University of Alberta

Plasticity after Damage to Peripheral and Central Nervous System

by

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Abstract

Adaptive plasticity is one of the main functions of the nervous system, which allows animals to survive in the ever-changing external world. Three studies are presented in this thesis, all of which concern CNS plasticity following injury to PNS or the brain. The first study addressed plasticity following partial denervation of the triceps surae muscles of the cat hindlimb. The hypothesis tested was that the gain in the stretch reflex pathway of cat MG muscle during locomotion increases after the denervation of its synergists. The results of the study showed changes in the pathways underlying short- and medium-latency stretch reflexes, but they were proportional to the changes in the descending locomotor drive. This indicates that adaptive plasticity following PNS damage does not involve a change in gain independent of activation level. The second and third studies addressed methods of augmentation of adaptive plasticity following damage to the brain by developing and testing the efficacy of FES-assisted exercise therapy. The results of the second study showed that the therapy was successful in improving motor function of the hemiplegic upper extremity in people with severe chronic hemiplegia. The results of the third study showed that in subacute stroke patients, the enhancement in functional recovery of the treatment group of subjects compared to controls did not reach statistical significance. This indicates that there may be an upper limit to the effectiveness of rehabilitation to increase functional plasticity of severely affected stroke patients during the subacute stage of their recovery. The second goal of the third study was to measure changes in cortical excitability induced by the therapy and to assess how well the functional gains exhibited by the subjects correspond to changes in cortical excitability. The study found that the map volume, a variable widely used in

TMS studies, was unreliable in measuring changes in cortical excitability in subacute stroke patients with severe hemiplegia. The studies described in the thesis have deepened our understanding of damage induced changes in CNS by investigating the neural sites of adaptive plasticity and methods of its augmentation.

I would like to dedicate this thesis to my family –

to my husband Sergiy for his love and unwavering confidence in my abilities,

to my mother Zoya for inspiring me to excel,

to my farther Vadim for nurturing my interest in science

and

to the rest of my family for their support and encouragement.

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Abbreviations

ACA – anterior cerebral artery;
AChA – anterior choroidal artery;
ADL – activities of daily living;
ANOVA – analysis of variance;
AOU – amount of use;
CES-D – center for epidemiological studies depression scale;
CIMT – constraint induced movement therapy;
CNS – central nervous system;
CMCT – central motor conduction time;
EMG – electromyogram;
fMRI – functional magnetic resonance imaging;
SCI – spinal cord injury;
FES – functional electrical stimulation;
FF – finger flexors;
FIM – functional independence measure;
FMA – Fugl-Meyer assessment;
FMT – Fugl-Meyer test;
FP – final performance;
FU – follow-up;
GABA - gamma aminobutyric acid;
H-reflex – Hoffman reflex;
LGS – lateral gastrocnemius/soleus;
LTD – long-term depression;
LTP – long-term potentiation;
M1 – primary motor cortex;
mA – mean amplitude of objects movement;
MAL – motor activity log;
MCA – middle cerebral artery;
MEP – motor evoked potential;
MG – medial gastrocnemius;
mMt – mean time taken to move an object;
mRt – mean time to reach and grasp an object;
MT – motor threshold;
MV – map volume;
nA – normal mean amplitude of objects movement;
NDT – neurodevelopmental treatment;
nMt – normal mean time taken to move an object;
nRt – normal mean time to reach and grasp an object;
OS – performance scores for each object;
PET – positron emission tomography;
PL – plantaris;
PNF – proprioceptive neuromuscular facilitation;
PNS – peripheral nervous system;
QOM – the quality of movement;
RS – slopes of regression lines;
SD – standard deviation;
SOL – soleus;
TA – tibialis anterior;
TH – thenar muscle;
TMS – transcranial magnetic stimulation;
VL – vastus lateralis;
WE – wrist extensors;
WMFT – Wolf motor function test;

CHAPTER 1

General Introduction

The question of how animals are able to survive in the ever-changing conditions of the external world has interested scientists for centuries. A wealth of knowledge has been collected on this subject. It has been known for some time, for example, that adult vertebrates are able to adapt to changes in external conditions (du Lac *et al.*, 1995; Knudsen, 1999; Krakauer *et al.*, 1999). Moreover, the nervous system is able to adjust to the effects of damage to its peripheral or central components (Barbeau & Rossignol, 1987; Waters *et al.*, 1994; Carrier *et al.*, 1997; Pearson *et al.*, 1999; Edgerton *et al.*, 2001), as well as to the changes in mechanical properties of limbs (Optican *et al.*, 1985; Loeb, 1999). However, the investigation of the mechanism and the extent of such plasticity is in its infancy.

1.1 Damage to peripheral nervous system

1.1.1 Role of afferent input in the control of locomotion

It is well documented that although there are circuits in the spinal cord capable of generating the basic locomotor rhythm, they strongly rely on afferent feedback for the adaptation to varying external conditions (Rossignol, 1996). The importance of large fiber afferent input for locomotion can be revealed by examining movements of people suffering from sensory neuropathies. Such patients show severe disturbances in their gait and other movements following the loss of large fiber afferents. For example, a case

study of one person, who regained the ability to walk after an acute episode of purely sensory neuropathy, reports that this patient was only able to recover function by devoting considerable attention to every task and by using visual control for feedback (Lajoie *et al.*, 1996). Thus, large fiber afferents seem to play a crucial role in the execution of any purposeful movements.

The question of which role various afferents play in the control of locomotion has been studied by a number of researchers. As a result, we now know more about the specific functions that different groups of afferents play in the control of locomotion. For example, the load-sensitive afferents from the muscles acting around the ankle joint and the length-sensitive afferents from the muscles acting around the hip joint are involved in controlling the timing of the stance phase of locomotion in animals (Orlovskii & Shik, 1965; Grillner & Rossignol, 1978; Duysens & Pearson, 1980; Andersson & Grillner, 1983; Conway *et al.*, 1987; Pearson *et al.*, 1992; Kriellaars *et al.*, 1994; Hiebert *et al.*, 1996). Similar roles that the afferents play in the timing of phase changes during locomotion have been also demonstrated in human adults (Misiaszek *et al.*, 2000) and infants (Pang & Yang, 2000).

Another role of afferent input is to control the magnitude of the forces generated by the muscles during locomotion. The supporting evidence comes from a number of animal studies. Firstly, a marked decrease in the extensor electromyogram (EMG) amplitude has been observed after a sudden removal of the afferent input (Gorassini *et al.*, 1994; Hiebert *et al.*, 1995). Secondly, the stimulation of the group I afferents has been shown to induce an increase in the EMG amplitude of extensors (Conway *et al.*, 1987; Gossard *et al.*, 1994; Guertin *et al.*, 1995). These results hold true for both healthy

and spinal cord injured (SCI) human adults (Yang *et al.*, 1991; Harkema *et al.*, 1997; Stephens & Yang, 1999; Sinkjaer *et al.*, 2000). Studies by Pearson *et al.* have further narrowed down the roles of specific afferent groups in the control of locomotion, by suggesting that the load sensitive afferents are primarily responsible for the modulation of the EMG magnitude of extensor muscles (Hiebert & Pearson, 1999) and flexor muscles (Lam & Pearson, 2001).

The role of cutaneous and joint afferents in the control of locomotion is much less well understood. The firing patterns of some of the afferents seem to correlate with certain parameters of locomotion. Most of the skin receptors, situated around the paw in cats, fire mainly around the time of foot touchdown, while the other receptors fire throughout the stance phase (Loeb *et al.*, 1977; Loeb, 1981). Some joint afferents fire throughout the step cycle while others fire only at the extremes of joint movements (Loeb *et al.*, 1977). Removal of cutaneous inputs distal to the ankle joint has little effect on the treadmill locomotion of otherwise intact cats, but it seems to affect severely the performance of more demanding tasks such as walking on a horizontal ladder or walking on inclined surfaces (Bouyer & Rossignol, 2003a). This indicates that cutaneous input may be more important for the performance of more challenging tasks.

1.1.2 CNS plasticity following a nerve transection or deafferentation

The first experiments tackling plasticity of the nervous system concentrated on the effects of severing nerves or dorsal roots on animal movements. Some of the earliest work addressing the effects of dorsal root transections was carried out by Claude Bernard in the middle of the 19th century (Bernard, 1858). Later Mott and Sherrington studied central nervous system (CNS) plasticity after the dorsal root transections in monkeys

(Mott & Sherrington, 1895) followed by Goldberger's work on cats (Goldberger, 1977). Results from these studies have demonstrated that plasticity, leading to the recovery of functional movements after deafferentation, is dependent on afferent feedback. The recovery has been shown to be much greater in the presence of *some* afferent feedback, i.e. after an incomplete deafferentation (Mott & Sherrington, 1895; Goldberger, 1988a). Afferent input has also been shown to be of great importance for adaptive plasticity to occur following peripheral nerve damage (Whelan *et al.*, 1995; Pearson *et al.*, 1999). Some of the neural pathways that are involved in the recovery of spinal cord from dorsal rhizotomies have been revealed by Goldberger's experiments. He discovered that plasticity, occurring in the presence of some afferent input, is more dependent on the reorganization of spinal circuitry and less on descending inputs. At the same time, he has shown that when all afferent input is removed, neural plasticity occurs mainly in higher order structures (Goldberger, 1988b).

Research on animals employing the technique of partial denervation of hind limbs has revealed plasticity occurring at both spinal and supraspinal levels. A number of studies have provided evidence that neural plasticity after partial denervation occurs at the spinal level. Whelan *et al.* have shown that after the transection of the lateral gastrocnemius/soleus (LGS) nerve in cats, the efficacy of the group I afferents from the intact medial gastrocnemius (MG) nerve to prolong stance phase duration increases (Whelan *et al.*, 1995). Another study has reported progressive increases in the amplitude of the midstance EMG in spinalised cats, which were also partially denervated (Bouyer *et al.*, 2001). Other studies have shown involvement of the supraspinal centers in the plasticity following partial denervation. For example, Carrier *et al.* reported a severe

impairment in the ability of chronically denervated cats to learn to walk after the subsequent removal of descending inputs (Carrier *et al.*, 1997). Pearson *et al.* suggested that the centrally programmed initial component of the stance-phase MG EMG changes along a different time course than the late component, which is thought to be primarily controlled by the ongoing afferent input (Pearson *et al.*, 1999). The late component of MG EMG increased shortly after the surgery, which suggested spinal plasticity in the form of an immediate increase in the efficacy of the afferent feedback from the spared MG muscle. In contrast, there was a more gradual increase in the amplitude of the initial EMG component over days after the denervation, which was interpreted as a gradual change in supraspinal control (Pearson *et al.*, 1999). These studies demonstrate that although the spinal cord has some capability to adjust to partial denervations, in non-spinalised animals higher-level structures seem to contribute significantly to the adaptive plasticity.

The interesting question is what kind of afferent feedback is important for driving plasticity after damage to the peripheral nervous system (PNS). A recent study argues that large fiber afferents are not necessary for plasticity to occur. When large fiber afferents in cats were ablated by pyridoxine, the animals recovered coordinated locomotion within a few weeks (Allum *et al.*, 1998). However, when cats with the same kind of deafferentation subsequently underwent partial denervation of hind limb muscles, they were not able to recover from the locomotor deficits induced by the partial denervation (Pearson *et al.*, 2003). These data show that while adaptive plasticity can occur in the absence of large fiber afferents, it is not robust enough to compensate for the

loss of both the afferent feedback and the voluntary control of individual muscles occurring after the partial denervation.

The importance of cutaneous afferents in adaptive plasticity was recently studied by Bouyer *et al.* The authors showed that after the complete cutaneous deafferentation distal to the ankle in cats, the locomotion on a horizontal ladder is severely impaired, while treadmill walking is affected very little. Three to seven weeks later the ladder walking improved, but never recovered to the same level as before the deafferentation (Bouyer & Rossignol, 2003a). Another study showed that animals with complete cutaneous deafferentation distal to the ankle did not recover plantar foot placement or weight bearing of the hindquarters after spinalisation, while animals with partial cutaneous deafferentation recovered both (Bouyer & Rossignol, 2003b). These studies demonstrate the crucial importance of cutaneous afferents for adaptive plasticity in the absence of descending inputs. However, when descending inputs are intact, cutaneous feedback appears to be less important for plasticity.

1.1.3 Reorganization of the motor cortex following a nerve transection or deafferentation

One of the striking examples of neural plasticity following peripheral damage is the recovery of patients suffering from damage of the brachial plexus after a surgical intervention. These patients undergo a procedure to surgically join intercostal and musculocutaneous nerves, after which not only voluntary control of biceps brachii muscle is restored, but also the biceps is eventually controlled independently from breathing (Mano *et al.*, 1995). Such plasticity can occur at multiple sites in CNS, but due to limited

scope of this Introduction I will mainly concentrate on the evidence for plasticity in the motor cortex. The motor cortex is subdivided into several distinct regions based on anatomic, physiologic, or functional criteria. These regions include the primary motor cortex (M1), the premotor cortex, the supplementary motor area, and the cingulate motor area (Picard & Strick, 1996; Wise, 1996; Preuss *et al.*, 1997; Wu *et al.*, 2000).

