chapter 5, in order to ascertain the usefulness of the grip-lift apparatus in detecting change in the upper limb following stroke over a period of time or as a result of an

intervention. Rather than comparing aspects of the task to age-matched controls, I considered that if the task were sensitive enough to detect a difference between the hands of individual stroke patients then it should be a useful measure of changes in dexterity following stroke. Results indicated not only which parameters were useful to detect a change between the hands, but also that these same parameters, when compared with basic speed and strength tests, explained a large proportion of the variance of standard stroke-specific tests of function.

Finally, I combined the findings from the above experiments to explore the potential of afferent stimulation to increase the excitability of the motor cortex and to induce functional changes in a group of subacute stroke patients. This longitudinal study involved two groups of ten stroke patients, randomly allocated to be given stimulation of two muscles of the paretic hand, or sham stimulation. All patients participated in a standardised rehabilitation program based on task-specific physiotherapy, to test the hypothesis that increased excitability of the motor cortex would make it more responsive to motor learning. At the end of the intervention, all patients improved their functional abilities, but the stimulation group also increased their ability to perform aspects of the precision grip-lift task. This study, presented in Chapter 6, confirms that methods that induce cortical plasticity can enhance the effect of rehabilitative strategies and may become a useful adjunct in the restoration of function following brain injury.

1. Literature review

The range of movements and functions that human hands are capable of is truly remarkable. We subconsciously perform countless precise and complex actions each day for basic hygiene, feeding and communication needs. Individuals such as concert musicians can master remarkable levels of motor skills by extensive training. In an instant, all of these can be taken away, for example by a stroke, sometimes making even the most basic of motor tasks impossible. This review will summarise the anatomical substrates that allow dextrous movement of the human hand, how this can be investigated, and the consequences of damage to this system in individuals suffering from stroke.

The capacity for the human nervous system to reorganise in response to activity or experience has been termed "plasticity", a concept that will also be discussed in this review. Plastic change of the motor cortex can be induced in a number of ways, and use of the non-invasive technique transcranial magnetic stimulation (TMS) can quantify these changes within the motor cortex. This review will outline methods of inducing cortical plasticity in normal individuals and also in stroke patients, and relate this to improvements in functional abilities of the hand.

1.1. The human motor cortex

1.1.1. Organisation of the motor cortex

The complex organisation of the human brain was elegantly demonstrated by Wilder Penfield in the mid–twentieth century, by direct electrical stimulation of the brains of awake humans who were undergoing brain surgery for epilepsy under local anaesthetic (Penfield and Rasmussen, 1950). This revealed which areas of the brain were responsible for different functions, in particular speech and voluntary movement. The part of the brain where motor

responses were most readily elicited was located on the precentral gyrus, and this region is now referred to as the primary motor cortex.

Subsequent to this, the motor cortex has been identified as a number of interconnected regions: the primary motor cortex or M1 (also known as Brodmann's area 4), the supplementary motor area (Brodmann's area 6), the premotor cortex and the cingulate motor area (Krakauer and Ghez, 2000; Nudo et al., 2001; Wu et al., 2000). These non-primary motor areas may be further subdivided; for a comprehensive review see Roland and Zilles (1996). The M1 gives rise to approximately 30% of neurons controlling voluntary movement (Galea and Darian-Smith, 1994), and is characterised by a relatively low threshold for eliciting movements using electrical stimulation (Krakauer and Ghez, 2000).

Mapping M1 with electrical stimulation revealed a topographical organisation, with ordered representation of areas controlling the foot, leg, trunk, arm, hand, digits and face arranged from medial-to-lateral along the surface of the cerebral hemisphere (Penfield and Rasmussen, 1952). The different body parts are not represented equally; the hands and face which are used in tasks requiring precision and fine control have greater representations in the motor cortex. It is important to note that the functional subregions are not discrete areas, but rather a network involving large populations of neurons, resulting in representations that are widely distributed, multiple and overlapping (Sanes and Donoghue, 2000). This distributed network allows for enormous flexibility. The ability to modify connections between neurons may be the basis for organisational change (plasticity) within the motor cortex.

The cellular organisation of the cerebral cortex varies in different regions depending on their function (Brodal, 1969). In the motor cortex, there are two main types of cells that are organised into six layers (I - VI, numbered from the outer surface of the cortex). These are the pyramidal cells, which have axons that leave the cortex, and stellate cells, which act as

interneurons within the motor cortex (Rothwell, 1994). Pyramidal cells are found in layers II – VI but are most prevalent in layers III and V (Porter and Lemon, 1995). Dendrites of pyramidal cells extend both horizontally and vertically into all layers of the cortex, forming extensive networks in layers II – IV. These intrinsic connections between dendritic spines presumably allow the flexible synaptic organisation of the motor cortex.

Stellate cells constitute approximately 25% of the neurons in the motor cortex, and are located in all layers. Their dendritic trees are organised radially and axons are almost exclusively intrinsic to the cortex. The most prevalent stellate cells in the motor cortex are basket cells, which make inhibitory synaptic contacts with pyramidal neurons, using the neurotransmitter gamma-aminobutyric acid (GABA) (Jones, 1983). In contrast, pyramidal cells use the excitatory amino acid glutamate as their primary neurotransmitter.

In addition to the distribution of neurons in layers, groups of cells work together in vertical units called cortical columns. This columnar organisation is characterised by extensive synaptic communication between neurons, the majority of which is inhibitory (Jones, 1983). Afferent inputs from the thalamus and inputs from other areas of the cortex also synapse onto pyramidal and stellate cell neurons, and these projections terminate in intermittently-distributed patches within the columns (Mountcastle, 1997). It has been shown that each cortical column is a discrete complex processing unit that communicates with adjacent columns and other regions of the cortex through extensive horizontal connections (Mountcastle, 1997).

1.1.2. Corticospinal tract

A number of descending fibre systems influence the activity of the spinal cord (Brodal, 1969). The largest of these is the pyramidal tract, containing fibres from the cortex which course

through the pyramids of the medulla oblongata and continue to the spinal cord, becoming the corticospinal tract (Brodal, 1969). The majority of these fibres (up to 60%) originate in layer V of the primary motor cortex and the adjacent pre-motor cortex while the remaining fibres arise from the primary somatosensory cortex and parietal cortex (Galea and Darian-Smith, 1994; Jane et al., 1967). In humans, approximately 90% of these fibres are slow-conducting, with speeds of up to 14 $m.s^{-1}$ and only a small proportion are fast-conducting, capable of conducting action potentials at 50 $m.s^{-1}$ (Lassek, 1942; Rothwell, 1994).

Corticospinal tract fibres leave the motor cortex and pass through the internal capsule as they descend to the brainstem, where about 75% of the fibres cross the midline at the junction of the medulla and the spinal cord (Brinkman and Kuypers, 1973; Ghez and Krakauer, 2000). These fibres continue on as the lateral corticospinal tract, to synapse with the motor neurons in the ventral horn of the spinal cord that innervate limb and trunk muscles. Some of the remaining uncrossed fibres descend in the ventral columns of the spinal cord as the ventral corticospinal tract and terminate in the thoracic spinal cord to innervate trunk muscles. The majority, however, descend ipsilaterally and join the crossed fibres as the lateral corticospinal tract (Brodal, 1969).

The unique ability of humans to produce relatively independent finger movement is believed to depend on direct, monosynaptic, excitatory connections from the motor cortex to spinal motor neurons innervating the hand and forearm (Porter and Lemon, 1995; Rothwell, 1994). Each cortical motor neuron synapses with many spinal motor neurons, and each spinal motor neuron receives input from many cortico-motoneuronal (CM) cells (Weber and Eisen, 2002). These CM connections involve both fast-conducting and slower corticospinal fibres and are most prominent in mammals with more developed digital dexterity (Porter and Lemon, 1995). Cortico-motoneuronal cells are discussed more fully in Section 1.2.1.

1.1.3. Techniques used to investigate human motor cortical function

The range of techniques available to investigate the structure and function of the human brain and its connections has expanded considerably over the last 25 years. For example, it is now possible to measure regional blood flow and metabolic changes associated with specific neuronal activity. Functional magnetic resonance imaging (*f*MRI) and positron emission topography (PET) are two such techniques that enable changes in local brain activity to be assessed while subjects perform a particular task during the scan. Disadvantages of these techniques are that their temporal resolution is poor and they indicate only total neuronal activity, but not whether this reflects inhibitory and/or excitatory synaptic transmission. However, the spatial resolution of these scans is high, allowing a detailed delineation of the areas of the brain that are associated with a particular act (Rossini and Dal Forno, 2004).

Direct stimulation of the human brain through the scalp has been used since 1980 to investigate the pathway from the motor cortex to the peripheral nervous system (Merton and Morton, 1980). Initially, electrical stimulation was applied through the scalp (transcranial electrical stimulation, TES) to activate pyramidal tract neurons directly at or close to the axon hillock (Day et al., 1987). While this technique still has a role in neuroscience research, application of TES is limited due to the discomfort caused. Only a small proportion of the current applied actually flows into the brain, with the remainder stimulating the scalp causing pain and contraction of the scalp muscles (Barker et al., 1988).

1.1.4. Transcranial magnetic stimulation

The development of TMS (Barker et al., 1985) has enabled safe and painless investigation of the motor cortex and the integrity of the central motor pathways. The magnetic stimulator consists of a tightly-wound coil of insulated wire, connected to a set of capacitors. The passage of a large but brief electric current through this coil induces a magnetic field

perpendicular to the plane of the coil which passes virtually unimpeded through the skull. This induces electrical eddy currents in the underlying neural tissue (Barker et al., 1988). If the intensity of the stimulus is sufficient it will depolarise nearby neurons, e.g. in the motor cortex, resulting in a number of descending volleys in neurons that synapse with the corresponding motoneuron pool and elicit a transient electromyographic response termed a motor evoked potential (MEP) in the target muscle (Burke et al., 1993). The latency of the MEP from the time of the cortical stimulus to the onset of the MEP indicates the CM conduction time.

Transcranial magnetic stimulation can be used in a number of ways to investigate the motor cortex. For example, it is possible to map the cortical representation of specific muscles using an appropriate coil (Cohen et al., 1998). Stimulating coils are either round, inducing strong and spatially dispersed electric fields, or figure-of-eight, producing a weaker but more focal field. To map the motor cortex, a figure-of-eight coil is moved over a number of scalp sites centred on the optimal position to evoke a MEP. The stimulus intensity must be above the motor threshold, which is operationally defined as the intensity at which five MEPs with minimum peak-to-peak amplitude of 50 μV can be elicited when ten successive stimuli are given while the target muscle is relaxed (Rossini et al., 1994). A number of stimuli are delivered at each scalp site delineated by a grid, with spacings of, for example, 1 cm x 1 cm (e.g. Uy et al., 2002). This enables a motor map to be constructed, which gives an indication of the cortical representation of the target muscle(s) contralateral to the stimulated motor cortex. This method of cortical mapping has been used to investigate changes in the area and excitability of cortical representations of muscles in healthy subjects (Brasil-Neto et al., 1992; Uy et al., 2002; Wassermann et al., 1992) and in individuals following amputation (Ridding and Rothwell, 1995) or brain injury (Liepert et al., 2000b; Liepert et al., 1998).

Two important parameters obtained from cortical mapping of individual muscles are the "centre of gravity", calculated mathematically to indicate the amplitude-weighted centre of the excitable area (Wassermann et al., 1992), and the optimal scalp position or "hot spot" where the maximal MEP amplitude is evoked in the target muscle (Siebner and Rothwell, 2003). In addition, the area of the cortical map for a particular muscle may be determined as the number of scalp sites where stimulation evokes a MEP within it. This depends on the TMS stimulus intensity employed (Siebner and Rothwell, 2003) and is highly sensitive to the excitability of the representation and thus may be more difficult to interpret. Nevertheless, mapping is used to indicate the size of the corticospinal representation of a particular muscle at a given stimulus intensity.

Transcranial magnetic stimulation is also used to ascertain the excitability of the corticospinal projection solely at the optimal position by recording electromyographic (EMG) activity evoked in specific muscles in response to stimulation at a range of stimulus intensities. The responses can then be plotted as a stimulus-response curve. For hand muscles, the relationship between intensity and output is sigmoidal, with a steeply rising slope terminating in a plateau (Carroll et al., 2001; Devanne et al., 1997; Pitcher et al., 2003a). The slope of the curve is influenced by the excitability of the CM cells underlying the stimulating coil and the spatial distribution of excitable elements in the cortex. As cortical representation increases the current will depolarise a greater number of cortical cells, resulting in a steeper slope (Siebner and Rothwell, 2003). Changes in motor cortical maps are also reflected in changes in the slope of stimulus-response curves. This has been shown in response to transient ischaemia in normals (Ridding and Rothwell, 1997), and in individuals following limb amputation (Ridding and Rothwell, 1997) or suffering from focal hand dystonia (Ikoma et al., 1996). Increased excitability of the corticospinal projection is evident from larger MEPs, resulting in a steeper slope of stimulus-response curves and greater area of the representational map.

Construction of stimulus-response curves requires careful determination of the motor threshold. Stimulus intensities are then chosen to cover the range of MEP amplitudes up to the maximal MEP elicited. In order to obtain other descriptive parameters, such as the slope of the curve, it is necessary to fit a mathematical function to the observed relationship, using the Boltzmann equation (Buccolieri et al., 2004; Capaday, 1997; Devanne et al., 1997; Kaelin-Lang and Cohen, 2000; Khaslavskaia et al., 2002; Kido Thompson and Stein, 2004). This gives an estimation of the slope of the curve, the maximal MEP amplitude defined by the function, and the stimulus intensity at which the size of the MEP is 50% of the maximal MEP. It has been shown that stimulus-response curves are reliable indicators of excitability of the corticospinal pathway projecting to the hand muscles (Carroll et al., 2001).

The technique of paired-pulse TMS is another valuable tool for investigating the excitability of circuits within the motor cortex (Kujirai et al., 1993). This involves the delivery of a TMS shock below the threshold for motor activation (the conditioning stimulus) at a series of short intervals before a suprathreshold (test) TMS stimulus. The interstimulus interval determines the net output of the cortex at the level of the resting target muscle: short intervals (1 - 4 ms) inhibit the test response via activation of GABAergic interneurons (Ilic et al., 2002) resulting in intracortical inhibition of corticospinal neurons (short interval intracortical inhibition, SICI). Intervals of 3 - 4 ms are preferable for estimating function of the GABAergic inhibitory system of the motor cortex as shorter intervals are influenced by the refractory period of target cells or collision of inhibitory interneuron impulses (Hanajima et al. 2003). Longer intervals (5 - 15 ms) reflect the activation of glutamatergic interneurons mediating intracortical facilitation, or ICF (Cicinelli et al., 2003; Kujirai et al., 1993; Ziemann et al., 1996).

1.1.5. Consequences of damage to the motor cortex caused by stroke

Impaired motor function due to disruption of output from the motor cortex is frequently caused by stroke, or cerebrovascular accident (Porter and Lemon, 1995). Stroke is the most common cause of adult disability in Australia (Australian Institute of Health and Welfare, 2004) and worldwide (Love, 2005). More than one third of people who survive a stroke will have severe disability, due primarily to impaired upper limb rather than lower limb function. The reason for this greater involvement of the upper limb is the increased prevalence of strokes in the territory of the middle cerebral artery, which supplies the surface of the cerebral hemispheres and the pre- and post-central gyri where the motor and sensory cortex for the face and arm are located.

Stroke can be ischaemic, i.e. occlusion of a cerebral vessel by a clot or other particle, or haemorrhagic. Ischaemic strokes occur five times more often and may be the result of a thrombus forming over an atherosclerotic plaque, abnormal clotting or an embolus dislodged from the vascular wall anywhere in the circulatory system. Infarction ensues in the area of the brain normally supplied by the occluded vessel if collateral circulation is not able to compensate for the ischaemia (Brust, 2000). Haemorrhage may occur at the brain surface or within the brain tissue. A haematoma forms and is accompanied by oedema, both of which increase pressure on the brain, further compromising blood supply and leading to more widespread damage. This contributes to the much higher mortality rates following haemorrhagic stroke (Australian Institute of Health and Welfare, 2004).

1.1.6. Investigating corticomotor function following stroke

Transcranial magnetic stimulation is a safe, non-invasive tool that may be used to investigate the integrity of the corticospinal system following stroke. In the early stage following stroke, TMS over the affected hemisphere may not elicit a MEP in relaxed muscle. When present,

MEPs tend to have increased latency, smaller amplitude and require a higher stimulus intensity to elicit a response (Rossini and Dal Forno, 2004). TMS has been proposed as a tool to predict functional recovery following stroke (Catano et al., 1995; Cruz Martinez et al., 1999; Heald et al., 1993; Pennisi et al., 1999; Trompetto et al., 2000) as MEPs are always present initially in individuals who later regain complete finger control (Heald et al., 1993; Turton et al., 1996). In contrast, the absence of TMS responses is associated with poor recovery of hand function (Binkofski et al., 1996; Heald et al., 1993).

In addition to this decreased representation or excitability of the CM projection to hand muscles, asymmetries in cortical excitability between the hemispheres is another important feature following stroke (Rossini and Dal Forno, 2004). Investigation of the motor cortex contralateral to the lesion commonly reveals hyperexcitability when tested with TMS, indicating disinhibition of the CM projection to the intact hand (Cicinelli et al., 1997; Liepert et al., 2000c; Shimizu et al., 2002; Traversa et al., 1997). That is, infarction within one hemisphere may lead to a transient hyperexcitability of the opposite hemisphere, which is mediated by transcallosal fibres. This asymmetry tends to re-balance progressively during functional recovery, with a reduction in motor threshold and larger MEP amplitudes in the affected hemisphere being associated with a reduction in responsiveness of the unaffected hemisphere (Traversa et al., 1998). The mechanism for this may be transcallosal diaschisis (Andrews, 1991), or altered function in a brain region remote to the original infarct, which in this instance is probably the intact motor cortex. Alternatively, abnormalities in interneuronal GABAergic activity within the affected hemisphere may play a role (Chen, 2004; Daskalakis et al., 2002). Balancing may occur as the affected hemisphere recovers from the original insult and transcallosal inhibitory pathways influencing the unaffected hemisphere recover (Traversa et al., 1998). Despite the changes that occur in the hemisphere contralateral to the lesion, I shall for simplicity refer to it as the "unaffected hemisphere" throughout this review.

Paired-pulse TMS can also be used to assess neurophysiological changes following stroke, by plotting the asymmetry of SICI/ICF in both hemispheres (Cicinelli et al., 2003). In the unaffected hemisphere, there is a decrease in SICI within two weeks of the stroke (Liepert et al., 2000d), which corresponds to findings in animal studies (Buchkremer-Ratzmann et al., 1996). This may be due to a deficiency in intracortical inhibitory GABAergic circuits, or it may reflect decreased inhibition from the opposite motor cortex. Intracortical facilitation is unchanged in both the affected and unaffected hemispheres following stroke (Cicinelli et al., 2003; Liepert et al., 2000d). Longitudinal analysis of SICI/ICF curves in both hemispheres has not yet been conducted, although it has the potential to indicate beneficial changes over time, if SICI decreases in parallel with functional recovery.

Longitudinal TMS studies have demonstrated that improvements in function correlate with reorganisation of the motor cortex (Cicinelli et al., 1997; Traversa et al., 1997). Mapping the representation of a small hand muscle in subjects undergoing rehabilitation two to four months post stroke revealed an increased number of excitable scalp sites (i.e. increased map area) and greater MEP amplitudes at the second recording session. The increased map area correlated significantly with improved hand function score, assessed by the Canadian Neurological Scale (Traversa et al., 1997).

1.2. The upper limb

The integrity of the fast-conducting, monosynaptic pathway from the motor cortex is essential for skilled movement of the upper limb and particularly the hand (Kuypers, 1981). In the following section I review the important features of skilled upper limb movements, and discuss ways in which this can be studied in normal subjects. I then discuss features of upper limb function following stroke and different ways in which this can be investigated.

1.2.1. Dexterity

Definitions of dexterity are as diverse as the spectrum of skills and functions that humans perform with their upper limbs. They range from "adroitness, skill" (Oxford Dictionary), to "readiness in performing an action which proceeds from experience or practice, united with activity or quick motion" (Webster Encyclopaedic Dictionary) and "the ability to solve a motor problem correctly, quickly, rationally, and resourcefully" (Bernstein, 1996). Dexterity depends on the ability to make fractionated, independent movements, especially for fine manipulation, as we interact with our environment (Carr and Shepherd, 1998).

The neural system that controls the multitude of muscles and joints in order to achieve dexterity is incredibly complex. Firstly, the target must be located, which requires coordination between eye and head movements (Biguer et al., 1982). Reaching is then performed to transport the hand in space, with appropriate postural adjustments by the trunk and upper arm (Jeannerod, 1984). This is followed by grasp, the form of which depends on the location, size and shape of the object to be grasped (Johansson and Edin, 1992). Finally, manipulation within the hand allows the desired use or interaction with the object in question.

The ability to perform fine and complex movements is attributed to the highly developed CM projections that are present in mammals with the greatest digital dexterity (Heffner and Masterton, 1975). It is not merely the number or size of corticospinal fibres that determines dexterity, for these measures correlate poorly with dexterity. Instead, it is the level at which the corticospinal tract terminates, and penetration into the deepest layers of spinal laminae that contributes to greater dexterity (Heffner and Masterton, 1975).

It is now accepted that the CM projection is vital for selective finger activation under voluntary control (Kuypers, 1981; Lemon, 1999; Lemon and Griffiths, 2005). In humans, the

corticospinal system exerts a greater excitatory influence over distal than proximal upper limb muscles (Colebatch and Gandevia, 1989; Palmer and Ashby, 1992), particularly with low-force voluntary contractions (Turton and Lemon, 1999). A significant number of connections from the motor cortex to the motoneurons are monosynaptic (Lang and Schieber, 2004). Corticomotoneuronal cells projecting to intrinsic hand muscles are most active when independent finger movement is performed, and less active during gross movements of the whole hand, despite the greater activity in the muscles involved in the task (Muir and Lemon, 1983). This apparent preference for involvement in fractionated finger movements is not seen in non-CM cells (Fetz et al., 1989) and may be attributed to the small number of hand muscles supplied by individual CM cells (Bennett and Lemon, 1996; Buys et al., 1986).

Performance of skilled hand movement requires more than a functioning motor output system. All movements generate vast amounts of sensory feedback, and this afferent input is crucial for the fine control of movement (Lemon, 1999). Cutaneous and other proprioceptive inputs project onto pyramidal cells in the motor cortex either via the thalamus or less directly via the somatosensory cortex (Asanuma and Arissian, 1984). Individuals with absent or impaired sensation have significantly reduced dexterity and accurate purposeful movements are possible only with vision (Jeannerod et al., 1984; Rothwell et al., 1982). However, vision is not able to compensate adequately in the event of loss of cutaneous sensation due to digital anaesthesia or deafferentation (Monzee et al., 2003). This further emphasises the importance of cutaneous mechanoreceptors in force coordination (Augurelle et al., 2003b; Brochier et al., 1999; Johansson and Westling, 1984; Nowak et al., 2004; Nowak et al., 2003a) and for reactive grip force adjustments in response to load perturbations (Nowak et al., 2002). Extensive cortico-cortical connections from areas of the motor cortex subserving cognition, learning, and attention are also important for the problem-solving aspect of human dexterity.

1.2.2. Investigation of normal upper limb function

The experimental investigation of digital dexterity in humans is frequently directed towards discriminating between the dominant and non-dominant hands. Much interest has centred on this prominent behavioural asymmetry to determine the mechanisms that cause us regularly to use one hand to stabilise an object while the dominant hand manipulates it. Superior performance of the dominant hand is most evident in coordinated movement sequences, rather than single-finger movements such as performing isolated finger movements in an opposition task (Hammond et al., 2004; Reilly and Hammond, 2004). More precise control can be demonstrated using repetitive finger tapping, where the transitions between flexion and extension are less variable and more rapid for the dominant hand (Hammond et al., 1988; Hammond et al., 2004). Kinematic analysis of drawing concentric circles or handwriting is another means of demonstrating superior performance of the dominant hand, with less variability in amplitude, peak velocity, and acceleration/deceleration than the non-dominant hand, indicating its more efficient sensorimotor performance (Henkel et al., 2001; Phillips et al., 1999).

Another method of discriminating between performance of the hands is the Purdue pegboard test (Tiffin, 1968). This involves retrieving small pegs from a well with the thumb and index finger and placing them in holes, with the aim of placing as many pegs as possible in 30 seconds (Reddon et al., 1988). The right hand is able to place pegs faster than the left in right-hand dominant subjects (Nielsen et al., 1989) although there is considerable variation in the performance when the left hand is dominant (Verdino and Dingman, 1998). The Grooved Pegboard Test (GPT) is a variation of the Purdue pegboard test. The apparatus consists of key-shaped pegs that must be rotated to match the groove in the corresponding hole in a horizontal board (Tremblay et al., 2003). One advantage of the GPT is that there is no effect of handedness; that is, left-handers complete the task in the same amount of time as right-

handers (Ruff and Parker, 1993). This limits the potential bias for left-handers, who receive more practice using their non-dominant (right) hand for everyday tasks than right-handers (Schmidt et al., 2000). Further, it assesses eye-hand coordination and motor speed and thus can be used to test sensorimotor integration and motor processing (Schmidt et al., 2000).

Westling and Johansson (1984) described an innovative method to determine the factors involved in force coordination when grasping and lifting a small object using the so-called "precision" or pinch grip, which is a key feature of dexterity (Westling and Johansson, 1984). Their purpose-built apparatus measured the grip force between the thumb and the index finger, the load force as the object was lifted from the surface, and the position of the object (Figure 1.1). Subjects were required to lift the object to a specified height, hold it steady, and then slowly move apart the thumb and index finger until they dropped the object. A number of different experimental conditions were examined, in which the weight of the object was varied and the texture of the touched surfaces was changed to alter the friction coefficient. Local anaesthesia of the index finger and thumb was also performed on several subjects (Westling and Johansson, 1984). In addition to grip and load forces, other data obtained from these experiments included the minimal grip force required to prevent slippage, or slip force (see Figure 1.2), the relationship between static grip force and surface structure and weight, and the influence of the previous trial on grip force (i.e. learning).

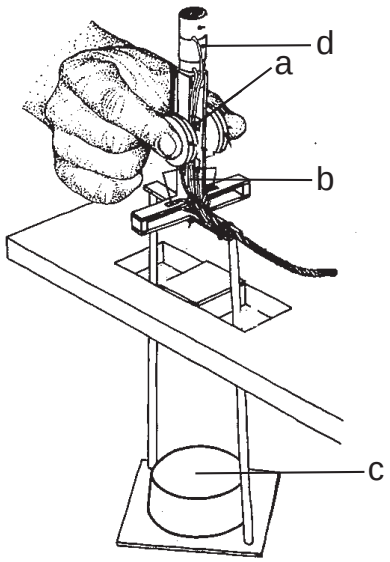

Figure 1.1 Grip-lift apparatus

Schematic drawing of grip-lift apparatus developed; (a) strain gauge force transducer measuring grip force, (b) strain gauge measuring load force, (c) exchangeable weight shielded from subject's view by the table, (d) accelerometer. Adapted from Westling and Johansson (1984).

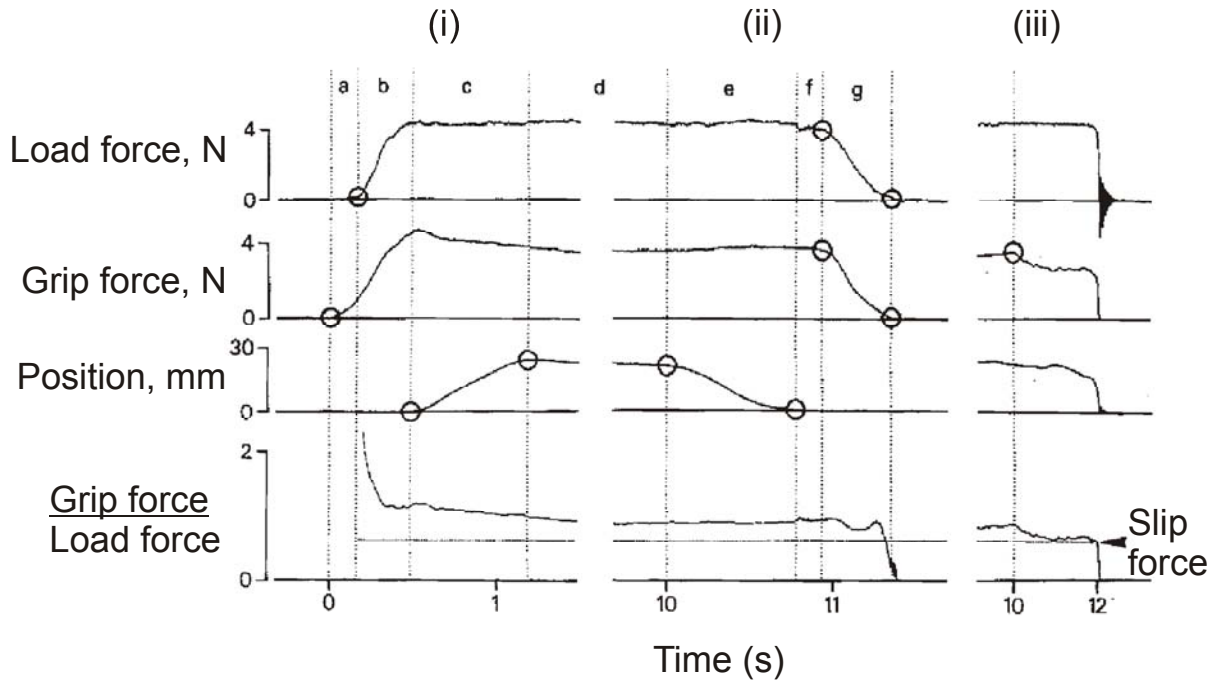

Figure 1.2 General form of data in lifting trials

General structure of the lifting trials with separate panels indicating (i) lift off, (ii) set down and (iii) measurement of the slip force (separate trial). The phases (a) – (g) were common for all lifting trials: (a) preload phase, (b) loading phase, (c) transitional phase, (d) static phase, (e) replacement phase, (f) delay, (g) unloading phase. Note the interrupted time scale and that the force ratio is not shown for the preload phase. The vertical dashed line in the slip trial indicates the start of slow voluntary separation of the fingers as the object was slowly released (adapted from Johansson and Westling, 1984).

A long series of studies by these researchers and others led to the following conclusions:

1. Grip force is critically balanced when gripping and lifting a small object with a precision grip, and is influenced by object weight, surface friction and a safety margin factor related to the individual (Westling and Johansson, 1984).
2. Different mechanisms control grip force with altered friction and weight changes: cutaneous mechanoreceptors are necessary to allow adjustment of grip force to different frictional conditions but not to adjustments in the weight of the object (Johansson and Westling, 1984; Westling and Johansson, 1984).
3. Different phases of the grip-lift task are centrally programmed and triggered by peripheral feedback, for they are disrupted by local finger anaesthesia (Johansson and Westling, 1984; Johansson and Westling, 1988a).

4. The coordination between grip and load forces depends on an anticipatory control strategy whereby the central nervous system predicts the consequences of self-generated load forces and anticipates the grip force required to maintain a stable grasp (Ehrsson et al., 2003; Flanagan and Wing, 1997; Johansson and Westling, 1984; Johansson and Westling, 1988b).
5. Anticipatory control of fingertip forces develops gradually, and a mature pattern of force coordination is not achieved until approximately eight years of age (Ehrsson et al., 2003; Forssberg et al., 1991; Forssberg et al., 1992).
6. When load force is changed unexpectedly between or within trials, grip force is programmed erroneously and somatosensory signals rapidly trigger compensatory actions and update the internal model or memory trace of the task (Johansson and Westling, 1984; Johansson and Westling, 1988a; Johansson and Westling, 1988b).
7. If the contralateral hand performed the same task, information gained thereby about the friction or weight of the object can be used to update the central program for grip force control, even in the presence of anaesthesia of the digits involved in the task (Johansson and Westling, 1984; Johansson and Westling, 1988b).
8. The coordination of grip and load forces is observed in other types of manipulatory tasks (Flanagan et al., 1993; Flanagan and Wing, 1993; Johansson et al., 1999; Johansson and Westling, 1988b) and can rapidly adjust to altered gravitational fields, such as during parabolic airplane flights (Augurelle et al., 2003a).
9. Varying the type of grip used influences the coordination of grip and load forces in children (Gordon and Duff, 1999) and adults (McDonnell et al., 2005).
10. Older adults continue to use anticipatory control but employ excessive grip forces, partly due to increased skin slipperiness. Other factors contributing to the increased safety margin may be declining cutaneous afferent function, attributed to changes in

Meissner corpuscle structure and function, and central processing delays (Cole et al., 1999).