More than 50 years ago Penfield was the first to reveal a somatotopic organization of M1 (Penfield & Boldrey, 1937; Penfield & Rasmussen, 1950). The size and organization of the cortical representations of body parts in M1, called motor maps, have been studied directly by stimulating cortical cells via microelectrodes or transcranially using functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and transcranial magnetic stimulation (TMS). These techniques have offered unique insights into the organization of the motor cortex. Nowadays, a large body of evidence suggests that the somatotopic organization of the motor cortex may not be as clear-cut as previously thought. Intracortical microstimulation studies in monkeys have shown that the motor maps of individual muscles overlap with each other (Donoghue *et al.*, 1992; Donoghue & Sanes, 1994). Studies using PET, fMRI and TMS have also demonstrated that the motor maps overlap in humans (Cohen *et al.*, 1991b; Grafton *et al.*, 1991; Rao *et al.*, 1995; Sanes *et al.*, 1995). Cortical projection neurons have been shown to have connections to multiple motoneuron pools in awake and behaving monkeys, providing electrophysiological evidence for overlapping motor maps (Fetz & Cheney, 1980; McKiernan *et al.*, 1998). Such complexity of the cortical motor maps may serve as a good medium for plasticity.

Numerous studies have shown that cortical plasticity following denervation of muscles occurs through the expansion of the motor maps of the intact muscles toward the representations of the denervated muscles. In humans, it has been shown that after limb amputation the motor maps of the proximal muscles in the stump increase compared to the maps of the corresponding muscles of the intact arm (Cohen *et al.*, 1991a). Another study has shown that temporary anesthesia of the arm below the elbow results in increased excitability of cortical projections to the adjacent non-anesthetized muscles (Brasil-Neto *et al.*, 1992). The changes in excitability were only recorded following TMS of the cortex, not electrical stimulation of the cortex or spinal cord (Brasil-Neto *et al.*, 1993). This indicates that reorganization occurred in the cortical circuitry associated with the corticospinal tract, not the tract itself or the spinal circuitry. Similar expansions of cortical representations have been shown in monkeys after forelimb deafferentation and in rats after peripheral nerve lesion or forelimb amputation (Donoghue & Sanes, 1988; Sanes *et al.*, 1990; Pons *et al.*, 1991).

1.2 Damage to the spinal cord

The incidence of SCI worldwide is 20 to 50 cases per million per year and approximately half of SCI people are under 30 years of age (da Paz *et al.*, 1992; Dincer *et al.*, 1992; Dixon *et al.*, 1993; Shingu *et al.*, 1995). Most SCIs nowadays are incomplete with some sensation and voluntary function left or recovered below the level of the lesion (Dixon *et al.*, 1993; Shingu *et al.*, 1995). Understanding the changes that the neuromuscular system undergoes after a SCI and developing better methods of promoting functional recovery are goals that will never lose their importance.

1.2.1 Changes in the spinal cord after injury

After a SCI the whole neuromuscular system experiences a number of pathological changes. Probably the most obvious results of the damage to the CNS are problems with muscle activation resulting in weakness (Rymer & Powers, 1987; Lenman *et al.*, 1989; Gerhart *et al.*, 1993; Haughton *et al.*, 1994; Little *et al.*, 1994; Levi *et al.*, 1996; Thomas *et al.*, 1997b; Drolet *et al.*, 1999) and loss of sensory function (Crozier *et al.*, 1991; Waters *et al.*, 1994). Abnormalities in EMG profiles during walking following a SCI have been especially closely studied. Although the EMG patterns are very different in each individual with SCI, due to the uniqueness of each injury, some common abnormalities have been documented. The common abnormalities include hyperactivity of tibialis anterior muscle during swing and a decrease and a prolongation of the activity of triceps surae muscles during the whole step cycle (Dietz *et al.*, 1981; Conrad *et al.*, 1983; Fung & Barbeau, 1989, 1994). Abnormal changes in the activity of the muscles acting on the knee and ankle joints have also been reported (Conrad *et al.*, 1985; Fung & Barbeau, 1989). All these changes in the musculoskeletal system result from both direct spinal cord damage and subsequent spinal plasticity.

Changes in non-neural tissue after SCI include an increase in stiffness of the tendons and connective tissue around some joints (Mirbagheri *et al.*, 2001); an increase in fatigability of motor units and a change in their biochemical properties (Cope *et al.*, 1986; Yang *et al.*, 1990); and, in some cases, an impaired functioning of the circulatory system during exercise and at rest (Hooker *et al.*, 1993; Raymond *et al.*, 1997; Bunten *et al.*, 1998; Schmid *et al.*, 1998; Yamamoto *et al.*, 1999).

1.2.2 Recovery pattern after SCI

After SCI humans and animals exhibit various levels of functional recovery as well as changes that impede recovery (Nathan & Smith, 1973; Eidelberg, 1981; Little *et al.*, 1988; Helgren & Goldberger, 1993; Ditunno *et al.*, 1995; Burns *et al.*, 1997; Galea & Darian-Smith, 1997). Volitional control of muscles can continue to increase and interlimb reflexes can start to appear as late as 21 months post-injury (Calancie *et al.*, 2000). This recovery is not continuous; rather it occurs in stages with, possibly, different mechanisms underlying improvements at each stage (Nathan & Smith, 1973; Little & Halar, 1985a). Immediately after the injury, spinal cord neurons hyperpolarize, becoming much less excitable (Barnes & Schadt, 1979). This effect is known as spinal shock and it may last in its complete form for up to 24 hours after the injury (Holdsworth, 1970). The recovery during this early period, although dependent on the severity of the lesion, consists mainly of improvements in the volitional control of muscles after about 24 hours and the appearance of Hoffman reflexes (H-reflexes) and delayed plantar reflexes occurring by 48 hours post-injury (Nathan & Smith, 1973; Cadilhac *et al.*, 1977; Nathan, 1994; Leis *et al.*, 1996).

Those with complete or severe incomplete injury demonstrate primarily late-phase changes, which start in the second week following SCI and may extend over months (Del Bigio & Johnson, 1989). During this time the volitional control of muscles continues to improve and amplitudes of reflexes change. These changes in voluntary movements and reflexes do not occur simultaneously, like in the early phase, indicating that the mechanisms underlying them may be different (Little *et al.*, 1999). Problems with hyperactive spinal reflexes and decreased modulation of the H-reflex and/or the short

latency stretch reflex during gait have been reported to occur in the late phase of recovery following SCI (Little & Halar, 1985b; Yang *et al.*, 1991; Calancie *et al.*, 1993; Fung & Barbeau, 1994; Lamontagne *et al.*, 1998). In patients with complete SCI, flexor and extensor spasms may develop during this phase (Riddoch, 1917; Kuhn & Macht, 1949).

The late-phase plasticity in CNS after SCI can be enhanced or limited by various factors. Activity in the remaining connections enhances plasticity, while competition between descending inputs and reflex pathways seems to limit motor recovery (Little *et al.*, 1989b; Maynard *et al.*, 1990). Studies of hyperreflexia provide evidence for the important role that neural activity plays in the occurrence and degree of spinal plasticity. Less hyperreflexia has been shown to develop in people, who had suffered both a SCI and an amputation of a distal limb (Nathan, 1980; Yu *et al.*, 1981). This indicates that removal of afferent input from the limb prevents maladaptive plasticity, which would lead to the development of hyperreflexia. The two mechanisms of plasticity, driven by afferent and descending inputs, have been shown to be in competition with each other. Studies on humans with SCI have shown that as hyperreflexia develops, it seems to limit or even erode voluntary motor recovery, indicating that synaptic growth in the reflex pathways limits or competes with synaptic growth in spared descending inputs (Little *et al.*, 1989a). At the same time, it has been demonstrated that people with better motor recovery seem to have less severe hyperreflexia, which indicates that synaptic growth in descending pathways limits sprouting in reflex pathways (Little *et al.*, 1989b; Maynard *et al.*, 1990).

1.2.3 Methods of augmenting spinal plasticity in order to increase functional improvement

Many types of intervention have been attempted to improve walking in incomplete SCI subjects. Pharmacological interventions rely on activation or inactivation of certain spinal locomotor networks via noradrenergic agonists, i.e. clonidine, serotonergic antagonists, i.e. cyproheptadine, or agonists of gamma aminobutyric acid (GABA), i.e. baclofen. Pharmacological treatments are usually oriented toward management of spasticity. Nonetheless, because severe spasticity impedes functional movements, the overall effect of the drugs often translates into improved locomotion in SCI subjects (Parke *et al.*, 1989; Fung *et al.*, 1990; Wainberg *et al.*, 1990).

Another method of augmenting spinal plasticity is based on research addressing the effects of training on treadmill stepping of spinalised cats (Barbeau & Rossignol, 1987; Muir & Steeves, 1997). Promising results of these studies led to the development of locomotor training therapy for incomplete SCI patients (Visintin & Barbeau, 1989; Dietz *et al.*, 1997; Muir & Steeves, 1997). The locomotor training of SCI patients comprises a daily regime of walking on a treadmill with partial weight support, which is progressively increased until full weight bearing is achieved (Visintin & Barbeau, 1989; Dietz *et al.*, 1997; Muir & Steeves, 1997). Exactly which mechanisms account for the enhancement of functional recovery after locomotor training is unknown. Recent work demonstrates that locomotor training in spinal cats may reduce the effectiveness of the glycinergic system, which is thought to tonically inhibit central pattern generator (CPG) neurons below the lesion (de Leon *et al.*, 1999).

1.2.4 Use of FES for restoration of walking

Functional electrical stimulation (FES) of leg muscles can be used as an active orthosis to assist with walking or as a therapeutic tool to enhance recovery of locomotion after SCI or stroke. A number of FES devices have been developed by researchers around the world. Devices such as Fepo (Vodovnik *et al.*, 1978), WalkAid (Wieler *et al.*, 1996), Reciprocating Gait Orthosis (Solomonow *et al.*, 1997a; Solomonow *et al.*, 1997b), Parastep (Graupe *et al.*, 1998; Graupe & Kohn, 1998) and the Odstock dropped foot stimulator (Taylor *et al.*, 1999) to name a few have been reported in the literature. The use of FES as an active orthosis in SCI subjects has been shown to increase the speed and decrease the metabolic cost of locomotion (Bajd *et al.*, 1989; Granat *et al.*, 1992; Stein *et al.*, 1993).

The therapeutic effects of FES were initially reported anecdotally (Vodovnik, 1981). For example, Granat mentioned in one of his publications that in some cases the walking speed stays higher after the stimulator is turned off (Granat *et al.*, 1993). Recently, more evidence has emerged suggesting that FES can induce long term improvements in locomotion when it is combined with locomotor training. The combined therapy has been reported to increase locomotion speed, improve kinematics of walking and decrease the physiological cost of walking in SCI subjects (Wieler *et al.*, 1999; Ladouceur & Barbeau, 2000). Such therapeutic effects of FES may be due to the plastic changes induced in the spinal cord (Knash *et al.*, 2003) or the motor cortex (Hamdy *et al.*, 1998; Ridding *et al.*, 2000; Khaslavskaia *et al.*, 2002).

1.2.5 Cellular mechanisms of spinal plasticity

Currently little is known about the cellular mechanisms of plasticity in the spinal cord. It is generally believed, that because recovery from SCI occurs in two separate stages, different cellular mechanisms underlie them (Little *et al.*, 1989b). The early phase recovery is generally considered to be mainly due to the diminution of spinal shock (Del Bigio & Johnson, 1989). Other mechanisms, such as the upregulation and dephosphorylation of neurotransmitter receptors in spinal cord neurons (Klein *et al.*, 1989; Shapiro, 1997; Grossman *et al.*, 2000) or the activation of plateau potentials in motoneurons (Kiehn & Eken, 1997; Schmidt & Jordan, 2000; Collins *et al.*, 2001), are also known to contribute to the early phase recovery.

The late phase recovery seems to be mainly driven by localized synapse growth as a number of studies have reported reorganization of the connections below the lesion site (Steward, 1989; Nacimiento *et al.*, 1995). Sprouting has been reported to occur in afferent fibers, their second-order interneurons and other interneurons following an SCI (Pullen & Sears, 1978; Bullitt *et al.*, 1988; Mendell, 1988; Trugman & James, 1992; de Groat, 1995; Wall, 1997). Anatomical data have demonstrated synaptic growth in the pathways which descend contralaterally to the injury site, indicating the potential importance of spared contralateral inputs for motor recovery (Nathan & Smith, 1973; Kato *et al.*, 1985; Little & Halar, 1985a; Aoki *et al.*, 1988; Ditunno *et al.*, 1997). Another type of synapse growth, such as the enlargement of the active zones of pre-existing terminals, has been reported to occur after SCI (Steward, 1989). Any or all of these types of synapse growth may contribute to spinal plasticity during the late phase of recovery. An additional site of plasticity may be located at the neuromuscular junction. Axonal

sprouting of motoneurons to reinnervate denervated motor units has been reported in SCI patients (Yang *et al.*, 1990; Gordon *et al.*, 1993; Thomas *et al.*, 1997a).