The grip-lift task has been used to quantify the temporal and force characteristics of the precision grip in a number of different pathological conditions (Johansson and Westling, 1984). This has been reported for children (Forssberg et al., 1999) and adolescents (Duque et al., 2003) with cerebral palsy, children with developmental coordination disorder (Pereira et al., 2001) and traumatic brain injury (Golge et al., 2004), adults with Parkinson's disease (Fellows et al., 1998), amyotrophic lateral sclerosis (Nowak et al., 2003c), focal hand dystonia (Odergren et al., 1996) and stroke (Hermsdorfer et al., 2003). The findings solely relating to stroke patients are discussed in Section 1.2.4.

1.2.3. Impaired dexterity due to hemiplegia

Many aspects of brain function are disrupted by a stroke: these include speech, language and cognitive abilities. However, it is the loss of independence due to physical impairment that is the greatest cost to stroke survivors and to the community (Pang et al., 2006). Despite intensive rehabilitative efforts, the functional outcome of patients with initially-severe hemiparesis is very poor (Nakayama et al., 1994a). It has been estimated that only 5% of patients with complete paralysis regain full arm function (Gowland et al., 1992; Richards and Pohl, 1999) and that 30-66% of survivors never regain any use of the affected arm (Nakayama et al., 1994b; van der Lee et al., 1999). While loss of skilled arm function is partially related to the location of the stroke (Wenzelburger et al., 2005), the extent and location of the stroke are less effective predictors of eventual function than the initial clinical findings of neurological loss (Feys et al., 2000; Kwakkel et al., 2003; Wade et al., 1983).

Weakness and loss of dexterity are considered to account for most of the disability following stroke (Burke, 1988; Landau, 1988) and, while both are commonly seen together, recovery of strength does not ensure recovery of dexterity (Canning et al., 2000). Carefully designed experiments have shown that loss of dexterity can occur independently of weakness, slowness of muscle activation, excessive co-contraction and spasticity (Canning et al., 2000). However, when relative contributions of strength and dexterity to recovery of function and their ability to predict functional recovery are compared, weakness makes a greater contribution to function than lack of dexterity (Canning et al., 2004).

Features commonly associated with impaired dexterity in the hemiplegic upper limb include the loss of individuated finger movement (Lang and Schieber, 2003; Lang and Schieber, 2004; Li et al., 2003), altered muscle properties due to contracture (O'Dwyer et al., 1996), slowing of coordinated movements (McCombe Waller and Whitall, 2004), increased sensation of heaviness or effort when moving (Gandevia, 1982; Rode et al., 1996) and reduced skilfulness of aimed and ballistic movements (Platz et al., 2001a). These features are independent of visuospatial disorders, such as apraxia, agnosia and neglect, which are more common following right hemisphere damage (Hermsdorfer et al., 1999).

Gradual recovery of dexterity can occur following stroke, although it is often incomplete. Functionally-beneficial reorganisation within the corticospinal system can occur provided approximately 20% of cortical pyramidal cells are spared (Cicinelli et al., 1997; Rossini et al., 2003; Seitz and Freund, 1997). Damage to the posterior limb of the internal capsule, which contains the most dense projections from M1, is strongly correlated with poor motor outcome, again emphasising the importance of the integrity of the corticospinal tract for the recovery of fine motor functions of the upper limb (Wenzelburger et al., 2005). Sensory deficits resulting from somatosensory cortex lesions are also associated with deficits in fine motor skill (Nudo

et al., 2000; Xerri et al., 1998) and may contribute to the overall motor deficit independently, or as a function of the extensive connections between M1 and a number of somatosensory areas in the parietal cortex (Nudo et al., 2000; Nudo et al., 1997).

1.2.4. Investigation of hemiplegic upper limb function

Traditionally, assessment of upper limb motor function following stroke has relied on qualitative descriptions of muscular control, strength and muscle tone (Poole and Whitney, 2001). Over time, a wide range of upper limb assessment scales were developed to quantify deficits in function, and to provide a means of documenting recovery during rehabilitation. More than a dozen reliable and valid stroke-specific scales are available for use (Finch et al., 2002). Each of these has various limitations in terms of sensitivity, completion time, ceiling and floor effects, equipment required and consideration of pre-existing hand preferences. Table 1.1 summarises the advantages and disadvantages of these assessments of motor function. Based on these observations, I chose to use two of these tests for the study described in Chapter 6 and they are briefly reviewed here.

The Action Research Arm Test (ARAT) is based on the Carroll test of upper extremity function (Carroll, 1965) and consists of 19 movements grouped into four subtests: namely grasp, grip, pinch and gross arm movement (Lyle, 1981). Each movement is scored on a four-point scale and items are organised hierarchically. The maximal total score is 57 points. Although not designed specifically for stroke patients, its use with this population has been validated (De Weerdt and Harrison, 1985; Hsieh et al., 1998; Lyle, 1981; Wagenaar et al., 1990) and intra-rater and retest reliability have been established (Hsieh et al., 1998; Lyle, 1981; van der Lee et al., 2001b; Wagenaar et al., 1990). In order to detect a clinically meaningful change, the measurement error of the ARAT must be smaller than the estimated minimal clinically important difference in scores. This was confirmed by van der Lee et al.

(2001) and an increase in score of 5.7 points was suggested to indicate a clinically-relevant change in function.

Rather than testing upper limb function, the Fugl-Meyer Assessment (FMA) tests impairment of the upper and lower extremities, balance and sensation (Fugl-Meyer et al., 1975). It has undergone the most extensive psychometric testing and is sensitive to change after intervention (Poole and Whitney, 2001). The 66-point upper limb section is commonly used in isolation to measure motor recovery. It consists of 33 items scored on a 3-point scale and grouped according to the categories shoulder/elbow/forearm, wrist, hand and coordination/speed. Validity (De Weerdt and Harrison, 1985; Dettmann et al., 1987) and reliability (Duncan et al., 1983; Sanford et al., 1993) have been established in multiple studies. Both the ARAT and the FMA are sensitive to motor changes in chronic stroke (van der Lee et al., 2001a).

While empirical measures of function and impairment are important in clinical studies, the ability of patients to use their affected upper limb for daily activities, or real-world use, is a primary focus for rehabilitation. The Motor Activity Log (MAL) was developed to measure this (Taub et al., 1993). The MAL is a semi-structured interview that determines the amount and quality of use of the affected arm when performing everyday tasks, scored on a 6-point scale. The number and characteristics of tasks included in the interview have not been standardised, with reports in the literature of between 14 and 30 activities (van der Lee et al., 2004). Recent assessment of the clinimetric properties of the MAL suggests that it is internally consistent and stable in chronic stroke patients, irrespective of the number of items included (van der Lee et al., 2004).

Table 1.1 Summary of assessment systems used for upper limb motor function post stroke

Assessment	Time (min)	Areas of assessment	Pros	Cons
Action Research Arm Test (Lyle, 1981)	10	Grasp and lift items Grip Pinch Gross arm movements	Reliability and validity well established Responsive to change in chronic stroke patients	Lacks assessment of performance time
Arm Motor Ability Test (Kopp et al., 1997)	30	13 functional tasks, unilateral and bilateral e.g. eating, dressing, combing hair, telephoning, tying shoelaces, opening a jar and door	Measures daily living skills	Complex scoring system Suffers from floor effects with more impaired patients
Box and Block Test (Mathiowetz et al., 1985)	5	Gross manual dexterity: grasping and transporting blocks	Normative data available for the elderly	Responsiveness to change not established
Chedoke-McMaster Stroke Assessment (Gowland, 1990)	20	Shoulder pain Arm movements Hand movements	Designed for the stroke population	Limited assessment of hand function Complex scoring system
Frenchay Arm Test (De Souza et al., 1980)	3	Tasks: stabilise ruler, grasp cylinder, drink from glass, place clothes peg on a dowel, comb hair	Quick to administer	Not responsive to gains in function at upper and lower ends
Fugl-Meyer Assessment – upper extremity component (Fugl-Meyer et al., 1975)	15	Shoulder/elbow/fore-arm Wrist Hand Coordination	Reliability and validity well established Measures impairment Sensitive to change following intervention	Based on Brunnstrom's stages of motor recovery (outdated)
Functional Test for the Hemiparetic Extremity (Wilson et al., 1984)	30	Tasks include stabilise items with arm/hand, grasp small items, in-hand manipulation, tasks scored on 7 functional levels	Hierarchical organisation of tasks	Complex scoring system

Table 1.1 Summary of assessment systems used for upper limb motor function post stroke (continued)

Assessment	Time (min)	Areas of assessment	Pros	Cons
Jebsen-Taylor Functional Hand Test (Jebsen et al., 1969)	20	Gross and fine motor function	Normative data available for stroke patients	Does not consider quality of movements Requires large amount of equipment
Motor Assessment Scale - upper extremity subscale (Carr et al., 1985)	10	Upper arm function Hand movements Advanced hand activities	Reliability and validity well established with stroke patients	Advanced hand tasks are not truly hierarchical and are influenced by hand dominance Limited sensitivity
Motricity Index (upper extremity subscale) (Collin and Wade, 1990)	5	Elbow flexion Shoulder abduction Pinch grip	Requires minimal equipment	Only tests strength of the three movements Not sensitive to quality of movement
Nine-hole Peg Test (Sharpless, 1982)	5	Grasp, transport, insertion of pegs into a wooden board, then removal	Timed	Floor effects with patients who cannot grasp pegs
Rivermead Motor Assessment–arm subscale (Lincoln and Leadbitter, 1979)	15	Tasks: grasp and release objects, tying a bow, cutting putty, bouncing a ball, rotating the forearm	Hierarchical organisation of tasks	Dichotomous scoring, no sensitivity to quality of movement
Test Evaluant les Membraes Superieurs des Personnes Agees (Desrosiers et al., 1993)	20	Functional activities including 5 bilateral tasks	Scores time taken to complete the task and subject's independence	Limited evidence of reliability and validity in stroke patients

(Australian Physiotherapy Association, 2001; Croarkin et al., 2004; Finch et al., 2002; Kopp et al., 1997; Poole and Whitney, 2001)

Other tests that have been used to characterise impairment following stroke are maximal finger-tapping rate (Heller et al., 1987) and grip strength (Sunderland et al., 1989). Objective measurement of grip strength is simple to measure objectively following stroke and can be a

powerful measure for detecting early recovery and predicting final functional outcome (Sunderland et al., 1989). The highest value from three successive trials is recommended for reproducible results (Hammer and Lindmark, 2003).

Investigation of impairments in manipulative grip force control in stroke patients has been undertaken comprehensively by Hermsdorfer et al. (2003). Rather than use an apparatus that could be gripped and lifted from a surface, they developed a lightweight instrumented object that was not physically connected to external devices. This allowed investigation of hold, transport and cyclical vertical movements, but not the initial stages of the grip-lift task as originally outlined by Westling and Johansson (1984). Although sensation was not thoroughly assessed, a perturbation task was designed to assess the capacity for processing sensorimotor information in a precision grip. The load between the grasping fingers was increased by altering the displacement between the fingers, and the time taken to respond was measured. Compared with age-matched healthy subjects, chronic cerebral stroke patients with mild to moderate paresis used excessive grip forces when holding and transporting the object despite a reduction in maximal grip strength. While there were some delays in responding to force changes in a grip perturbation task and decreased speed of movement during object transport, the feedforward mechanisms required for the cyclic vertical movements were intact, suggesting that anticipatory control was largely preserved. Significant correlations between the delay in the perturbation task and increased grip force and delay in achieving peak grip force during object transport led the authors to conclude that impaired sensibility and sensorimotor processing accounted for force control deficits in stroke patients (Hermsdorfer et al., 2003).

Other studies of grip-force control in stroke patients have involved different tasks, investigating maintenance of a constant grip force, matching a required force level

(Hermsdorfer and Mai, 1996) or responding to sudden load perturbations in a drawer-opening task (Grichting et al., 2000). The only other study to investigate stroke patients did use the grip-lift task but analysis was concentrated on the temporal characteristics of the lift and comparing these results to an age-matched control group (Wenzelburger et al., 2005). Recruitment was limited to patients with a "pure motor stroke" due to a lesion of the internal capsule. These patients demonstrated a moderate increase in precision grip force, and a significant delay in both the time taken to establish grip and to commence lifting the object. Although sensory deficits were not reported for individual patients, group data indicated that some subjects had mild impairments in sensation to light touch and proprioception, so it is unclear whether the deficits seen were due purely to corticospinal tract involvement or in part due to sensory impairments.

Improvements in the hardware and software required to construct a grip-lift apparatus have led to the suggestion that grip force control may be easily included in clinical examination of hand function following cerebral lesions (Hermsdorfer and Mai, 1996). The examination is brief, non-invasive, easy for patients to complete, and data obtained can provide detailed information that may assist in directing therapeutic intervention (Hermsdorfer and Mai, 1996). In order to detect changes in the affected (treated) upper limb during rehabilitation, it is advantageous to be able to compare changes in the affected and unaffected (untreated) limb over the same time period. The relationship between grip-lift parameters of both upper limbs in subacute stroke patients and function is presented in Chapter 5. The grip-lift task was also used to detect changes in dexterity during a novel intervention to facilitate recovery following stroke, discussed in Chapter 6.

1.3. Cortical plasticity

The ability of the adult nervous system to change constantly and to be remodelled throughout life offers exciting prospects for researchers in neuroscience. In the following section I will discuss mechanisms underlying this ability to change, and ways in which plastic changes can be achieved experimentally. I will discuss conventional rehabilitation approaches to impaired upper limb function following stroke, and introduce novel techniques that are currently being investigated to facilitate upper limb recovery following stroke.

1.3.1. Mechanisms of cortical plasticity

The human nervous system retains the potential for functional reorganisation throughout life (Sanes and Donoghue, 2000). This potential for change has been termed plasticity and has been defined as "any enduring change in cortical properties either morphological or functional" (Donoghue et al., 1996). Plasticity encompasses mechanisms of self-repair or reorganisation of neural connections at the synaptic level (Rossini and Dal Forno, 2004), but it can also be demonstrated at the regional level where changes can be effected in larger cell networks in response to lesions or training (Siebner and Rothwell, 2003). Plastic changes are believed to be the foundation for learning, memory and the repair of damage following brain injury (Rossini and Dal Forno, 2004). Plasticity has been demonstrated in the rodent hippocampus (Bear and Abraham, 1996; Castro-Alamancos and Connors, 1997), rodent visual cortex (Antonini et al., 1999; Kirkwood et al., 1996) and sensory cortex (Finnerty et al., 1999), primate (Recanzone et al., 1993) and human auditory cortex (Jancke et al., 2001), and the human motor cortex (Donoghue, 1995; Hamdy et al., 1998; Karni et al., 1995).

Central nervous system reorganisation occurs at many levels. Rapid changes in organisation are attributed to the unmasking of synapses that are functional but are not currently active

(Jacobs and Donoghue, 1991). This may be due to increased excitatory neurotransmitter release, increased density of postsynaptic receptors or the removal or reduction of tonic inhibition (Chen et al., 2002; Kaas, 1991). Less inhibitory inputs onto excitatory synapses is the most likely mechanism in short-term plastic changes and is believed to be due to reduction of GABAergic inhibition (Chen et al., 2002). Pharmacological blockade of GABA-mediated inhibition through the application of the GABA antagonist bicuculline into the rodent motor cortex resulted in significant and rapid changes in size and distribution of cortical representational areas, suggesting that GABAergic neurons play a vital role in cortical map reorganisation (Jacobs and Donoghue, 1991).

Rapid plastic changes have been demonstrated in the human motor cortex following the change in pattern of tonic afferent input by prolonged (30–40 minute) forearm ischaemia (Ridding and Rothwell, 1995; Ziemann et al., 1998). The removal of tonic inhibitory inputs from cutaneous and other afferent input influences the dynamic equilibrium between excitation and inhibition acting on cortical output neurons. This allows the cortical representation zone to expand into the full extent of anatomical connectivity which is greater than the usual zone of functional influence (Jacobs and Donoghue, 1991; Muellbacher et al., 2002). This is associated with reduced intracortical inhibition in muscles proximal to the ischaemia that have expanded into the deafferented zone (Chen et al., 2002).

Another important process involved in short-term reorganisation is the ability to modulate synaptic efficacy. Increased effectiveness of synaptic transmission was first described in the rabbit hippocampus (Bliss and Lomo, 1973) where it was noted that stimulation of any of the three major input pathways resulted in increased amplitude of excitatory postsynaptic potentials in the target hippocampal neurons. This was termed long-term potentiation (LTP) and has since been defined as “an artificially induced change in synaptic strength produced by

electrical stimulation of synaptic pathways" (Kandel et al., 2000, p. 1264). It requires high-frequency stimulation of excitatory afferents (Bliss and Lomo, 1973); in contrast, low-frequency stimulation can induce long-term depression (LTD) (Dudek and Bear, 1992).

In general, the induction of LTP has four requirements: cooperativity, associativity, input-specificity and involvement of *N*-methyl-D-aspartate (NMDA) and GABA receptors (Bi and Poo, 2001; Bliss and Collingridge, 1993; Paulsen and Sejnowski, 2000). Cooperativity requires that several axons be activated together, which can be considered as an intensity threshold for inducing LTP by tetanic stimulation (Bliss and Lomo, 1973). Associativity refers to convergent activity of "weak" and "strong" synaptic inputs (Bi and Poo, 2001), or concomitant activation of pre- and post-synaptic cells (Debanne et al., 1998). This is consistent with Hebb's postulate:

> "When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased" (Hebb, 1949, p. 62).

Hebbian plasticity is dependent upon input specificity so reversing the temporal order of paired inputs may result in LTD rather than LTP (Levy and Steward, 1983). Cortical plasticity is NMDA receptor dependent and frequently requires reduction of local inhibition mediated by GABA receptors (Bliss and Collingridge, 1993).

While longer-term changes in cortical reorganisation may also involve LTP, other mechanisms have been proposed, such as axonal regeneration and sprouting, and alterations in synapse shape, number, size and type (Chen et al., 2002; Kaas, 1991; Toni et al., 1999). Dendritic spines, at least in the adult mouse barrel cortex, are constantly remodelled, with new synapses being formed and eliminated in response to sensory experience (Trachtenberg

et al., 2002). The ability to form new synapses in the adult cortex is carefully balanced by the retraction of existing but perhaps unused synapses, so that the density of stable synapses remains unchanged (Trachtenberg et al., 2002). Homeostatic regulation of neural circuits is necessary to prevent them from becoming hyper- or hypo-active (Turrigiano and Nelson, 2004). Circuits must be flexible in responding to change but stable enough to avoid developing uncontrolled excitation or quiescence (Miller, 1996). In order to maintain this homeostasis, it is proposed that changes in synaptic weight, rather than wiring, may underlie cortical plasticity (Chklovskii et al., 2004; Turrigiano, 1999).

1.3.2. Learning and use-dependent plasticity

Since the pioneering studies of Bliss and Lomo, the induction of LTP has been described in the neocortex of animals (Castro-Alamancos et al., 1995; Hess and Donoghue, 1994; Rioult-Pedotti et al., 2000) and also the human hippocampus (Beck et al., 2000). Recent studies investigating activity-dependent plasticity in the human motor cortex have suggested that repetitive TMS (rTMS; Ziemann et al., 1998) and motor learning (Ziemann et al., 2004) result in LTP and LTD-like plastic changes. Evidence to support this hypothesis includes the similarities between the observed changes and LTP/D, in particular the duration of the effect (> 60 mins), input specificity and dependence on NMDA-receptor activation (Stefan et al., 2002; Stefan et al., 2000; Wolters et al., 2003). Thus the remodelling of synapses, and reorganisation of cortical networks, may be significantly influenced by use or experience (Biernaskie and Corbett, 2001; Johansson and Belichenko, 2002).

Direct investigation of representational maps of somatosensory cortical areas in animals by intracortical microelectrode recording has revealed the capacity for substantial reorganisation in response to manipulation of sensory inputs (Clark et al., 1988; Kaas, 1991; Nudo et al., 1996a; Recanzone et al., 1990). This plasticity occurs in response to behavioural experience

as well as pathological disturbance, and suggests that the sensory cortex is constantly remodelled throughout life (Nudo et al., 1996a). This has also been demonstrated in the rodent motor cortex, through the manipulation of peripheral inputs (Donoghue and Sanes, 1987) or by using repetitive electrical stimulation to induce changes in movement representations (Nudo et al., 1990). Simply changing the position of the forelimb of anaesthetised adult rats can alter motor output representations in M1 (Sanes et al., 1992), an observation that highlights the importance of changes in proprioceptive input to organisation within the motor cortex.

The induction of plastic changes accompanying motor learning has been studied in human subjects who have undergone extensive motor training. The somatosensory cortical representation of digits involved in the dextrous task of fingering strings is enlarged in string musicians, and the increase is correlated with the age at which they started playing (Elbert et al., 1995). Similarly, the motor representation of the reading finger of Braille readers is expanded; this occurs with blind individuals or sighted individuals who have undergone the process of learning Braille (Elbert and Rockstroh, 2004; Rockstroh et al., 1998). Motor cortical reorganisation has also been reported in elite racquet players (Pearce et al., 2000).

There is a strong association between learning a novel motor task and changes in cortical organisation, suggesting that the ability to acquire a new skill may be dependent on increased cortical excitability (Pascual-Leone et al., 1999). TMS has been used to investigate changes in motor maps in subjects trained to perform a one-handed, five-finger exercise on the piano and compared with those engaged in mental practice or random key presses. Five days of the learning condition resulted in improved playing skills and increased excitability of the motor cortex (Pascual-Leone et al., 1995). These changes were not observed in the mental practice or random key press groups. In another experimental paradigm, the performance of

synchronised thumb and foot movements led to a temporary (less than one hour) alteration in the location of the cortical motor map of the thumb, towards the foot area of the cortex (Liepert et al., 1999). Asynchronous thumb and finger movements did not induce any plastic changes (Liepert et al., 1999), which is consistent with the observation that plastic changes in the motor cortex do not occur following repetitive, unskilled movement, but instead require the element of skill (Nudo et al., 2001). Similarly, passive movements do not lead to lasting changes in the memory of kinematic details of a task to the same extent as active movements, which highlights the importance of voluntary drive for skill acquisition (Kaelin-Lang et al., 2005). These findings are consistent with data from animal models. Repetitive skill learning increased the number of synapses in adult rats in comparison to inactive animals and those allowed to perform unskilled motor tasks (Kleim et al., 1996). In adult squirrel monkeys, simple, repetitive motor activity alone was insufficient to induce representational plasticity in cortical motor maps (Plautz et al., 2000).

1.3.3. Methods of inducing cortical plasticity

The potential for learning new skills to induce cortical plasticity has led researchers to investigate other techniques for inducing cortical plasticity. Changes in afferent input can lead to a reduction of cortical inhibition. For example, withdrawal of sensory inputs has revealed rapid and dramatic alterations in representational maps of M1 that mimic changes which occur following limb amputation. In particular, temporary ischaemic nerve block (as discussed in Section 1.3.1) has been used experimentally to induce motor cortex disinhibition (Brasil-Neto et al., 1993; Ridding and Rothwell, 1995; Ziemann et al., 2001). This is consistent with the view that the pattern of somatosensory input to the central nervous system plays an important role in maintaining cortical representation (Brasil-Neto et al., 1993).

Conversely, the addition of relevant sensory stimulation can induce plastic changes that increase the representation of target muscles. Prolonged sensory stimulation, designed to mimic repetitive natural stimulation over a large skin surface, applied to adult cats (Recanzone et al., 1990) and adult owl monkeys (Jenkins et al., 1990) resulted in significant remodelling of the primary somatosensory cortex, with stimulated receptive fields expanding considerably. Godde et al. (1996) extended this work, replacing repetitive nerve or digital stimulation with paired sensory inputs, according to Hebb's postulate. So-called "associative pairing" of tactile stimulation involved weak electrical stimuli to two non-overlapping receptive fields of the digits of adult rats, with both fields being stimulated simultaneously but with random intervals between pulses. The resultant cortical reorganisation was manifest as enlargement of the stimulated receptive fields. A control experiment stimulated only one skin site with the same temporal characteristics and induced no change in receptive fields (Godde et al., 1996).

A similar paradigm was then applied to human subjects to determine whether increased somatosensory information could lead to changes in perception. Two skin sites were stimulated, as described above, resulting in a significant improvement in spatial discrimination performance in the stimulated digits only (Godde et al., 1996). This work forms the basis for the associative stimulation technique used by Ridding and co-workers (Pyndt and Ridding, 2004; Ridding and Uy, 2003) with the important modification of stimulating the afferents of target muscles, rather than skin regions, to allow direct investigation of the effect on the stimulation on the motor cortex. This paradigm was chosen to induce plasticity in Chapters 3 and 5.

Another experimental paradigm widely used to induce plasticity in the human motor cortex is paired associative stimulation (PAS) (Ridding and Taylor, 2001; Stefan et al., 2002; Stefan et

al., 2000; Stefan et al., 2004; Wolters et al., 2003; Wolters et al., 2005; Ziemann et al., 2004). This is similar to the associative stimulation technique insofar as it requires activation of paired inputs to the sensorimotor cortex, but the paired inputs are repetitive median nerve stimulation and cortical stimulation. The electrical nerve stimulation and cortical TMS pulses are timed so that the peripheral signal and the central stimulus occur synchronously or near-synchronously at the motor cortex. The interval between the two modes of stimulation is critical; initially 25 ms was chosen to allow for peripheral conduction time from the periphery to the somatosensory cortex (~ 20 ms) and from there to the motor cortex (~ 3 ms). However, Stefan et al. (2000) discovered subsequently that interstimulus intervals up to 35 ms were effective, provided the peripheral volley arrived prior to the cortical stimulus. Reversing the sequence of arrival of the afferent signals so that the peripheral volley arrived after the cortical stimulus induced depression of cortical excitability, as proposed by the strict temporal Hebbian rules (Levy and Steward, 1983; Wolters et al., 2003). This is consistent with the idea that induction of plasticity in this way is similar to LTP and LTD (Section 1.3.2).

Repetitive stimulation of either the periphery or the cortex, while not strictly fulfilling the requirements for associative LTP-like plasticity, may also induce plastic change in the somatosensory cortex. Prolonged peripheral nerve stimulation (Charlton et al., 2003; Kaelin-Lang et al., 2002; Khaslavskaia et al., 2002; Kido Thompson and Stein, 2004; Knash et al., 2003; Ridding et al., 2000; Ridding et al., 2001; Wu et al., 2005), muscle vibration (Rosenkranz and Rothwell, 2004) or high frequency stimulation of the motor cortex with rTMS (Berardelli et al., 1998; Maeda et al., 2000; Pascual-Leone et al., 1994) also result in enhanced cortical excitability of the target muscles. In contrast, low-frequency rTMS may depress motor cortical excitability (Chen et al., 1997). Studies with combined peripheral and central stimulation (Pitcher et al., 2003b) and rTMS (Pascual-Leone et al., 1994) have

demonstrated that corticospinal excitability is bi-directionally modifiable, with the frequency of stimulation determining the direction of excitability change.

An alternate method of inducing plastic changes, which is believed to involve mechanisms other than LTP-like changes, is transcranial direct current stimulation (tDCS). This form of non-invasive stimulation modifies cortical excitability in a polarity-specific manner: anodal stimulation increases neuronal firing rates and cortical excitability, and cathodal stimulation suppresses firing rate and responses to TMS (Lang et al., 2004). The mechanism of action is thought to be direct-current induced changes in resting neuronal membrane potential (Lang et al., 2004), leading to a change in NMDA-receptor activation (Liebetanz et al., 2002).

In addition to these studies investigating cortical plasticity following stimulation of the limbs, cortical plasticity has also been demonstrated in human cortical swallowing pathways. Repeated high-frequency stimulation of the pharynx increased the excitability of the pharyngeal muscles to TMS for at least 30 minutes, without changes in excitability at the level of the brainstem (Hamdy et al., 1998). Interestingly, the same result was obtained with repetitive stimulation over the swallowing motor cortex (Gow et al., 2004), although the effect was quite specific for a particular frequency (5 Hz). Significant facilitation in the absence of sensory afferent activation, as is the case with subthreshold cortical stimulation, implicates cortical interneurons as the critical pathway to be activated for these changes to occur.

1.3.4. Cortical plasticity following stroke

The neurological deficit observed following acute stroke is largely due to the death of neuronal tissue in the affected region. In addition, this central necrotic core is surrounded by an ischaemic penumbra, or region of neurons still alive but dysfunctional due to poor

circulation (Hossmann, 1994). While this penumbra contributes significantly to the severity of the early clinical deficit, neurons can survive in this ischaemic state for a short period of time only. Restoration of viable blood supply to this region, and resolution of perilesional oedema and inflammation are factors possibly contributing to rapid recovery of function following stroke (Rossini et al., 2003).

Another important consideration following stroke is the disruption of neuronal networks in undamaged brain regions that are remote from the original injury but are functionally connected, such as subcortical regions or the contralateral motor cortex. Originally, this concept was termed diaschisis and was proposed as a principle for recovery following brain lesions (von Monakow, 1914) but evidence of this has only recently been provided (Seitz et al., 1999). Resumption of function of remote brain structures initially influenced by the stroke, or resolution of diaschisis, is another substrate of post-stroke reorganisation.

Neurological deficits following stroke can continue to improve for weeks to months (Twitchell, 1951), long after the resolution of acute stroke-related pathology. Long-term recovery involves changes in the anatomy and physiology of intact cortical and subcortical tissue due to the lesion itself as well as to alterations in the patterns of use and sensory input. In addition to the mechanisms of brain plasticity outlined in Section 1.3.1, including changes in synaptic efficacy and unmasking of latent synapses, recovery may involve reorganisation of intracortical connections and activation of other adjacent regions of the cortex.

Post-stroke reorganisation differs from other forms of brain plasticity in several ways. Damage to cortical neurons may lead to changes in neuronal-membrane excitability, removal of inhibition due to destruction of GABAergic interneurons and loss of perilesional GABAergic inhibition, and increased glutamatergic activity (Buchkremer-Ratzmann et al.,

1996; Rossini et al., 2003). Activation of perilesional areas is increased after partial damage of M1 in animals (Nudo and Milliken, 1996) and humans (Cramer et al., 1997). The shift in the excitation-inhibition balance towards excitation in the perilesional area may facilitate other forms of plasticity, such as increased synaptic efficacy.

Activation of the contra-lesional ("unaffected") hemisphere has been observed during movements of the paretic hand (Carey et al., 2002; Ward et al., 2003b), leading to support for the proposal that post-stroke reorganisation involves plastic changes of connections within the opposite M1 (Cao et al., 1998; Caramia et al., 1996; Marshall et al., 2000; Pineiro et al., 2001; Trompetto et al., 2000). Further investigation of this phenomenon has revealed that functional ipsilateral CM connections from the unaffected hemisphere to the paretic hand are more common in patients with poor motor recovery (Bastings et al., 2002; Johansen-Berg et al., 2002; Netz et al., 1997; Turton et al., 1996). Furthermore, temporary disruption of transmission from the unaffected hemisphere to the paretic hand does not increase simple reaction times in chronic stroke patients (Werhahn et al., 2003), suggesting that the unaffected hemisphere does not contribute to functional recovery. Recent evidence now supports the hypothesis that successful recovery of motor function requires reorganisation predominantly in the affected hemisphere (Carey et al., 2002; Fridman et al., 2004; Murase et al., 2004; Werhahn et al., 2003).