Since the long-distance axonal growth is markedly limited in the adult CNS by the inhibitory proteins on the surface of myelin (Tatagiba *et al.*, 1997), the synaptic growth appears to be primarily important for the strengthening of pre-existing pathways. The data supporting this hypothesis come from reflex studies, which have reported that hyperactive lumbosacral reflexes ipsilateral to the hemisected spinal cord appear on a time-scale consistent with local synaptic growth (Aoki *et al.*, 1976; Hultborn & Malmsten, 1983).

1.3 Damage to the brain

Although there are a number of causes for brain injury, in this thesis I will mainly concentrate on the damage to the brain following a stroke. According to the statistical data of the Heart and Stroke Foundation of Canada, there are between 40,000 to 50,000 strokes in Canada each year. Of all people who have had a stroke, on average 15% die, 10% recover completely and the rest have to live with various levels of impairment or disability (HSFC, 2002).

1.3.1 Pathophysiology of stroke

The abrupt development of a focal neurologic deficit is called a stroke when the deficit is due to a local disturbance of cerebral circulation. In most cases the disturbance results from an obstruction of an intracranial artery or a vein producing an ischemic infarction. Approximately 80% of strokes encountered in clinical practice are cerebral infarcts most of which occur in the distribution of the middle cerebral artery (MCA)

(Kase, 1987; Sharp *et al.*, 1998). The main trunk of the MCA gives off 10 to 15 deep penetrating branches, which supply the basal ganglia and the internal capsule. Distal to these branches, the MCA stem is divided into two main trunks: the upper and lower divisions. The upper division of the trunk supplies the lateral and inferior aspects of the frontal lobe, including the anterior parietal areas, while the lower division supplies the rest of the parietal lobe and the upper two-thirds of the temporal lobe. Infarction of the deep penetrating branches results in the interruption of the corticospinal tract, which leads to hemiplegia. If only the corticospinal tract is involved, hemiplegia affects the limbs and face to an equal extent and is frequently associated with difficulty in articulating words (dysarthria), but lacks features associated with cortical infarcts, like sensory and visual field deficits, aphasia or hemineglect. Infarcts in the branches supplying the basal ganglia result in contralateral hemichorea without detectable hemiparesis. Larger infarcts involving the longest penetrating branches involve both the basal ganglia and the internal capsule. These are characterized by hemiplegia with visual and sensory disturbances and sometimes aphasia. Occlusion of the upper division of the MCA is clinically manifested by severe contralateral hemiparesis with weakness predominating in the upper limb, sensory defects and conjugate ocular deviation. If the dominant hemisphere is affected, global or motor aphasia accompany the disabilities, while in case of non-dominant hemisphere involvement aphasia is replaced with hemi-inattention syndrome. Occlusion of the lower division of the MCA in the dominant hemisphere results in sensory (Wernicke's) aphasia and a visual field defect in the absence of contralateral hemiparesis (Caplan & Stein, 1986; Kase, 1987; Sharp *et al.*, 1998). Hemiplegia may also result from infarctions along the superficial distribution of

the anterior cerebral artery (ACA) or a full occlusion of the anterior choroidal artery (AChA). The ACA infarction results in contralateral hemiparesis predominating in the lower extremity and affecting distal musculature more severely than proximal, while the AChA infarction produces hemiparesis with involvement of the face and limbs to a similar extent mostly due to the involvement of the internal capsule and the medial peduncle (Caplan & Stein, 1986; Kase, 1987). Occlusion of the deep penetrating branches of the basilar artery results in small pontine infarcts, clinical outcomes of which are various combinations of motor hemiparesis with cerebellar ataxia (ataxic hemiparesis) (Caplan & Stein, 1986; Kase, 1987).

Significant recovery of function occurs within the first 6 months following a stroke. The extent of the recovery is thought to depend on the severity of the initial deficits (Duncan *et al.*, 2000). The earliest limiting factor for motor recovery is the onset of diaschisis. Diaschisis is a depression of blood flow and metabolism, which affects various areas of the brain and may involve parts of both the affected and unaffected hemispheres (Lenzi *et al.*, 1982; Feeney & Baron, 1986; Seitz *et al.*, 1999). PET studies have reported that the presence of depressed blood flow or metabolism within the thalamus or the motor cortex of either hemisphere correlates with the decreased motor outcome, supporting the notion of an inverse relationship between the amount of diaschisis and the amount of motor recovery (Baron *et al.*, 1986; Binkofski *et al.*, 1996; Pantano *et al.*, 1996). However, there is some evidence that diaschisis lasts well past the initial recovery period and that the long lasting effects of stroke include not only inhibition and hypometabolism (Infeld *et al.*, 1995) of surrounding tissues, but also

disinhibition and hyperexcitability (Andrews, 1991). This indicates that there may be other mechanisms underlying early recovery, not just the reduction of diaschisis.

The neurological damage produced by a stroke results in a number of changes in the rest of the body that influence motor recovery. Ischemic or hemorrhagic damage to certain areas of the brain may disrupt functioning of the circulatory system during exercise and at rest (Adams & Imms, 1983; Takeyasu *et al.*, 1989; Mori *et al.*, 1994), cause problems with muscle activation and result in the loss of sensory function (Belmont *et al.*, 1972; Dietz *et al.*, 1981; Conrad *et al.*, 1985; Dannenbaum & Dykes, 1988). Other consequences of stroke include abnormal muscle tone, abnormal posture, inappropriate muscle synergies, loss of interjoint coordination (Twitchell, 1951; Wade *et al.*, 1985; Nakayama *et al.*, 1994a, b; Cirstea & Levin, 2000) and increased stiffness of non-contractile components of the soft tissues around the joints (Thilmann *et al.*, 1991; Svantesson *et al.*, 2000; Lamontagne *et al.*, 2002).

It is worth mentioning, that some recovery of function after a stroke occurs due to the development of compensational strategies seen in both humans and animals (Cirstea & Levin, 2000; Whishaw, 2000). For example, about 20% of change in the Functional Independence Measure (FIM), an ordinal scale used for the assessment of disability, is attributed to the appearance of compensatory strategies rather than recovery of motor control (Shelton *et al.*, 2001).

1.3.2 Cortical and subcortical plasticity: role in functional recovery after a stroke

The first studies addressing changes in the neocortex following brain damage were undertaken by Leyton and Sherrington in the early 20th century. They observed recovery of hand function in chimpanzees one month after the ablation of the hand motor areas, but concluded that the undamaged cortex did not assume the function of the damaged hand area (Leyton & Sherrington, 1917). After that, a number of studies demonstrated the importance of the undamaged cortex in the recovery of function. To the best of my knowledge, the first study to report changes in cortical motor maps following brain lesions was by Glees and Cole in 1950 (Glees & Cole, 1950). In this study the ablated thumb motor representations have been shown to reappear in the adjacent intact cortical areas in monkeys. A more recent study showed that when monkeys were left to spontaneously recover from a partial lesion of the hand motor area, the area first decreased in size and then gradually increased over months of recovery (Nudo & Milliken, 1996). The damaged hand area rarely recovered to the pre-lesioned size and on average reached about 75% of the original size after 4 months of spontaneous recovery (Friel *et al.*, 2000). Similar shifts of the motor maps after lesions toward the surrounding unaffected cortex have also been documented in rats (Castro-Alamancos & Borrel, 1995). This study also showed that the ablation of the newly formed motor maps results in the reappearance of functional deficits.

In a number of studies TMS was used to measure the role of cortical excitability and cortical reorganization in functional recovery after a stroke. Generally, the absence of EMG responses to TMS of the affected hemisphere, i.e. motor evoked potentials (MEPs),

early after a stroke seem to indicate poor functional recovery (Heald *et al.*, 1993; Catano *et al.*, 1995; Misra & Kalita, 1995; Catano *et al.*, 1996; Pennisi *et al.*, 1999). However, the opposite is not automatically true, that is the presence of MEPs does not necessarily indicate good functional recovery (Turton *et al.*, 1996). Other parameters measured with TMS and used to assess the potential for functional recovery include the central motor conduction time (CMCT), the excitability threshold for evoking MEPs and the number of excitable locations over the scalp. A longer CMCT has been reported to correlate with a higher degree of impairment (Heald *et al.*, 1993; Misra & Kalita, 1995). Higher excitability threshold values have been reported to indicate poor functional outcome (Heald *et al.*, 1993; Catano *et al.*, 1996). Increased numbers of responsive locations to TMS of the affected hemisphere have been reported to correlate with functional recovery (Cicinelli *et al.*, 1997; Traversa *et al.*, 1997). Also, recent studies have reported medio-lateral shifts in the centers of the cortical maps occurring together with spontaneous functional recovery (Byrnes *et al.*, 2001) or as a result of treatment (Liepert *et al.*, 1998; Liepert *et al.*, 2000). There is some controversy, however, about the prognostic value of the various parameters of TMS. One study argues that the CMCT is less useful in predicting the amount of functional recovery than the amplitudes of MEPs (Rapisarda *et al.*, 1996). Another study reports that neither CMCT, nor MEP amplitudes, nor the threshold values are useful in predicting functional recovery (Catano *et al.*, 1995).

Recent animal studies have addressed the role of cortical areas besides M1 in the functional recovery following a stroke. Injections of muscimol, the GABA agonist, into the premotor cortex resulted in the reappearance of functional deficits originally induced by damage to M1, indicating that the premotor cortex took over the functions originally

performed by M1 (Liu & Rouiller, 1999). In another study, reorganization of the supplementary motor area was shown to correlate with functional recovery (Aizawa *et al.*, 1991). Furthermore, human studies using PET have demonstrated that a number of neural sites can exhibit plasticity after a stroke. For example, increased bilateral activation of the cerebellum, the primary sensorimotor, inferior parietal and premotor cortices has been shown to accompany movements of the impaired hands of stroke patients compared to movements of the unimpaired hands (Chollet *et al.*, 1991). Comparison of the brain activation of stroke patients with controls showed that the movements of both impaired and unimpaired hands of stroke patients coincided with increased cortical activity, especially in the premotor cortex and the basal ganglia of the unaffected hemisphere (Weiller *et al.*, 1992).

In addition to revealing the sites of cortical reorganization outside the M1, these and other studies indicate a possible involvement of the ipsilateral pathways from the unaffected hemisphere in the recovery of function after a stroke (Chollet *et al.*, 1991; Weiller *et al.*, 1992; Honda *et al.*, 1997; Seitz *et al.*, 1998). How important the unaffected hemisphere is for functional recovery is, however, a matter of some debate. Several studies have suggested that the ipsilateral pathways may contribute to maladaptive plasticity. For example, stroke patients with mirror movements have been reported to also show the activation of the sensorimotor cortex of the unaffected hemisphere (Weiller *et al.*, 1993; Cao *et al.*, 1994). In contrast, a more recent study using fMRI reported a positive correlation between changes in activation of the ipsilateral sensorimotor cortex and the changes in functional recovery (Cramer *et al.*, 1997). A rather convincing piece of case-based evidence was presented by Fisher in 1992. He reported that when a second

stroke developed in the unaffected hemisphere in two stroke patients, it produced re-paralysis of the hemiplegic arm, indicating that ipsilateral connections were crucial for recovery after the first stroke (Fisher, 1992). Evidence from the TMS studies for the importance of ipsilateral pathways is not clear. Some studies have shown that ipsilateral MEPs appear more often and at a lower threshold in the recovered hemiplegic hands of stroke subjects, signifying the importance of the ipsilateral connections in the recovery of motor control (Caramia *et al.*, 1996; Turton *et al.*, 1996). In contrast, other studies have shown that ipsilateral MEPs seem to be more prevalent in the subjects with poor functional recovery (Turton *et al.*, 1996).

There is some evidence for plasticity occurring at subcortical sites following lesions of sensorimotor cortex in neonatal animals (Nah *et al.*, 1980; Rouiller *et al.*, 1991). These studies have reported changes in corticorubral, corticopontine and corticospinal projections. However, the existence of subcortical plasticity after a cortical lesion in adult animals or humans needs further study.