While activity in descending pathways from the unaffected hemisphere cannot compensate for disruption to the CM pathway from the damaged hemisphere, imbalance between the hemispheres may contribute to functional deficit and hence recovery following stroke. Hyperexcitability of the unaffected motor cortex occurs following stroke (Liepert et al., 2000c) and is associated with a disruption of transcallosal inhibition, but the significance of this hyperexcitability to motor function is unclear (Shimizu et al., 2002). Longitudinal studies

using TMS have documented a reduction in excitability of the unaffected hemisphere as functional recovery occurs (Cicinelli et al., 1997; Manganotti et al., 2002; Traversa et al., 1998). Longitudinal *f*MRI studies report a similar finding: improved function is associated with decreased activity in ipsilateral (unaffected) brain areas and increased activity in the affected sensorimotor cortex during the performance of a task (Greenberg et al., 2002; Jang et al., 2003; Ward et al., 2003a). A shift of activation towards the primary motor cortex of the unaffected hemisphere suggests less-effective reorganisation, perhaps as a result of a large lesion, and probably indicates maladaptive plasticity (Johansen-Berg et al., 2002; Rossini et al., 2003). Activation of the unaffected hemisphere may also reflect an increase in task complexity, which even in normal subjects is associated with a shift from contralateral to bilateral activation (Rao et al., 1993; Shibasaki et al., 1993).

Cortical reorganisation within the affected hemisphere is believed to be the most effective mechanism for functional recovery of the motor control of the hand and upper limb following stroke (Byrnes et al., 2001; Cicinelli et al., 1997; Rossini and Dal Forno, 2004; Traversa et al., 1997; Traversa et al., 1998). Although this has been most widely reported in the motor cortex, which is the primary focus of the current review, extensive remodelling of the primary somatosensory cortex has also been reported in animal models (Jenkins and Merzenich, 1987; Xerri et al., 1998). Motor representations in areas other than M1 can undergo reorganisation, in particular the premotor cortex, the supplementary motor area and the cingulate motor cortex, all of which have projections to the spinal cord (Nudo, 1999). Enlargement of the hand representation area into the ventral premotor cortex following damage to M1 was observed in adult squirrel monkeys, with the enlargement proportional to the amount of hand representation damaged in M1 (Frost et al., 2003). The functional significance of this premotor cortex reorganisation was provided by Liu and colleagues (Liu and Rouiller, 1999), who demonstrated that, in monkeys that had recovered some dexterity following a brain

lesion, inactivation of the premotor cortex (by infusion of ibotenic acid) reinstated the deficit, while inactivation of M1 had no effect. In humans with a middle cerebral artery infarct, moving digits of the recovered hand can result in increased regional cerebral blood flow to the premotor and parietal cortices, not the primary sensory and motor cortices (Seitz et al., 1998), suggesting that reorganisation of these regions allows recovery of hand use following stroke in some individuals.

The reorganisation of adjacent areas of cortex following M1 damage has been widely reported in animal studies (Aizawa et al., 1991; Castro-Alamancos and Borrel, 1995; Nudo et al., 1996b), but the cortical region involved in this reorganisation is not consistent in either animal studies or following stroke in adult humans. TMS maps of the topography of the corticomotor representation of a paretic hand muscle in patients suffering subcortical stroke have revealed that corticomotor maps shift on the affected side relative to the unaffected side (Byrnes et al., 2001). Similar findings were reported in subcortical stroke patients examined with *f*MRI (Pineiro et al., 2001). The direction of the shift may be along either the anteroposterior or mediolateral axis and the lack of consistent asymmetries in map position is in agreement with other mapping studies (Liepert et al., 1998; Traversa et al., 1997). Serial imaging with *f*MRI supports these findings, with no consistent pattern of brain regions demonstrating a recovery-related increase in activation in a group of subacute stroke patients (Ward et al., 2003a). Despite the presumed primary roles of different motor cortical regions (Lawrence and Kuypers, 1968), the extensive connections between cortical areas and the distributed nature of parallel motor systems in the human motor cortex may account for the large variability seen as the central nervous system adapts after damage to the primary sensorimotor areas.

1.3.5. Rehabilitation following stroke

Some of the earliest observational studies of stroke patients suggested that motor disabilities were, to a large extent, the result of disuse (Franz et al., 1915). This was confirmed by experiments investigating the effect of a combination of treatments in monkeys with large motor cortical lesions, e.g. restraint of the unaffected limb, and passive and/or active treatment. It was observed that monkeys that regained full recovery after one month were those that had received active treatment, with or without restraint (Ogden and Franz, 1917), confirming that use of the upper limb is essential for recovery. These observations have been replicated by subsequent researchers (Nudo and Milliken, 1996; Taub et al., 1994) and form the basis for constraint-induced movement therapy (CIT; Taub et al., 1999) and forced use therapy (Wolf et al., 1989). Both techniques aim to reverse the effect of learned non-use, first observed in deafferented monkeys (Knapp et al., 1958; Twitchell, 1954). As attempts to move the affected extremity were repeatedly unsuccessful, the animals gradually ceased to use the limb at all.

The proposition that adult humans who sustain a brain injury also demonstrate learned non-use was tested in two separate studies applying CIT to patients following stroke (Taub et al., 1993) and traumatic brain injury (Wolf et al., 1989). The findings supported the hypothesis and indicated that an intensive period of restraint of the unaffected limb, and performance of intensive goal-directed movement of the affected hand, resulted in increased use of the affected upper limb in the real-world situation, with improvements maintained for at least one to two years. In an effort to demonstrate neuroplastic changes occurring in conjunction with CIT, Liepert et al. (2000a) used TMS to map the motor representation of a small hand muscle before and after two weeks of CIT. The increase in motor output area and amplitude of MEPs was associated with an increase in the use of the affected upper limb. In addition, a shift in centre of gravity of the motor output map suggested that recruitment of motor cortical areas

adjacent to the original lesion also occurred. Another imaging study in which *f*MRI studies were carried out on two subjects undergoing CIT found increased activation of perilesional areas in association with functional improvements. Recent feasibility studies have adapted CIT and report on the success of implementing this technique in the acute (Dromerick et al., 2000) and subacute (Page et al., 2002; Page et al., 2001; Ploughman and Corbett, 2004) periods following stroke.

Conventional rehabilitation following stroke aims to restore full movement and function to enable patients to achieve activities of daily living independently. Ward et al. (2003a) performed serial *f*MRI scans on acute stroke patients undergoing conventional rehabilitation for six months in order to identify changes in motor-related brain activation patterns occurring during recovery. Significant correlations were found between recovery and decreases in task-related brain activation in motor related regions, such as the unaffected hemisphere and cerebellum, but there was no consistent pattern of increased activation across the group of eight patients. This study supports the view that conventional rehabilitation is associated with neuroplasticity, but again highlights the complex nature of the reorganisation. Increases in peak sensorimotor activation were not consistent between sessions and were not correlated with lesion site (Ward et al., 2003a).

Because of the impact of upper-limb impairment on disability (Olsen, 1990) and the poor recovery of function despite intensive therapeutic efforts (Nakayama et al., 1994b; Wade et al., 1983), rehabilitation of the upper limb is a current focus for many research groups. The strong association between weakness and loss of function (Chae et al., 2002; Olsen, 1990) has led to suggestions that exercises designed to increase strength are crucial to decrease disability following stroke (Ada et al., 1996; Boyd and Ada, 2001; Canning et al., 2004; Carr et al., 1995). A recent randomised controlled study compared three different approaches to

rehabilitation in acute stroke patients. These were standard care, strength training and functional task practice (Winstein et al., 2004). Standard care was delivered by occupational therapists and included muscle facilitation techniques, stretching and self-care activities. Strength training involved progressive resistance training with weights or elastic bands and functional training focussed on the systematic practice of daily tasks that were within the available range of motion. The greatest increases in strength and reductions in impairment were found in the strength and functional task practice groups, with greater long-term gains in the less-severely impaired functional task practice subjects. This type of task-specific physiotherapy is based on the motor relearning approach devised by Carr and Shepherd (1987) and is widely advocated as a more effective treatment than traditional approaches (Bayona et al., 2005; Hanlon, 1996; Langhammer and Stanghelle, 2000; Page, 2003; Shepherd, 2001; Winstein et al., 2004). Nelles et al. (2001) used PET scanning to compare patients with acute subcortical strokes who received task-oriented training with a control group receiving non-specific exercises. The task-oriented group had increased activation of bilateral parietal and premotor areas, which may be indicative of training-induced plasticity (Nelles et al., 2001). Recently, Jang et al. (2003) used *f*MRI to demonstrate increased activation in the affected hemisphere, and decreased activation of the unaffected hemisphere, in a group of chronic stroke patients undergoing four weeks of task-oriented training. For these reasons, I chose task-specific physiotherapy, incorporating the principles of motor learning, as my strategy to rehabilitate subacute stroke patients in the study described in Chapter 6.

1.3.6. Novel approaches to rehabilitation following stroke

A number of different strategies have been developed to augment conventional therapies, most of which involve repetitive motor activity. Adding fifteen-minute sessions of repetitive wrist and hand exercises against increasing loads twice daily to the usual care regimen for

subacute stroke patients resulted in increased grip strength and peak acceleration in the paretic hand over four weeks. This was not observed in the control group who were given transcutaneous electrical nerve stimulation (Bütefisch et al., 1995). Muellbacher et al. (2002) trained patients to perform repetitive pinching movements between the paretic index finger and thumb over several weeks until they became proficient in the task. Following this, the upper arm was anaesthetised with the aim of enhancing the effects of motor practice of the hand by depriving the motor cortex of sensory inputs from the upper arm. This led to greater improvements in pinch force and acceleration than following the exercises alone, and the increase in peak pinch force correlated significantly with the increase in MEP amplitude in the involved thumb muscle (Muellbacher et al., 2002). Neither of these studies reported improved function as a result of these interventions, so the potential impact of repetitive simple movements on rehabilitation is unclear.

Another technique to increase paretic arm activity in chronic stroke patients involves bilateral arm training with a custom-built arm trainer (Whitall et al., 2000). In this study, patients participated in three twenty-minute sessions per week for six weeks of bilateral repetitive pushing/pulling movements. Results revealed increased function (as assessed with the FMA) and increased strength and active range of motion. The specificity of this type of training cannot be ascertained as there was no control group comparison. The concept that bilateral movements allow facilitation of the paretic arm from the non-paretic arm either through spared ipsilateral CM projections, indirect ipsilateral corticospinal pathways or ipsilateral corticospinal pathways from the unaffected hemisphere has also been investigated (Mudie and Matyas, 2000). A series of multiple-baseline single-case experiments were conducted and the authors developed a scale to quantify kinematic characteristics during the bilateral tasks to demonstrate that during bilateral training, performance was superior than during the baseline phase where patients practised other unilateral or active-assisted bilateral tasks. Again, the

lack of clear evidence that this approach results in functional improvements that are superior to conventional physiotherapy limits the clinical relevance of these studies.

Other techniques that aim to induce cortical reorganisation involve increased cognitive demands in conjunction with increased arm use. This includes tracking a moving target across a screen (Carey et al., 2002), computerised arm training with a robotic arm trainer either on the affected arm alone (Aisen et al., 1997; Fasoli et al., 2003; Fasoli et al., 2004; Volpe et al., 1999) or bilaterally (Hesse et al., 2005; Lum et al., 2002), use of a "virtual reality" computer game (Broeren et al., 2004), and a form of task-specific therapy known as arm ability training (Platz et al., 2002; Platz et al., 2001b). In general these studies have involved small sample sizes, lack appropriate control groups, and require complex training and/or equipment, and thus are not commonly used in mainstream rehabilitation.

An area of research that has gathered increasing evidence and is becoming mainstream is the use of electrical stimulation in stroke rehabilitation. The basis of this approach is to employ electrical stimulation to maintain and improve tone in weak muscles and also to increase strength through peripheral mechanisms. Stimulation of the posterior deltoid and supraspinatus muscles is effective in reducing glenohumeral subluxation and decreasing shoulder pain following stroke (Faghri et al., 1994; Kobayashi et al., 1999; Linn et al., 1999; Price and Pandyan, 2001) and the implementation of this approach in patients with severe weakness has been recommended in recent best-practice guidelines (National Stroke Foundation, 2005). Electrical stimulation of the wrist and finger extensors enhances upper limb motor recovery in acute stroke patients (Chae et al., 1998) and increases function compared with a control group (Powell et al., 1999). In other studies, muscle activation (EMG) was used to trigger the stimulator to ensure that patients participate actively with at least weak voluntary movement. Greater improvements in strength and function than control

interventions were demonstrated (Bowman et al., 1979; Cauraugh et al., 2000; Cauraugh and Kim, 2003; Francisco et al., 1998; Kimberley et al., 2003; Kraft et al., 1992). Recently, a combined orthosis-stimulation system was developed that enabled daily home-based stimulation-assisted training to increase hand function. While this was achieved, there was no control intervention for comparison (Alon et al., 2003).

In contrast to the studies described above peripheral stimulation has, more recently, been employed to induce central changes that might be beneficial for rehabilitation. Somatosensory stimulation in the absence of muscle contraction is able to influence cortical reorganisation, and the application of peripheral nerve stimulation to chronic stroke patients was tested in a randomised crossover design (Conforto et al., 2002). Pinch grip strength increased following a two-hour session of median nerve stimulation but not control stimulation, and patients reported improved ability to write and hold objects. This type of stimulation increased the amount of use-dependent plasticity seen in chronic stroke patients when tested using TMS (Sawaki et al., 2006), supporting the hypothesis that somatosensory input is able to drive plastic changes in the motor cortex even in stroke-damaged brains (Asanuma, 1981; Porter, 1990; Sawaki et al., 2006). A single session of peripheral nerve stimulation improved the ability of stroke patients to complete the Jebsen-Taylor Functional Hand Test (Wu et al., 2006) but to date, no longitudinal studies have investigated the effects of repeated application of somatosensory stimulation in stroke patients.

Paired associative stimulation (Section 1.3.3) modulates motor cortical excitability in a manner similar to associative LTP in animal experiments (Classen and Ziemann, 2003; Stefan et al., 2000). In a recent study, this type of stimulation was applied daily for four weeks to increase the excitability of the corticospinal projection to paretic ankle dorsiflexors and evertors in a group of chronic stroke patients (Uy et al., 2003). In some subjects, this induced

significant improvements in the gait characteristics cadence, stride length and time-to-heel-strike, even in the absence of gait training. Increased MEP amplitude and maximal voluntary contraction force was demonstrated in five of the nine subjects, but there was no overall group effect in this small sample. Although this study lacked a control group, it suggests that in some subjects the application of repeated sessions of dual stimulation can result in plastic changes in the motor cortex that lead to functional improvements.

As discussed above (Section 1.3.4), stroke alters the balance between excitation and inhibition between the hemispheres, which suggests that down-regulation of the unaffected M1 may facilitate motor recovery following stroke (Murase et al., 2004). The ability of rTMS to modulate motor cortical excitability in a frequency-dependent manner has been exploited in studies investigating stimulation of either the affected or unaffected hemispheres of stroke patients. Low-frequency rTMS decreases cortical excitability (Maeda et al., 2000) and has been applied to the unaffected motor cortex to decrease hyperexcitability in chronic stroke patients (Takeuchi et al., 2005). A single session of 1 Hz rTMS decreased cortical excitability and transcortical inhibition, and led to a short-lasting increase in pinch acceleration of the paretic hand, while no change was seen following sham stimulation. In contrast, a recent study applied 3 Hz rTMS in conjunction with routine rehabilitation in acute stroke patients, and found that real, but not sham, stimulation decreased disability over a two-week period, although there was no increase in motor cortical excitability as predicted (Khedr et al., 2005). These studies suggest that decreasing inhibition in the affected M1, and perhaps other motor related areas such as the dorsal premotor cortex, can unmask pre-existing, functionally latent neural connections around the lesion and contribute to cortical reorganisation (Takeuchi et al., 2005).

A case study highlighting the functional gains made after three weeks of motor cortex stimulation via implanted epidural electrodes during structured occupational therapy sessions adds further support to the hypothesis that cortical stimulation could contribute to recovery of motor function in stroke patients (Brown et al., 2003). Non-invasive motor cortical stimulation with tDCS, which is believed to increase cortical excitability (see Section 1.3.3; Nitsche and Paulus, 2000), has also been used during the performance of a motor training task. Hummel et al. (2005) studied stroke patients as they practised an upper limb training task, the Jebsen-Taylor Hand Function Test or JTT. When their performance had plateaued they received a session of stimulation while continuing to perform the JTT. Performance time decreased significantly after stimulation, but not after sham stimulation, with greater improvement in tests requiring fine motor control than tasks involving proximal arm control tasks. Stimulation increased the amplitude of MEPs recorded using recruitment curves and SICI was significantly reduced, suggesting that GABA receptor-dependent inhibitory processes were involved (Hummel et al., 2005). The significant correlation between improvement in JTT time and increased recruitment curve slope suggests that tDCS can influence motor cortical excitability and can improve skilled motor functions of the paretic hand in chronic stroke patients.

1.3.7. Functional significance

There is increasing evidence in both animal and human studies to suggest that a variety of methods that are known to induce cortical plasticity may have a role in rehabilitation of patients following brain injury. Recent developments have led two research groups to suggest that cortical stimulation combined with motor training can lead to greater functional gains in stroke patients than rehabilitative training alone (Bütefisch et al., 2004; Hummel et al., 2005). Despite this, the only study that specifically combines stimulation and training is a single case study in which the cortex was stimulated via implanted electrodes, which is invasive and

expensive (Brown et al., 2003). Studies that have applied interventions in the short term either lack control groups or appropriate measures of increased function, or have not investigated the long-term benefit of these novel approaches. In the present study, I have addressed some of these issues by investigating the therapeutic potential of stimulating peripheral afferents of the upper limb in subacute stroke patients undergoing an outpatient rehabilitation program, and comparing these results with a control group receiving rehabilitation but a sham stimulation. I hypothesised that the afferent stimulation would increase the excitability of the motor cortex, making it more responsive to the motor training tasks and resulting in greater improvements in hand function than the group receiving the sham stimulation. This experiment is detailed in Chapter 6.

2. Comparison of alternate methods of analysing motor evoked potentials

2.1. Abstract

This study assessed the reliability of alternate methods of analysis of motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS). We recorded two sets of MEPs (TIME 1 and TIME 2) at the optimal scalp sites for both the right first dorsal interosseus (FDI) and flexor carpi ulnaris (FCU) at two different stimulation intensities in 10 healthy subjects. MEP magnitude was determined in each of the following three ways: the mean peak-to-peak amplitude and area of the 20 individual responses; the amplitude and area of the ensemble averaged waveform; and the amplitude and area of the maximal response. We hypothesised that calculating the mean peak-to-peak values would be result in the greatest reliability for both muscles. There was no significant difference in amplitude or area for either muscle using any of the three methods between TIME 1 and 2. However, the ensemble average (area and amplitude) was significantly smaller than the mean MEP and the maximal MEP amplitude was significantly larger. Intraclass correlation analysis demonstrated that reliability of MEP measures over time was poor regardless of method. Reliability was similar between methods for FDI, but FCU had lower reliability values for the mean and ensemble average methods than the maximal method. Results indicate that measuring the peak-to-peak amplitude of each MEP and then taking the average over a number of trials is the most appropriate method for analysing MEPs from FDI, while the maximal MEP should be used for FCU.

2.2. Introduction

Since the introduction of TMS two decades ago (Barker et al., 1985), the application of this method for the investigation of the properties of the cortico-spinal pathway in humans in both research and clinical environments has broadened enormously (Carroll et al., 2001). Many

neurophysiological variables can be measured using this technique, including the stimulus intensity threshold for evoking MEPs, central motor conduction time, MEP amplitude and area, silent period, trans-callosal conduction time, and intracortical inhibition and facilitation. Each of these variables depends on measurements of various parameters of the MEP, but there is little data on the reproducibility of the different approaches that are used for analysis. Here we investigated which of the common methods of analysis is the most reproducible, and how the values obtained with the different analysis methods correlate with each other.

Because the MEP can vary markedly in amplitude from one trial to another, it is customary to elicit a number of MEPs at the optimal scalp site for stimulation. Following this, the peak-to-peak amplitude and area of each MEP are identified and then averaged to determine the mean value of the individual trials (Carroll et al., 2001; Kiers et al., 1993; Magistris et al., 1998; Miranda et al., 1997; Ridding and Rothwell, 1997). Alternatively, an ensemble averaged MEP can be generated and the peak-to-peak amplitude and area of this waveform then determined (Bastings et al., 2002; Pitcher and Miles, 2002; Pitcher et al., 2003a). Less commonly, the largest MEP at a set stimulus intensity is identified and the peak-to-peak amplitude of this response is used (Eisen et al., 1991).

We examined MEPs in both a distal muscle and a more proximal muscle, since their MEP characteristics are known to differ. In particular, the MEP thresholds in proximal muscles are higher and the responses vary more in amplitude from trial to trial than in distal muscles (Brasil-Neto et al., 1992). Furthermore, the morphology of MEPs in proximal muscles is often more complex than in distal muscles. Thus we sought to determine whether one method of analysis was more reproducible than the others and whether this was influenced by the muscle in which the MEPs were evoked.

2.3. Methods

Experiments were conducted on 10 normal individuals (five males, five females; age 19-38 years). All were assessed by the Edinburgh Handedness Inventory to be right-handed. The Human Research Ethics Committee at The University of Adelaide approved the protocol and all subjects gave informed consent.

The surface electromyograms (EMG) of the right FDI and FCU were recorded with silver/silver chloride surface electrodes (9 mm diameter) after careful skin preparation. For FCU, one electrode was placed over the muscle belly and the other 2 cm distal to this. For FDI, one electrode was placed over the muscle belly and the other over the metacarpophalangeal joint of the index finger. The signals were amplified in the bandwidth 20-1000 Hz, sampled at 5 kHz with a laboratory interface (Micro1902®, Cambridge Electronic Design, Cambridge, UK) and stored for off-line analysis.

TMS was performed with a Magstim 200 (Magstim Co. Dyfed, UK). We used a round coil (external diameter 14 cm) because the MEPs evoked using this type of coil are less susceptible than figure-of-eight coils to placement variability (Wassermann, 2002). The coil was placed so that the current flow in the coil was anticlockwise, which preferentially stimulates the left motor cortex. The optimal sites for eliciting MEPs in FDI and FCU were marked on the scalp. Resting motor threshold (RMT) was operationally defined as the minimal TMS intensity that evoked MEPs of 50 μV in at least five of 10 successive trials, and was determined for each muscle.

Subjects kept their arm relaxed while 20 stimuli were given at the optimal sites for both FDI and FCU. For each subject, stimuli were applied in four blocks as follows: FDI at an intensity of 110% ; FDI at 120% RMT; FCU at 110% RMT; FCU at 120% RMT. The order of

presentation of the blocks was randomised between subjects. This process was then repeated to evaluate the reproducibility of the responses. Thus, for each subject there was a total of eight blocks (four blocks at TIME 1 and another four blocks at TIME 2). The entire testing procedure lasted approximately one hour.

2.3.1. MEP data analysis

MEPs were analysed using the following three methods:

a) Mean

Cursors were set to encompass the time within which the MEP began and ended for both muscles. The peak-to-peak amplitude of the unrectified MEP and the area of the full-wave rectified MEP were then measured automatically in each of the 20 trials in each block, and their average was calculated for each condition to give the "mean" peak-to-peak amplitude and area.

b) Ensemble average

The ensemble average waveform of 20 consecutive MEPs for each condition was obtained by averaging the MEP waveforms across multiple frames using commercially-available software (Signal 2®, Cambridge Electronic Design, Cambridge, UK). The peak-to-peak amplitude and area of this averaged waveform were then measured.

c) Maximum MEP

The largest amplitude MEP in each block of 20 trials was identified and the peak-to-peak amplitude and area of this "maximal" response measured.

2.3.2. Statistical analyses

A three-way analysis of variance (ANOVA) was performed with factors TIME (1 and 2), INTENSITY (110% and 120%), and METHOD (mean, ensemble average and maximal). GenStat software (6th edition, VSN International Ltd) was used to allow for blocking the

variability between subjects as a source of variance between the main factors. Initial ANOVA revealed differences between muscles, so each muscle was analysed separately for both amplitude and area: that is, the ANOVA was repeated four times (FDI amplitude, FDI area, FCU amplitude, FCU area). The test-retest reliability of the amplitude and area data was assessed using intraclass correlation coefficients (ICC) on the basis of each ANOVA. We report the ICC (A,1) for absolute agreement of MEPs from TIME 1 to TIME 2.

2.4. Results

Neither the amplitude nor the area of the MEPs changed significantly over time (TIME, $P > 0.05$ for all four ANOVAs) regardless of which of the three methods of data analysis was used. Figure 2.1 illustrates three consecutive MEPs with the ensemble average MEP from the 20 stimuli superimposed. The dotted lines indicate the placement of the cursors to identify the limits of the MEP.

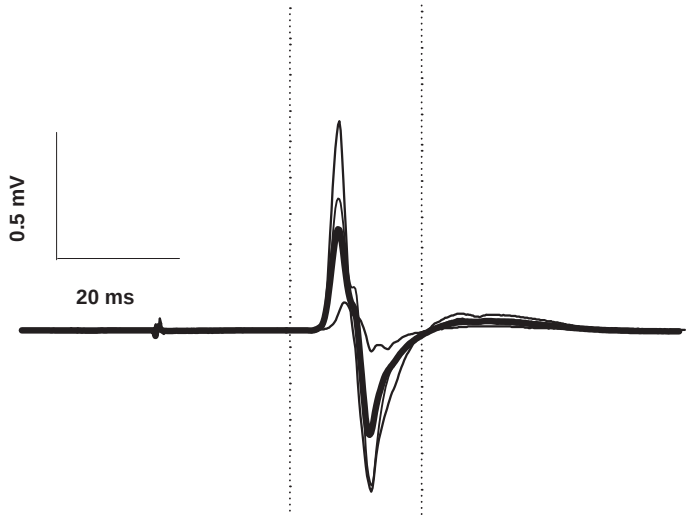

Figure 2.1 Trial-to-trial variability of MEPs in right FDI muscle

Three consecutive MEPs (thin lines) are superimposed on the ensemble average MEP (thick line).

There was a significant effect of METHOD for both area and amplitude measures when analysing data from each muscle separately (for all muscles $P < 0.001$, ANOVA). The ensemble average value (both amplitude and area) was significantly smaller than the mean and maximal values (Pairwise comparisons with Bonferroni correction, $P < 0.05$), and the maximal value was significantly larger (Pairwise comparisons with Bonferroni correction, $P < 0.05$) than the mean or ensemble average values (see Figure 2.2).

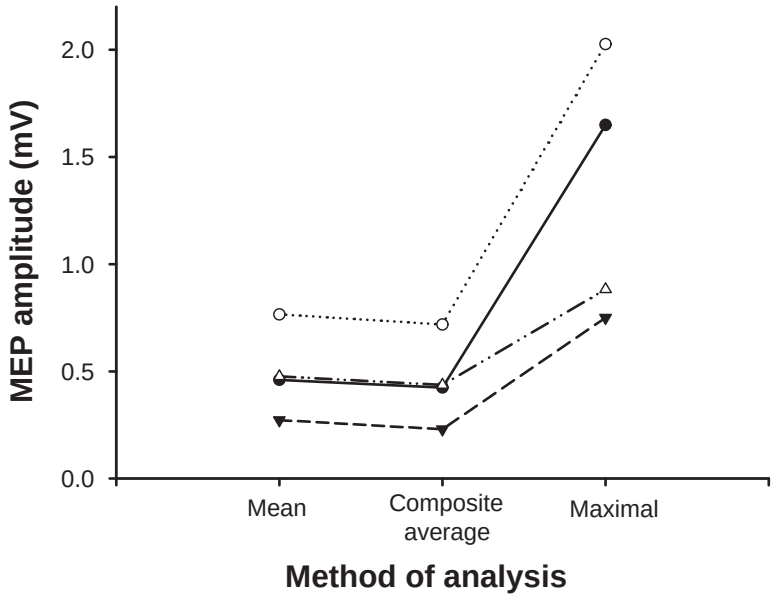

Figure 2.2 MEP amplitude data for each muscle and intensity
Data are from TIME 1 with the solid line and filled circle representing FDI 110%, dotted line and open circle FDI 120%, dashed line and filled triangle FCU 110%, dotted and dashed line and open triangle FCU 120%.

Both the amplitude and the area of the mean MEP were highly correlated with the amplitude and area of the ensemble average MEP (amplitude $r^2 = 0.9932$, area $r^2 = 0.9477$). Figure 2.3 shows the strong correlation between the ensemble average and mean MEP amplitude values but also that the ensemble average MEP value was always smaller than the mean. Linear regression analysis showed no difference in intercepts or slopes for either muscle or intensity,

indicating that a common regression line could describe the relationship. This relationship could be expressed as:

For amplitude Ensemble average value = -0.036 + 0.97mean

For area Ensemble average value = -6.129 + 0.95mean

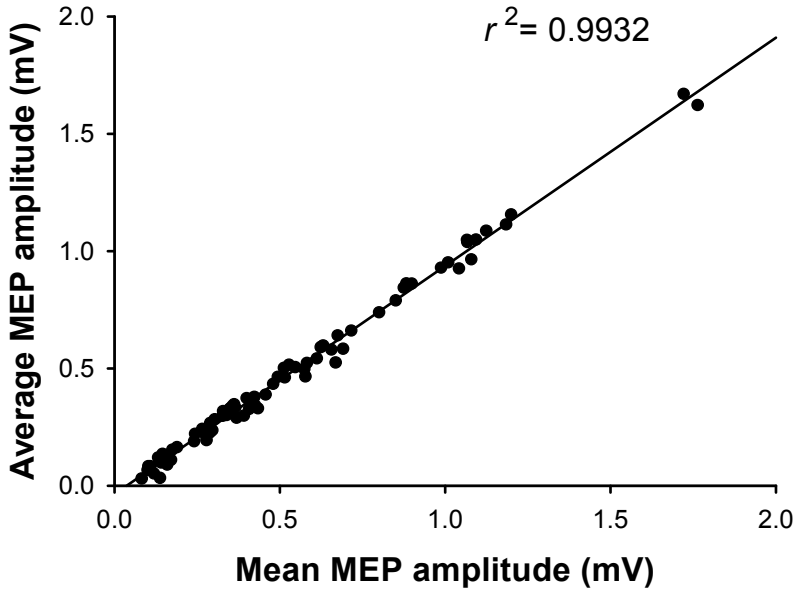

Figure 2.3 Relationship of mean and ensemble average MEP amplitude
Data represent all muscles and intensities (linear regression analysis, r^2=0.9932).

To compare the relative reliability of each data analysis method between TIME 1 and 2, amplitude and area measures were analysed using ICCs for each muscle and method. As there was no interaction between METHOD and INTENSITY (ANOVA, $P > 0.05$) data from both intensities of stimulation were pooled for the ICC analysis. The ICC values obtained for these muscles and these methods of analyses ranged from ICC = 0.16-0.55 (see Figure 2.4). ICCs were generally higher for FDI muscle than FCU, suggesting that agreement between TIME 1 and 2 was more likely to occur in FDI than in FCU. Reliability of the maximal MEP (both amplitude and area) measure was greater for FCU than the mean or ensemble average methods.

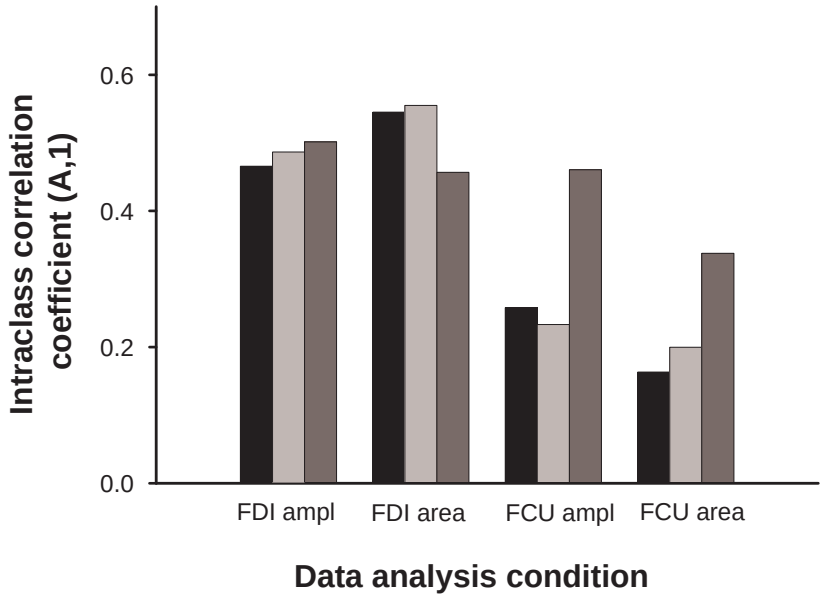

Figure 2.4 Reliability of data analysis methods
Intraclass correlation coefficients are shown for all methods of analysis, with black columns representing the mean, light grey the ensemble average and medium grey the maximal value.

2.5. Discussion

The aim of this study was to determine the reproducibility of different methods of analysis of MEPs evoked by TMS in two arm muscles. We attempted to control the factors that are known to affect variability such as the level of alertness (Kiers et al., 1993), muscle relaxation (Thickbroom et al., 1999) and attention to the stimulus (Hess et al., 1987) by directing the attention of all subjects to the stimuli and giving EMG feedback. However, as observed in earlier studies, MEP amplitudes varied widely from trial to trial (Kobayashi and Pascual-Leone, 2003; Wassermann, 2002), possibly due to changes in the excitability of both the corticospinal pathway and the motoneurons (Funase et al., 1999; Weber and Eisen, 2002). Other potential sources of within-subject variability of MEP responses include small alterations in the position of the coil (Ellaway et al., 1998), varying desynchronisation of the efferent volley (Magistris et al., 1998), stimulation frequency and subthreshold activation of corticospinal outputs (Wassermann, 2002).

Under the conditions of the present study, there was no significant difference in the amplitude or area of the MEPs from TIME 1 to TIME 2 within the same testing session. However, the ICC analysis indicates that none of the methods described gave highly reliable (i.e. reproducible) measures of MEP magnitude for either FDI or FCU. That is, the variability in MEPs recorded under standard conditions is sufficiently large that no significant differences in their average value over time were revealed by the conventional statistical analysis (ANOVA). It may be inferred from this that, in studies in which a change in MEP size is expected as the result of the experimental protocol or intervention, the magnitude of the changes must be large, or many trials must be included in the analysis, before significant differences can be demonstrated.

ICC analysis expresses the ratio of the variance between subjects over the total variance of the group. The variability between subjects should be similar across each method of analysis; hence differences in the ICCs obtained can be interpreted as differences in the relative reliability of the different methods of measurement. Generally, ICC values above 0.75 indicate good reliability between measures and those below 0.75 show poor to moderate reliability (Portney and Watkins, 2000). Reliability was comparable between all three methods of analysis for FDI (ICC = 0.46-0.55) suggesting that no method is more reliable than any other. In contrast, for FCU, the reliability of the mean and ensemble average values (both area and amplitude) was lower than the maximal value. Therefore, the maximal MEP values may give a more reliable measure of corticospinal excitability for FCU at these intensities, although with ICCs of 0.34-0.46 this still indicates poor inter-trial reliability.

The peak-to-peak amplitudes and areas of ensemble average MEPs were consistently smaller than the mean MEP values (i.e., across all muscles and intensities). This is likely to be the result of small phase shifts in the peaks of individual MEPs which leads to minor phase

cancellation (Magistris et al., 1998). The phase-shifting of the action potentials of individual motor units accounts for much of the trial-to-trial variability in MEPs (Magistris et al., 1998).

We conclude that, at these intensities, there is little difference in the reliability of each of these three methods of MEP analysis for FDI despite the susceptibility of the ensemble average to phase shifts. For FCU, the ICCs are low overall but slightly greater reliability is seen when using the maximal MEP measure. Further investigation would be warranted to determine if these findings generalise to other distal and proximal muscles.

3. Afferent stimulation facilitates performance on a novel motor task

3.1. Abstract

Training on a motor task results in performance improvements that are accompanied by increases in motor cortex excitability. Also, periods of afferent stimulation result in increased motor cortex excitability. There is increasing evidence to suggest that raised motor cortical excitability may facilitate movement and learning. Here we examined the hypothesis that a period of electrical stimulation of hand afferents ("associative stimulation"), known to increase motor cortex excitability, would facilitate performance of a complex sensorimotor task. Three groups of nine normal subjects participated in these studies. All subjects were trained on the grooved pegboard test (GPT). Training consisted of three blocks, each of five trials, of placing pegs as quickly as possible. The time to complete each block was recorded. One group of subjects had a 1-hour period of associative stimulation prior to training on the GPT. A second group received non-associative stimulation (which does not change cortical excitability) of the same hand afferents, and a third group received no stimulation prior to training. Motor evoked potentials (MEPs) were recorded from the right first dorsal interosseus (FDI) and abductor digiti minimi (ADM) prior to and following stimulation and performance of the GPT. In contrast to non-associative stimulation, associative stimulation increased motor cortical excitability, evidenced by an increase in the amplitude of MEPs evoked in FDI, one of the stimulated muscles, but not ADM. Training on the GPT resulted in significant improvements in the time taken to complete the task for all three groups. However, in subjects who had preconditioning associative stimulation, performance on the GPT improved more rapidly. Additionally, there was a trend for the improvement in performance of the stimulated group to be greater than that of the control group. The results of the present study suggest that increased motor cortical excitability, induced by associative stimulation, may facilitate performance of a novel complex sensorimotor task.

3.2. Introduction

The organisation of the human motor cortex may be modified by changes in afferent input. For example, increases in motor cortical excitability are seen following electrical stimulation of peripheral nerves (Hamdy et al., 1998; Ridding et al., 2000), or paired peripheral and cortical stimulation (Ridding and Uy, 2003; Stefan et al., 2000). Practice of simple motor tasks also results in reorganisation of the primary motor cortex (Bütefisch et al., 2004; Classen et al., 1998; Karni et al., 1998). This is evidenced by an increase in MEP amplitude seen following transcranial magnetic stimulation (TMS) in muscles involved in the training task. Further, increases in performance have been positively correlated with MEP facilitation (Garry et al., 2004; Muellbacher et al., 2001).

There is increasing evidence that experimentally induced increases in motor cortical excitability may facilitate motor learning. Firstly, Bütefisch and co-workers (Bütefisch et al., 2004) have recently shown that applying focal TMS to the motor representation of a muscle involved in a simple motor task enhanced the encoding of the motor memory of that task. Secondly, increases in motor cortical excitability induced by transcranial direct current stimulation facilitate movement in a reaction-time task (Nitsche et al., 2003). Finally, a recent study has shown that transcranial direct current stimulation can also facilitate functional improvement in a small group of chronic stroke patients (Hummel et al., 2005).

Here we investigated whether preconditioning the motor cortex of normal subjects with a period of afferent stimulation, known to increase motor cortical excitability, facilitates the performance of a novel and complex sensorimotor task, in this instance the GPT. The GPT is a task routinely used to assess manual dexterity (Tremblay et al., 2003) and requires fine manipulation of grooved pegs between the thumb and the index finger.

3.3. Methods

3.3.1. Subjects

A total of 27 subjects participated in the study (age range 20-58 years, 15 males and 12 females). Subjects had no relevant medical history and all investigations were performed on the dominant hand, which was the right hand as assessed by the Edinburgh Handedness Inventory. All subjects gave written, informed consent to the studies, which were conducted in accordance with the Declaration of Helsinki and were approved by The University of Adelaide Human Research Ethics Committee.

3.3.2. Recording

Surface electromyographic (EMG) activity was recorded from the right FDI and ADM muscles using disposable silver-silver chloride surface electrodes. EMG activity was amplified (x1000), filtered (20 Hz to 1 kHz) and then sampled at 5 kHz (Cambridge Electrical Design 1401, Cambridge, UK). Data were stored on a computer for off-line analysis.

3.3.3. Stimulation

Focal TMS was performed using a flat figure-of-eight shaped coil (external wing diameter 9 cm) connected to a Magstim 200 magnetic stimulator (Magstim, Whitland, Dyfed, UK). The coil was held over the scalp with the handle pointing posteriorly and oriented approximately 45 degrees to the sagittal midline so that the induced current flowed perpendicular to the estimated alignment of the central sulcus. The optimal position for evoking responses in FDI and ADM was established and marked on the scalp with a soft-tip pen to ensure reliable coil placement between trials.

3.3.4. Experimental procedures

Subjects were randomly assigned to one of three groups; associative stimulation (AS), non-associative stimulation (NS) or control and were naïve to both the hypothesis and the training task. The groups were matched with respect to age and sex (AS group five males, age 30 ± 12 (mean ± SD) years; NS group five males, 32 ± 11 years; control group five males, age 32 ± 9 years). Resting motor threshold was determined and defined as the minimum stimulator intensity needed to produce an MEP of at least 50 μV in the relaxed FDI muscle in at least five out of 10 successive trials (Rossini et al., 1994). Following threshold determination, the intensity of the TMS was adjusted to evoke an MEP of approximately 0.5 – 1 mV in both the relaxed FDI and ADM prior to afferent stimulation. This procedure was also followed for all subjects prior to motor training; this required a reduction of stimulator output intensity after the associative stimulation for the AS group subjects, due to an increase in the MEP amplitude. Fifteen MEPs were recorded with all muscles relaxed and trials in which background EMG activity was present were excluded from analysis. Muscle relaxation was monitored by giving subjects visual feedback of their EMG with a high gain oscilloscope and auditory feedback.

Pre-training MEPs were recorded in FDI and ADM for all groups (Pre Train). Following the motor training task, MEPs were recorded immediately following (Post Train), and 10 minutes following (Post $Train_{10}$) the task. Additionally, for the AS and NS groups only, MEPs were recorded before associative or non-associative stimulation (Pre Stim), immediately following (Post Stim) and 10 minutes following stimulation (Post $Stim_{10}$). This resulted in a total of three time points at which MEPs were recorded for the control group, and six time points for the two stimulation groups.

3.3.5. Afferent stimulation paradigm

Subjects in the AS group received a period of associative stimulation prior to the motor training task. The AS paradigm previously reported by Ridding and Uy (2003) was used to increase the excitability of the corticospinal projection to the stimulated muscles. Short-duration electrical stimuli were delivered to FDI and abductor pollicis brevis (APB) simultaneously (Digitimer DS7A stimulators, Digitimer Ltd, Welwyn Garden City, UK). The timing between successive pairs of stimuli was randomised in the range 0.15 - 2.85 s. Stimulus intensity (range 10 - 30 mA) was adjusted for each muscle and set at a level just sufficient to evoke a visible motor response. This stimulation paradigm was applied for one hour and was painless for all subjects. Subjects in the NS group received similar stimulation to the two muscles at the same rate. However, in contrast to the AS paradigm, in this condition the two muscles (FDI and APB) never received synchronous stimulation. This afferent stimulation paradigm does not produce a significant change in motor cortical excitability (Ridding and Uy 2003). The same number of stimuli were applied to each muscle as in the AS protocol. This paradigm was used to control for general attentional effects. Subjects in the control group were permitted to move freely in the hour prior to performing the motor training task.

3.3.6. Motor training task

All subjects participated in the motor training (MT) task, which consisted of repeated trials using the grooved pegboard test (Lafayette, IN, USA). The pegs are key shaped and must be rotated appropriately to match the groove in the corresponding hole. Subjects were encouraged to place the 25 pegs as quickly as possible and the time taken to complete the test was recorded. Instructions were standardised, and subjects repeated the test in blocks of five trials, with two minutes rest between blocks. A total of three blocks were completed. On average this gave a total training time of approximately 15 minutes.

3.3.7. Data analysis

Data from the AS and NS paradigms and MT task were assessed separately. Two repeated measures analysis of variance (ANOVA) were performed with within-subject factors of TIME (3 levels: Pre Stim, Post Stim and Post $Stim_{10}$), and MUSCLE (2 levels; FDI and ADM) to determine the effect of AS or NS on MEP amplitude. A separate ANOVA assessed the effect of MT on MEP amplitudes for all three groups with within-subject factors TIME (3 levels; Pre Train, Post Train, Post $Train_{10}$) and MUSCLE (2 levels), and between-subject factor GROUP (3 levels). An additional ANOVA was conducted on the GPT performance data, with factors GROUP (3 levels) and BLOCK (3 levels). *Post hoc* testing with Bonferroni corrections was performed where appropriate.

Pearson's correlation coefficients were used to investigate the relationship between changes in MEP amplitude following AS and GPT performance improvement.

The significance level was set at $P < 0.05$ and, if not stated otherwise, all group data are given as mean ± S.D.

3.4. Results

3.4.1. MEP changes following associative stimulation

Analysis of variance revealed a significant effect of MUSCLE ($F_{1,8} = 23.1$, $P = 0.001$) on MEP amplitude, therefore the analysis was repeated for each muscle separately. This revealed a significant main effect of TIME ($F_{2,16} = 3.9$, $P < 0.05$) for FDI but not ADM ($F_{2,16} = 0.5$, $P > 0.05$). Further analysis of FDI MEP amplitudes revealed that this was due to a significant difference between Pre Stim MEP amplitude and Post $Stim_{10}$ values (Pre Stim FDI MEP amplitude 1.1 ± 0.1 mV, Post $Stim_{10}$ FDI amplitude 1.7 ± 0.3 mV; paired two-tailed t-test, $P < 0.05$; see Figure 3.1).

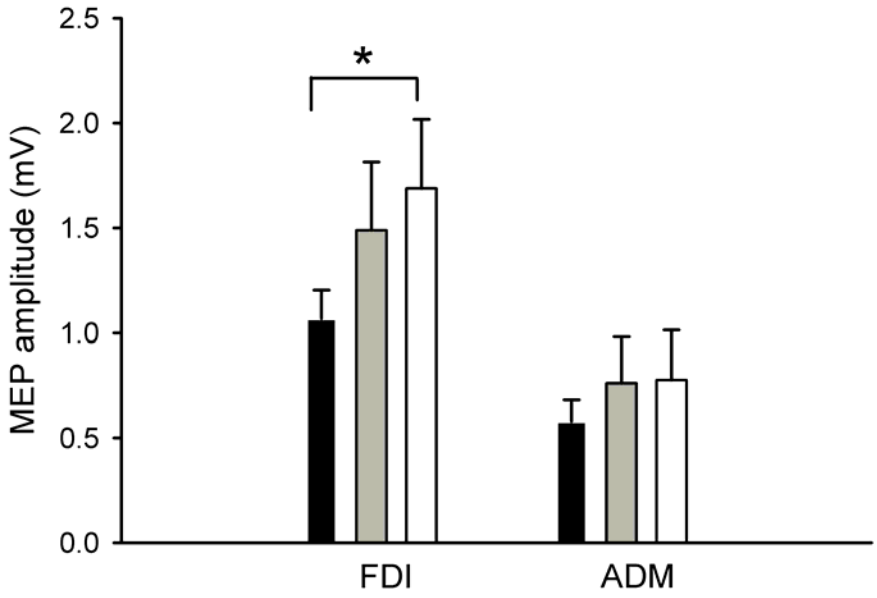

Figure 3.1 MEP amplitudes in FDI and ADM following associative stimulation
*Data represents the group mean (n = 9) and error bars illustrate the standard error of the mean (SEM). Columns represent Pre Stim values (black bar), immediately following the stimulation (Post Stim, grey bar) and 10 minutes following the stimulation (Post $Stim_{10}$, white bar). At Pre Stim, stimulation intensity was adjusted to elicit a MEP of approximately 1 mV. There was a significant increase in FDI MEPs 10 minutes following the end of the associative stimulation (*P < 0.05).*

3.4.2. MEP changes following non associative stimulation

MEP amplitudes were unchanged following the period of NS for both FDI (Pre Stim FDI MEP amplitude 0.8 ± 0.4 mV, Post $Stim_{10}$ FDI amplitude 1.2 ± 0.9 mV) and ADM (Pre Stim ADM MEP amplitude 0.7 ± 0.6 mV, Post $Stim_{10}$ ADM amplitude 0.6 ± 0.5 mV). There was no difference between muscles, and no main effect of time (ANOVA, $P > 0.05$).

3.4.3. MEP amplitude changes following MT

In order to obtain test MEPs prior to training of 0.5 - 1 mV the intensity of stimulation was adjusted for subjects in the AS group. This resulted in a test intensity of 43.9 ± 18.3% being used (reduced from 51.8 ± 12.7% prior to AS). In two of the subjects in the NS group stimulation intensity was adjusted. This resulted in a stimulation intensity of 53.5 ± 10.3%

being used (reduced from 55.5. ± 11.5% prior to NS). In the control subjects a stimulus intensity of 54.4 ± 11.4% was employed. Subjects in both stimulation groups performed the MT task 10 minutes following the stimulation, while the control subjects were permitted to move freely in the period prior to training. There were no significant differences in pre-training MEP amplitudes between the three groups for either muscle (AS group FDI = 0.9 ± 0.2 mV, ADM = 0.6 ± 0.1mV; NS group FDI = 1.2 ± 0.8 mV, ADM = 0.6 ± 0.5, Control group FDI = 0.9 ± 0.1 mV, ADM = 0.6 ± 0.1mV; ANOVA $F_{2,24} = 0.71$, $P = 0.5$).

Following the pegboard training task, analysis of the MEP amplitude data revealed a significant main effect of MUSCLE ($F_{2,24}= 28.8$, $P < 0.001$). The analysis was then repeated for each muscle separately. Although there was no main effect for TIME or a TIME*GROUP interaction for either muscle ($P > 0.05$) the raw data suggested that MEP amplitude gradually increased following MT in FDI and to a lesser extent in ADM (see Figure 3.2). Paired, two-tailed t-tests revealed that the MEP amplitude increased in FDI in the AS group only following MT (Post $Train_{10}$ FDI MEP amplitude 1.3 ± 0.2mV, $P < 0.05$). There were no significant changes in the amplitude of MEPs in ADM following the training for any of the three groups.

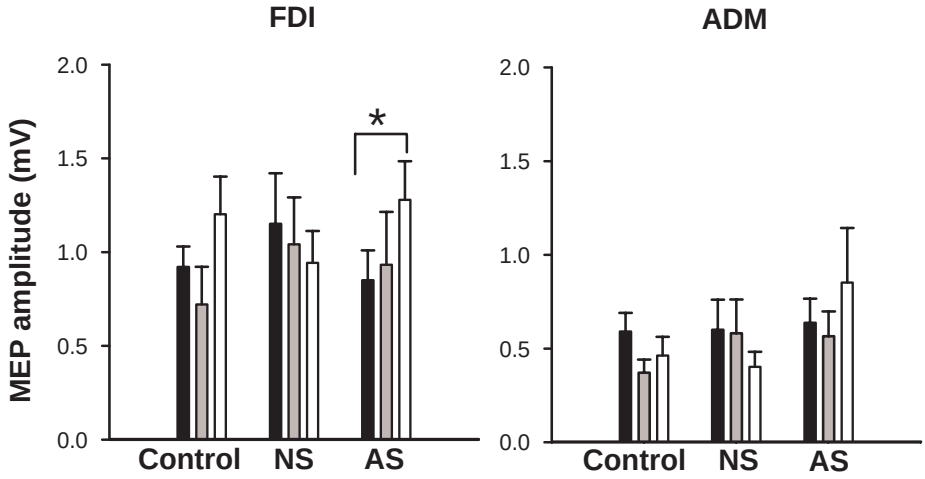

Figure 3.2 MEP amplitudes in FDI and ADM following the motor training task
*The mean (and SEM) data of the control group, who performed the task without any intervention, are shown on the left of each panel, the data of the non-associative stimulation group in the middle of the panel and the data of the associative stimulation group are shown on the right of each panel. Columns represent Pre Train values (black bar), immediately following the training (Post Train, grey bar) and 10 minutes following the training (Post Train$_{10}$, white bar). Following the MT task, MEP amplitudes increased for FDI in the associative stimulation group (*P < 0.05).*

3.4.4. Changes in GPT performance

There was no difference between GPT completion times for the three groups at block one (control group 57.4 ± 7.9 s, AS group 59.1 ± 8.7 s, NS group 59.0 ± 8.6 s; ANOVA, $P > 0.05$). When the data for the three training blocks were examined, there was a significant reduction in time taken to complete the task across the three blocks (effect of BLOCK, $F_{2,48} = 100.2$, $P < 0.001$; Figure 3.3). There was no significant difference between the three groups when data from all three training blocks were examined (GROUP, $P > 0.05$). However, there was a trend towards a difference between the groups in the rate of performance improvement, indicated by the interaction between the factors of BLOCK and GROUP ($F_{2,48} = 2.5$, $P = 0.052$). Inspection of the raw data suggested that the difference between the groups was greatest between blocks 1 and 2. Therefore, given this trend in the data an additional repeated measures ANOVA was used to compare block 1 and block 2 across the three groups. This analysis revealed a significant BLOCK*GROUP interaction ($F_{2,24} = 5.8$, $P = 0.009$), as shown in Figure 3.3. This was due to a greater increase in performance for the AS group when

compared with the control group ($P < 0.001$, unpaired t-test) between blocks 1 and 2, while there was no difference when comparing the performance of the control and NS groups ($P > 0.05$).

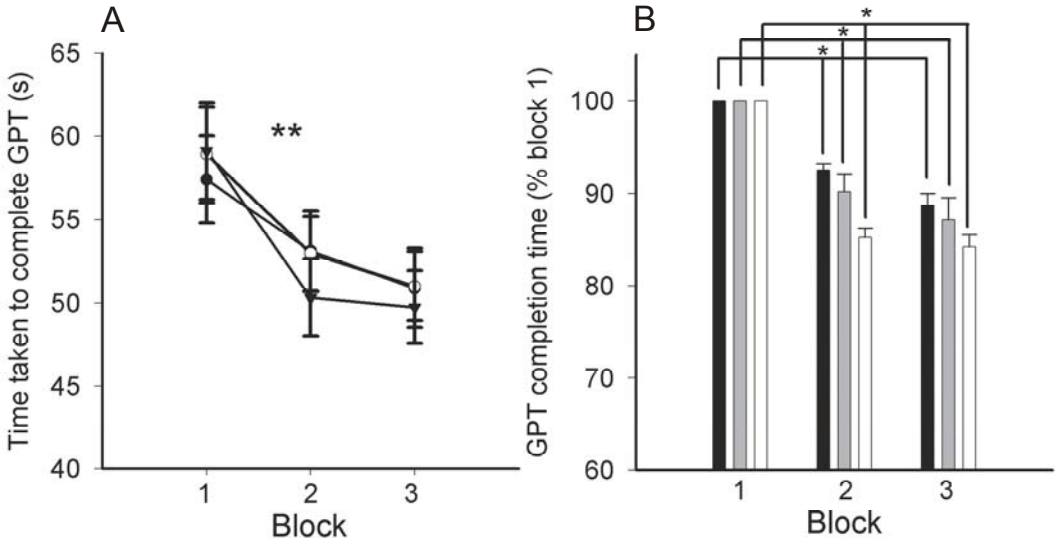

Figure 3.3 GPT completion times for each group

*(A) Time taken to complete the GPT for the control (filled circles), NS (open circles) and AS groups (filled triangle). The mean of 5 trials in each block is shown and error bars indicate ± 1 SEM. There was a significant GROUP*BLOCK interaction (**P = 0.009) due to a greater reduction in GPT completion times for the AS group than the control and NS groups when comparing Block 1 and 2. The GPT completion time is significantly different between Block 1 and 2, and 2 and 3 for all groups (* P < 0.05).*

(B) Normalised (to block 1) GPT times for control subjects (black bar), NS subjects (grey bar) and AS subjects (white bar). Times are different in each block for all subjects (P < 0.05).*

When comparing percentage improvement between block 1 and 3, there was a trend for subjects in the AS group to improve their performance more than the control group (independent samples t-test, $P = 0.056$). Across the three training blocks control subjects improved GPT completion times by 11.3 ± 3.3%, the NS group improved 12.9 ± 7.4% while the AS group improved by 15.6 ± 5.4%.

There was no correlation between increased MEP amplitude in either FDI or ADM following AS and improved performance on the GPT ($r^2 < 0.1$, $P > 0.05$).

3.5. Discussion

The main, and novel, finding of this study was that increasing the excitability of the motor cortex by the application of peripheral associative stimulation facilitated the performance of a complex sensorimotor training task involving the hand. Non-associative stimulation did not result in performance facilitation. This suggests that the effects of associative peripheral stimulation on performance are related to the increased motor cortical excitability and not general attentional effects. Therefore, these findings suggest that enhanced motor cortical excitability may facilitate processes important for motor performance and movement.

The associative stimulation paradigm employed in the present study has been shown to increase the excitability of the corticospinal projection to the stimulated muscles (FDI and APB) for more than one hour, with the change in excitability increasing over this period (Ridding and Uy 2003). The results from the present study support this previous finding as MEPs in the FDI muscle were larger in amplitude immediately following the associative stimulation but not significantly so until 10 minutes following the end of the stimulation period. Additionally, the intensity of the test stimulus needed to evoke a MEP in FDI of 0.5 – 1 mV at the Pre Train timing was less than that needed at the Pre Stim time. This is further evidence that there was a lasting increase in the excitability of the corticospinal projection to the stimulated muscles. Therefore, it seems very likely that the excitability of the corticospinal projection to FDI and APB was increased during performance of the GPT in the stimulation group.

The NS paradigm, in contrast to the AS intervention, did not produce a significant change in MEP amplitudes. This finding, again, confirms the results of a previous study (Ridding and Uy 2003). Non-associative stimulation involves application of the same number of stimuli, at the same average frequency, and the same stimulus intensity over the one hour stimulation

period as given during the AS. However, in the NS paradigm the two muscles never receive synchronous stimulation. Therefore, subjects in the NS group served as an important control for general effects of peripheral stimulation that may have resulted from subjects attending more to the stimulated hand.

Peripheral associative stimulation, as used in the present study, induces an increase in motor cortex excitability that is associated with an enhancement of intracortical facilitation (Pyndt and Ridding, 2004). Similar changes in motor cortex excitability and intracortical facilitation have been reported following a paradigm using paired peripheral and central stimulation, known as paired associative stimulation or PAS (Stefan et al., 2000; Ridding and Taylor, 2001). Based upon the time course of the induced excitability change, its specificity and its dependence on *N*-methyl-D-aspartate (NMDA) receptor activation, PAS is likely due to a long-term potentiation (LTP)-like mechanism (Stefan et al., 2002). The mechanism responsible for the excitability change induced by the AS paradigm employed in the present study is not known. However, given the similarity of the excitability changes induced by AS (Pyndt and Ridding, 2004) and those seen following PAS, it may also involve LTP-like mechanisms.

Several other lines of evidence suggest that increased motor cortex excitability may facilitate movement or motor learning. For example, Bütefisch and colleagues (Bütefisch et al., 2004) demonstrated that by combining a simple movement with TMS it was possible to enhance the motor memory of kinematic details of the trained movement. Also, it has recently been shown that hand function improved in a small group of stroke patients following a single session of anodal transcranial direct current stimulation (Hummel et al., 2005), which is known to increase motor cortical excitability (Nitsche and Paulus, 2000). This form of stimulation can also improve visuo-motor learning (Antal et al., 2004) and implicit motor learning (Nitsche et al., 2003). The findings of the present study extend these observations in that we have

demonstrated that preconditioning with peripheral associative stimulation, which increases motor cortical excitability, can facilitate performance improvements of a complex sensorimotor task. Specifically, AS increased the rate at which naïve subjects improved their performance on the GPT. Additionally, there was a trend for the amount of performance improvement to be increased.

The time taken to complete the first five trials of the GPT task (block 1) did not differ between the three groups, despite the demonstrated increase in cortical excitability in the AS group prior to commencing the task. Further, the increase in MEP amplitude in FDI following the stimulation did not correlate with increased performance on the GPT for the AS group. This suggests that increased motor cortical excitability, per se, would not be sufficient to explain GPT performance. Rather, an ability to become proficient in the task more rapidly than the other two groups characterises the performance of the AS group, as evidenced by the significant improvement in block 2 completion times for the AS group only.

Motor training on simple ballistic tasks increases motor cortical excitability and the increase in excitability correlates positively with measures of performance change (Muellbacher et al., 2001). This suggests that the MEP facilitation seen during training might be related to the induced functional change. Additionally, both training induced functional change, and the associated MEP facilitation, can be blocked by NMDA receptor antagonists (Bütefisch et al., 2000) suggesting that both mechanisms are dependent on LTP-like processes. Therefore, it is likely that both motor training and AS result in increases in motor cortical excitability that are dependent on a LTP-like mechanism.

Recently, it has been shown that training on a ballistic thumb task prevented subsequent induction of LTP-like plasticity by PAS (Ziemann et al., 2004). The results of these studies parallel closely those of cortical slice studies conducted on rats (Rioult-Pedotti et al., 1998; Rioult-Pedotti et al., 2000) and together they provide evidence that the excitability changes induced by PAS and motor learning in human subjects share, at least in part, similar cortical networks that may rely on LTP-like processes. However, this finding by Ziemann and colleagues (Ziemann et al., 2004) might also suggest that an increase in cortical excitability, induced by PAS, may block subsequent training induced changes in performance. Here we have demonstrated that motor performance is facilitated at a time at which motor cortical excitability is increased. The reason for this apparent anomaly is most likely due to the difference between the motor training tasks. The GPT task was chosen because it is a complex sensorimotor task that reflects functional abilities. Practise of this task resulted in performance improvements. However, in contrast to the ballistic training task used by Ziemann and colleagues (Ziemann et al., 2004), it did not result in a change in MEP amplitude. This suggests that the performance improvement seen with the GPT task in the present study may not have been associated with LTP-like changes (see below). Therefore, the lack of LTP change following training on the GPT may at least partly explain why AS did not block performance changes following training. In the present study, although subjects in the control and NS groups improved their performance on the training task this was not accompanied by a significant increase in the MEP amplitude in a muscle involved in the task (FDI). This finding may appear to be contradictory to previous studies that reported significant MEP facilitation in muscles employed in motor training tasks (Muellbacher et al., 2001). However, the training period employed in the present study was only approximately 15 minutes in duration. This duration is shorter that that used in many other studies (Muellbacher et al., 2001; Ziemann et al., 2004) and may not induce similar LTP-like changes. However, in the AS group, motor training of the same duration was accompanied by a larger performance

improvement and a significant increase in MEP amplitude. It may be that the increased MEP amplitude is due to a progressive increase in motor cortical excitability, which is known to persist for up to one hour following peripheral associative stimulation (Ridding and Uy, 2003).

In conclusion, the results of the present study demonstrate that increased motor cortical excitability, induced by peripheral associative stimulation, can facilitate performance of a complex motor task. Whether this reflects facilitated movement or an increase in the rate of learning is not clear although the present data suggest the latter. The mechanism by which performance is facilitated is not known but may involve LTP-like mechanisms. Given the obvious therapeutic potential of this result, further studies are warranted. In particular, the investigation of whether a period of associative stimulation can facilitate performance of other fine motor tasks in normal subjects and individuals with neurological disorders.

4. Effect of human grip strategy on force control in precision tasks

4.1. Abstract

Alternate grip strategies are often used for object manipulation in individuals with sensorimotor deficits. To determine the effect of grip type on force control, 10 healthy adult subjects were asked to grip and lift a small manipulandum using a traditional precision grip (lateral pinch), a pinch grip with the fingers oriented downwards (downward pinch) and a "key grip" between the thumb and the side of the index finger. The sequence of grip type and hand used was varied randomly after every 10 lifts. Each of the three grips resulted in different levels of force, with the key grip strategy resulting in the greatest grip force (GF) and the downward pinch grip using the least amount of GF to lift the device. Cross-correlation analysis revealed that the ability to scale accurately the rate of grip force and load force (LF) changes was lowest in the downward pinch grip. This was also associated with a more variable time-shift between the two forces, indicating that the precise anticipatory control when lifting an object is diminished in this grip strategy. There was a difference between hands across all grips, with the left non-dominant hand using greater grip force during the lift but not the hold phase. Further, in contrast with the right hand, the left hand did not reduce grip force during the lift or the hold phase over the 10 lifts, suggesting that the non-dominant hand did not quickly learn to optimise grip force. These findings suggest that the alternate grip strategies used by patients with limited fine motor control, such as following stroke, may partly explain the disruption of force control during object manipulation.