1.3.3 Cellular mechanisms of cortical plasticity

Changes in the motor maps can occur in very brief periods of time. Training to perform synchronized thumb and foot movements has been reported to result in a shift of the thumb motor map toward the map of the foot muscles and back within an hour (Liepert *et al.*, 1999). Another study showed that training to perform thumb movements in a direction opposite to that evoked by TMS produces a progressive shift in the TMS-evoked thumb responses toward the trained direction in less than half an hour (Classen *et al.*, 1998). Both of the described changes in the motor maps occurred and disappeared within a very short time, too short for any sprouting to occur. One of the mechanisms

which could account for such rapid cortical plasticity, would be a change in the borders of the motor maps resulting from a modulation in the strength of the connections between them by long-term potentiation (LTP) or long-term depression (LTD). Such horizontal connections between motor maps have been known to exist within cortical layers II and III (Huntley & Jones, 1991; Keller, 1993b, a; Weiss & Keller, 1994; Huntley, 1997). Supporting evidence for this mechanism comes from recent studies of the rat motor cortex, reporting that LTP and LTD can be induced in the horizontal connections within the layers II and III (Hess & Donoghue, 1994; Hess *et al.*, 1996; Hess & Donoghue, 1996, 1999). Other studies have shown that when the sensorimotor cortex is repeatedly stimulated with implanted electrodes, LTP and LTD can be induced in awake and behaving rats (Trepel & Racine, 1998; Froc *et al.*, 2000).

The mechanism underlying long-term changes in cortical organization appears to be synaptogenesis. A study by Kleim *et al* showed that the motor cortical neurons of rats trained in skilled reaching tasks have more synapses per cell than neurons in the motor cortex of untrained animals (Kleim *et al.*, 2002). Another study showed that induction of LTP in cortical layer III is associated with alterations in dendrite morphology and with increased spine density, similar to those found in rats exposed to complex environments (Ivanco *et al.*, 2000). Yet another study showed that the size of the dendritic trees of pyramidal cells in the motor cortex of rats correlates with the use of the contralateral limb (Jones & Schallert, 1994). Increased use of the limb coincided with increased dendritic arborization of pyramidal neurons, while decreased use of the limb coincided with the pruning of dendritic trees. In contrast, other studies have not shown use-dependant arborization in intact hemisphere of rats and monkeys recovering from cortical damage

inflicted using different methods (Recanzone *et al.*, 1992; Forgie *et al.*, 1996). This indicates that the presence of synaptogenesis may depend on the type of cortical damage.

The learning-dependent synaptogenesis appears to be specific to the cortical area involved in reorganization. A recent study has demonstrated that rats trained to perform skilled reaching tasks, showed increases in the size of the caudal, but not rostral, forelimb motor map (Kleim *et al.*, 1998). An increased number of synapses per neuron within layer V in only the caudal forelimb area was later found in these same animals (Kleim *et al.*, 2002).

1.3.4 Methods of augmenting recovery after stroke

Plastic reorganization of the motor maps in M1 can be induced by changes in behavior or training (Nudo *et al.*, 1992; Kleim *et al.*, 1998). Some of the early evidence for this idea came from studies on the interhemispheric differences between hand motor maps in monkeys. Concurrent with the more extensive use of the dominant hand, the hand maps in the dominant hemispheres have been shown to be larger than the corresponding representations in the nondominant hemispheres (Nudo *et al.*, 1992). Numerous other studies have shown that the sizes of the motor maps correlate with the amount of use of the muscles represented by these maps. Classical studies by Elbert in humans and Nudo in monkeys showed that the motor training of muscles increases the size of their representations in the motor cortex (Elbert *et al.*, 1995; Nudo *et al.*, 1996a).

A number of studies have explored the effect of various interventions aimed at promoting use-dependent cortical plasticity and aiding in recovery from cortical damage in animals. Some interventions consisted of restraining the use of the unaffected arm in order to promote greater use of the affected arm (Friel *et al.*, 2000), while other

approaches combined restraint of the unaffected arm with repetitive training of the affected arm (Nudo *et al.*, 1996b). These studies have shown that both the combination of restraint with training and the restraint on its own result in increased cortical representations of the affected hands beyond those occurring spontaneously. They also showed that training, not restraint, was crucial for the maintenance of these changes beyond the duration of the intervention (Friel *et al.*, 2000). Other studies, addressing the issue of what kind of intervention promotes cortical reorganization, have shown that repetition of unskilled movements does not induce cortical reorganization, while activities that include learning of a new task do (Kleim *et al.*, 1998; Plautz *et al.*, 2000).

Human studies have also shown that training can induce cortical reorganization. Finger representations in the somatosensory cortex of the trained hand of string musicians and blind Braille readers have been reported to be larger than those of the untrained hand (Pascual-Leone *et al.*, 1993; Elbert *et al.*, 1995). The same size difference between the M1 representations of the trained and untrained hands has been reported for skilled badminton players (Pearce *et al.*, 2000).

Another crucial issue for achieving the maximum recovery of function is the timing of intervention following damage to CNS. Some animal studies have indicated that there is a period after a brain injury, when early rehabilitative intervention may exacerbate damage to the nervous tissue and worsen the outcome. A study on rats has shown that the overuse of the impaired extremity immediately after brain damage enlarges the lesion and worsens the motor impairment (Kozlowski *et al.*, 1996). When forced overuse of the impaired extremity had been delayed by 7 days, the effect on the lesion size disappeared, but the worsening of the motor impairment remained (Humm *et*

al., 1998). These studies suggest that there may be vulnerable periods after brain damage, when maladaptive effects of training interventions prevail.

1.3.5 Treatment of hemiplegia in clinical practice

A large portion of the treatment of stroke patients in clinical practice, following the initial stabilization of their condition, is dedicated to dealing with hemiplegia. Hemiplegia is defined as the paralysis of one side of the body and often occurs in various levels of severity following a unilateral stroke. One of the most widespread therapies for the treatment of hemiplegia in use today is the Bobath approach or "Neurodevelopmental treatment" (NDT). NDT is based on a theory developed in Britain by K. Bobath and B. Bobath, neurologist and physiotherapist respectively (Bobath, 1977). The main principle of the approach is to retrain normal, functional patterns of movement by first eliminating the abnormal muscle activity and tone on the affected side and then "reeducating" muscles to produce normal patterns appropriate for various activities (Levit, 1995). The goals of NDT are 1) to avoid activities that increase muscle tone, 2) to promote development of the normal patterns of posture and movement, 3) to incorporate the hemiplegic side into all activities in order to reestablish symmetry, 4) to produce a change in the quality of movement of the affected side.

Another approach used by clinicians to treat hemiplegia is the movement therapy of Brunnstrom. The approach was developed by trial and error, applying procedures that S. Brunnstrom derived from her experience as a physiotherapist and from the motor control literature of the day (Trombly, 1995). The principles of the therapy are 1) treatment progresses sequentially from reflex to voluntary to functional, 2) when the patient is flaccid, movement is facilitated using reflexes, associated reactions,

proprioceptive facilitation and exteroceptive facilitation to develop muscle tension in preparation for voluntary movement, 3) the voluntary effort is encouraged and assistance with movements is gradually decreased, 4) the repetition of "correct" movements is encouraged (Brunnstrom, 1970).

Another therapy, "Proprioceptive Neuromuscular Facilitation" (PNF), was developed for treatment of hemiplegia by a number of people from both neurophysiologic and physiotherapeutic backgrounds. The approach is based on the assumption that the stimulation of proprioceptors promotes recovery of voluntary movements (Voss *et al.*, 1985). The principles of the therapy are 1) everyone has a potential for recovery, 2) normal motor development proceeds in a cervico-caudal and proximo-distal direction, 3) voluntary movement consists of spinal and supraspinal reflex components, 4) appropriate movement patterns develop from correct interaction between agonists and antagonists, 5) appropriate motor behavior develops according to specific sequences of movement patterns, 6) functional improvement depends on motor learning, which is largely based on proprioceptive feedback, 7) goal-directed activities assisted by appropriate facilitation techniques are used to achieve learning of functional tasks (Voss, 1967).

To the best of my knowledge NDT, PHF and the Brunnstrom therapy were all developed 30-40 years ago and have not been modified since. The books written by the founders of each approach are simply periodically re-released and successive generations of therapists are taught to believe that the therapies work without thorough research to back up the claims. I have found only one paper that compares the effects of different approaches. The study compares NDT and the Brunnstrom therapy and reports no difference between the two (Wagenaar *et al.*, 1990).

The latest therapy for the treatment of hemiplegia is Constraint Induced Movement Therapy (CIMT), which was developed by E. Taub based on his research using deafferented monkeys (Taub, 1980). The goal of the therapy is to reverse learned non-use of the affected arm, which develops during the initial period of recovery following damage to the brain (Taub, 1994). The therapy includes restraint of the unimpaired hand and arm for 90% of waking hours and a 6-hour per day exercise regime. The exercise sessions consist of the repetition of tasks performed with the impaired arm under the supervision of a therapist. The tasks are chosen specifically for each patient and their difficulty is gradually incremented (Taub *et al.*, 1998). Only those stroke patients who have some voluntary control of their wrist and finger joints, can participate in CIMT (Taub *et al.*, 1998). Unlike the other therapies, the efficacy of CIMT has been and continues to be scientifically studied. CIMT has been shown to produce large gains in hand function of chronic and subacute stroke patients (Wolf *et al.*, 1989; Taub *et al.*, 1999). The attempt to apply CIMT to lower-functioning stroke patients has had limited success (Taub *et al.*, 1999).

1.3.6 Use of FES for restoration of reaching and grasping

The upper-extremity application of FES is aimed at restoration of reaching and grasp in SCI and stroke patients (Cozean *et al.*, 1988; Keith *et al.*, 1988; Kralj & Bajd, 1989; Kraft *et al.*, 1992). A variety of devices, such as the neuromuscular assist (Waters *et al.*, 1985), Handmaster (Hendricks *et al.*, 2001), Mesh-glove (Dimitrijevic & Soroker, 1994), the Belgrade Grasping System (Popovic *et al.*, 2001) and the Bionic Glove (Prochazka *et al.*, 1997), use surface electrodes to deliver electrical current to the hand and arm muscles. Other systems include implantable electrodes, such as the Freehand

system (Smith *et al.*, 1987) and the Cleveland multichannel percutaneous FES system (Marsolais & Kobetic, 1987). The newest development among FES systems are fully implantable stimulators called Bions, which can be injected into the muscles and controlled wirelessly by an external circuit (Cameron *et al.*, 1997).

Various functional gains occur after repeated use of FES. A number of studies have demonstrated improvements in voluntary range of motion and muscle strength following various FES treatment regimens for upper and lower extremities of people with hemiplegia (Baker *et al.*, 1979; Bowman *et al.*, 1979; Merletti *et al.*, 1979; Cozean *et al.*, 1988; Bogataj *et al.*, 1989; Dimitrijevic *et al.*, 1996; Weingarden *et al.*, 1998; Cauraugh *et al.*, 2000) and SCI (Keith *et al.*, 1988; Prochazka *et al.*, 1997). Some of these improvements were maintained months after the FES treatment was administered (Kraft *et al.*, 1992), while others decreased to become indistinguishable from the natural progression of functional gains in control subjects (Powell *et al.*, 1999). Other reported benefits of FES therapies include decreased muscle coactivation (Dimitrijevic *et al.*, 1996), decreased spasticity (Bajd *et al.*, 1989; Stefanovska *et al.*, 1989), reversed muscle atrophy with positive changes in other muscle characteristics (Pette & Vrbova, 1985; Vodovnik *et al.*, 1986). When FES treatment was administered to subjects in the subacute stage of their recovery, another beneficial effect of the treatment was prevention of flexor contractures (Baker *et al.*, 1979).

1.4 Objectives of the thesis

The main objective of the thesis was to study CNS plasticity following an injury to PNS or the brain. The specific questions addressed in separate chapters are outlined below.

CHAPTER 2. In this chapter CNS plasticity following partial denervation of the triceps surae muscles of the cat hindlimb was studied. The hypothesis tested was that the gain in the stretch reflex pathway of cat MG muscle during locomotion increases after the denervation of its synergists, lateral gastrocnemius (LG), soleus (SOL) and plantaris (PL) muscles.

CHAPTER 3. In this chapter CNS plasticity following the chronic damage to the brain was studied in a group of stroke patients. The goal of the study described in this chapter was to develop and test the efficacy of an FES-assisted exercise therapy system to improve motor function of the hemiplegic upper extremity in chronic stroke subjects.

CHAPTER 4. In this chapter CNS plasticity following recent damage to the brain was studied in a group of subacute stroke patients. The first goal of the study was to measure the effect of FES-assisted therapy on the upper-extremity function of subacute stroke subjects. The second goal was to measure changes in cortical excitability induced by the therapy and to assess how well the functional gains exhibited by the subjects are reflected in the changes in cortical excitability.

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CHAPTER 2

Adaptive changes in locomotor control after partial denervation of triceps surae muscles in the cat

Adapted from Gritsenko, V., Mushahwar, V. and Prochazka, A. (2001) Adaptive changes in locomotor control after partial denervation of triceps surae muscles in the cat. *J Physiol*, **533**(1), pp 299-311.