4.2. Introduction

The precise regulation of muscle forces exerted when an object is lifted from a table and then replaced has been intensively studied since the original experiments of Johansson and Westling (Johansson and Westling, 1984; Westling and Johansson, 1984). It is now clear that,

during a so-called "precision grip" in which a load is held by adduction of the tips of the forefinger and thumb, GF is accurately scaled to prevent slip without crushing the object or using a force that is unnecessarily high and may lead to accelerated muscle fatigue (Hermsdorfer et al., 2003). When a load is to be lifted, the motor program for the GF estimates the LF needed on the basis of previous experience, and the GF then becomes closely coupled temporally with the LF (Augurelle et al., 2003b). This close coupling is not disrupted by walking, jumping, moving the arm or even using a two-handed grip (Flanagan and Tresilian, 1994; Flanagan et al., 1999; Flanagan and Wing, 1997). The acquired internal model pre-programs GFs while glabrous skin receptors provide information about the friction between the object and the skin and update the internal model when the load changes unexpectedly (Grichting et al., 2000; Monzee et al., 2003).

Impairments in fine motor performance of the hand are often characterised by a diminished ability to perform a precision grip with the thumb and the index finger. Gordon and Duff (1999) observed that children with hemiplegic cerebral palsy lift objects between the thumb and the lateral surface of their index finger or use other fingers in addition to the thumb and index finger. When a group of age-matched children without cerebral palsy lifted the object using these grip strategies, their GFs were larger and more variable than with the precision grip. The use of alternate strategies in children with cerebral palsy did not limit their ability to use anticipatory control, but they required more trials than the controls to optimise this.

Adults with impaired motor control due to hemiplegia also use different grip strategies. These include a downward pinch, in which the fingers are oriented downwards with the wrist flexed because of the inability to maintain wrist extension, or a "key grip" between the thumb and the lateral side of the index finger at the proximal interphalangeal joint. The downward pinch posture with the wrist fully flexed results in considerable shortening of the extrinsic finger

flexors (Werremeyer and Cole, 1997), which reduces the maximum GF that can be generated in this position. Fifteen degrees of wrist flexion has been shown to decrease grip strength to 73% of normal (O'Driscoll et al., 1992). In the key grip, on the other hand, there is a larger surface area of skin contact with the object: the increased friction between the object and the fingers may therefore influence the GF exerted.

The present study addressed the following questions: (1) What effect do various grip strategies have on the ability to scale GF to LF in normal adults? (2) Is there a difference between the dominant and non-dominant hands when lifting loads with three different grip strategies?

4.3. Methods

Ten healthy subjects (six men, four women, aged 22-56 years) participated in the study. All were right-hand dominant according to the Edinburgh Handedness Inventory. The experimental procedures were conducted in accordance with the ethical standards prescribed by the Human Research Ethics Committee at The University of Adelaide. All subjects gave informed consent in accordance with the Declaration of Helsinki.

The manipulandum that was used was similar in concept to that described by Westling and Johansson (1984) (see Figure 1.1). The GF, applied by the fingers and thumb onto polished brass surfaces 35 mm apart, and the LF were measured with lightweight load cells (MLP-10, Transducer Technologies, Temecula, CA). An accelerometer attached to the apparatus signalled the onset of a lift. The device weighed 340 g and was positioned on a custom-made box.

Subjects washed their hands with soap and water, and sat at a low table facing the device. The lifting movement was performed primarily by elbow flexion and subjects rested their forearms on their upper thighs between trials. Subjects used three different grip strategies in randomised sequence to lift the apparatus; namely, a key grip between the thumb and the side of the flexed index finger, a pinch grip between the thumb and index finger with the fingers directed horizontally (lateral pinch) and a pinch grip with the fingers directed downwards and the wrist fully flexed (downward pinch).

The first experiment compared the results of the three grip strategies in the left and right hands. Explicit verbal instructions and demonstration of the three grips were provided prior to the first attempt to lift the apparatus. Subjects were instructed to "Lift the device off the table to the height indicated (10 cm). Hold the device there for three seconds and then replace it on the table. I will tell you when to start". Subjects practised the different grips and lifted the device with the lateral pinch grip until they were familiar with the height and timing of the lifts. Subjects were randomly assigned to begin with either the left or the right hand. The three grips were then randomly varied so that each subject performed a series of 10 lifts with each grip (three blocks in total). This was repeated for the other hand after a brief rest period. At the end of the experiment, subjects were asked to lift the object with each grip and then slowly separate the fingers to release it, to provide an estimate of the “slip ratio”, which is the minimal GF:LF ratio required to prevent the object from slipping (Johansson and Westling, 1984). For each subject, three such trials were carried out with each grip and each hand. The entire testing procedure took approximately one hour.

The second experiment examined the maximal GF generated in each of the three grips. Subjects were instructed to lift the device and perform a maximal voluntary contraction

(MVC) against the load cell with each grip type. This was performed three times for each grip, on both hands.

4.3.1. Data analysis

For each lifting trial, the data acquisition started 0.5 s prior to the load reaching 1.0 N force and ended when the apparatus was replaced on the flat surface. The GF and LF signals and acceleration were low-pass filtered (100 Hz), digitised, and stored on a computer for off-line analysis.

The lift phase and the hold phase were analysed separately. The lift phase was assessed in two ways. Firstly, the maximal GF (GF_{max}) as the object was lifted from the surface was determined. Secondly, the temporal relationship between GF and LF was assessed by cross-correlating the rate of change of GF (dGF/dt) and LF (dLF/dt) using the method described by Duque et al. (2003). That is, the correlation coefficient (*r*) for these two signals was obtained at each of a series of time points to which the plot of dGF/dt was shifted in increments of 2.5 ms relative to the plot of dLF/dt (Fig. 4.1, lowermost row). The time-shift at which the maximal *r* value was obtained indicated the time difference between the change in GF relative to LF, and indicates whether the grip strategy was primarily anticipatory or reactive.

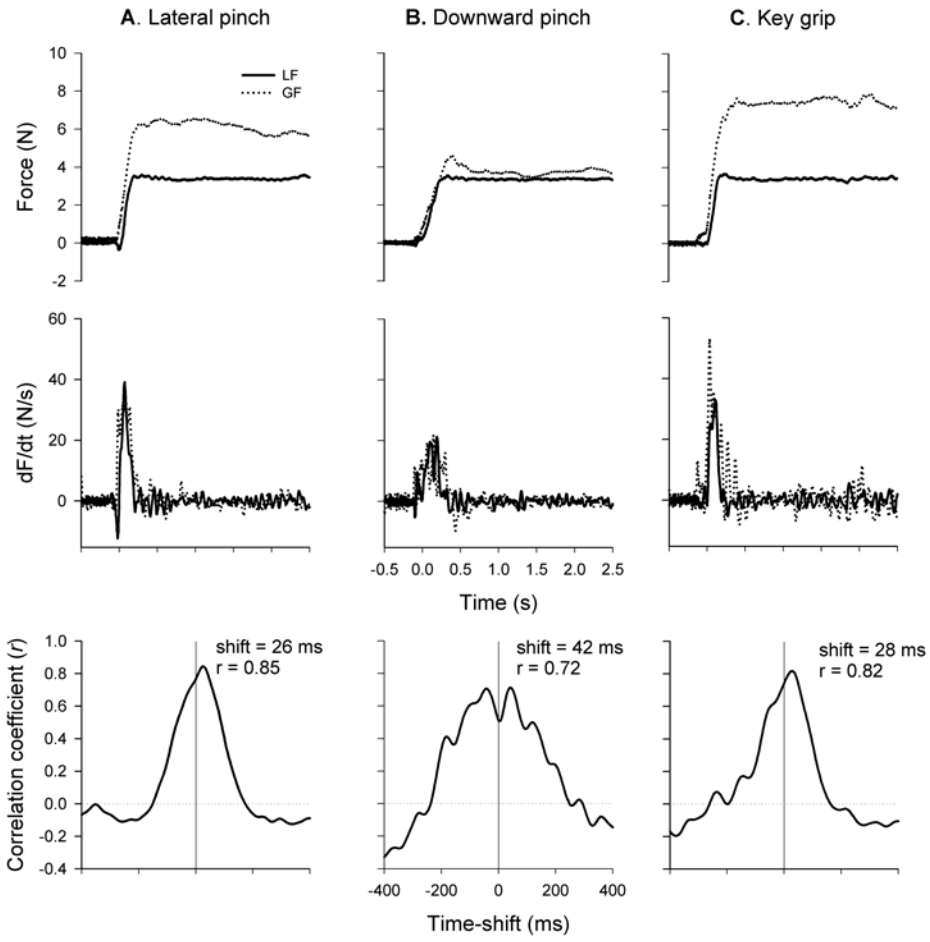

Figure 4.1 Characteristics of the three different grip strategies in a single subject
The top row shows the grip force (GF, dotted line) and load force (LF, solid line) as the object (mass 340 g) is lifted from the surface. The key grip resulted in the largest GF_{max} and the downward pinch the lowest; all were significantly different ($P < 0.001$). The concurrent rates of change of GF and LF are shown in the middle row. The profiles of dGF/dt are similar for the lateral and key grips but the downward pinch grip resulted in lower peak lift velocities, without the single peak characteristic of the other grips. The values of the correlation coefficients for each of the three grip strategies when dGF/dt was shifted in 2.5 ms time increments against dLF/dt are plotted in the lowermost row. The maximum correlation coefficient is significantly lower for the downward pinch grip ($P < 0.001$).

The hold phase was defined as a 1-s interval starting 1 s after the time of GF_{max}, when a stable GF was established (see Fig. 4.1): the average GF:LF during this interval was calculated. The slip ratio was obtained at the time point at which GF suddenly fell; this is the minimum GF required to support the weight of the object (Johansson and Westling, 1984).

Statistical analysis was performed using a two-way analysis of variance (ANOVA) with factors GRIP and HAND on the following parameters: GF_{max}, maximal correlation coefficient (*r)* and time shift, hold ratio, slip ratio and MVC for each lift. An additional ANOVA was performed to assess learning. Data were combined for lift one and two (Lift A), and for nine and ten (Lift B) to give an additional factor of LIFT in a three-way ANOVA. *Post hoc* analyses were performed using Bonferroni's comparison with corrections. Statistical significance was accepted at $P \leq 0.05$. Group means ± standard error of the mean are shown.

4.4. Results

The general form of the data for the three grips is shown in Figure 4.1. Across all subjects, there was a significant difference in the GF_{max} for all three grips (ANOVA, $P < 0.001$). The key grip resulted in the largest GF_{max} (11.5 ± 0.8 N; mean ± standard error). The lateral pinch GF_{max} (7.9 ± 0.4 N) was significantly greater than the downward pinch grip (6.9 ± 0.4 N). The absence of a significant GRIP*HAND interaction indicates that this was consistent across hands. The MVC for each grip was also significantly different (ANOVA, $P < 0.001$), with a similar pattern to GF_{max} (key grip 107.4 ± 9.4 N, lateral pinch 81.1 ± 10.0 N, downward pinch 64.5 ± 8.2 N).

The GF_{max} data analysis revealed a significant effect for HAND ($P < 0.001$), which was the result of the left hand exerting larger GFs to lift the object across all grips (9.2 ± 0.6 N) than the right (8.4 ± 0.5 N). There was no effect of HAND for the MVC data ($P = 0.15$).

Further differences between the three grip strategies were revealed by correlating the rate of change of GF with the rate of change of LF. The maximal correlation between dGF/dt and dLF/dt was very high for both the key and the lateral pinch grips due to the close similarity

between the profiles of GF and LF rates, e.g., Fig. 4.1A and 4.1C lower panels. The ANOVA revealed a significant effect of GRIP ($P < 0.001$) but no effect of HAND ($P = 0.8$). *Post-hoc* tests demonstrated that the difference was due to the lower r values for the downward pinch grip ($r = 0.79 \pm 0.01$) across both hands, compared with the other two grips (lateral pinch $r = 0.84 \pm 0.01$, key grip $r = 0.83 \pm 0.01$).

The time-shift indicates the temporal relationship between the rates of change of GF and LF. There was a significant effect of GRIP ($P < 0.001$) due to a greater time-shift for the key grip (-23.1 ± 4.5 ms) compared with downward pinch (3.6 ± 3.6 ms) and lateral pinch (1.1 ± 2.2 ms). The distribution of time-shifts indicated a clear difference in the range of values for both the key and downward pinch grips (Figure 4.2). There was no effect of HAND ($P = 0.13$).

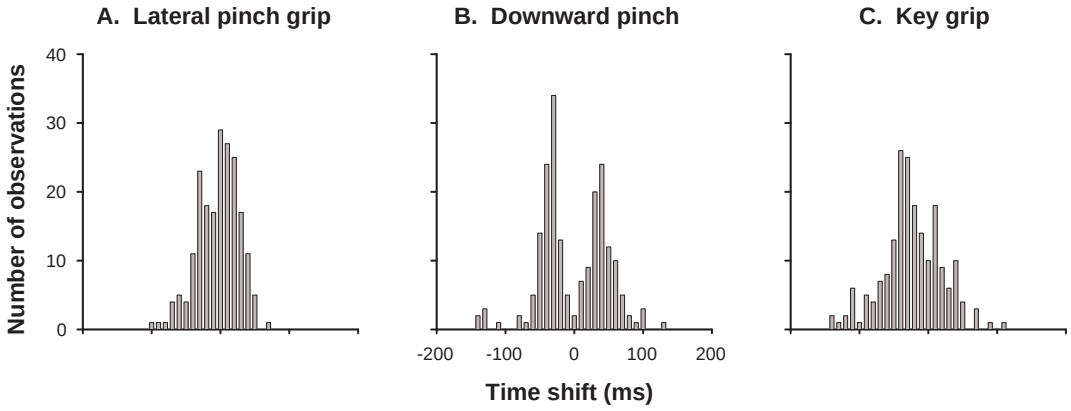

Figure 4.2 Results of the correlation analyses for each of the three grips
Data shown are results of the correlation analyses made at different time shifts of dGF/dt relative to dLF/dt for each of the 10 lifts, combining both hands. The distribution of the time-shift values for the lateral pinch and key grips are similar, although there is a net negative shift for the key grip indicating the use of a reactive strategy. The downward pinch grip resulted in a bi-phasic distribution, with dGF/dt matched poorly to dLF/dt.

The average GF:LF during the hold phase of the lift was analysed for each grip. ANOVA revealed a significant effect of GRIP ($P < 0.001$) with all three grips resulting in different values. The key grip had the largest GF:LF and therefore the largest safety margin for holding the object stationary (2.5 ± 0.2). There was a small but significant difference between the

lateral pinch grip (1.8 ± 0.1) and the downward pinch (1.5 ± 0.1). There was no effect of HAND (P = 0.08).

The slip ratio was different for the three grips (P < 0.001) due to a significantly higher GF:LF ratio required to prevent slipping for the key grip (0.66 ± 0.06) than for the lateral pinch (0.35 ± 0.02) or the downward pinch (0.36 ± 0.02). These correspond with approximate minimum GFs of 1.98 N, 1.05 N and 1.08 N respectively. There was no effect of HAND (P = 0.15).

The ability of subjects to learn to optimise the GF from the first to the last lift was analysed in two additional ANOVAs, with factors LIFT, HAND and GRIP. There was a significant interaction of LIFT*HAND for both the GF_{max} data (P = 0.016) and the hold ratio data (P = 0.015). *Post-hoc* tests indicated that this was due to a larger difference in GF and GF:LF for the right hand from the first two lifts to the last two lifts (Lift A GF_{max} = 9.4 ± 1.1 N, ratio 2.1 ± 0.3; Lift B GF_{max} = 8.0 ± 1.1 N, ratio 1.8 ± 0.3) whereas the left hand did not change from the first to the last lifts (Lift A GF_{max} = 9.4 ± 1.3 N, ratio 2.0 ± 0.4; Lift B GF_{max} = 9.2 ± 1.3 N, ratio 2.0 ± 0.3) as shown in Figure 4.3.

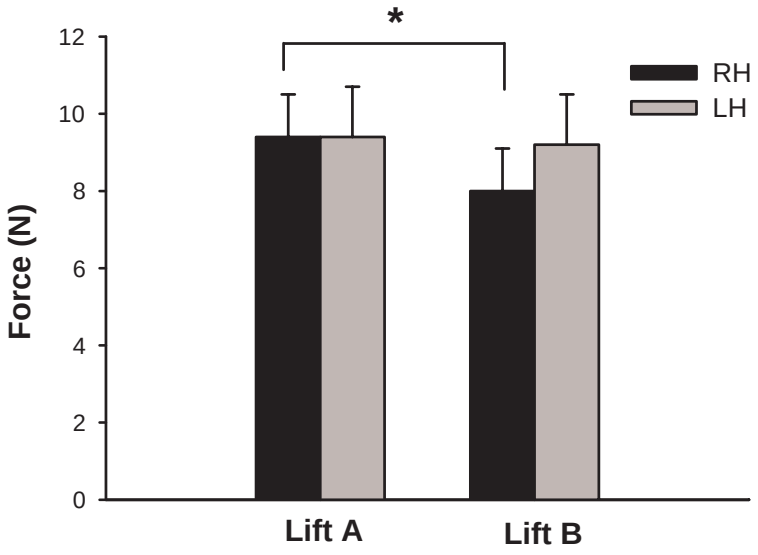

Figure 4.3 GF_{max} for each hand as the device is lifted

Data from the first two lifts (Lift A) and the last two lifts (Lift B) combined to provide an index of learning across the ten trials. GF_{max} decreased for the right hand (black columns) across the trials (P = 0.016) but there was no difference in the maximal force generated by the left hand (grey columns).*

4.5. Discussion

All three grip strategies investigated in this grip-lift task resulted in significantly different GF_{max}, GF:LF, MVC, and slip ratio. The differences in GF_{max} and GF:LF in the hold phase confirm our hypothesis that the grip strategy used to lift an object influences the accuracy of scaling GF to LF.

The MVC was greatest for the key grip, presumably as the result of the biomechanics of the hand. The lateral pinch MVC was about 20% higher than for the downward pinch. The explanation for this is likely also to be biomechanical, as the extreme wrist flexion posture in the downward pinch places the extrinsic finger flexors in a shortened position, reducing their ability to generate large forces (Werremeyer and Cole, 1997). GF_{max} was also larger with the key grip than the precision grips. The key grip also resulted in significantly greater values for the time-shift in the correlation analyses, with an average value of –23 ms, indicating that GF lags LF. When an object is lifted, the rate of GF increase is based on an estimate of the

expected LF and therefore the rate of LF increase as the object starts to move. A positive time-shift indicates that changes in the GF preceded the changes in LF, i.e., the subject's movement plan correctly anticipated the change in load. Subjects using the key grip strategy tended to react to the rate of LF increase *as* it started to move, resulting in a negative time-shift. This may reflect the relative unfamiliarity of this task compared to a precision grip, and hence a less well-developed internal representation of this strategy.

There were quite marked differences in the matching of GF to LF in the pinch grip task when the hand was horizontal with the wrist in a neutral position (lateral pinch), compared with the downward pinch in which the wrist was fully flexed. The GF_{max} and GF during the hold phase were significantly lower in the downward pinch than in the lateral pinch grip, although the slip ratio was similar in both postures. The explanation for this is not clear. It is known that cutaneous mechanoreceptors in the fingertips are able to scale the amplitude and direction of forces applied to the skin (Wheat et al., 2004), so it is possible that the different pattern of activation of sensory receptors in the downward pinch may modulate the muscle activity in a manner that gives a lower safety margin (see below). This is consistent with the observation that the rate of change of GF during the lift phase in the downward pinch was less well correlated temporally with the rate of change of LF than it was in the lateral pinch in both hands (Fig. 4.2). The cross-correlograms of the downward pinch data frequently had bi-phasic peaks of similar amplitude which were not seen in the lateral pinch analyses (e.g., Fig. 4.1). These bi-phasic peaks led to a different pattern of distribution of time-shifts of the cross-correlograms across the grouped data. Figure 4.2 shows that, while the time-shifts for the lateral pinch and the key grip for all trials in all subjects are distributed fairly evenly around zero, the downward pinch data are distributed in a highly bi-phasic pattern. We interpret this to mean that in individual downward pinch trials, the movement plan was less accurate than for the other grips. Subjects were more likely either to anticipate the LF by increasing their

GF before the load increased, or to compensate after the LF increased, so that GF was less accurately matched to LF. This may in part be due to the fact that the downward pinch is a less-familiar task than lateral pinch, so that movement plans are less accurately programmed, and perhaps to the biomechanics of the wrist and hand, i.e., the MVC data suggest that a given effort in the downward pinch posture may result in about 20% less force than in the lateral pinch posture.

It was therefore interesting to compare the mean safety margin for the downward pinch during the hold phase with the other grip strategies. The safety margin equals the GF above that which is necessary to prevent the object from falling in the hold phase. This equals the hold-phase GF minus the frictional force from the skin-object contact that would prevent the object from falling. The frictional force was calculated from the slip ratio, namely the minimal GF:LF required to support the object in the hold phase, which is an index of the static coefficient of friction between the skin and the object's surface (Johansson and Westling 1984). The slip ratio for the downward pinch was 0.36. That is, the minimal GF that would support the 340 g weight (equivalent to a force of 3.3 N) was 1.2 N: the remaining 2.1 N force was the result of friction between the object and the skin. Hence the mean safety margin in the downward grip was the 5 N hold-phase GF minus the 2.1 N friction, i.e., 2.9 N. In contrast, the safety margin for the lateral grip was 3.8 N and for the key grip was 7.2 N. The relatively low safety margin for the downward grip is consistent with the observation from the temporal correlations of GF and LF that follow-up corrections to the GF were often necessary.

The slip ratio for the key grip was about twice as high than for the other two grips, indicating lower friction at the time of release of the manipulandum. This was unexpected, as we anticipated that the friction arising from the (apparently) larger skin-to-object contact area and therefore friction in the key grip would be greater rather than less than in the pinch grips, and

that the slip ratio would therefore be smaller. However, inspection of the skin contact areas during determination of the slip ratio revealed that, while these areas declined only slightly as the GF was decreasing prior to release of the two pinch grips, the contact areas on both the thumb and the lateral surface of the index finger in the key grip declined markedly as the GF decreased just prior to release. Accordingly, the frictional force supporting the manipulandum at the moment of release was lower in the key grip than in the other grip strategies. Hence, the minimal GF required to support the manipulandum during the hold phase was relatively larger when the key grip was used: despite this, the 7.2 N safety margin is much higher than is required for supporting it safely. This did not decrease even after many lifts with both hands, which suggests that the sensory information did not update the central motor program further. Afferent information from glabrous skin receptors is used to update the central program in order to optimise the forces involved with the grip-lift task (Johansson and Westling, 1988a). It is likely that the afferent information from the skin overlying the proximal joint of the index finger differs from the rich sensory innervation of the tip of the forefinger and this may explain the large safety margin that was observed with this grip.

Our data reveal a difference between the left and right hands in two aspects of the grip-lift task. Firstly, the left hand used larger GFs than the right hand in the lift but not the hold phase, although there was a trend towards greater GF during the hold phase ($P = 0.08$). All subjects were right-hand dominant, suggesting that they performed precision tasks less often with the left hand. The relative novelty of the task may explain the greater GF and safety margin employed with all grips on the left hand. Secondly, the left hand did not optimise GF_{max} or GF:LF during the hold phase over the course of the 10 lifts. There was a significant reduction in both of these variables during lifts of the right hand only. Again, the left hand may be inexperienced in a repetitive precision task in comparison to the dominant hand, and may require more than 10 lifts to optimise the forces involved.

Damage to the corticospinal tract, for example by stroke, often leads to deficits in sensorimotor control. Depending on the degree of impairment, hemiplegic patients who are unable to use the normal precision grip often use alternative strategies such as key grip and downward pinch grip. Stroke patients with mild motor deficits who are able to lift and transport a spherical object use excessive GFs, and the coupling of GF to LF is impaired (Hermsdorfer et al., 2003). Our results suggest that even with normal sensorimotor control, the use of the alternate grip strategies may result in sub-optimal force control.

In conclusion, it is clear that alternate grip strategies influence force control and scaling of GF to LF during the grip-lift task in subjects with normal sensorimotor control. The altered biomechanics of the downward pinch and key grip may contribute to the differences seen in these grips compared to a standard precision grip. Hand dominance also affects force control in right-handed subjects, for the left hand employs greater GFs and does not learn to optimise force control over a short series of lifts. This may have implications when studying the grip-lift task in patients who are unable to perform a lateral precision grip, particularly if their affected arm is non-dominant.

5. Impairments in precision grip correlate with functional measures in adult hemiplegia

5.1. Abstract

Analysis of a precision grip-lift task provides measures to assess functional disability of the hand, but the correlation between these measures and accepted tests of motor function in stroke patients has not been established. Seventeen subacute stroke patients were studied to compare parameters of a precision grip-lift task between the affected and unaffected side, and to correlate them with function. Functional impairment was assessed with the Action Research Arm Test (ARAT) and the Fugl-Meyer Assessment (FMA), as well as grip strength and maximal finger-tapping speed. The grip force (GF) and load force (LF) were recorded as patients lifted a custom-built manipulandum. All measures were recorded on two separate occasions, at least one week apart. There was good reproducibility between testing sessions for the grip-lift and functional measures. The affected hand gripped the manipulandum for longer prior to lift-off than the unaffected hand, and the normal close temporal coupling between the rate of change of GF and LF during the lift was disrupted. These two measures correlated more highly with the ARAT than the FMA and, when combined with measures of grip strength and tapping speed, explained 71% of the variance of the ARAT. In summary, the grip-lift task is a sensitive measure of impaired dexterity following stroke and provides measures which correlate well with a commonly applied functional assessment scale. It may be used clinically to detect changes in the hemiplegic upper limb during rehabilitation and recovery.

5.2. Introduction

Despite advances in medical care and rehabilitation, the recovery of arm function following stroke is often limited. Functional abnormalities in the hemiplegic upper limb are often

quantified with the ARAT, the upper-limb components of the Motor Assessment Scale and the FMA. However, it is common for patients to score well on these tests but still to complain of clumsiness when performing fine manipulative tasks.

To lift an object between the finger and thumb (the so-called "precision grip") requires accurate force coordination to prevent the object slipping or excessive forces that might crush it (Johansson and Westling, 1984). Individuals with poor dexterity due to disorders of the basal ganglia (Fellows et al., 1998), cerebellum (Serrien and Wiesendanger, 1999), or children and adolescents with cerebral palsy (Duque et al., 2003; Forssberg et al., 1999) demonstrate deficits in efficient GF scaling and temporal precision of GF to LF coupling. Manual dexterity is strongly correlated with a global score for the development of grip-lift synergy in children with cerebral palsy (Forssberg et al., 1999). Furthermore, Forssberg and colleagues (1999) reported a significant correlation between impaired grip-lift synergy and location and size of brain lesions. However, the relationship between individual grip-lift task parameters and functional measures has not been systematically investigated in stroke patients.

The aims of the present study were to compare a range of grip-lift parameters in the affected and unaffected upper limbs in a heterogeneous sample of stroke patients and to correlate them with two widely-used indices of motor function. We hypothesised that the grip-lift task parameters would correlate well the functional assessment tools and that significant differences between the affected and unaffected hands would be evident.

5.3. Methods

5.3.1. Subjects

Seventeen adults who suffered a first-ever stroke causing paresis of the upper limb were recruited (details summarised in Table 5.1). All patients were right hand dominant. The study was approved by the Human Research Ethics Committee of The University of Adelaide and all patients gave written informed consent. Patients were tested on two separate occasions at least one week apart.

Table 5.1 Demographic and clinical data of patients

Patient	Sex	Age (yrs)	Infarct site on CT scan	Months since stroke	Hypoaesthesia (0-2)[a]	Proprioception (0-2) [a]	ARAT (/57)	FMA (/66)
1	F	70	R MCA and PCA	2	1	2	12	25
2	F	63	R parietal	7	1	1	17	27
3	F	94	R posterior limb IC	3	2	2	23	43
4	M	70	R thalamic and occipital	3	2	2	24	38
5	F	79	R cortical parietal	4	1	1	32	54
6	M	77	R parietal	2	1	2	41	45
7	F	76	L subcortical parietal	6	2	2	41	46
8	M	57	L corona radiata	3	2	2	48	56
9	M	66	L IC	2	2	2	51	43
10	M	55	L IC	7	2	2	54	58
11	M	68	R IC	7	2	2	55	55
12	F	63	L ACA	7	2	2	57	62
13	M	45	R post aspect MCA	3	1	2	49	63
14	M	54	L medial medulla	7	2	2	53	57
15	F	69	R lacunar	4	2	2	53	55
16	M	63	L IC	2	2	2	44	60
17	F	48	R MCA	5	1	2	47	40

F = female; M = male; MCA = middle cerebral artery; PCA = posterior cerebral artery; IC = internal capsule; ACA = anterior cerebral artery

[a] Hypoaesthesia/proprioception: 0 = no sensation, 1 = reduced sensation , 2 = intact sensation (Fugl-Meyer et al., 1975)

The authors acknowledge that the hand ipsilateral to the lesion is not "unaffected" by the stroke (Sugarman et al., 2002; Thilmann et al., 1990), but have used this expression for simplicity.

5.3.2. Upper limb assessment

Hemiplegic upper limb function was assessed by an experienced physiotherapist using the ARAT (Lyle, 1981) and FMA (Fugl-Meyer et al., 1975) functional outcome scales. Both tests have high reliability and established validity (Poole and Whitney, 2001). The maximal scores for these tests are 57 and 66, respectively: the total raw score achieved on each scale was used in the analyses. The ARAT tests overall upper limb function with 19 items divided into subtests of grasp, grip, pinch and gross arm movement. Items within each of these groups are ranked on an ordinal scale with four levels from 0 (cannot perform any part of the test) to 3 (performs test normally). Sensation and proprioception were also assessed using a 3-point ordinal scale (Fugl-Meyer et al., 1975).

A hand-held dynamometer (North Coast Medical Precision Instruments, USA) was used to assess maximal hand-grip strength. Patients were asked to squeeze the dynamometer as hard as possible for 3 - 5 s. Maximal tapping speed was determined by tapping the index finger as quickly as possible on a load cell for 5 s. Each hand was tested three times with both measures, with a rest period of 30 s between trials. The highest value of the three attempts was recorded.

5.3.3. The grip-lift task

The grip-lift manipulandum was based on that described by Westling and Johansson (Westling and Johansson, 1984) and weighed 340 g. The GF applied by the index finger and

thumb onto polished brass surfaces 35 mm apart, and the LF were measured with load cells (MLP-10, Transducer Technologies, Temecula, CA).

Patients washed their hands thoroughly and sat at a low table with their arms resting on the upper thighs. The lifting movement was performed primarily by elbow flexion. They were instructed to lift the manipulandum to the height indicated (10 cm), hold it there for 3 s, then lower it. They practised this until they were comfortable with the task. The manipulandum was lifted 15 times with the unaffected hand, then 15 times with the affected hand.

Data acquisition started 1 s before the GF reached 1.0 N force and ended when the manipulandum was replaced on the table. GF and LF signals were low-pass filtered (100 Hz), sampled at 400 Hz, digitised, and stored on a computer for off-line analysis.

The following grip-lift parameters were analysed for each lift (Figure 5.1):

1. *preload duration*: time between onset of GF and onset of positive LF as the manipulandum was lifted from the surface.
2. *minimum load*: maximal downwards load during grasping of manipulandum.
3. GF_{max}: peak GF during lift phase.
4. *GF:LF ratio*: ratio of GF to LF at GF_{max}.
5. *maximal correlation*: the maximal correlation coefficient obtained when dGF/dt and dLF/dt were cross-correlated, as dGF/dt is shifted in 2.5 ms steps against dLF/dt (Duque et al., 2003).
6. *time-shift*: time difference between dGF/dt and dLF/dt at which the maximal correlation occurred. This is an objective measure of the temporal asynchrony between dGF/dt and dLF/dt.
7. *average GF*: mean GF during hold phase.

8. *hold ratio*: average GF:LF as object is held stationary after lifting. Hold phase was defined as a 1-s interval starting at least 1 s after GF_{max}, when a stable GF is established.

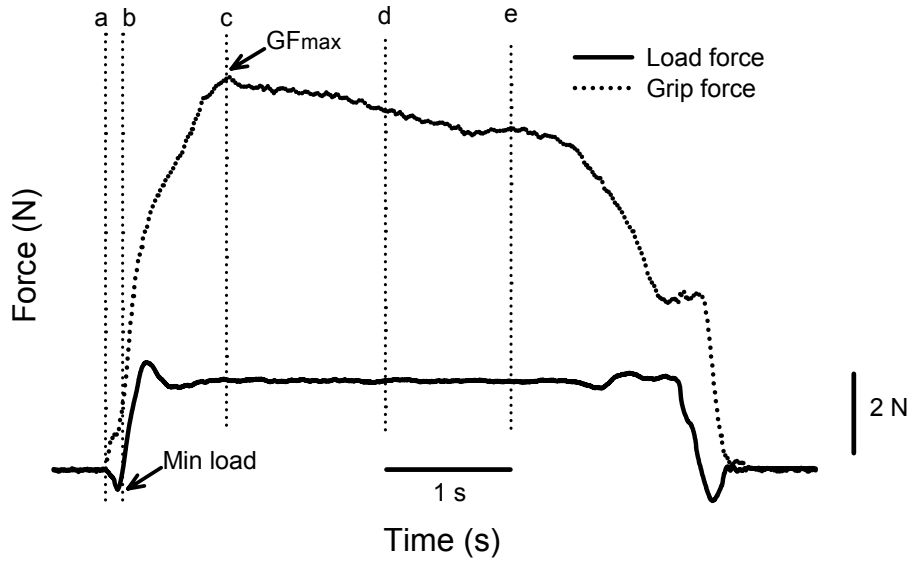

Figure 5.1 Raw data obtained from the grip-lift task

Typical GF (dotted line) and LF (solid line) profiles as the manipulandum is lifted with the paretic hand after several practice trials. Dotted lines indicate specific events: (a) onset of GF; (b) onset of positive LF; (c) GF_{max}; (d) – (e) the hold phase which commences at least 1 s after GF_{max} and lasts for a duration of 1 s. Preload duration is the time between (a) and (b), and the lift phase is defined as time between (a) and (c). Other grip-lift parameters obtained from these data are minimum load and GF_{max} (indicated on the figure), GF:LF ratio at GF_{max}, maximal correlation and time shift (see Figure 5.2 below), and GF:LF and average GF during the hold phase.

5.3.4. Statistical analyses

Reliability was assessed using Intraclass Correlation Coefficients (ICC) for each hand to determine the agreement between testing sessions (SPSS, Chicago, IL, USA). Data from both sessions were then averaged and variables were grouped into measures of function (ARAT, FMA, grip strength and tapping speed) and dexterity (eight grip-lift parameters).

To assess for differences between hands with the ordinal functional data, Wilcoxon signed-rank tests were used with Bonferroni sequential corrections. For the continuous data obtained

from the grip-lift task, log-transformation was applied if data failed Kolmogorov-Smirnov normality testing. Data were then analysed with a one-way multivariate analysis of variance to investigate the effect of hand on grip-lift parameters. Significance was set at $P < 0.05$. Data are presented as mean ± SD.

Each grip-lift parameter was correlated with the functional measures using Spearman's rank correlation coefficient (ρ). When ρ was > 0.6, these parameters were entered into a hierarchical multiple regression to determine which parameters could predict the total score of the ARAT and the FMA.

5.4. Results

All measures were reliable between testing sessions for the unaffected hand (mean $ICC_{(3,1)}$ = 0.86 ± 0.07, range 0.78 – 0.99) and, except for the time-shift ($ICC_{(3,1)}$ = 0.18), in the affected hand (mean $ICC_{(3,1)}$ = 0.93 ± 0.05, range 0.83 – 0.99). The data for ARAT, FMA, grip strength, tapping speed and grip-lift variables were therefore pooled for further analysis.

5.4.1. Comparison between affected and unaffected hands

Table 5.2 presents the results of the functional and dexterity measures for the affected and unaffected hands. There was a significant difference between hands for all functional measures, as seen in the significant effect of hand. There was no main effect of hand on the combined grip-lift variables ($F_{8,25}$ = 1.1, P = 0.4). When each variable was considered separately, there was a significant effect of hand for preload duration, negative load and the maximal correlation coefficient, as shown in Table 5.2.

Table 5.2 Comparison of functional and dexterity measures between hands

Parameter	Affected side			Unaffected side			
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	Hand difference *P* value*
ARAT (/57)	42.8±13.2	47	12-57	57±0	57	57	<0.001
FMA (/66)	48.2±12.7	54	25-65	66±0	66	66	<0.001
Grip strength (N)	117±104	103	0-372	295±153	155	93-642	<0.001
Tapping speed (taps per 5 s)	18±7	17	2-32	26±5	26	14-37	<0.001
Preload duration (ms)	601±586	424	87-2701	247±192	190	33-444	0.003
Minimum load (N)	-0.64±0.6	-0.5	-1.51-0	-0.3±0.2	-0.2	-0.6-0	0.018
GF:LF ratio	3.4±2.8	2.9	0.7-15.3	3.1±2.2	2.6	0.3-9.9	0.770
Max correlation	0.62±0.2	0.66	0.20-0.92	0.74±0.1	0.75	0.49-0.95	0.020
Time-shift (ms)	-36.5±70	-26	-262-126	-11±43	-0.3	-184-37	0.118
Hold ratio	3.0±2.3	2.6	0.91-11.4	2.6±1.8	2.1	0.3-6.4	0.609
GF_{max} (N)	12.0±7	10.6	6.2±36.7	10.4±6.5	8.6	3.6-26.9	0.208
Average GF (N)	10.1±6.7	9.0	2.3-32.2	8.4±5.3	6.9	3.4±29.6	0.154

*Wilcoxon Signed Rank test with Bonferroni sequential corrections for functional data; grip-lift data were analysed with multivariate analysis of variance

The performance of the affected hand in the grip-lift task varied markedly between patients. The object was dropped in a small number of trials and these were excluded from analysis. Figure 5.2 shows the performance of patient 1 who scored poorly on the ARAT, and patient 12 who scored maximal points. Panels (i) and (ii) refer to the affected and unaffected hands, respectively. The poorly-recovered patient could barely lift the object and could not generate sufficient GF to hold the object steady. In contrast, patient 12 could lift and hold the manipulandum steady with either hand, although the affected hand used excessive GF. The large inter-subject differences in GF_{max} resulted in no significant difference between the hands across the group ($P = 0.2$).

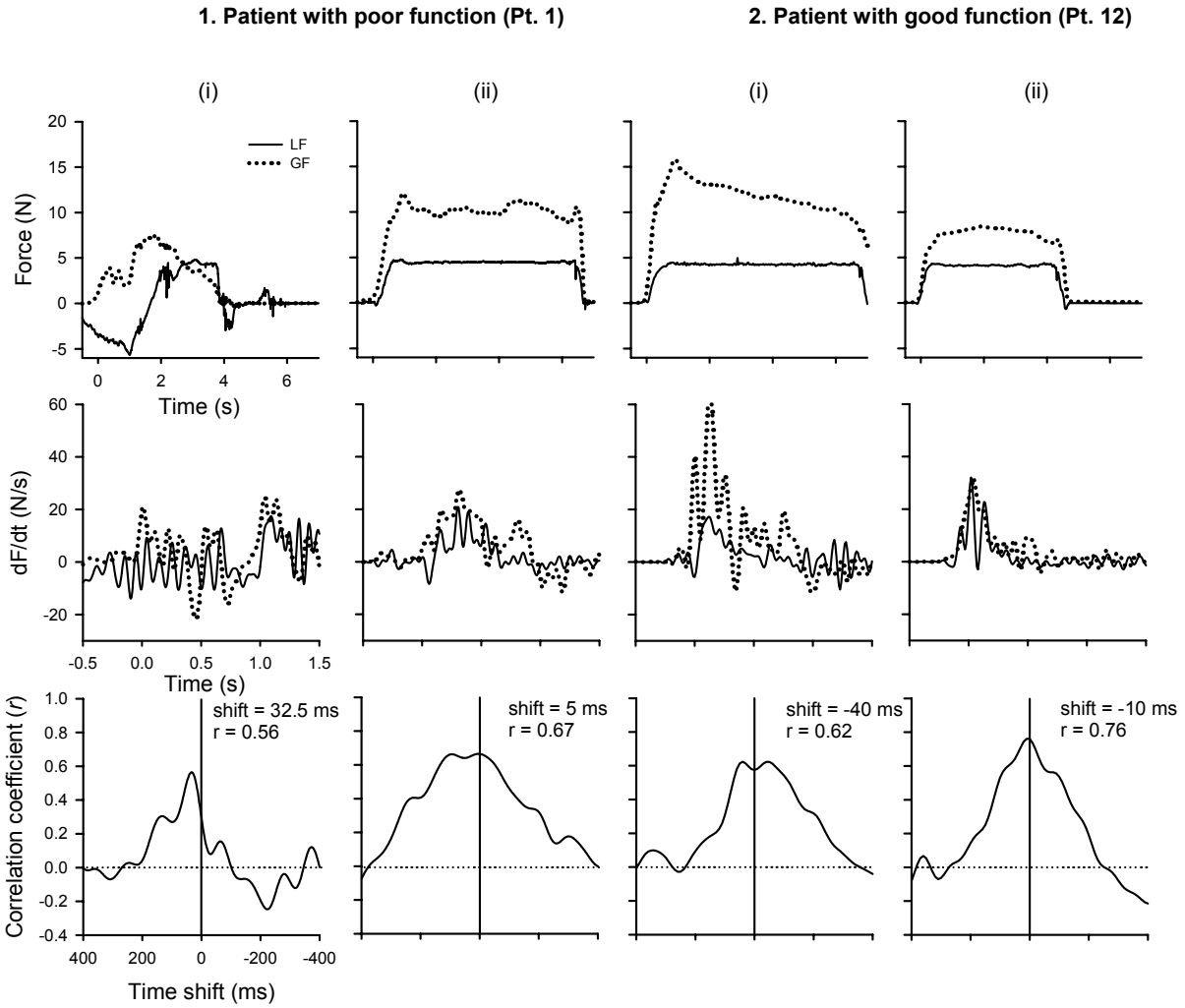

Figure 5.2 Data from representative stroke patients performing the grip-lift task
Data from a poorly recovered patient (Patient 1) who scored 12/57 on the ARAT, and a well-recovered patient (Patient 12, ARAT = 57/57) with data from the affected and unaffected hands in panels (i) and (ii) respectively. Uppermost row: GF and LF profiles; middle row: rates of change of GF and LF; note change in y-axis scale to N/s. The profiles of dGF/dt are similar for Pt. 12 and the unaffected hand of Pt. 1 but the grip employed by the poorly-recovered patient resulted in substantially lower peak load velocities and without the single peak characteristically seen. Values of maximal correlation when dGF/dt was shifted in 2.5 ms time increments against dLF/dt are plotted in the lowermost row. The maximal correlation coefficient is significantly lower for the affected hand of Pt. 1 and time-shifts are greater on the affected side for both patients.

All patients used the maladaptive strategy (not seen in normal individuals) of pushing the device down into the table prior to lifting which resulted in an initial negative load only in the affected hand ($P = 0.018$). Preload duration was also significantly longer in the affected hand ($P = 0.003$) and the rates of change of GF and LF did not increase in parallel, as indicated by the lower maximal cross-correlation values ($P = 0.02$).

5.4.2. Correlation between functional measures and grip-lift parameters

The ARAT and the FMA were significantly correlated ($\rho = 0.75$, $P < 0.001$), but the ARAT correlated more highly than the FMA with grip strength ($\rho = 0.73$, $P < 0.001$) and tapping speed ($\rho = 0.61$, $P < 0.001$) and thus was chosen as the primary dependent variable for the correlation analysis. Univariate analysis revealed a significant negative correlation between the ARAT and preload duration ($\rho = -0.72$, $P < 0.001$) and a positive correlation with the maximal dGF/dt and dLF/dt correlation coefficient ($\rho = 0.83$, $P < 0.001$). These correlations are illustrated in Figure 5.3. This relationship was not influenced by whether the affected hand was dominant or non-dominant.

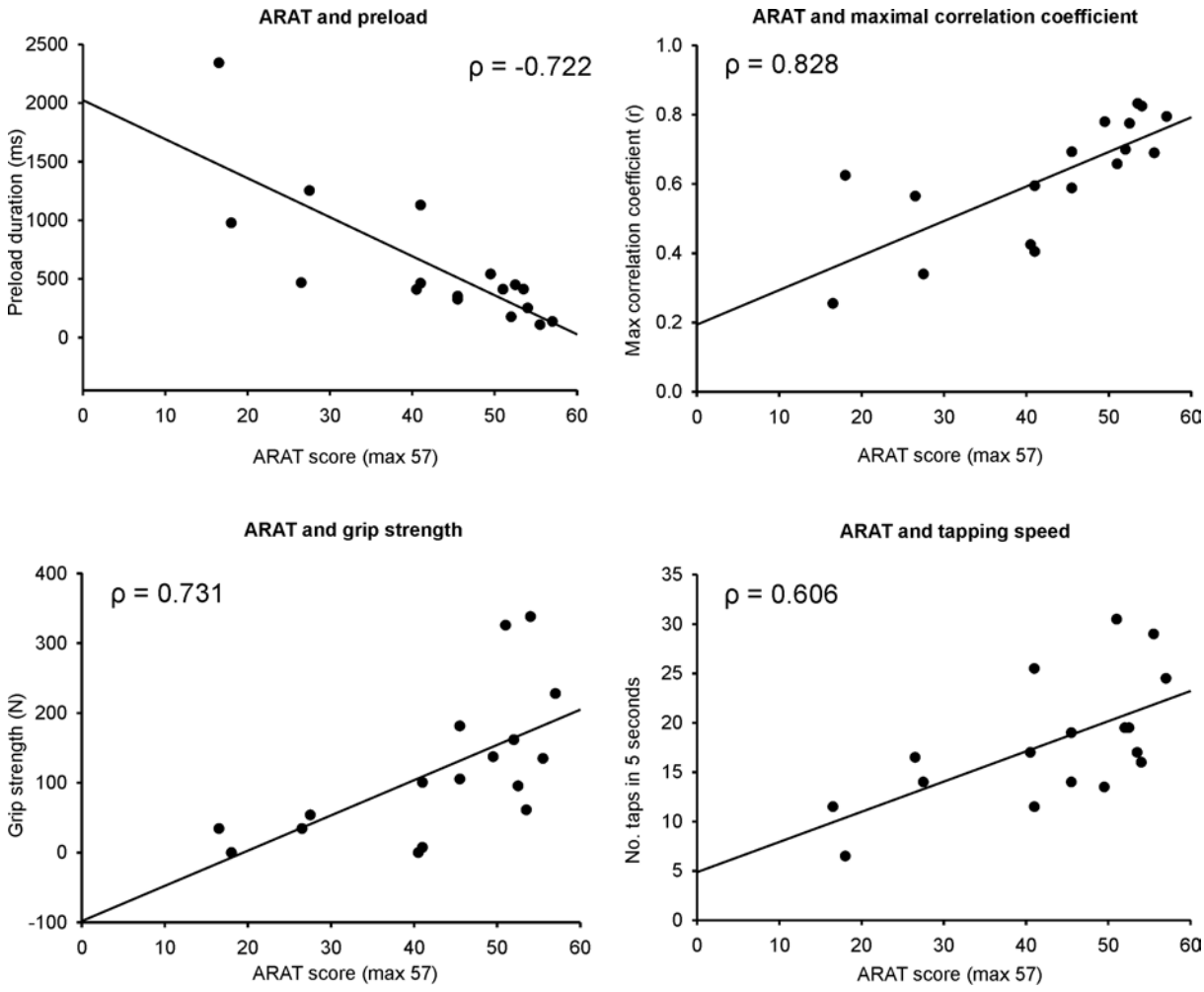

Figure 5.3 Correlation between the ARAT and other functional and grip-lift parameters
The ARAT was significantly correlated with the preload duration and maximal correlation coefficient (r) (upper row), and also with grip strength and tapping speed (lower row). All correlations are significant (P < 0.001). Data is from the affected hand only.

A hierarchical multiple regression was performed to determine the contributions of measures to the total scores of motor function. The combination of preload duration and maximum correlation coefficient explained 60% of the variance of the ARAT, and 38% of the FMA. Adding grip strength and tapping speed increased this to 71% of the ARAT and 59% of the FMA.

5.5. Discussion

Our sample of subacute stroke patients was heterogeneous, with some patients suffering extensive and multifocal lesions resulting in a wide range of functional deficits across the group. However, it is known that, even with a larger group of patients, it is difficult to demonstrate any correlation between lesion site and functional deficit, and clinical tests are more useful for predicting upper limb function following stroke (Feys et al., 2000). It is a strength of the present study that relationships between function and grip-lift parameters can be demonstrated even in a group of patients with heterogeneous lesion sites.

The grip-lift task is a sensitive measure for the detection of subtle deficits in skilled performance of the hand (Forssberg et al., 1999; Golge et al., 2004; Pereira et al., 2001). The present study shows that two objective parameters of the grip-lift task, namely, the preload duration and the coupling of changes in GF to changes in LF, differ in the affected and non-affected hands of this heterogeneous group of stroke patients, and that these parameters correlate well with a common functional upper-limb assessment tool, the ARAT. The greater the delay between onset of grip and onset of lift, the worse patients performed tasks within the ARAT; the greater the correlation between the coupling of grip and load force rates, the better patients performed the various grip, pinch and grasp tasks of the ARAT. This linear relationship was confirmed with regression analysis, as shown in Figure 5.3.

When an object is lifted, there is a brief (~ 80 ms) delay while grip is established prior to lift-off in normal subjects (Westling and Johansson, 1984). We found that the duration of this preload phase was significantly longer on the affected side in stroke patients. A similar difference has also been observed in children with hemiplegia (Duque et al., 2003) or traumatic brain injury (Golge et al., 2004), and in adults with internal capsule lesions (Wenzelburger et al., 2005). The delay in establishing GF could partly be the result of sensory changes in stroke. However, an increased duration of the preload phase also occurs in patients without sensory loss (Wenzelburger et al., 2005), and most of the patients (11/17) in the present study had no identifiable sensory deficits (Table 5.1). It seems more likely, therefore, that this delay is the result of abnormal integration into the movement plan of the sensory signal arising from the initial contact with the manipulandum.

The ability to coordinate temporal parameters of the grip-lift task precisely is regarded as evidence for anticipatory scaling of force output (Forssberg et al., 1991; Gordon et al., 1992): again, this is consistent with the notion of abnormal sensorimotor integration on the stroke-affected side. Several studies have examined the temporal relationship between GF and LF by cross-correlating dGF/dt and dLF/dt. This analysis has revealed subtle differences between grip strategies in normal adult subjects when they lifted an object using sub-optimal grip strategies (McDonnell et al., 2005). This approach has also been used to demonstrate impaired coordination of changes in the rate at which GF is matched to LF in adolescents with congenital hemiplegia (Duque et al., 2003).

The present study confirms that there are significant differences in the temporal coupling of changes in GF to changes in LF between the affected and unaffected hands in stroke patients. These are indicated by the reduction in the maximal cross-correlation of dGF/dt and dLF/dt and by the time-shift of this relationship. Lifting the object with the unaffected hand first did

not improve these parameters, indicating that patients did not use information from the unaffected hand about the mechanical properties of the object to optimise subsequent lifts by the affected hand.

The key finding in the present study was a demonstration of the relationship between specific parameters of the grip-lift task and commonly-used clinical assessments of upper limb function (Figure 5.3). The ARAT and the FMA are based on assessments of a number of everyday upper-limb motor tasks. Of the 57 possible points in the ARAT, 48 are derived from grip-related tasks such as pinching, lifting objects with the fingers and placing them on a surface. On the other hand, the FMA scores gross movement and impairment with less emphasis on fine motor tasks. Hence, it is not surprising that objective parameters of the grip-lift task correlate more strongly with ARAT than with FMA scores. This further validates the use of the ARAT as a clinical test of hand function.

It is essential to be able to measure functional changes objectively in studies of the effectiveness of rehabilitative strategies following stroke (Duncan et al., 1994; Wade et al., 1983). The ARAT and the FMA have been used extensively in such studies. Perhaps the most valuable feature of these tests is that they are based on normal functional tasks such as gripping and lifting objects, etc. However, scoring them requires a significant level of clinical judgment, they can suffer from floor and ceiling effects (Poole and Whitney, 2001), and their scoring systems are based on non-linear ordinal scales.

In contrast, the key parameters in the grip-lift task are quantitative and measured objectively. This is a clear advantage in studies measuring the progress of recovery of stroke patients, or the effectiveness of interventions that are designed to improve hand function. Furthermore,

grip-lift parameters were correlated with functional measures regardless of whether the dominant hand was used, further supporting our observation that the grip-lift task is a useful measure of hand function in stroke patients.

Previous investigations of the grip-lift task following stroke have compared the performance of the hemiplegic upper limb with age-matched control subjects (Hermsdorfer et al., 2003; Nowak et al., 2003b; Wenzelburger et al., 2005). However, it is useful to monitor changes in performance of the affected upper limb during the course of rehabilitative therapy in stroke patients, and to contrast them to changes in the unaffected limb. We therefore consider that the quantitative data obtained with the grip-lift task may be a valuable adjunct to the clinical physiological assessment of hand function during treatment for motor disorders in stroke.

6. Combined afferent stimulation and task-specific physiotherapy improves dexterity following stroke

6.1. Abstract

Reorganisation of the human motor cortex can be induced by specific patterns of peripheral afferent stimulation. We sought to determine whether combining appropriate afferent stimulation with task-specific training resulted in greater improvements than training alone in patients with impaired upper limb function following stroke. Twenty patients with hemiparesis due to stroke were allocated randomly to either a stimulation or control group. All received nine sessions of task-specific physiotherapy training over three weeks. Prior to each training session, associative electrical stimulation of the motor point of two hand muscles was given in the stimulation group, while the control group received sham stimulation. Results showed that both groups made similar improvements in functional measures of upper limb function. The stimulation group exhibited significantly greater improvements in an objective measure of dexterity than the control group. There was no significant change in corticospinal excitability in either group. These findings support the use of targeted afferent stimulation to facilitate the response to conventional rehabilitation in patients with hemiparesis due to stroke.

6.2. Introduction

Stroke is a leading cause of long-term disability in adults, with upper limb paresis the primary functional impairment (Lai et al., 2002; Olsen, 1990). Despite intensive rehabilitative efforts, functional outcome of patients with severe hemiparesis is poor (Nakayama et al., 1994a). Only 5% of patients with complete paralysis regain full arm function (Gowland et al., 1992; Richards and Pohl, 1999) and 30-66% never regain use of the affected arm (Nakayama et al., 1994b; van der Lee et al., 1999). Of those who regain purposeful upper limb movement, fine

motor control or dexterity often remains impaired due to sensory loss and impairments in sensorimotor integration (Hermsdorfer et al., 2003).

Corticospinal excitability can be increased in normal subjects by performance of simple ballistic movements (Muellbacher et al., 2001) or more complex tasks such as the Purdue pegboard task (Garry et al., 2004). In stroke rehabilitation, specific training or repetitive exercise also increase corticospinal excitability (Liepert et al., 2000b; Muellbacher et al., 2002) and function of the paretic hand. Task-specific physiotherapy involving repetitive practice of meaningful daily activities is more effective than traditional approaches to rehabilitation of the upper limb (Bayona et al., 2005; Page, 2003; Winstein et al., 2004), and can lead to increased activation of the affected sensorimotor cortex (Jang et al., 2003).

Periods of peripheral (Ridding et al., 2000), central (Nitsche and Paulus, 2000) or combined peripheral and central stimulation (Stefan et al., 2000) also increase motor cortical excitability. Repeated sessions of stimulation over a number of days increase cortical representation of targeted muscles which persists beyond the final stimulation session for several days (McKay et al., 2002). Increasing motor cortical excitability can facilitate motor performance in normal subjects performing complex tasks (McDonnell and Ridding, 2006). Ridding et al. (2000) suggested that stimulation of afferents might increase the excitability of corticospinal projections to stroke-weakened muscles, and that this in turn may facilitate functional recovery. While these different stimulation protocols have been used extensively in normal subjects, their application to stroke patients has remained limited, although promising preliminary results have been reported (Hummel et al., 2005; Uy et al., 2003; Wu et al., 2006).

Despite evidence that stimulation-induced and exercise-induced plasticity can be beneficial for recovery in hemiplegia, the combination of these approaches has not been investigated hitherto. Our hypothesis was that combining stimulation techniques that influence plasticity with rehabilitative treatment would result in greater functional gains than rehabilitation alone (Bütefisch et al., 2004). We tested this hypothesis in a group of patients with hemiparesis due to stroke. The aim of the study was to determine whether repeated sessions of afferent stimulation targeted at two intrinsic hand muscles, combined with task-specific training of the upper limb, would result in greater improvements in dexterity than training alone.

6.3. Methods

6.3.1. Patients

Twenty patients, aged 45-94 years (mean ± SD = 65.6 ± 11.8 years) with mild to moderate hemiparesis due to stroke completed the study (Table 6.1). All were studied between one and eight months after the stroke (4.4 ± 2.4 months). Patients were recruited according to the following criteria: (1) first-ever ischaemic cerebral infarct; (2) active range of antigravity motion of the affected side of at least 60º shoulder elevation and 10º wrist extension; (3) passive range of motion of the affected side of at least 75% normal in the shoulder, elbow, wrist and hand with minimal or no pain; and (4) discharged from upper-limb rehabilitation services. Patients were excluded if they had a cardiac pacemaker, metallic intracranial implants, epilepsy, complete loss of hand sensation, or language deficits that impaired cooperation in the study. All patients gave written informed consent to participate in the study, in accordance with the Declaration of Helsinki. The study was approved by the relevant Human Research Ethics Committees.

Table 6.1 Baseline patient characteristics

Patient No.	Sex	Age (yrs)	Months since stroke	ARAT (/57)	FMA (/66)	Site of infarct/ arterial territory
Control group						
1	F	63	7	57	62	L ACA
2	M	55	7	54	58	L IC
5	M	68	7	55	55	R IC
10	M	66	2	51	25	L IC
11	F	70	2	12	25	R MCA and PCA
13	M	45	3	49	63	R MCA
14	M	54	1	53	57	L medial medulla
18	M	54	4	4	31	L frontoparietal
19	M	78	8	10	32	L basal ganglia and IC
20	F	48	5	47	40	R MCA
Mean±SD		60.1±10.5	4.6±2.6	39.7±20.6	47.9±14.2	
Stimulation group						
3	M	70	3	24	38	R thalamus and occiput
4	F	79	4	32	54	R parietal - cortical
6	F	76	6	41	46	L parietal - subcortical
7	M	57	3	48	56	L corona radiata
8	F	63	7	17	27	R parietal
9	F	94	3	23	43	R IC
12	M	77	2	41	45	R parietal
15	F	69	4	53	55	R lacunar
16	M	63	8	32	51	L frontoparietal
17	M	63	1	44	60	L IC
Mean±SD		71.1±10.8	4.1±2.2	37.6±11.8	47.3±10.6	

F = female; M = male; ARAT = Action Research Arm Test; FMA = Fugl-Meyer Assessment; R = right; L = left; ACA = anterior cerebral artery; IC = internal capsule; MCA = middle cerebral artery; PCA = posterior cerebral artery

6.3.2. Experimental design

Patients were randomly assigned to the stimulation or control group at the time of enrolment into the study. Allocation was determined by a computerised random number generator

performed by an independent researcher and assignments were enclosed in sequentially-numbered, opaque sealed envelopes until entry into the study, at which time baseline measures were recorded (see Figure 6.1). These measures were repeated one week later. Following this, both groups participated in a standardised training protocol designed to improve upper limb function which was conducted three times a week for three weeks (Winstein et al., 2004). Patients in the stimulation group (N = 10) were given a period of afferent nerve stimulation (details below) immediately before the training period in each session, while patients in the control group (N = 10) were given sham stimulation (below). All patients were told that they would receive weak electrical stimulation but the strength would vary between patients; hence, those in the sham group were unaware they were not receiving the "true" stimulation.

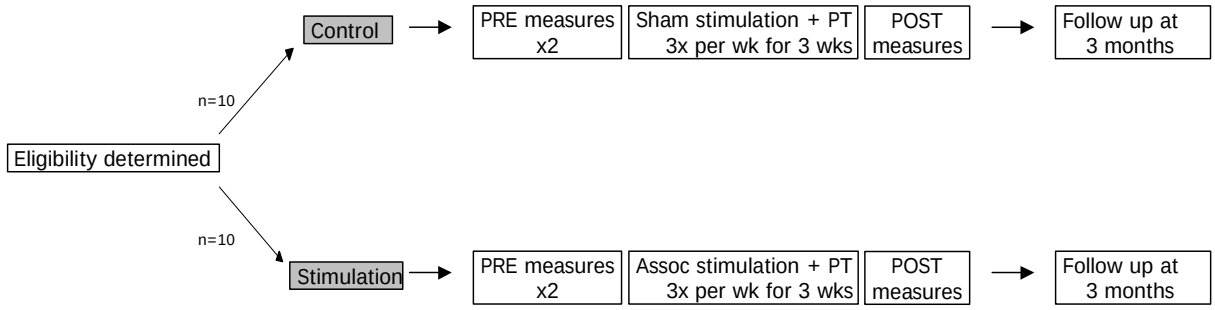

Figure 6.1 Experimental design

Intervention

Training protocol

A standardised training protocol was developed to provide upper limb rehabilitation to all patients. Major impairments of upper limb function were identified, according to the following categories: sensation, active and passive range of movement, and uni- and bimanual dexterity. Deficits in each of these areas were identified and strategies to reduce the

impairments were implemented. Task-specific training involving repetitive practice of everyday tasks was chosen as the training method (Winstein et al., 2004). Tasks were standardised and repeatable and included items such as reaching, wrist extension against resistance and performing fine motor tasks like placing items in a box, writing and manipulating putty. The assessment of impairment and interventions applied during training are detailed in Appendix I. Each patient performed only those tasks that were relevant to their impairments. In accordance with the principles of motor learning (Winstein, 1987), patients were given feedback of their performance and tasks were progressed to maintain interest and motivation. Sessions lasted for one hour and were conducted by an experienced physiotherapist (MMcD). All patients completed home exercises and documented the duration of exercise in a logbook.

6.3.3. Afferent stimulation

Patients in the stimulation group were given a period of peripheral nerve stimulation prior to each session of training. This peripheral stimulation protocol, referred to as "associative stimulation", induces an increase in cortical excitability in normal subjects (Ridding and Uy, 2003). Patients sat in a comfortable armchair with both arms supported and relaxed. Surface Ag-AgCl disposable electrodes (9 mm diameter) were placed over the motor point of the paretic first dorsal interosseus (FDI) and abductor pollicis brevis (APB) muscles with reference electrodes placed over the corresponding metacarpophalangeal joints. Stimuli were square-wave electrical pulses of 0.1 ms duration, delivered simultaneously to the FDI and APB muscles by a constant-current stimulator (Digitimer DS 7, Digitimer, UK). The timing between successive pairs of stimuli was randomised in the range 0.15 - 2.85 seconds. Stimulus intensity (range 10 - 30 mA) was set for each muscle at a level just sufficient to evoke a visible motor response. Patients were instructed to pay attention to the relaxed, stimulated hand and this was reinforced regularly during the session to maintain their

attention to the stimulus. This stimulation paradigm was applied for one hour and was painless. Associative stimulation increases the excitability of the corticospinal projection to stimulated hand muscles for at least one hour (Ridding and Uy, 2003). Therefore, it was likely that the excitability of the corticospinal projection to FDI and APB was increased during the following period of motor training in the stimulation group.

6.3.4. Sham stimulation

Prior to the upper limb training protocol, patients in the control group underwent the same experimental set up as the treatment group except that the stimulus current was switched off and patients were told: "You are about to receive weak electrical pulses to your finger and thumb that you may or may not feel". Patients were asked to focus on maintaining complete relaxation of their hand and this was reinforced regularly during the one-hour period of sham stimulation.

6.3.5. Evaluation

Functional measures were tested on four occasions. Patients attended two sessions, one week apart, for baseline measures prior to commencing the intervention (Pre). Post-intervention measures were taken immediately following the last training session and follow-up measures were recorded three months later.

Grip-lift task and manual dexterity

The ability of patients to initiate and scale grip force (GF) to load during a precision lifting task with the thumb and index finger was investigated with a purpose-built manipulandum. This grip-lift manipulandum was similar in concept to that originally described by Westling and Johansson (Westling and Johansson, 1984). The base held an exchangeable mass, allowing the weight of the manipulandum to be varied in 100 g increments from 240 g to

440 g. The GF, applied by the index finger and thumb onto polished brass surfaces 35 mm apart, and the load force (LF) were measured with lightweight load cells (MLP-10, Transducer Technologies, Temecula, CA).