2.1 Introduction

Carrier *et al.* (1997) recently described adaptive changes in the control of hindlimb flexion in cats after denervation of ankle flexors. Certain aspects of these adaptive changes persisted after the cats were spinalized, suggesting that enduring changes in segmental transmission had occurred. Since the adaptive changes did not develop in cats spinalized before the partial denervation, Carrier *et al.* suggested that signals descending from supraspinal centers were responsible for inducing adaptive changes in the wiring of spinal interneuronal networks associated with the locomotor pattern generator. As the workings of the pattern generator are strongly influenced by sensory inputs (Pearson, 1995; Rossignol, 1996), one might suspect that changes in sensory pathways could be involved in these adaptations. Indeed it has been shown that operant conditioning in rats can be used to produce long-tern augmentation or attenuation of transmission in stretch reflex pathways and that descending input mediated by the corticospinal tract is necessary for the relevant changes to occur in the wiring of the spinal cord (Chen & Wolpaw, 1997). There are numerous mechanisms by which

sensorimotor transmission may be modulated in both the short and long term, including fusimotor action (Prochazka, 1996), presynaptic inhibition (Rudomin, 1999) and the action of neuromodulators such as serotonin (Rossignol *et al.*, 1998). Finally, there is the practical question of whether intensive training could be used to augment desirable adaptive changes in spinal motor responses in spinal-cord-injured people (Carrier *et al.*, 1997).

In experiments that followed on from those of Carrier *et al.* (1997), Pearson *et al.* (1999) reported large increases in stance-phase MG EMG activity following denervation of its synergists LG, SOL and PL. Early (pre-ground-contact) and late (mid-stance) components of EMG both increased after denervation, the latter within a day and the former more gradually over several days. Because the late EMG components were correlated in size with the amount of muscle stretch, Pearson *et al.* suggested that they were mediated by afferent signals generated soon after the onset of stance. It was suggested that partial denervation led to an adaptive facilitation of transmission of these afferent signals in reflex pathways, reinforcing the central drive to MG motoneurons. The authors argued that their previous results ruled out changes in the monosynaptic group Ia pathway, but they hinted that group Ib tendon organ afferents might be involved. Considerable importance was attached to the slower time course of increase in the early (pre-contact) component of EMG activity. It was suggested that changes in the early components reflected a gradual re-scaling of internal models of muscle stiffness that in turn depended on error signals provided by group Ia afferents.

Our study was designed to test some of these ideas. In normal cats, before denervation, rapid ankle dorsiflexions were applied at the onset of the stance phase of

step cycles to elicit EMG stretch responses in MG. The day after denervation of LG, SOL and PL, these responses had increased in size, as had the centrally-generated pre-ground-contact EMG. Over the ensuing days and weeks pre-contact and reflex responses increased further. There was no significant difference in the time course of these respective increases. The results are consistent with adaptive augmentations of extensor locomotor drive that in turn cause increases in the size, but not the gain of stretch reflexes.

2.2 Methods

The experiments were performed on 4 cats with the ethical approval of the University of Alberta Health Sciences Animal Welfare Committee. They conformed to the guidelines of the Canadian Council on Animal Care.

2.2.1 Surgical Implantation

In a single 2-3 hour aseptic procedure under pentobarbitone anaesthesia (35 mg/Kg intraperitoneal, maintained intravenously), EMG wires (632ss Cooner, Chatsworth CA) were sewn into MG, tibialis anterior (TA) and vastus lateralis (VL) muscles of each hindlimb. The intramuscular portions of the wires were deinsulated over about 4 mm. The wires were led subcutaneously to the cat's head where they were embedded in an acrylic headpiece secured to the skull by three bone screws. Incisions were closed with 4/0 nylon monofilament sutures. Buprenorphine (0.03 mg/kg) was administered subcutaneously: this powerful analgesic has an effect lasting about 12 hours. The animals were placed on blankets in a heated enclosure. Typically they were

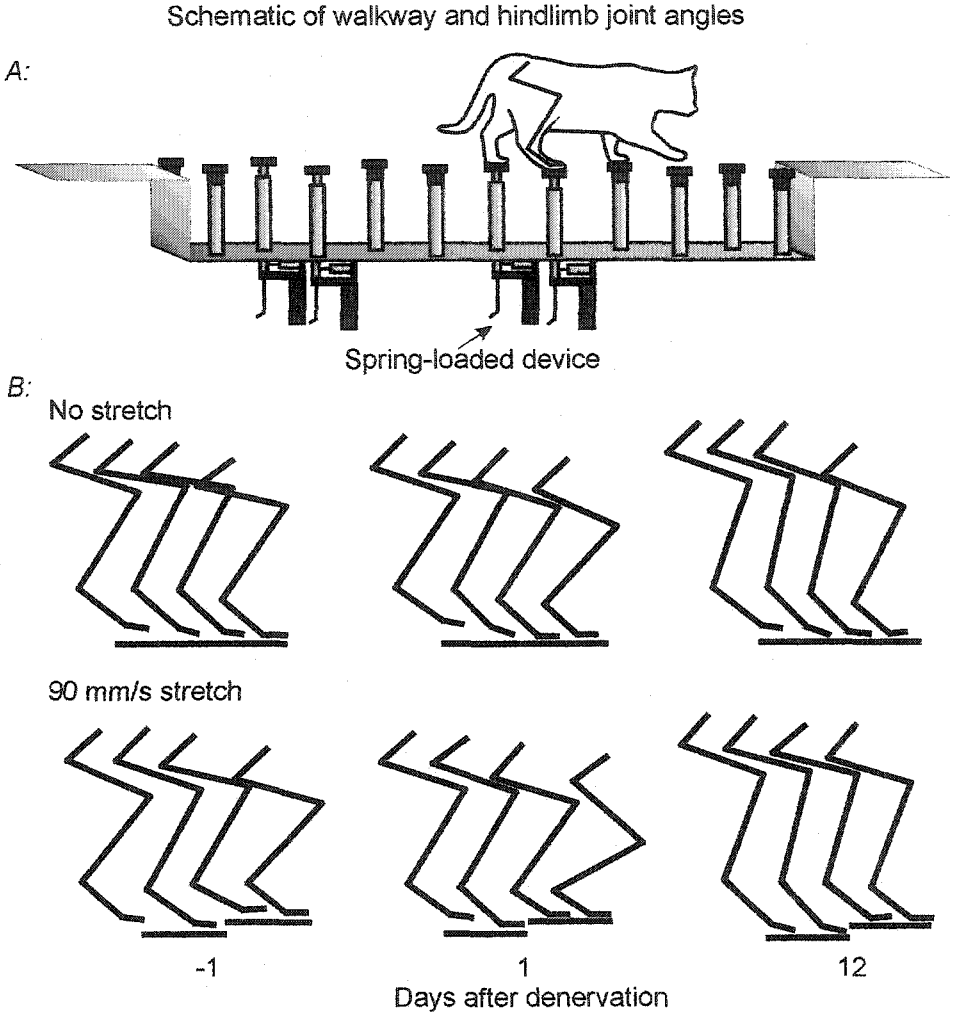

Figure 2-1. Setup diagram and stick figures of cat hindlimb. A. Schematic of walkway. Any one of four spring-loaded pegs could be triggered to release at the moment of foot contact, which was detected by light sensors mounted on the top of the loaded peg. B. stick figures constructed by tracing hip, ankle and toe markers from video still frames (the toe markers were on the lateral side of the foot, so they are slightly above the contact surface). Knee joint position was inferred by assuming constant hip-knee and knee-ankle segment lengths. Top row: unperturbed trials, bottom row: peg-popping trials. Each column represents data collected on a different day. Left: one day before denervation of lateral gastrocnemius (LG), soleus (SOL) and plantaris (PL); middle: one day after denervation; right: 12 days after denervation. Each set of 4 stick figures were taken from video frames corresponding from left to right to 30 ms before foot touchdown, touchdown, 30 ms after touchdown and 120 ms after touchdown respectively.

conscious and moving around within 6 - 10 hours and showed no obvious sign of pain or discomfort. A second similar dose of Buprenorphine was given 10 hours after the first to guarantee a comfortable and pain-free recovery. Antibiotics were not needed during recovery and therefore were not used.

2.2.2 Denervation

Denervation of the muscles was carried out following the methods of Pearson *et al.* (1999). In a 45 minute aseptic procedure conducted under Halothane anesthesia, an incision was made proximal and dorsal to the knee joint on the medial side of the left hindlimb. Nerves to LG, SOL and PL were identified with the help of electrical stimulation and cut. The incision was sutured shut and the cat recovered with Buprenorphine analgesia.

2.2.3 Locomotor trials

Cats walked along a 2m-long walkway for food rewards (Fig. 2-1). The walkway comprised 12 vertical pegs, 18 cm in height, each offering a 3cm diameter flat surface for foot support. Four of the pegs were spring-loaded with an electromagnetic release mechanism. Three photoelectric sensors mounted less than 1mm above the support surfaces of each active peg detected the moment the cat's paw interrupted light directed across the surface from corresponding photodiodes on the opposite side. This triggered a solenoid, releasing the spring-loaded portion of the peg, which moved upwards by 1 to 1.5 cm, rapidly dorsiflexing the cat's foot. Fig. 2-1B shows stick figures obtained from 30 frames/s video films of a cat 1 day before and 1 and 12 days after partial denervation, walking on a locked peg (top, no stretch) and a peg that popped up at the moment of foot

contact (bottom panels). Springs of three grades of stiffness were available to produce peg velocities of 250, 450 and 1000 mm/s respectively, corresponding to triceps surae stretch velocities of 50, 90 and 200 mm/s, respectively, assuming a lever ratio around the ankle joint of 1:5. Each active peg was equipped with custom-made length gauges to monitor peg displacement. Force transducers were embedded in the support surfaces of the active pegs to measure reaction forces but unfortunately the signals depended crucially on where the paw was placed on the surface, so these measurements were not considered in this report. EMG responses were recorded in MG, TA and VL.

2.2.4 Foot pad anaesthesia

To determine the effect of cutaneous input on EMG responses, two animals were anaesthetised with Halothane and 1ml of 1% lidocaine hydrochloride was injected into the paw pads of the partially denervated hindlimb. The animals recovered from the anaesthesia within about 20 minutes and data collection resumed. Foot anaesthesia was monitored continuously and data collection was discontinued at the first sign of reactions to pin prick in the locally anaesthetised foot were observed.

2.2.5 Terminal surgery

In order to verify the denervation at the end of the experiment, cats were anaesthetised with pentobarbitone (40 mg/kg i.p.). Nerve branches innervating triceps surae and the stumps of severed nerves were dissected, electrically stimulated and any resulting contractions were identified visually. The animals were then euthanised with an overdose of pentobarbitone. Triceps surae and PL muscles were removed from both limbs and weighed.

2.2.6 Data collection and analysis

EMG signals were amplified (x500 to x2000), high-pass filtered (30Hz), full-wave rectified and low-pass filtered (1000Hz). EMG and peg displacement signals were digitized (2000 samples/s) and stored using Signal 1.82 software and a CED1401 interface (Cambridge Electronic Design, Cambridge UK) and a personal computer. The data were analyzed offline using MATLAB5.0 software (Mathworks Inc. Natick, MA). Data from individual steps were aligned to the photoelectric contact signal, whose time of occurrence we defined as t_0. This signal triggered the solenoid to release the peg. The first detectable peg displacement commenced at about (t_0 + 5) ms. We estimated that the earliest possible latency of monosynaptic reflex responses was therefore (t_0 + 10) ms (Prochazka *et al.*, 1976). Accordingly, MG EMG responses were divided into four bins, representing pre-stretch EMG, and short-, medium- and long-latency reflexes (corresponding to M1, M2 and M3 stretch reflexes in monkeys (Lee & Tatton, 1975) and cats (Ghez & Shinoda, 1978)). The pre-stretch bin ("a" in Figure 2-2) encompassed the pre-contact build-up of MG EMG and terminated at (t_0 + 10) ms. The onset time of pre-contact build-up was computed in each individual trial as follows. First, the background mean (m_b) and standard deviation (σ_b) of MG EMG were computed in mid-swing over a 50 ms interval centered at (t_0 - 200) ms. The moving window mean (m_w) and standard deviation (σ_w) of the EMG signal were then computed over consecutive 10ms intervals starting centered at (t_0 - 40) ms and moving back in time in 5ms increments. When m_w and σ_w fell below the criterion levels defined below, the time in the middle of the window was taken as the onset time.