Patients washed their hands thoroughly with soap and water and sat at a low table. They were instructed to lift the manipulandum to the height indicated (10 cm), hold it still for 3 s, and replace it on the table. They practised this until they were comfortable with the task. Testing consisted of three blocks of five lifts with the weight of the manipulandum changed pseudo-randomly between blocks (either 240, 340 or 440 g). The lifting task was performed by both hands, starting with the unaffected hand.

For each lifting trial, data acquisition started 1 s before GF reached 1.0 N and ended when the apparatus was replaced on the table. The GF and LF signals were low-pass filtered (100 Hz), sampled at 400 Hz, digitised, and stored on a computer for off-line analysis.

The following grip-lift parameters were analysed for each lift (see Figure 6.2): (1) *preload duration*: defined as the time between onset of GF and onset of positive LF as the manipulandum was lifted from the surface; (2) *minimum load*: maximal downwards force that occurred during the initial grasping of the manipulandum; (3) GF_{max}**:** maximal GF during the lift phase; (4) *maximal correlation*: the maximal correlation coefficient obtained when dGF/dt and dLF/dt are cross-correlated. That is, the correlation coefficient (r) for these two signals was obtained at each of a series of time points to which the plot of dGF/dt was shifted in increments of 2.5 ms relative to the plot of dLF/dt. The maximal value of the correlation coefficient thus calculated is an objective measure of the ability to scale GF to the changing LF during a lift (Duque et al., 2003).

The average of 15 lifts on each occasion was calculated for all parameters other than GF_{max} which was calculated separately for the three weights by averaging five lifts.

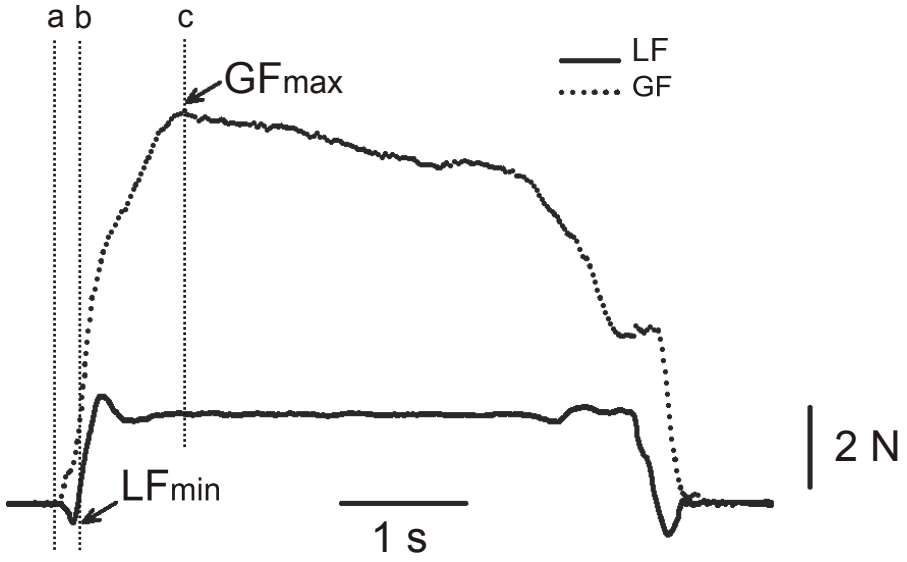

Figure 6.2 Typical grip-lift trace

GF (dotted line) and LF (solid line) are shown as the device is lifted from the surface. Vertical lines indicate (a) onset of GF, (b) onset of positive LF, (c) GF_{max}. Periods between (a) and (b) correspond to the preload phase and (a) and (c) the lift phase. The minimum load (LF_{min}) is shown.

Corticospinal excitability

We measured the amplitude and latency of motor evoked potentials (MEPs) evoked in the relaxed FDI and APB muscles by transcranial magnetic stimulation (TMS). Focal TMS was performed using a flat figure-of-eight shaped coil (external wing diameter 9 cm) connected to a Magstim 200 magnetic stimulator (Magstim, Whitland, Dyfed, UK). The coil was held over the scalp with the handle pointing posteriorly and oriented approximately 45° to the sagittal plane so that the induced current flowed perpendicular to the estimated alignment of the central sulcus. The optimal position for evoking responses in FDI and APB was established and marked on the scalp with a soft-tip pen to ensure reliable coil placement between trials. The location of this point relative to the vertex was measured and recorded for future sessions.

Resting motor threshold, defined as the minimum stimulator intensity needed to produce a MEP of at least 50 μV in the relaxed FDI muscle in at least 5 out of 10 successive trials was determined (Rossini et al., 1994). The stimulator intensity was then set to 90% of motor threshold, and increased in steps of 5 - 10% of stimulator output to obtain stimulus-response curves (Ridding and Rothwell, 1997). Eight stimuli were delivered at each intensity step and intensity was increased either until MEP amplitude reached a plateau or 100% stimulator output was reached. MEPs were recorded with all muscles relaxed, and trials in which background electromyographic (EMG) activity was present were excluded from analysis. Muscle relaxation was monitored by giving patients visual feedback of their EMG with a high-gain oscilloscope and auditory feedback.

The average peak-to-peak amplitude of MEPs at each stimulus intensity was plotted for each patient, and the Boltzmann sigmoidal function was used to fit the data points by the Levenberg-Marquand nonlinear least-mean-squares algorithm (Carroll et al., 2001; Devanne et al., 1997; Kaelin-Lang and Cohen, 2000; Khaslavskaia et al., 2002; Pitcher et al., 2003a). The parameters obtained from this function were: (1) the maximal value or plateau of the relation; (2) the stimulus intensity required to obtain a response of 50% of the maximum; (3) the slope parameter.

Functional measures

All performance-based functional measures were conducted by a single investigator who was blinded to group assignment (SLH). The ARAT was used to assess upper limb function (Lyle, 1981). It consists of 19 tests divided into the categories of grasp, grip, pinch and gross arm movement. Each item is scored on a 4-point ordinal scale, with a total possible score of 57. In addition, the 66-point upper limb component of the FMA was used to measure impairment. Both of these measures have been extensively used to evaluate response to intervention

following stroke (De Weerdt and Harrison, 1985; Page et al., 2004; van der Lee et al., 1999; Ward et al., 2003b).

The Motor Assessment Log (MAL) was used to assess the ability of patients to use their arm for daily activities (Page et al., 2004). This is a semi-structured interview, adapted from Taub et al. (1993), which determines the amount and quality of use of the affected arm when the patient performs 13 everyday items, scored on a 6-point scale. Other measures of upper limb function were maximal pinch-grip strength between the thumb and the index finger, recorded with a calibrated load cell, and maximal tapping speed, determined by asking the subject to tap with the index finger as quickly as possible on a load cell for 5 s. Each hand was tested three times, with a rest period of 30 s between each trial. The highest value of the three attempts was recorded on each occasion.

6.3.6. Data analysis

All baseline data from the two pre-intervention testing sessions were analysed with paired t-tests and correlated with the Spearman rank order test to show that data obtained on the two occasions were well correlated ($r > 0.80$) and the two samples were not different ($P > 0.05$). Data were then combined to provide an average of the two sessions and these averages were used as the pre-intervention values. Unpaired t-tests were used to investigate differences between the two groups at baseline.

Linear mixed effects model analysis of variance was fit to the data to compare results pre- and post-intervention and between post-intervention and follow-up. In the models, group status and time were treated as fixed effects, while subject was treated as a random effect. A Spearman rank order correlation was used to determine the correlation between the functional

measures, grip-lift parameters and corticospinal excitability. Paired t-tests were used to compare changes in subscores of the ARAT and FMA for each group separately.

Data are reported as mean ± 1 SD, and results were considered significant when $P \leq 0.05$.

6.4. Results

Patients in each group attended all sessions and were available for follow-up, and there were no adverse events. All patients participated in their home exercise program with no difference in the amount of time spent between the two groups (time spent on daily exercises control group 21.0 ± 6.1 mins, stimulation group 21.5 ± 8.2 mins; unpaired t-test, $P = 0.88$).

Grip-lift task

Three patients from each group were unable to lift and hold the manipulandum with the paretic limb (Patients 11, 18 and 19 in the control group and 3, 8 and 16 in the stimulation group). Therefore the data from the remaining seven patients in each group were used in this analysis.

There was a significant reduction in the time taken to establish grip prior to lifting the device from the table (the preload duration) for all subjects post-intervention. Analysis of variance revealed a significant TIME effect ($F_{1,12} = 23.0$, $P < 0.001$) but no overall effect of GROUP ($P > 0.05$). There was however, a significant GROUP*TIME interaction ($F_{1,12} = 4.75$, $P = 0.05$) due to greater improvement in the stimulation group (Figure 6.3).

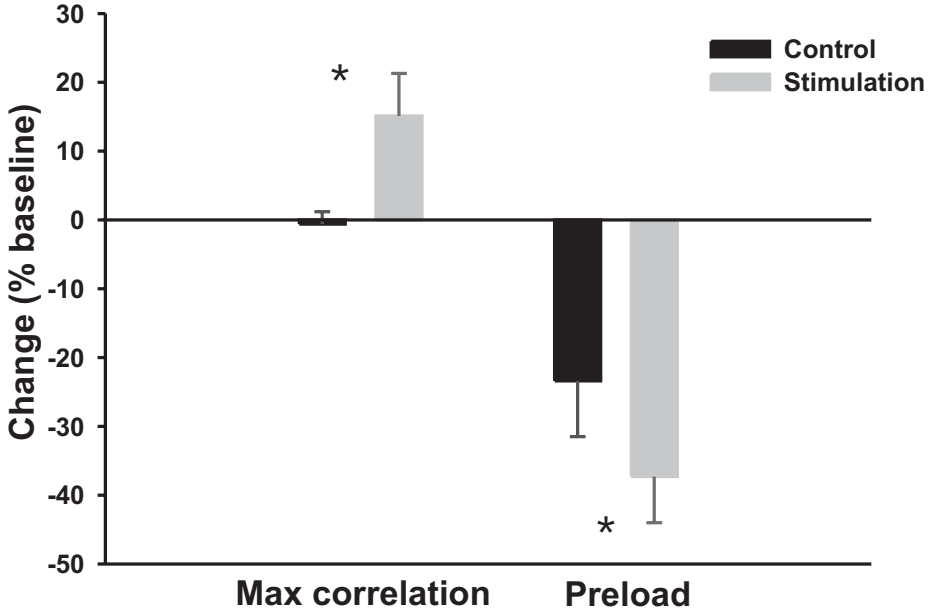

Figure 6.3 Changes in grip-lift characteristics shown as percentage of baseline values
*Control group data are shown in black and stimulation group in grey. The maximal correlation between rate of grip and load force rates during the lift phase is calculated by cross-correlating the rate of change of GF and LF during the lift phase, and is an objective measure of the ability to scale the GF to the changing LF during a lift (Duque et al. 2003). An increase in the maximal correlation coefficient indicates improved scaling of the rate of change of grip force to the load force rate during the lift. A decrease in preload duration occurs when patients reduce the time between establishing grip and commencing the lift. All subjects improved on these measures over time, but the superiority of the stimulation group was evident as a significant GROUP*TIME interaction for maximal correlation and preload duration (*$P \leq 0.05$).*

All patients used a maladaptive strategy of pushing the device down onto the table prior to lifting which resulted in an initial negative load. The magnitude of this minimum load decreased over time across all patients (TIME $F_{1,12} = 6.4$, $P = 0.03$) with no difference between the groups.

All patients were able to re-scale their GF when the weight of the device (LF) was altered, as reflected by a significant effect of WEIGHT ($F_{2,24} = 38.4$, $P < 0.001$). There was no main effect of TIME, GROUP or GROUP*TIME interaction, indicating that there was no difference between the groups or over time.

The maximal correlation value changed over time across both groups (time $F_{1,12} = 5.2$, $P = 0.04$). The stimulation group improved more than the control group following the intervention (GROUP*TIME interaction $F_{1,12} = 6.0$, $P = 0.03$; Figure 6.3).

Corticospinal excitability

The responses to TMS were highly variable between patients. It was possible to evoke MEPs from all patients in the stimulation group and all but one (Pt. 19) in the control group. MEP latency was not different at baseline between the two groups (GROUP, $P > 0.05$) and did not change over time (average latency across all sessions: Control group FDI 24.9 ± 1.5 ms, APB 24.9 ± 1.7 ms; Stimulation group FDI 24.3 ± 2.6 ms, APB 23.9 ± 2.6 ms; all $P > 0.05$). There were no differences in resting motor threshold between the groups for either muscle at baseline (GROUP, $P > 0.05$), or over time (Control group FDI pre 46.4 ± 10.6, post 49.1 ± 11.3%; APB 46.2 ± 10.8, post 45.5 ± 11.8%; Stimulation group FDI pre 46.7 ± 17.6, post 52.2 ± 10.6%, APB pre 52.0 ± 17.2, post 45.8 ± 20.4%; all $P > 0.05$).

The maximal MEP amplitude for FDI and APB did not change significantly over time in either patient group (TIME, FDI $P = 0.38$, APB $P = 0.30$) and there was no difference between the groups (GROUP, FDI $P = 0.84$, APB $P = 0.90$; Figure 6.4). Similarly, there was no change in the slope of the curve for either muscle over time (TIME, FDI $P = 0.84$, APB $P = 0.68$) and no difference between groups (GROUP, $P = 0.75$; APB $P = 0.70$; Figure 6.4). The midpoint of the sigmoidal curve, or the stimulus intensity required to obtain a response of 50% of the maximum, was also unchanged (Control group FDI pre 59.1 ± 13.6 → post 57.0 ± 10.5%; APB 49.4 ± 15.7 → 54.1 ± 10.9%; Stimulation group FDI 60.3 ± 18.1 → 63.7 ± 13.6%, APB 64.0 ± 16.8 → 61.8 ± 14.1%; all $P > 0.05$).

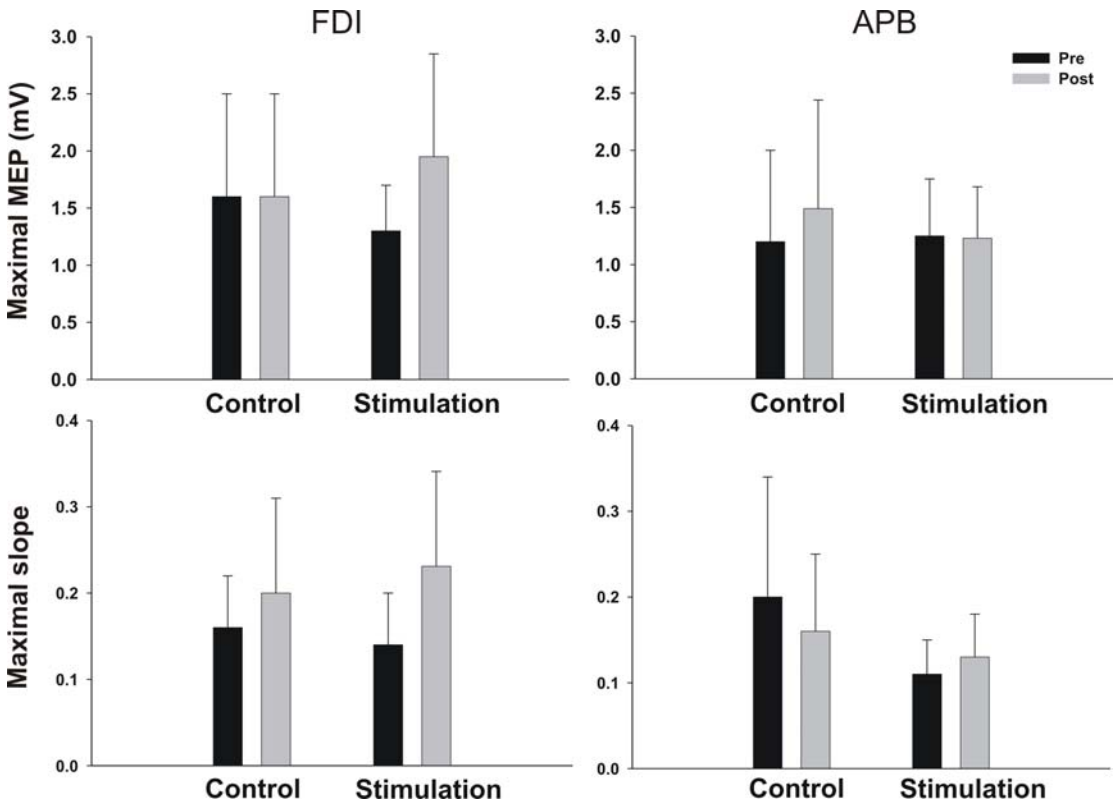

Figure 6.4 Changes in corticospinal excitability measures

Maximal MEP results (top row) and maximal slope (bottom row) are shown with FDI pictured on the left and APB on the right. Baseline data are shown in black and post-intervention data in grey. There are no significant differences between the groups or over time. Error bars indicate standard error.

Functional measures

Baseline performance was not significantly different between the intervention and control groups on either the ARAT (P = 0.79) or FMA (P = 0.91). All patients demonstrated improved function on either the ARAT or the FMA, resulting in a significant effect for the factor TIME (Table 6.2). The magnitude of improvement was greater for the stimulation group for both measures: the average improvement was 6 points for the stimulation group and 4 points for the control group for both the ARAT and the FMA. However, this difference between groups was not statistically significant. Improvements were evident for both groups of patients in the secondary outcome measures the MAL, grip strength and tapping speed (Table 6.2). Analysis of variance revealed a significant effect of TIME (all measures, P < 0.05) but there was no GROUP*TIME interaction to indicate that the groups behaved differently over time.

Table 6.2 Changes in functional performance over the three-week intervention period

	Control		**Stimulation**		**Effect of time**
	Pre	**Post**	**Pre**	**Post**	***P* value***
ARAT	39.7 ± 20.6	43.0 ± 19.1	37.6 ± 11.8	43.3 ± 14.1	< 0.001
FMA	47.9 ± 14.2	52.0 ± 16.9	47.3 ± 10.6	53.4 ± 9.4	< 0.001
MAL-amount	2.5 ± 1.7	3.9 ± 1.7	2.1 ± 1.1	3.6 ± 1.5	< 0.001
MAL- quality	2.7 ± 1.5	3.9 ± 1.6	2.3 ± 1.0	3.7 ± 1.3	< 0.001
Pinch strength (N)	40.4 ± 21.9	45.5 ± 24.0	30.2 ± 12.3	36.8 ± 16.3	0.009
Tapping speed (/5 s)	16.6 ± 10.0	18.8 ± 9.6	15.4 ± 4.9	18.4 ± 3.9	0.003

MAL amount = motor activity log amount of use score, MAL quality = quality of use score. **P* values indicate the effect of time in linear mixed effects model analysis of variance

Paired t-tests were used to investigate which components of the ARAT and FMA changed the most over time (Pre/Post). Both groups improved significantly for the ARAT sub-score grip but only the stimulation group improved in the FMA sub-scores for shoulder wrist and coordination; see Table 6.3.

Table 6.3 Change in subscores of the ARAT and FMA over time

		Effect of time*	
		Control group	Stimulation group
ARAT	Grasp	0.31	0.17
	Grip	**0.02**	**0.04**
	Pinch	0.23	0.07
	Gross arm	0.07	0.10
FMA	Shoulder	0.08	**0.001**
	Wrist	0.23	**0.02**
	Hand	**0.01**	0.14
	Coordination	0.39	**0.03**

* paired, two tailed t-test. Significant correlations are shown in bold.

Correlations

There were significant correlations between baseline functional scores and several grip-lift parameters. This was most evident with the preload duration, which had a significant negative correlation with the ARAT (r = -0.78, P = 0.001). There was also a positive correlation between the maximal correlation value and the ARAT (r = 0.56, P = 0.04). However, there was no correlation between the change in ARAT scores, grip-lift parameters or corticospinal excitability measures.

Follow-up measures

At three months follow-up, there was no difference in any of the measures of function, the grip-lift task or corticospinal excitability compared with post-intervention values (all P > 0.05), indicating that improvements made during the intervention were maintained to a similar extent for both groups.

6.5. Discussion

This is the first study to examine whether combining afferent stimulation targeted at hand muscles and task-specific training leads to a greater gain in dexterity and upper limb function in a group of patients with hemiparesis due to stroke than training alone. All patients showed improvement in scores of upper limb function with time. The stimulation group, but not the control group, improved significantly on two key features of the dextrous grip-lift task. However, this improvement was not accompanied by measurable changes in cortical excitability. The results of this study provide some support for the hypothesis that this combined approach may increase the effectiveness of standard rehabilitative techniques.

The grip-lift task is a sensitive measure of dexterity that can distinguish differences between the dominant and non-dominant hands of normal subjects (McDonnell et al., 2005), and

between affected and unaffected sides of stroke patients (McDonnell et al., 2006). While the grip-lift task may be a more sensitive indicator of dexterity than the ARAT, we have shown that a number of grip-lift parameters correlate well with the ARAT, in particular the maximal correlation coefficient and the preload duration (McDonnell et al., 2006). This was confirmed in the current study, indicating that patients who cannot coordinate their GF to conduct a smooth grip and lift of the object perform more poorly when attempting to grasp, grip and transport objects as required by the ARAT. Possible factors contributing to poor grip force control are the presence of a sensory impairment limiting the ability to feel contact between the fingers and the object, deficits in scaling motor output to the desired level, inappropriate central commands required to anticipate the load and therefore modulate the grip force as the object is lifted from the surface, or a combination of these factors. The greater improvement seen in patients receiving associative stimulation targeting muscles of the digits involved in the grip-lift task suggests that the combined intervention improved sensorimotor integration.

The fast-conducting corticomotoneuronal pathway is critical for independent skilled hand movements (Lemon and Griffiths, 2005) which are typically lost following stroke. Cerebral infarction involving the primary motor cortex and corticospinal tract reduces cortical excitability to TMS (Byrnes et al., 2001; Byrnes et al., 1999; Traversa et al., 1997). Changes in motor cortical excitability correlate with upper limb strength following stroke (Thickbroom et al., 2002), suggesting the pathway tested by TMS is involved in recovery following stroke. In the present study, repeated sessions of afferent stimulation were designed to increase the excitability of the corticospinal projection to paretic hand muscles. Despite a significant increase in upper limb functional ability across patients in both groups, there was no change in any of the TMS/MEP parameters over time. This differs from previous reports of increased MEP amplitudes and enlarged cortical maps over a period of 2 - 4 months after stroke (Traversa et al., 1997). It has been reported that the centre of gravity of TMS maps shifts

following two weeks of constraint-induced therapy (Liepert et al., 2000a; Liepert et al., 1998). In both these studies changes in MEPs and maps were associated with significant functional improvements, although not specifically with measures of dexterity.

The relationship between MEP amplitude and dexterity is complex. For example, MEP suppression induced by fatiguing exercise does not affect performance of a task requiring dextrous hand control in normal subjects (Lazarski et al., 2002). Secondly, Thickbroom et al. (2002) found no relationship between a measure of dexterity employing a subset of the McCarron test battery and MEP amplitude in a group of subcortical stroke patients. The present finding that changes in dexterity are not associated with significant changes in MEP measures is consistent with these reports. It is possible that changes in the excitability or organisation of the secondary motor areas that are not reflected by TMS are important for recovery of dexterity. For example, there is evidence the premotor and parietal cortices play a role in recovery following brain injury (Fridman et al., 2002; Johansen-Berg et al., 2002; Miyai et al., 1999). Inactivation of the premotor cortex in monkeys that had recovered some dexterity following a brain lesion reinstated the deficit, while inactivation of the primary motor cortex had no effect (Liu and Rouiller, 1999). In humans, movement of the paretic hand following recovery from middle cerebral artery infarction resulted in increased regional cerebral blood flow to the premotor and parietal cortices, not the primary sensory and motor cortices (Seitz et al., 1998), suggesting that reorganisation of regions other than the fast-conducting corticospinal pathway from the primary motor cortex may contribute to recovery of hand function following stroke.

Patients in both groups improved significantly following the interventions, and for some measures (e.g. the ARAT), patients in the stimulation group improved more than those in the control group. While these differences in performance between the groups were not

statistically significant, possibly due to the small number of patients, the overall improvement in the stimulation group exceeded the minimal clinically significant difference, reported to be 5.7 points, for the ARAT (van der Lee et al., 2001b). Therefore, the overall improvement made by the stimulation group on the ARAT would be considered a clinically significant change (6 points) while that of the control group would not (4 points). A larger sample size may reveal a significant effect in these relatively gross measures of upper limb function.

It is interesting to note that, despite the fact that the stimulus was targeted at intrinsic hand muscles, proximal limb function in the patients in the stimulated group improved more than the controls. The reasons for this are unclear, but one plausible explanation is that it is due to greater use of the arm as a result of improved hand motor function.

In summary, this study demonstrates that combining associative stimulation with task-specific training can increase aspects of dexterity more than training alone. There are several limitations of this study which may have influenced the outcome. The intervention physiotherapist was not blinded to group allocation, which may have influenced the training, and the sample size was small. It may have been preferable to use non-associative stimulation for the sham condition, but due to the limited number of stroke patients available it was not possible to perform pilot studies to ascertain that this stimulation paradigm does not affect cortical excitability in stroke patients. Despite these limitations, we believe that further exploration of approaches to rehabilitation of stroke patients that combine physical rehabilitation with techniques that encourage neuroplasticity with larger sample sizes is warranted.

7. General discussion

The studies described within this thesis have investigated the induction of plastic changes in both the intact and damaged nervous system, and considered whether increased corticospinal excitability is associated with improved fine motor performance of the hand. I chose to use associative stimulation to induce plasticity in both healthy subjects and stroke patients, and used the precision grip-lift task to record the forces involved in precision grip in order to discern whether there was a functional benefit. I have shown that inducing plasticity does give a functional benefit in the healthy and damaged nervous system, but the use of TMS to detect a change in excitability is not straightforward in stroke patients.

The following general discussion outlines how the specific findings of the studies described herein contribute to the understanding of this area.

7.1. Methods of analysing MEPs

The advent of TMS for the non-invasive investigation of the structure and function of the corticospinal pathway has greatly expanded our understanding of the human nervous system. TMS allows detailed investigation of the healthy and diseased or damaged nervous system, or the effects of manipulation of peripheral inputs or cortical processes such as attention. In all circumstances, the integrity of the corticospinal tract or intracortical circuits is inferred from measuring the MEP in target muscles. The amplitude and area of these muscle responses is characteristically variable between trials, necessitating the recording of a number of trials to obtain a valid population mean or average.

Review of the literature revealed that three alternate methods had previously been used to analyse MEPs, but that the reliability of each method had not been addressed. I began by investigating which was the most reliable method to use in both a small hand muscle and a

more proximal forearm muscle. I found that all three methods had low reproducibility, but recording the maximal MEP from a series of trials was in fact the most reliable method of analysing MEPs for a forearm muscle. This was not the case for hand muscles; instead, calculating the peak-to-peak amplitude for each trial and then calculating the mean amplitude was superior to recording the maximal MEP or the ensemble average (calculated online using commercially-available software). Although the mean and ensemble average values were comparable in terms of reliability, the ensemble average was always smaller than the mean due to the effect of small phase shifts in the peaks of individual MEPs, leading to minor phase cancellation. This preliminary investigation, described in Chapter 2, led me to measure the average peak-to-peak amplitude of individual MEPs to obtain the MEP amplitude for all further studies of small hand muscles.

7.2. Precision grip lift task in normal subjects and stroke patients

Recording the forces involved as an object is lifted with a precision grip has provided a vast amount of information about sensorimotor control of the hand and how anticipatory control systems operate in concert with sensory feedback systems. Both are important for dextrous manipulation. However, the sensorimotor experience gained by individuals through many years of handling objects is used to develop a central program before any voluntary movement begins. This is updated by sensory feedback in the event of unexpected consequences e.g. if the object is heavier or more slippery than expected. Studies of the precision grip-lift task in patient groups has also allowed greater understanding of the mechanisms involved in pathological conditions such as Parkinson's disease or dystonia.

Recent studies investigating patients with hemiplegia due to stroke or cerebral palsy have highlighted the inability of these patients, even with good recovery of hand function, to scale grip and load forces accurately in the initial stages of lifting the object. Grip forces tend to be

excessive, despite weakness of the precision grip; time taken to reach peak grip force during lift off is prolonged; and the precise coupling between grip and load forces is impaired (Duque et al., 2003; Hermsdorfer et al., 2003). These characteristics have been clearly demonstrated when comparing patients with healthy controls, but the performance of the hand ipsilateral to the lesion has not previously been investigated.

The grip-lift task is a sensitive measure of the ability to perform a fine motor task requiring considerable dexterity and I used it to detect change in the affected hand of individuals undergoing rehabilitative training. In order to achieve this goal, I first examined the performance of both hands of healthy subjects when lifting the device using three different grip strategies, for it has been shown that the type of grip used influences grip force in children with cerebral palsy (Gordon and Duff, 1999). These studies, described in Chapter 4, revealed that the grip strategy affects the amount of grip force used, the safety margin, and the close temporal coupling of grip force and load force rates as the object is lifted. These differences are most likely due to biomechanical differences between the three postures – the maximal amount of force generated by the key grip is greater than a lateral precision grip, with the downwards grip being the weakest of the three grips and ultimately being the least precise. Also, the relative familiarity of each grip is an important factor when considering that anticipatory control predicts the amount of grip force to be used prior to lifting the object.

I have shown, for the first time, that the non-dominant hand used excessive grip forces when lifting the object with all three grips, perhaps due to the unfamiliarity of performing a precision task with this hand. This is supported by the analysis comparing the maximal grip force from the first two to the last two lifts, which revealed a greater ability of the dominant hand to optimise grip force over a series of lifts. The finding, then, that there was no difference between the hands in temporal parameters of grip force control was somewhat

unexpected, especially considering the relative unfamiliarity of the non-dominant hand in manipulating objects with the key or downwards pinch grip. However, this observation is consistent with previous reports that tactile and weight-related information can be transferred between hands (Gordon et al., 1994; Johansson and Westling, 1988b). This study thus confirms that some sensorimotor control processes for aspects of the grip-lift task are more readily transferable between hemispheres than others.

When using the grip-lift task in the assessment of hand function in stroke patients it is thus important to standardise the type of grip used by a patient throughout the study. This was achieved in the experiments detailed in Chapter 5 and Chapter 6. Some stroke patients needed to use a key grip due to severe weakness preventing use of the lateral precision grip, and in this event the use of this grip was used throughout the study. When comparing the grip-lift characteristics of the affected and unaffected hands, I found only three parameters that were significantly different across the group: (1) minimum load or magnitude of load force downwards into the table prior to commencing lift off, (2) the preload duration or time necessary to stabilise grip prior to lift off, and (3) the maximal correlation coefficient obtained as the rate of change of grip and load force rates are cross-correlated, indicating the temporal coupling of grip and load force rates as the object begins to move. The latter two parameters correlated significantly with other measures of function: grip strength, tapping speed and with the stroke-specific functional outcome scales the ARAT and the FMA. This suggested that these measures might be sensitive to change over time in association with a change in function, although this had not been investigated previously.

The use of the grip-lift task as an objective measure of dexterity, as described in Chapter 6, is the first such study of its kind. The two parameters that were highly correlated with the ARAT, preload duration and maximal correlation coefficient, were selected as the important

outcome variables from the grip-lift task. Results confirmed the usefulness of the grip-lift task to detect change in the affected hand of stroke patients, as these two measures were indeed sensitive to changes in function as a result of a novel intervention strategy (see below). This supports the role of the grip-lift task as a quantitative and sensitive assessment of dextrous hand function which may be used to assess changes in hand function in other therapeutic trials.

7.3. Afferent stimulation to facilitate functional performance

A number of different paradigms have now confirmed that it is possible to increase the excitability of corticospinal projections to target muscles. While these changes have been associated with improved motor performance in simple ballistic tasks (Classen et al., 1998), it was uncertain whether this would improve any other aspects of hand function. The experiments described in Chapter 3 aimed to resolve whether a period of preconditioning afferent stimulation would indeed result in improved performance on a complex sensorimotor task. The Grooved Pegboard Test (GPT) was chosen for this task as it is dependent upon dextrous control and requires greater attention and concentration than simple ballistic tasks.