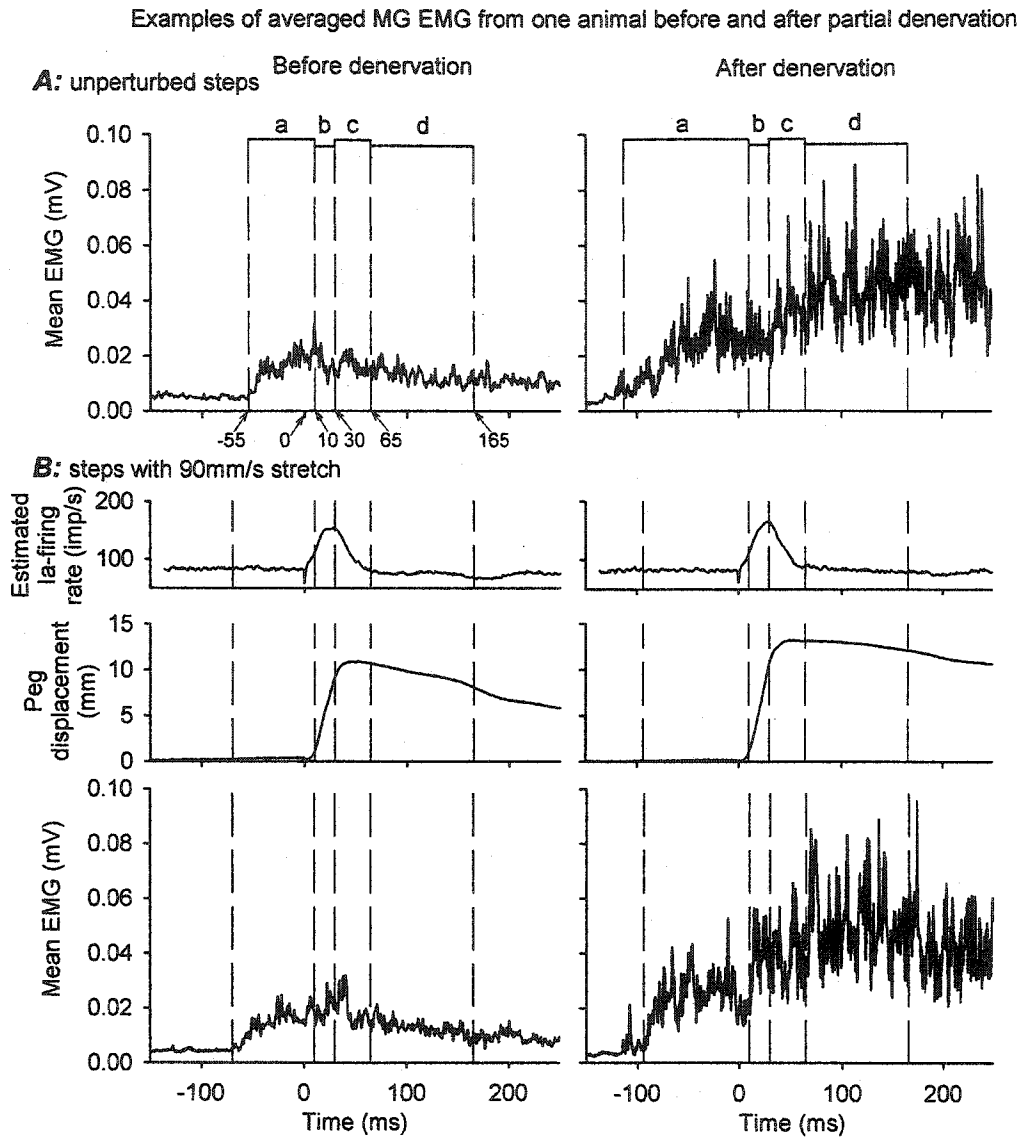

Figure 2-2. Examples of averaged EMG of medial gastrocnemius (MG) from one animal before and after the denervation. A. Normal steps on pegs recorded one day before (left) and 12 hours after (right) the denervation surgery. B. Steps one day before (left) and 12 hours after (right) partial denervation with a medium speed stretch applied at the moment of foot touchdown. Bottom trace: mean EMG; middle trace: peg displacement signal; top trace: change in firing rate of Ia-afferents modelled from the displacement signal. Dashed lines demarcate time intervals a, b, c and d corresponding to pre-stretch, short, medium- and long-latency components of MG EMG. Sweeps were aligned to the foot contact signal at time zero (t_0).The mean onset time of bin a shown by the dashed lines is the mean of individual onset times computed in each trial according to specific criteria (see Methods). Data are from cat #3, each panel represents >12 trials.

1) $100*(m_w - m_b)/m_w < 20$ (difference between moving window mean and background mean < 20%).

2) $100*(\sigma_w - \sigma_b)/\sigma_w < 40$ (difference between moving window SD and background SD < 40%).

The short-latency bin ('b') spanned the 20 ms following the termination of the pre-stretch EMG (i.e. +10ms to +30ms), the medium latency bin ('c') the next 35ms (+30ms to +65ms) and the long-latency bin ('d') the final 100ms (+65ms to +165ms). The long-latency bin was chosen to correspond approximately to the late component of Pearson *et al.* (1999) (note that these authors did not use a fixed latency from foot contact, but rather centered the long-latency component around the peak EMG in the stance phase).

The mean EMG within each bin was computed for an average of 15 steps in a given experimental condition. EMG varied in absolute amplitude from one cat to another due to electrode characteristics so to give the data from each cat equal weight, all EMG signals from a given cat were normalized to the peak of the averaged step cycle EMG profile obtained from 45 unperturbed steps prior to denervation. A set of stretch trials was performed in each cat during quiet stance. In these cases peg displacement was triggered manually. Because there was steady tonic EMG activity prior to stretch in these static trials, the pre-stretch bin, a, was set to encompass the interval -95ms to +10ms with respect to the trigger signal, corresponding to the mean span of bin a in the locomotor trials. Bins b and c spanned the same intervals as in the locomotor trials.

2.3 Results

Figure 2-2 shows mean stance phase MG EMG profiles recorded from one animal for normal (A) and perturbed (B) walking before (left) and 12 hours after (right) denervation. In B, peg displacement signals are shown, in these cases medium-stiffness springs were used that produced 450mm/s peak peg velocity, corresponding to 90mm/s peak stretch velocity of triceps surae muscles. It is assumed here that in the 25ms it took for the peg to pop, little rotation of the tibia occurred and therefore most of the motion of the paw was transferred by lever action to the triceps surae muscles acting about the ankle. A frame-by-frame analysis of video films supported these assumptions (Fig. 2-1B).

As the springs were not quite stiff enough to produce maintained step displacements or perfectly matched displacement signals before and after denervation, we felt it important to estimate the responses of muscle spindle Ia afferents to the actual displacements. Profiles of modulation of Ia ensemble firing rate were computed from the peg displacement signals using Ia models selected from the literature and implemented in Matlab Simulink software (Prochazka & Gorassini, 1998). Fig. 2-2B, upper traces show profiles generated by the following model: Ia firing rate modulation = $4.3*\text{velocity}^{0.6}$ +2*displacement. The profiles were surprisingly transient in nature, the relatively slow decline in length after the initial jump being enough to return the Ia rate close to background levels. From the point of view of our experiment, the estimated Ia profiles showed only minor differences before and after denervation. The fact that they were transient and not maintained was important in relation to the interpretation of long-latency responses. Similar profiles were obtained with the Hasan model (Prochazka & Gorassini, 1998).

In Fig. 2-2 it is clear that pre-stretch EMG and short, medium and long-latency EMG components all increased after denervation in both unperturbed (Fig. 2-2A) and perturbed (Fig. 2-2B) steps.

Figure 2-3 shows mean EMG responses of MG, VL and TA to 200mm/s stretches before (A) and after (B, C) denervation in three cats. The number of trials in which EMG recordings were available from all three muscles in each of the three cats varied from 5 to 17, so to maintain equal weighting, each EMG value in Fig. 2-3 was computed from the mean of three individual EMG means. Each individual EMG average was normalized to the muscle's *peak* mean EMG in unperturbed step cycles on three consecutive days prior to partial denervation.

The stretches were more than double the speed of those in Fig. 2-2B, and the transient responses in all three muscles were therefore very prominent, which explains why the pre-stretch EMG levels appear so small compared to those in Figure 2-2. Interestingly, there were large short-latency responses in VL as well as MG and delayed responses in TA that were essentially reciprocal with those in MG. The mean MG and VL responses had increased 6 days after denervation whereas that in TA had significantly decreased (see Discussion).

Figure 2-4 shows the time course of change of short-latency (A), medium-latency (B) and long-latency (C) responses to perturbations before and after denervation in 4 cats. Again, to ensure equal weighting per cat, each point in Fig. 2-4 represents the mean of four cats. Each panel also shows the time course of change of the mean amplitude of pre-stretch EMG. The first column shows data from steps on locked pegs. In these cases triceps surae stretch was associated with the yield during weight-bearing at the onset of

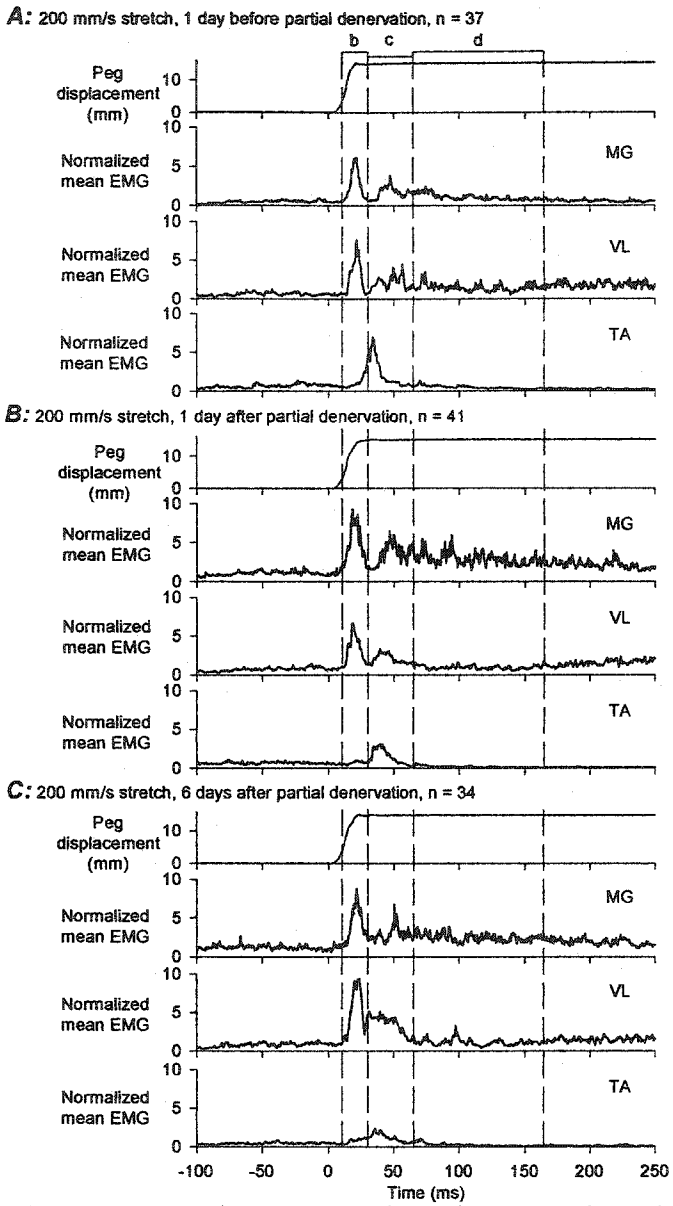

Figure 2-3. Mean stretch responses in MG, VL and TA before and after partial denervation. Mean EMG responses of MG, vastus lateralis (VL) and tibialis anterior (TA) to 200 mm/s stretches (A) before partial denervation, (B) 1 day after partial denervation, (C) 6 days after partial denervation. The transient responses in all three muscles were much more prominent than in Figure 2-2 because the stretch rates were more than twice as large. Note the similar latencies of MG and VL responses and the longer latency of TA responses. MG and VL responses had increased, while TA responses had declined 6 days after denervation. Data from cats #1, #2, #4; normalisation and averaging described in text, n = total number of trials per condition.