Associative stimulation increased corticospinal excitability to the two hand muscles stimulated. This did not result in increased performance time immediately following the stimulation, however subjects were able to decrease the time taken to perform the GPT to a greater extent than subjects who received no input or a control stimulation during the 1 hour period prior to performing the task. I contend that this heightened excitability arising from the stimulation may have facilitated the processes involved in learning this novel motor task, rather than simply enabling faster movement. Corticospinal excitability was also increased following the task for this group only, although the lack of direct correlation between

increased MEPs and increased performance suggests that this relationship is not a direct linear one.

A number of research groups have suggested that increasing corticomotor excitability may lead to functional improvements in stroke patients, alone or in combination with physical training (Ridding et al., 2000; McKay et al., 2002; Brown et al., 2003; Bütefisch et al., 2004; Hummel et al., 2005; Khedr et al., 2005). Preliminary studies performed within our research group (Uy et al., 2003) suggested that while stimulation alone has the potential to increase function in some patients, patients who were more motivated to improve may have practised the desired movements, or other movements more, ultimately leading to improved function. For this reason, the study described in Chapter 6 combined peripheral afferent stimulation with rehabilitative training in order to test the hypothesis that combining stimulation techniques that result in plastic changes with rehabilitative treatment could result in greater behavioural gains than stimulation alone.

The three-week intervention, consisting of task-specific physiotherapy and associative or sham stimulation, improved function in all patients involved in the study. Improvements were greater in the stimulation group but this difference did not reach a significant level for many of the measures (e.g. ARAT). This is likely to be the result of the small sample size and large variability within each group. Despite these limitations, there was a significant improvement in the ability of patients in the stimulation group to perform the precision grip-lift task using the digits that received the stimulation, the index finger and the thumb. The precise mechanism involved in this improvement is difficult to determine, with possible contributing factors being improvements in sensation, accurately controlling motor output, more precise anticipatory control or improved sensorimotor integration.

Stroke patients who received associative stimulation to hand muscles showed functional improvement in the absence of changes in hand muscle corticospinal excitability. There was no change in the slope of the stimulus response curve, the maximal MEP or the intensity required to achieve a half-maximal MEP in either group, although there were clear functional improvements in all subjects. One possible explanation for this is that changes in MEP characteristics which occurred following initial stimulation and training sessions were transient, so that no overall difference was observed at the end of the three-week intervention. This is consistent with the observation that MEPs increase when learning new motor skills, but cortical activity decreases after skills are learned and become automatic (Pascual-Leone et al., 1995).

Another important feature of the corticospinal excitability testing was the prevalence of extremely small TMS-evoked responses in a large proportion of patients, indicating severe disruption of the corticospinal pathway to the target muscles. In these individuals, cortical reorganisation is likely to have involved pathways other than the direct, fast conducting corticospinal pathway and thus would not result in changes to MEP amplitude. It has been shown that even in complete recovery of hand function, neurophysiological abnormalities still persist (Pennisi et al., 2002).

Despite these limitations, this pilot study has demonstrated that associative stimulation improved dexterity when performing the precision grip-lift task in a group of subacute stroke patients, in comparison to patients receiving only task-specific physiotherapy. This supports the call for further studies to combine techniques that may enhance cortical plasticity with functional rehabilitation.

7.4. Concluding remarks

As we strive to understand how the human adult nervous system can be modified as a result of learning or movement, we also hope that furthering our understanding of these basic processes can some day help those who have suffered damage to the nervous system. Stroke is the leading cause of disability in adults, with function restricted by limb paresis due to a large extent to disruption of the corticospinal pathway to the affected hand and leg. Now that changes within the intact motor cortex can be induced using specific interventions, there is hope that these discoveries may lead to new approaches to assist stroke patients.

This thesis takes a small step in that direction. Using the precision grip-lift task, I have shown that afferent stimulation can lead to improvements in dexterity that may allow patients to perform fine tasks such as writing and doing up button holes more accurately. This was achieved in patients who had been discharged from formal rehabilitation programs, and was above and beyond the improvements due to task-specific physiotherapy. As the effectiveness of other, perhaps shorter paradigms are investigated, the optimal method of enhancing brain plasticity may be uncovered that will significantly enhance the effectiveness of rehabilitation following stroke.

8. Appendices

8.1 Appendix I: Details of task-specific physiotherapy

A clinical algorithm was used to determine the appropriate tasks to complete as part of the task-specific physiotherapy. The assessments were used to determine whether patients had an impairment that required treatment, and this determined the type of intervention the patient participated in according to the algorithm. For example, if a patient had no deficit in sensation this was not addressed in therapy. Alternatively, if a patient had weakness of wrist extensors then this was addressed using the interventions explained below. For convenience, the therapist will always be referred to as 'she' and the patient as 'he'. Included below are the clinical algorithm and operational definitions of the assessment procedures, and the interventions applied.

Altered sensation

Proprioception	**Normal** ->	No intervention
	Decreased->	A. Locating body parts with eyes closed
		B. Passive drawing
		C. Guess distance between hands
		D. Identify the position of the hand
		E. Discriminate between thick and thin rods
	Absent->	Increased reliance on vision with above tasks and then without vision as subject has some success
Light touch	**Normal** ->	No intervention
	Decreased->	A. Identify touch/shapes drawn on arm
		B. Identify which part of the arm was touched
		C. Discrimination of texture
	Absent ->	Excluded from the study

PROM

Shoulder elevation	=90º ->	No intervention
	<90º ->	A. Active-assisted reach along table
		B. Passive mobilisation in supported sitting
		C. Prolonged stretch in sitting
Elbow extension	=-10º ->	No intervention
	>-10º ->	A. Mobilise elbow flexors
		B. Weight-bearing stretch in sitting
Wrist extension	=45º ->	No intervention
	<45º ->	A. Brief stretch with hand on wall or tabletop
		B. Passive mobilisation of the wrist complex
Supination	=120º ->	No intervention
	<120º ->	A. Mobilise radio-ulnar joints
		B. Brief manual stretch to pronators or prolonged stretch
		C. Mobilisation into supination
MCP Extension	=10º ->	No intervention
	<10º -=	A. Prolonged stretch of finger flexors
		B. MCP joint mobilisation
Thumb opposition		
To base of 5th finger		No intervention
Unable to reach 5th ->		A. Mobilise CMC of thumb finger passively

Weakness

Shoulder elevation	=4+/5 ->	No intervention
	4/5 ->	A. Active reach
	<4/5 ->	B. Reaching with arm supported on table
		C. Pushing towel/ball away
Elbow extension	=4+/5 at EOR->	No intervention
	=4/5 ->	A. Arm supported on table, slide glass back and forwards
		B. Weight bearing elbow extensions in sitting
Elbow flexion	=4+/5 ->	No intervention
	<4+/5 ->	A. Sliding glass on table, arm supported
		B. Bring hand to mouth
		C. Bring hand to other body parts
Supination	=4+/5 ->	No intervention
	<4+/5 ->	A. Pour seeds into affected hand
		B. Make imprints in putty with knuckles
		C. Supinate forearm with long ruler in hand, beat drum
Wrist extension	4+/5 at EOR ->	No intervention
	<4+/5 ->	A. Slide glass on table, forearm supported
		B. Wrist extension exercises with hand over the edge of the table
		C. Exercise with theraband, dumbbells
MCP extension	=4+/5 ->	No intervention
	4/5 ->	A. Resisted exercises with manual pressure or theraband
		B. Light and rapid finger tapping
	<4/5 ->	C. Active assisted finger extension in lengthened range

Impaired dexterity - Unilateral tasks

Grasp	Lift 10 cm woodblock -> from one shelf to another 5 times in less than 7 s	No intervention
	Lift 10cm woodblock from -> one shelf to another in more than 7 s	A. Lift cones B. Lift cup using a spider grip C. Drop tennis ball into affected hand D. Place objects in a box E. Pick up objects between thumb and ring and little fingers
	Unable to lift 10cm woodblock ->	F. Stack dominoes G. Use a stopwatch
Grip	Pour water from glass to glass -> 5 times in less than 8 s	No intervention
	Pour water from glass to glass-> in more than 8 s	A. Write with pencil B. Move pencils from one cup to another C. Turn a pencil clockwise
	Unable to pour water from glass -> to glass	D. Move ruler/cardboard cylinder around the clock E. Write with marker pen F. Pick up glass of water and drink

Pinch	Pick up 6 mm ball bearing -> between thumb and middle finger and lift up to shelf 5 times in 10 s	No intervention
	Pick up marble between -> middle finger and thumb and lift to shelf 5 times in >10 s	A. Turn over pages of a magazine, cards B. Use pegboard C. Make rapid dots with a pencil
	Unable to pick up marble -> between middle finger and thumb	D. Pick up small objects from inside a cup E. Tap fingers to table and fingers to thumb F. Repetitive pinching movements

Impaired dexterity - Bilateral tasks

Open and close jar, lid diameter -> 2 cm 5 times in 10 s	No intervention
Open a jar, lid diameter 6 cm ->	A. Manipulate putty into shapes B. Use knife and fork to cut putty C. Use telephone D. Turn pages of paper while holding it up E. Throwing and catching a ball F. Folding paper into an envelope
Unable to open a jar ->	A. Arm cycling B. Use a plunger C. Scoop coins off the table into unaffected hand D. Fold a towel E. Reach for objects with both hands F. Roll a rolling pin G. Push-ups against a wall H. Open can of tennis balls I. Turn pages of paper – on the table

Operational definitions - Sensation

Assessment (Fugl-Meyer et al., 1975)
Proprioception: Very small alterations in position of a joint are accomplished by the therapist and patient reports whether it was moved up or down. Performed for the shoulder, elbow, wrist and thumb.
Normal = all answers correct
Decreased = at least ¾ answers correct but considerable difference in sensation compared with joint on the unaffected side
Absent = poor awareness, less than ¾ answers correct

Light touch: touching the patient with a tissue, comparing the qualitative and quantitative impression of light touch on the arms and palmar surface of the hands
Normal = patient reports both sides equal
Decreased = altered sensation, either hypersensitive or slightly numb but patient can localise the sensation
Absent = no awareness of sensation

Interventions
Locating body parts with eyes closed: therapist takes patient's affected thumb and places it in an alternate position in space e.g. behind the ear, across the body, down by the leg. If the patient has difficulty the therapist can wiggle the thumb or tie a ribbon to it. Once the patient locates the thumb he can open his eyes (Yekutiel, 2002).

Passive drawing: therapist puts a pencil or marker pen in the patient's hand, then holds his hand and makes a drawing which the patient has to identify, without looking. The patient can be offered a selection of possible shapes or numbers that can be progressed from easy to hard to distinguish (Yekutiel, 2002). In order to make the patient more involved in the process he should be encouraged to identify shapes that he thinks would be easy/hard to distinguish and express ideas regarding special features of the shape. This can be repeated in front of the patient first and then to his left/right side.

Guess distance between the hands: therapist places the patient's hands to face each other and asks whether the gap is large enough to fit an object e.g. your head, football, shoulders etc. (Yekutiel, 2002).

Identify the position of the hand: therapist arranges the patient's hand in a certain position and asks the patient to either describe the position or imitate with his other hand. The hand can be open or closed, with fingers together or separated and involve functional positions such as opposition, pinch grip and lumbrical grip (Yekutiel, 2002).

Discriminate between thick and thin rods: therapist provides the patient with a series of rods of different thicknesses and asks him to determine which is the thinnest, thickest or order them in series. The rods can be placed between the thumb and index finger initially and progressed to the other fingers (Yekutiel, 2002).

Identify touch/shapes drawn on arm: therapist can start with simple tasks like drawing lines on the arm with a pen lid or pencil and ask the patient to identify whether the line is going up or down the arm; touching the arm and asking the patient to identify how many points were drawn on the arm and then how many lines; drawing letters and numbers on the arm and

getting the patient to identify them. This can be performed on the arm initially and then down the arm to the hand (Yekutiel, 2002).

Identify which part of the arm was touched: therapist can touch the arm with an object and identify which part of the arm was touched. The object used can be sharp initially if the patient has difficulty with recognising light touch and then progressed to tissues. Alternatively, a grooved object covered in Velcro can be moved across the surface. Also, the therapist can grasp the patients hand, especially the fingers, and move them if necessary to help with identification (Yekutiel, 2002).

Discrimination of texture: therapist provides the patient with a collection of objects/materials to perform this task. A selection is listed below:

Hairbrush
Coarse sandpaper
Fine sandpaper
Leather
Glass
Metal
Newspaper
Magazine
Pinecone
Sheepskin
Hessian sacking
Wool
Corduroy
Flannel
Velvet
Silk (Smits and Smits-Boone, 2000; Yekutiel, 2002)

The patient can first select two items that he thinks he can discriminate between and then try this with eyes closed. If the patient is unable to move his hand over the material he may be allowed to use his unaffected hand to rub the material over the affected hand but he should be encouraged to use a repetitive lateral shearing movement. As he progresses the therapist can choose the object and ask the patient to identify it (Yekutiel, 2002).

Operational definitions - Passive Range of Motion

Assessment (Reese and Bandy, 2002).
Shoulder elevation: patient sits in a chair with a supportive backrest. Passive flexion of the humerus is measured with a goniometer on the lateral aspect of the acromion with one arm following the line of the humerus toward the lateral epicondyle, and the other on the line of the thorax.

Elbow extension: patient sits in a chair with a towel supporting the arm just proximal to the elbow. Passive extension of the elbow joint in full supination is measured with a goniometer on the lateral humeral epicondyle, one arm along the line of the humerus toward the lateral aspect of the acromion process and the other along the line of the radius towards the radial styloid.

Wrist extension in palmar alignment: patient sits with forearm comfortably supinated and wrist and hand off the table. The goniometer is aligned with the midline of the arm toward the biceps tendon and the moving arm is aligned with the midline of the 3rd metacarpal.

Supination: patient is seated with the shoulder adducted, elbow flexed to 90 degrees and forearm in neutral rotation. Goniometer is placed over the palmar surface of the wrist, in line with the ulnar styloid. The stationary arm is aligned parallel to the anterior midline of the humerus and the moving arm is in line with the palmar surface of the wrist.

MCP extension: patient is seated with the arm supported on a table. The goniometer is placed over the dorsum of the MCP joint with the stationary arm in line with the dorsal midline of the metacarpal and the moving arm in line with the dorsal midline of the proximal phalanx.

Thumb opposition: patient is seated with the forearm comfortably supinated. The thumb is moved towards the palmar crease of the fifth digit. A ruler is placed on the palmar digital crease used to measure the distance between the flexor crease of the interphalangeal joint of the thumb and the palmar digital crease.

Interventions

Active-assisted reach along the table: sitting with the arm supported and the shoulder flexed to a comfortable position, the patient is encouraged to reach forwards towards an object, with assistance from the therapist (Carr and Shepherd, 2003).

Passive mobilisation in supported sitting: therapist supports the weight of the upper arm and has the other hand on the scapula to encourage protraction of the scapula as the humerus is flexed.

Prolonged stretch in sitting: patient sits with the arm supported on a table with the height of the table adjusted with towels if necessary to increase shoulder joint flexion. This position is maintained for 30 minutes.

Mobilise elbow flexors: therapist performs massage with a lumbrical grip to lift and lengthen the biceps and brachioradialis muscles to allow elbow extension.

Weight-bearing stretch in sitting: patient sits with the palm flat on the support surface and leans his body weight onto the affected arm. Therapist provides some pressure to the humerus to encourage elbow extension.

Brief stretch with hand on wall or table top: Patient either stands facing the wall with the palm touching the wall or with palm flat on table top and pressure is applied to the wrist flexors for approximately 20 s, then after a short relaxation period it is repeated 4-5 times (Carr and Shepherd, 2003).

Passive mobilisation of the wrist complex: therapist grasps the medial border of the patient's hand with her thumb against the dorsum of his metacarpals and her fingers in his palm. Her other hand is positioned proximal to the carpus, stabilising midway between supination and pronation. The method consists of extending the wrist from the mid position to the fully extended position (Grade III+) (Maitland, 1991).

Mobilise radio-ulnar joints: a) Superior radioulnar joint: therapist supports the adducted upper arm under the elbow and with the other hand grasps the supinated wrist from the medial side, with fingers spreading across the front of the wrist complex and the thumb at the back. The movement is performed from mid pronation to full supination (Grade III+) (Maitland, 1991).
b) Inferior radioulnar joint: therapist grasps the patient's hand between her two hands, with thumbs covering the dorsal surface of the wrist and fingers reaching across the palmar surface. The heel of each hand cups around the distal radius and ulna. The movement is produced by a twisting movement between the therapist's hands, into pronation and supination (Grade III+) (Maitland, 1991).

Brief manual stretch to pronators: patient sits with arm supported on a table with forearm pronated and elbow extended to lengthen pronator teres. Therapist applies pressure to the thenar eminence using her thumb (Carr and Shepherd, 2003). A prolonged stretch can be applied with sandbags for 20-30 mins.

Mobilisation into supination: therapist performs massage using a lumbrical grip to lengthen the pronator teres muscle.

Prolonged stretch of finger flexors: patient has an object placed in the hand to encourage MCP extension and stretching of the web space for 20-30 mins.

MCP joint mobilisation: therapist holds the proximal phalanx of the patient's finger between her proximally directed thumb and index finger, with her other hand stabilising the metacarpal with a similar grip. The joint is extended to a comfortable range (Grade III+) (Maitland, 1991). Both medial fingers and then lateral fingers and performed together.

Mobilise CMC of thumb: therapist stabilises the wrist with the index finger crossing in front of the trapezium and the thumb stabilising the back of the trapezium. The thumb is grasped in the other hand and the metacarpal joint is moved into flexion and opposition (Grade III+) (Maitland, 1991). The hypothenar eminence can also be mobilised to bring the little finger towards the thumb.

Operational definitions - Weakness

Assessment

Grades (Medical Research Council, 1990)
0 No contraction
1 Flicker or trace of contraction
2 Active movement, with gravity eliminated
3 Active movement against gravity

4 Active movement against gravity and moderate resistance
4-Movement against slight resistance
4+ Movement against strong resistance
5 Normal power

Shoulder elevation: patient stands with shoulder flexed to 90° and abducted to 45° (or as close to this position as possible). Therapist provides resistance against the arm just proximal to the elbow in the direction of extension and abduction.

Elbow extension: patient's elbow is supported on a table and therapist supports the forearm just proximal to the wrist. Patient extends the forearm against resistance.

Elbow flexion: therapist supports the standing patient's arm at the elbow and grips firmly at the wrist with forearm supinated. Patient flexes elbow against resistance.

Supination: patient stands with elbow extended and palm facing forwards. Therapist stabilises the arm at the distal humerus and grasps the patient's hand with her thumb on the dorsum of the hand and the fingers on the medial border. Patient supinates the forearm against resistance.

Wrist extension: patient's arm is supported on the table with fingers comfortably flexed. Therapist places her hand on the dorsum of the hand and the patient extends the wrist against resistance; therapist avoids any bias towards ulnar or radial deviation.

MCP extension: patient's arm is supported on the table. Therapist places two fingers of one hand over the metacarpals, supporting the palmar surface of the hand with her thumb. The other hand applies resistance over the proximal phalanges.

Interventions

Active reach: patient reaches to various objects in the room and points to different parts of a target (Carr and Shepherd, 2003). Reaching in a lateral direction is also encouraged, to facilitate external rotation. Theraband can be added in if patient has enough strength to hold the elastic in his hand.

Reaching with arm supported on table: patient's arm is supported on the table with elbow extended and patient is encouraged to reach for an object at arm's length e.g. pushing a sandbag off the table or passing a cup to the therapist (Carr and Shepherd, 2003). Assistance may be provided by placing the arm on a towel to decrease resistance through friction or light guidance from the therapist.

Pushing towel/ball away: patient's arm is supported on a table and therapist stabilises their hand on a ball or a towel and encourages the patient to push the object away through shoulder flexion.

Arm supported on table, slide glass back and forwards: patient's arm is supported on a table with a glass placed just lateral to his forearm. Patient is encouraged to move the glass towards targets marked on the table by extending the elbow (Carr and Shepherd, 2003).

Weight bearing elbow extensions in sitting: patient places hand on supporting surface and leans some body weight through the arm, allowing the elbow to bend slightly. He then returns to upright through the action of extending the elbow.

Sliding glass on table, arm supported: as previously described, but the targets are placed between the patient's arm and their trunk.

Bring hand to mouth: patient initially has elbow supported on the table and therapist can provide assistance if required to bring the hand to the patient's mouth. Can be progressed to bringing a cup to the mouth.

Bring hand to other body parts: patient is encouraged to bring the hand to the ear, forehead, opposite ear, behind the head etc.

Pour seeds into affected hand: patient holds cup with seeds in the unaffected hand and pours the seeds into the affected hand and back into the cup (Carr and Shepherd, 2003).

Make imprints in putty with knuckles: patient's arm is supported on a table and Theraputty is placed next to patient's pronated forearm, in line with the knuckles. Patient is encouraged to supinate the arm until the knuckles make an imprint in the putty, aiming for the knuckle of the index finger in particular (Carr and Shepherd, 2003).

Supinate forearm with long ruler in hand, beat drum: with patient's forearm supported on the table and a long ruler in hand, therapist encourages the patient to touch the end of the ruler to the table. Can be progressed to holding a tendon hammer or beating a drum placed on the table (Carr and Shepherd, 2003).

Slide glass on table, forearm supported: patient's arm supported on the table with a glass placed next to the dorsum of the hand. Therapist encourages the patient to slide the glass along the table towards targets by extending the wrist (Carr and Shepherd, 2003).

Wrist extension exercises with hand over the edge of the table: patient's forearm is supported on the table with wrist and hand over the end of the table (Carr and Shepherd, 2003). Initially patient can practise lifting the hand alone and then the therapist can add objects to the hand of increasing size e.g. small then larger piece of putty, Styrofoam cup.

Exercise with theraband, dumbbells: with patient's hand over the edge of the table therapist can place a piece of theraband over the dorsum of the hand and patient repeats the lifts of the hand with slight resistance. If the patient can grasp a weight, light dumbbells may be used (Johansen-Berg et al., 2002).

Resisted exercises with manual pressure or theraband: patient's fingers are placed over the end of the table with the forearm and MCP joints supported. Therapist places either a piece of theraband or her fingers over the patient's fingers and encourages him to extend.

Light and rapid finger tapping: with patient's arm supported on the table and forearm in pronation patient is encouraged to perform light and rapid finger tapping with all fingers (Carr and Shepherd, 2003). Wrist flexion is discouraged.

Active assisted finger extension in lengthened range: patient's arm is supported with fingers over the edge of the table and MCP joints supported. Assistance may be provided initially to extend the fingers, and the therapist may stimulate the belly of extensor digitorum to facilitate this.

Operational definitions - Impaired dexterity (Unilateral)

Assessments (Lyle, 1981)

Grasp:

patient able to lift a 10 cm^3 block of wood from the table to a shelf 37cm above it
patient able to lift a 7.5 cm diameter cricket ball from the table to a shelf 37 cm above it
patients attempts to lift a 2.5 cm^3 block, he is unable to lift the cricket ball

Grip:

patient able to pour water from one plastic tumbler (11 cm by 6 cm) to another
patient able to grip a metal tube with a diameter of 1 cm and move it across the table horizontally
patient attempts to grip a 2.25 cm tube; he is unable to grip and move the 1 cm tube

Pinch:

patient able to pick up a 6 mm ball bearing and lift it from the table to the shelf 37 cm above
patient able to pick up a marble with diameter 1.5 cm between middle finger and thumb and lift it to the shelf 37 cm above
patient attempts to pick up a marble with diameter 1.5 cm between index finger and thumb; he is unable to perform this task with the index and middle fingers

Interventions

Lift cones: cones are placed on top of each other and patient is required to lift cones off each other and place them on the table (Johansen-Berg et al., 2002).

Lift cup using spider grip: patient lifts cup or a lid from a large jar with a grip in which the hand spans the whole diameter, thumb extended to the maximum, fingers stretched wide (Carr and Shepherd, 2003).

Drop tennis ball into affected hand: patient releases the ball from the unaffected hand.

Pick up objects between thumb and ring and little fingers: patient attempts to lift objects of various sizes and weights (Carr and Shepherd, 2003); e.g. putty, golf ball, squash ball, tennis ball.

Place objects in a box: patient grasps items of large diameter into a box e.g. jar lids, tennis ball, cones.

Stack dominoes: patient attempts to move dominoes and stack them (Carr and Shepherd, 2003); therapist can assist by standing the domino on its end if necessary.

Use a stopwatch: therapist assists patient to grasp stopwatch and then patient is encouraged to stop and start the stopwatch in order to time events (Carr and Shepherd, 2003).

Write with pencil: patient is instructed to write personal details e.g. name, address.

Move pencils from one cup to another: patient may grab several pencils at once initially and progress to picking up one at a time. He may use the unaffected hand to separate the pencils if they bunch up (Smits and Smits-Boone, 2000).

Turn a pencil clockwise: patient is instructed to pick up pencil, put it down on the table, turn it anticlockwise to point in the opposite direction, then clockwise, according to target lines on the table top (Carr and Shepherd, 2003; Smits and Smits-Boone, 2000).

Move ruler/cardboard cylinder around the clock: starting with a cylinder e.g. paper towel roll, patient is to move the cylinder to instructed times on a clock face. Can progress to using a ruler.

Write with marker pen: patient instructed to write personal details e.g. name, address.

Pick up glass of water and drink: patient brings either glass or Styrofoam cup to the mouth to drink (Carr and Shepherd, 2003). Therapist can vary the amount of water in the cup to increase the difficulty.

Turn over pages of a magazine, cards: patient instructed to perform these tasks with the index finger and thumb of the affected hand, starting with playing cards and progressing to a magazine or newspaper (Carr and Shepherd, 2003).

Use pegboard: patient to make designs on the pegboard (Carr and Shepherd, 2003); e.g. a cross

Make rapid dots with a pencil: patient holds a pencil and makes rapid consecutive dots on a sheet of paper, at least 2 dots/second for 5 seconds.

Pick up small objects from inside a cup: patient encouraged to use thumb and index finger at times, and thumb and several fingers at others (Carr and Shepherd, 2003).

Tap fingers to table and fingers to thumb: patient taps individual fingers to the table, then touch each finger tip to thumb in sequence as rapidly as possible (Carr and Shepherd, 2003); patient is instructed to pinch together his thumb and index finger, with assistance from therapist if required. Patient progresses to performing rapid pinching movements independently (Muellbacher et al., 2002).

Operational definitions - Impaired dexterity (Bilateral)

Assessments

Open a jar, lid diameter 2 cm: patient able to lift jar, turn lid and replace both the jar and the lid on the surface; patient able to chose the hand with which to turn the lid.

Open a jar, lid diameter 6 cm: patient able to lift jar, turn lid and replace both the jar and the lid on the surface; patient able to chose the hand with which to turn the lid.

Unable to open a jar: patient attempts to open the 6 cm jar but fails.

Interventions

Manipulate putty into shapes: patient is instructed to roll the putty into a ball, a thin strip, make it into a cube etc.

Use knife and fork to cut putty: encourage patient to hold the cutlery between the ring finger, little finger and palm (Carr and Shepherd, 2003; Johansen-Berg et al., 2002).

Use telephone: patient holds the phone with the unaffected hand and practises punching in the numbers on a touch pad (Carr and Shepherd, 2003).

Turn pages of paper while holding it up: patient is to hold paper and turn pages at the same time (Carr and Shepherd, 2003).

Throwing and catching a ball: patient can start by rolling the ball between hands, then throw from one hand to the other (Carr and Shepherd, 2003), then either bounce or throw/catch with therapist.

Folding paper into an envelope: patient can start with a large envelope and progress to smaller ones (Johansen-Berg et al., 2002).

Arm cycling: patient performs cycling with an arm ergometer (Carr and Shepherd, 2003); affected hand can be strapped to the pedal initially if required (with supervision).

Use a plunger: patient alternates hands with which to stabilise the caffetiere and move the plunger (Carr and Shepherd, 2003). Therapist adds water to provide resistance.

Scoop coins off the table into the unaffected hand: patient can progress to performing this task with each hand (Carr and Shepherd, 2003).

Fold a towel: patient folds a towel with both hands (Carr and Shepherd, 2003).

Reach for objects with both hands: patient uses both hands to pick up and place large objects of different shapes and weights (Carr and Shepherd, 2003).

Roll a rolling pin: patient rolls a rolling pin back and forth over putty (Carr and Shepherd, 2003).

Push-ups against a wall: patient places hands on the wall and brings trunk towards the wall and then pushes away with both arms (Carr and Shepherd, 2003).

Open can of tennis balls: patient practises removing the lid from a can (Carr and Shepherd, 2003).

Turn pages of paper - on the table: patient is encouraged to hold the paper between both hands on the table and use one hand only to turn the page (Carr and Shepherd, 2003).

8.2 Appendix II: Publications arising from this thesis

McDonnell MN, Hillier SL, Ridding MC, Miles TS. Impairments in precision grip correlate with functional measures in adult hemiplegia. *Clin Neurophysiol* 2006 117:1474-1480.

McDonnell MN, Hillier SL, Miles TS, Thompson PD, Ridding MC. Combined afferent stimulation and task-specific training improves dexterity following stroke *in preparation*

McDonnell MN and Ridding MC. Afferent stimulation facilitates performance on a novel motor task. *Exp Brain Res* 2006 170: 109-115.

McDonnell MN, Ridding MC, Flavel SC, Miles TS. Effect of human grip strategy on force control in precision tasks. *Exp Brain Res* 2005 161: 368-373.

McDonnell MN, Ridding MC, Miles TS. Do alternate methods of analysing motor evoked potentials give comparable results? *J Neurosci Methods* 2004 136: 63-67.

8.3 Appendix III: Other related publications

McDonnell MN, Orekhov Y, Ziemann U. The role of $GABA_B$ receptors in intracortical inhibition in the human motor cortex. *Exp Brain Res, in press*

McDonnell MN and Ridding MC. Transient motor evoked potential suppression following a complex sensorimotor task. *Clin Neurophys* 2006 117:1266-1272.

McDonnell MN, Thompson PD and Ridding MC. The effect of cutaneous input on intracortical excitability in focal hand dystonia. *Mov Disorders,* s*ubmitted for publication*

8.4 Appendix IV: Presentations and abstracts arising from this thesis

McDonnell MN (2005) Facilitating recovery of upper limb function following stroke. Research Update lecture evening, Neurology Group of Australian Physiotherapy Association South Australian (APA SA) Branch, October 18 (invited seminar).

McDonnell MN, Hillier SL, Ridding MC, Miles TS (2005) Facilitating recovery of upper limb function following stroke. Proceedings of the Joint Conference of the National Neurology and Gerontology Groups of the APA, November 2005, p. 40.

McDonnell MN (2005) Facilitating recovery of upper limb function following stroke. AFaR CRCCS, Neuroscience Department, Ospedale Fatebenefratelli, Rome, Italy, July 12 (invited seminar).

McDonnell MN (2005) Facilitating recovery of upper limb function following stroke. Neurology Department, Universita Cattolica, Rome, Italy, July 11 (invited seminar).

McDonnell MN (2005) Facilitating recovery of upper limb function following stroke. Neurology Department, Goethe-University Frankfurt, Germany, June 15 (invited seminar).

McDonnell MN (2005) Facilitating recovery of upper limb function following stroke. Inaugural meeting of the South Australian Stroke Unit Network, March 15 (invited seminar).

McDonnell MN, Hillier SL, Ridding MC, Miles TS (2005) Impairments in precision grip correlate with functional measures in adult hemiplegia. Motor Control Satellite Symposium, February 3.

McDonnell MN, Ridding MC and Miles TS (2005). Effect of human grip strategy on force control in precision tasks. Proceedings of the 25th Annual Australian Neuroscience Society Meeting, p. 102.

Miles TS, **McDonnell MN** and Ridding MC (2004). Grip strategy affects force control in simple lifting tasks. Proceedings of the 22nd International Australasian Winter Conference on Brain Research, 5.1.

McDonnell MN (2004) Constraint-induced therapy: Implementing the evidence into practice. Lecture evening, Neurology group of APA SA Branch, October 27 (invited seminar).

McDonnell MN, Hillier SL, Ridding MC, Miles TS (2004) Induction of functionally beneficial reorganisation following stroke: a case study. Proceedings of the Eighth International Physiotherapy Congress, p. 156.

McDonnell MN (2003) Neuroplasticity following stroke. Lecture evening, Neurology Group of APA SA Branch, November 26 (invited seminar).

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