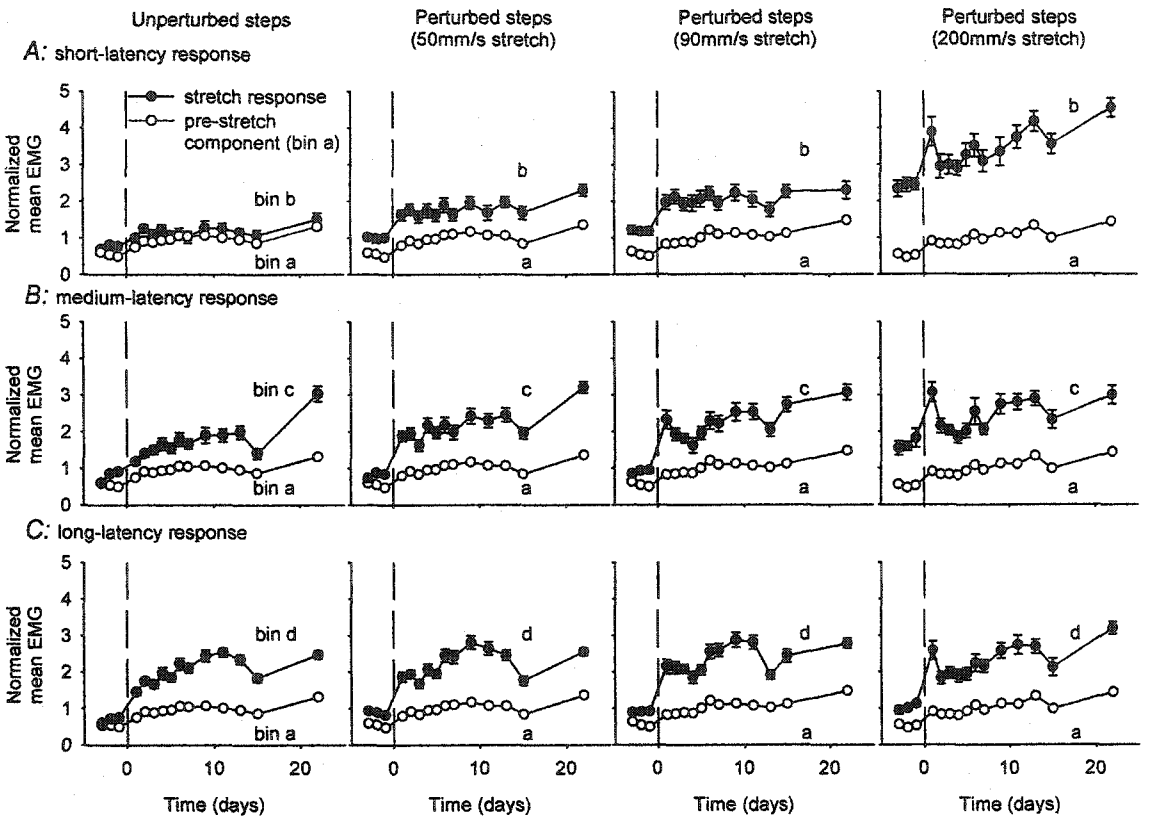

Figure 2-4. Mean normalized MG EMG data from all animals recorded over a 22-day period after the denervation. Each column displays data from trials with different speeds of muscle stretch. Left to right: unperturbed steps (unknown stretch rate), 50mm/s, 90mm/s, 200 mm/s. A, B, C: plots of the time courses of short-, medium- and long-latency bins defined in Fig. 2-2 (filled circles) and corresponding pre-stretch bins in the same trials (unfilled circles). First three pairs of data points in each graph, to the left of the vertical dashed lines, represent data collected on the three days before denervation. Error bars: $\pm$ SEM. Note the similar time course of pre-stretch and stretch-response components in all graphs. Each data point represents 64 trials, 4 cats.

the stance phase of the normal step cycle. The second, third and fourth columns show data from trials in which pegs popped, stretching triceps surae at estimated speeds of 50, 90 and 200 mm/s respectively. The first three points in each plot in this figure correspond to the mean normalized MG EMG within the relevant time bin on each of three days before denervation of synergists. Comparing these three values across the four top panels, the short-latency responses increased with stretch velocity, as would be expected if they were mediated by group I muscle afferents.

Mean pre-stretch EMG amplitude averaged over all trials had risen by at least 60% two days post-denervation and by about 140% 10 days post-denervation. There was no significant difference between pre-stretch EMG in trials with and without perturbations, indicating that the cats were not anticipating which peg would pop. The short, medium and long-latency EMG response components all increased in parallel with the mean level of the pre-stretch components. This was true of the large increases on the day after denervation (day 1) as well as of the more gradual increases on subsequent days (note that Pearson *et al.* (1999) restricted their comparisons to day 1 onward). The *duration* of pre-stretch components of MG EMG also increased abruptly after denervation (Fig. 2-5) but thereafter it slowly declined.

As the mean amplitudes of all EMG components, including the pre-stretch EMG, increased more or less in parallel after denervation, we were interested to know whether the *ratios* of the stretch reflex components to pre-stretch components (i.e. the reflex gain) increased after partial denervation. Using the set of single-sweep data that gave rise to Fig. 2-4, we computed all the gain ratios per condition per cat and their means $\pm$ SEM. The means of these sets of means (1 per cat per condition) were computed and plotted in

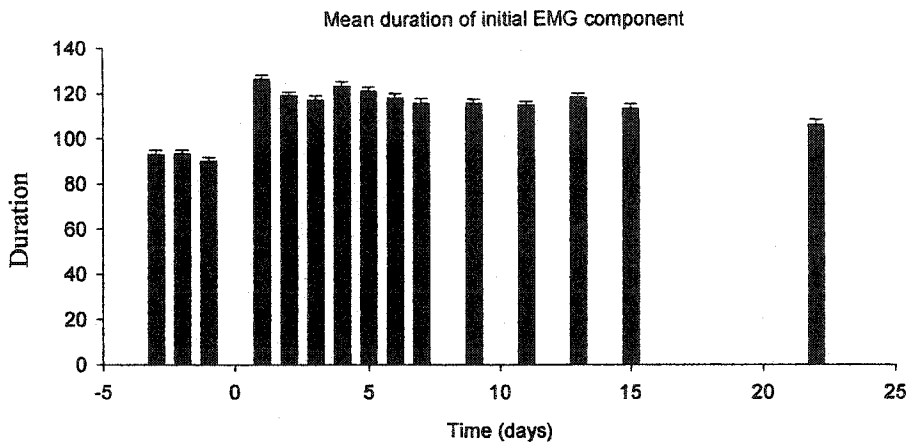

Figure 2-5. Mean duration of pre-stretch components of MG EMG before and after the denervation. The onset and termination of pre-stretch components were identified quantitatively and included a 10 ms period *after* foot contact (see Methods). Note the immediate increase in duration from 90ms to around 120ms the day after denervation and a slow decline thereafter. Each bar in the histogram represents 256 trials (mean $\pm$ SEM), 4 cats.

Fig. 2-6. With the exception of the 200 mm/s short and medium latency data, there were no consistent trends in the ratios over time after denervation, i.e. the stretch responses retained the same proportional relationship to pre-stretch components in the three days before denervation of synergists as well as in the days and weeks after denervation. The only significant trends were seen in the short and medium latency responses to 200 mm/s stretches. In these cases, there was a 25% to 30% fall in the ratios immediately after denervation, which was maintained for the 3-week duration of the study (this is attributable to the reduced afferent input from synergists: see Discussion). If there had been a sudden increase in the reflex responses with a more gradual increase in the pre-stretch component (Pearson et al., 1999), this would have shown up as an increase in the ratio on days 1 through 4 followed by a gradual decline. In other words there is no compelling reason to think that there had been a sudden adaptive increase in the gain of spinal stretch reflexes in the first few days after denervation. Rather, the increases in the amplitudes of the stretch responses can be explained by simple scaling of reflex responses to the increased background (pre-stretch) EMG after denervation.

We performed a similar analysis in 3 cats of stretch reflexes elicited by triggering peg displacement as the cats stood still on them. The difference in these trials was that by slightly adjusting the posture of the cat on the peg by varying the position of a food reward, background EMG levels could be matched reasonably well across trials. The left panels in Figure 2-7 show that under these conditions pre-stretch EMGs as well as short and medium latency MG EMG responses to 200 mm/s stretches did not change

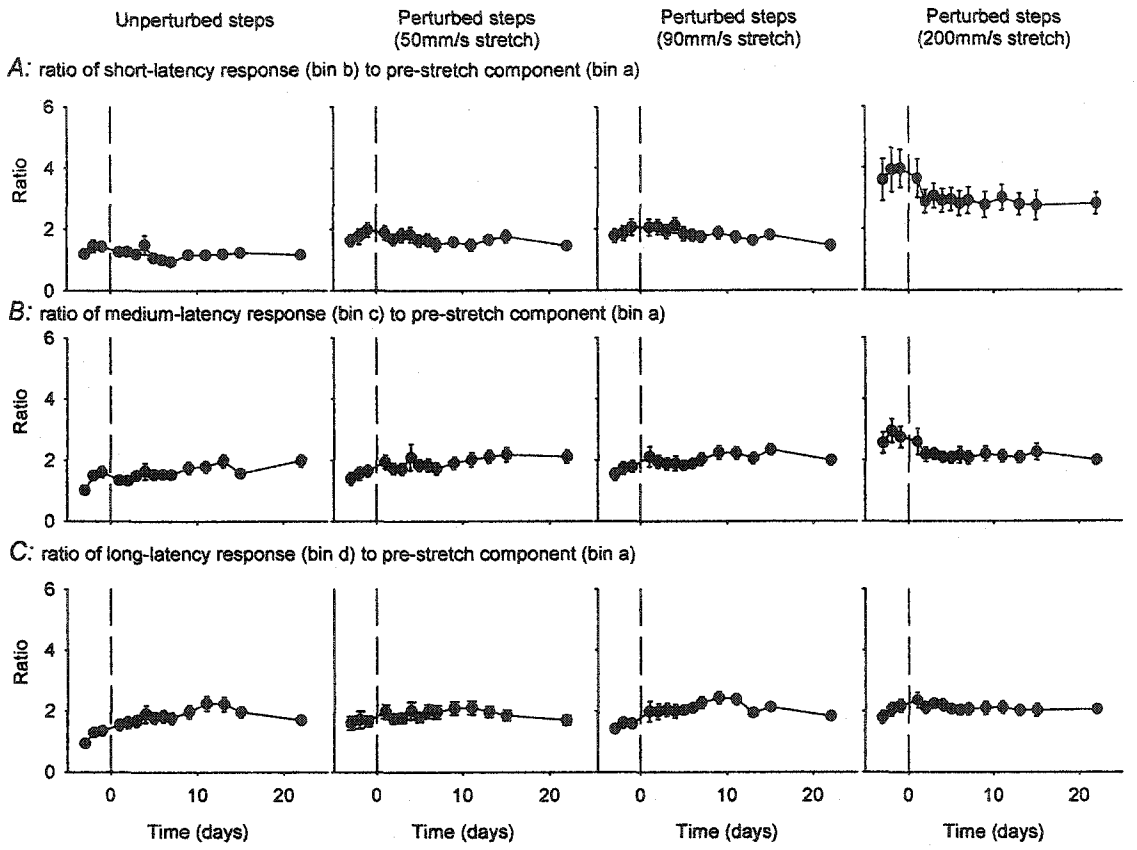

Figure 2-6. Time course of reflex gain: means of ratios of individual reflex components (b, c or d) to pre-contact component (a). Same set of data as in Fig. 2-4. In most cases, the mean ratios remained the same or decreased after denervation (i.e. pre-stretch and reflex components increased with a similar time course after denervation and reflex gain did not increase significantly). Means $\pm$ SEM from all 4 cats.

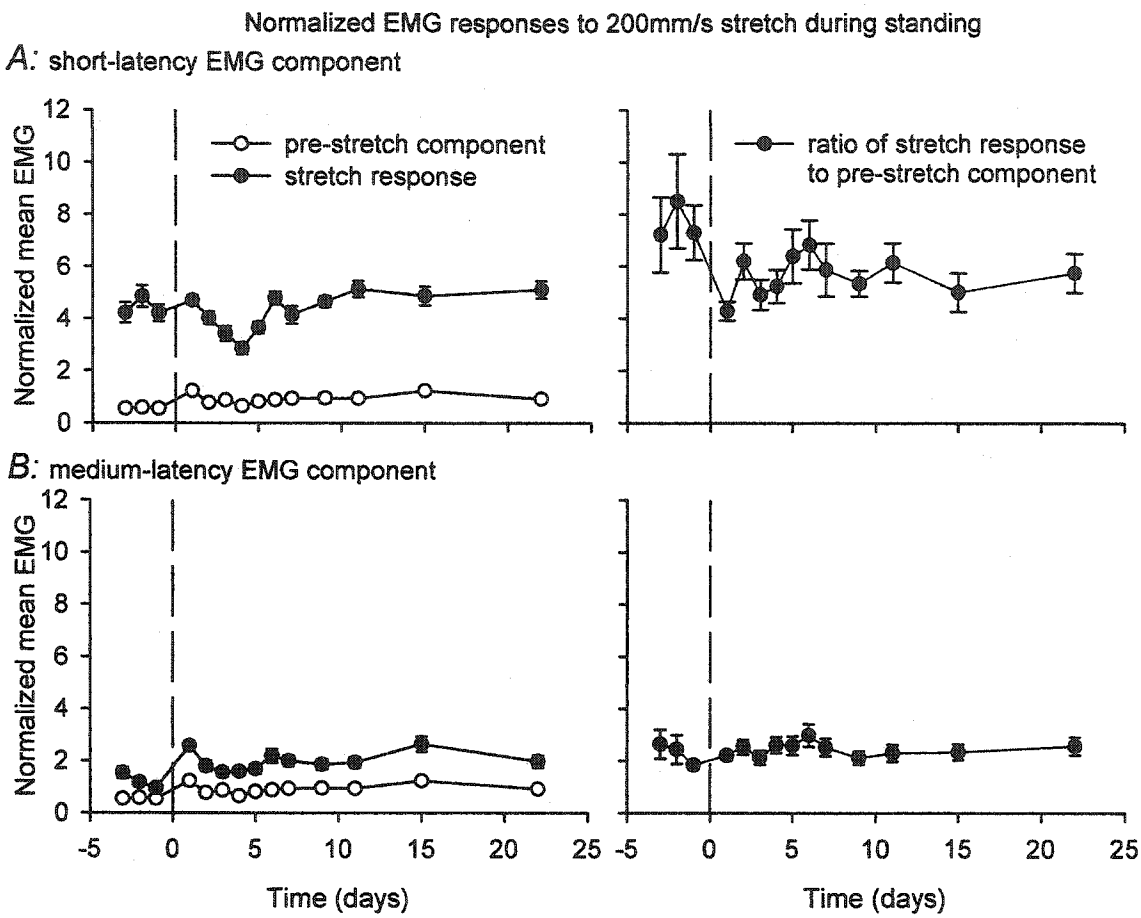

Figure 2-7. Responses to rapid (200 mm/s) perturbations applied during static stance. Left panels: time courses of short- (A) and medium-latency (B) bins (filled circles) and corresponding pre-stretch bins in the same trials (unfilled circles). First three pairs of data points in each graph, to the left of the vertical dashed lines represent data collected on the three days before denervation. Error bars: $\pm$ 1 SEM. Right panels: mean ratios of reflex to pre-contact components, same set of data as in the left panels. The mean ratios did not show a significant increasing trend from day 1 after denervation. Data from cats #1, #2, #3, 6-17 trials per cat.

significantly after partial denervation. Reflex gain, estimated as the mean ratio of stretch EMG responses to pre-stretch EMG (Fig. 2-7, right panels) showed a 25% to 30% fall in short-latency components as it had in corresponding stepping trials (Fig. 2-6A, right) and stayed fairly constant for medium latency components (Fig. 2-7, right panels).

Local anaesthesia of the footpads was performed in two cats. In cat 1 it was done 33 days after denervation. In cat 2 it was done two days prior to denervation as well as 61 days after denervation. Complete insensitivity was tested by applying pinprick stimuli to several locations on each pad. After a few minutes of complete footpad anaesthesia the cats displayed no obvious abnormalities in locomotion overground or on the pegs. Fig. 2-8 shows EMG averages (A: TA, B: MG) of steps before and during footpad anaesthesia for stretches of 90 mm/s and 200 mm/s. The non-anaesthesia control trials (thin lines) were done the day before the anaesthesia trials (thick dashed lines). There was remarkably little difference between matched trials, suggesting that the results were valid (different cats) and reliable (different days).

Figure 2-9 summarizes the detailed statistical comparisons: mean $\pm$ SEM of pre-stretch, short- medium and long-latency EMG components are shown before footpad anaesthesia (open bars) and during footpad anaesthesia (filled bars). There were small, but statistically significant ($p<0.05$) differences in two pairs of pre-stretch components before denervation in cat #2 (Fig. 2-9 B, C, left). Statistical significance was also reached in the long-latency responses (both cats, 200 mm/s, bottom right). Overall however the data suggest that skin input from the footpads did not contribute significantly to the EMG responses to perturbations. This does not exclude skin input from other parts of the foot or leg playing an important role (see discussion).

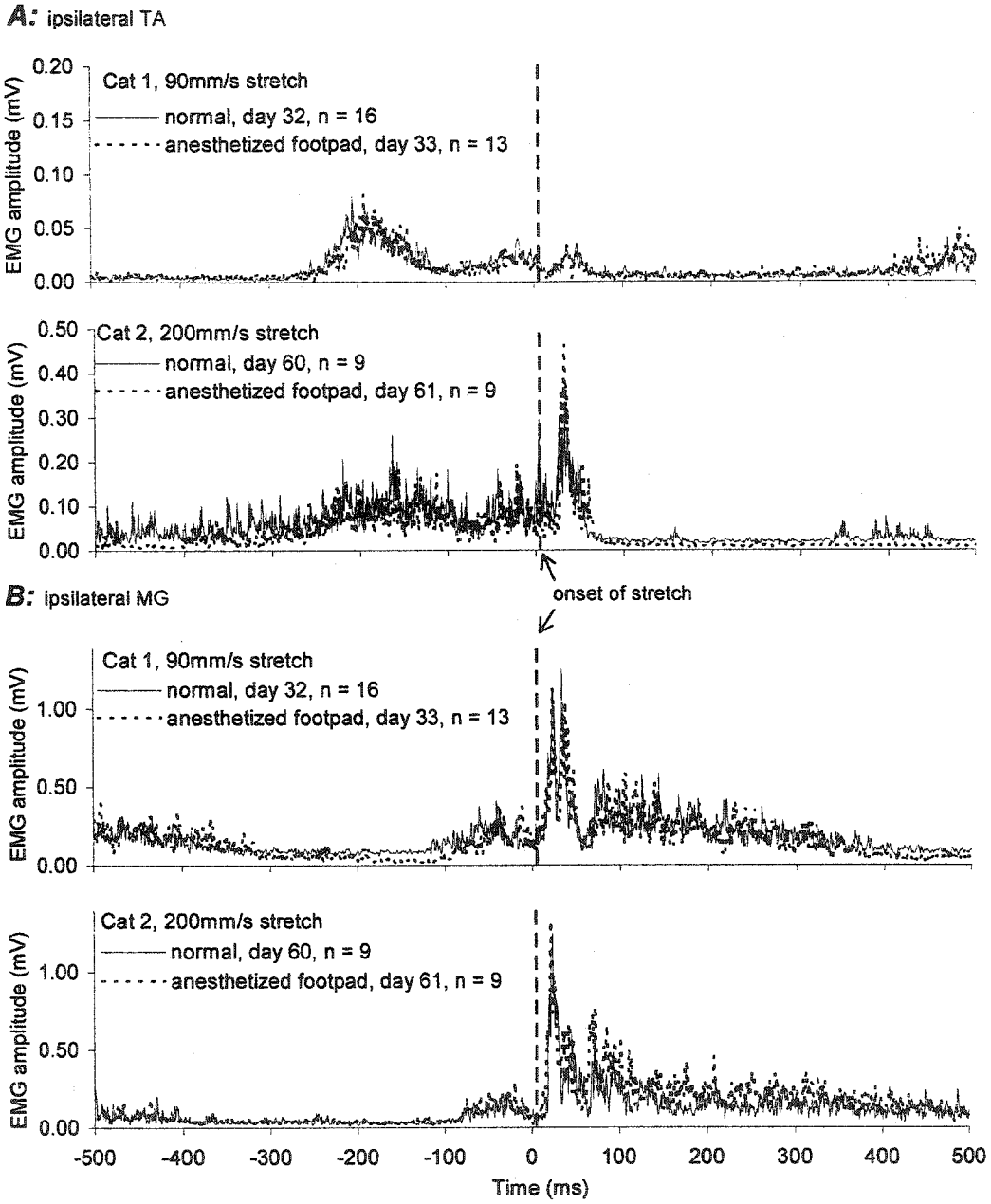

Figure 2-8. Stretch responses in TA and MG before and after partial denervation. EMG averages of responses of TA (A) and MG (B) in cats #1 and #2 to 90 mm/s and 200 mm/s perturbations before (thin lines) and during (dashed lines) footpad anaesthesia. The control trials (thin lines) were done the day before the anaesthesia trials (dashed lines). There is remarkably little difference between corresponding trials with and without local anaesthesia.

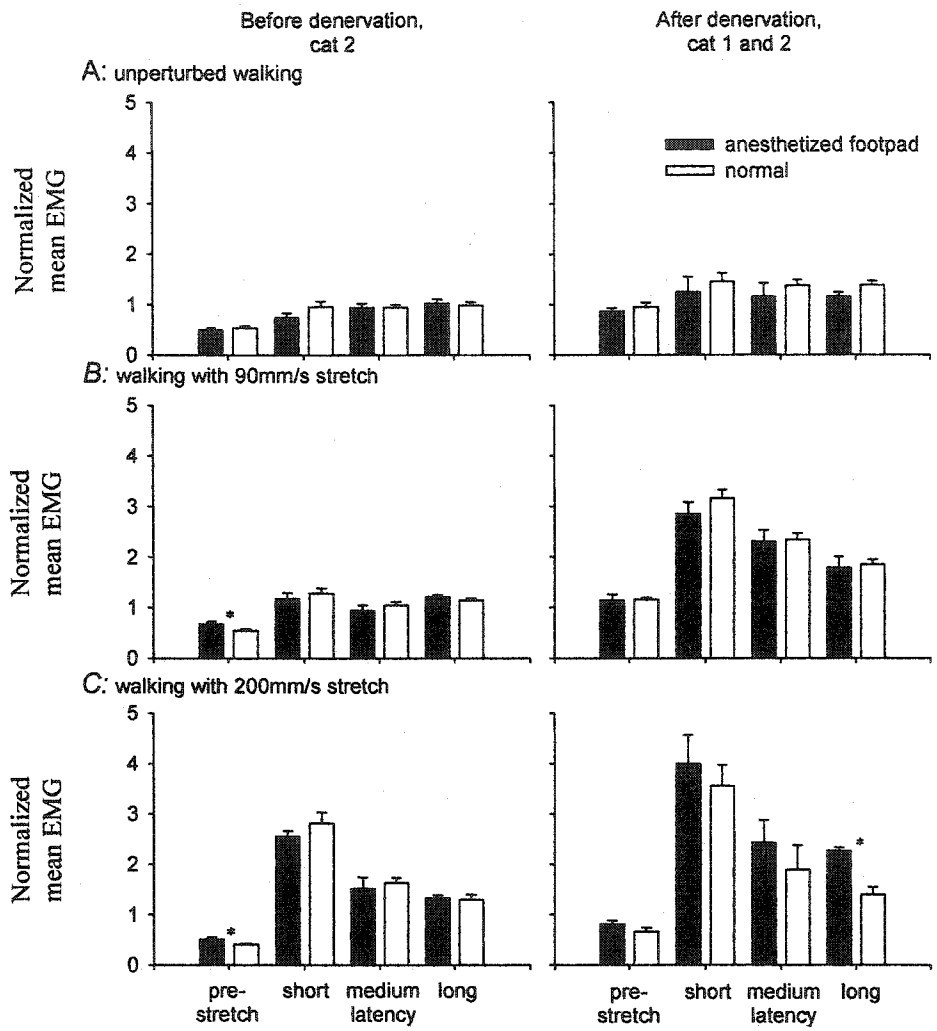

Figure 2-9. Normalized mean MG EMG data from normal and foot anaesthetised walking conditions. Left column: data from cat #1 before partial denervation; right column: lumped data from cat #1 32 days after denervation and cat #2 61 days after denervation. A. Unperturbed steps; B. 90 mm/s muscle stretch; C. 200 mm/s muscle stretch. In each graph mean $\pm$ SEM of four EMG components are plotted for normal (open bars) and anaesthetised (black bars) conditions. Two pairs of values in cat #2 (pre-stretch, pre-denervation) showed small differences that just reached significance (B and C, left; * $p<0.05$). One pair of post-denervation values (both cats) showed a large and significant difference (C, right; * $p<0.01$).

2.4 Discussion

As shown by Pearson *et al.* (1999), pre- and post-contact EMG activity in MG during unperturbed stepping increased following denervation of the synergistic muscles LG, SOL and PL. Our experiments were designed to evaluate and compare the time course of the centrally generated (pre-contact) and reflex-mediated (post-contact) components of this adaptation. Short- and medium-latency components of response to perturbations increased with increasing speed of the applied displacement of the foot which suggests that stretch reflexes contributed to them. Increases in these components in the days following denervation (Figure 2-4) therefore support the hypothesis that stretch reflexes increase in absolute amplitude after partial denervation. The timing of the short latency responses and the lack of effect of local anaesthesia of the paw on them suggest that they were mediated by group I muscle afferents.

The long-latency components of MG EMG did not change appreciably with a fourfold increase in stretch speed (see Fig. 2-4C, compare first three data points in each panel: no significant increase as stretch speed increased from 50mm/s to 200mm/s). This was surprising, not least because the reflex gain hypothesis we were testing was derived from late components of EMG in the step cycle rather than early components (Pearson *et al.*, 1999). However it became clear from the brief time course of the modelled Ia responses to the stretches (Fig. 2-2B) that Ia input was unlikely to contribute significantly to the long-latency EMG responses in MG in our experiments. Given that the MG muscle was active and remained stretched by the perturbations throughout the long-latency EMG responses, tendon organ Ib firing was probably elevated during this time (Prochazka & Wand, 1980) and may have contributed to these long-latency components. If Ib reflex

gain was significant, the only way we can explain the lack of correlation between the speed of peg motion and the size of long-latency components is that within 160ms of stretch onset, ground reaction force and therefore MG Ib firing reached the same steady-state value determined by the gravitational load of the cat's body weight rather than the speed of stretch.

The main new finding in our study is that short- and medium-latency stretch reflex responses to the perturbations increased in proportion to the increases in pre-stretch EMG. There was little evidence in our data for the notion that MG reflexes increased sooner after denervation than the centrally-generated pre-stretch EMG components. The proportional scaling of the amplitude of stretch reflexes to ensemble motoneuronal activity is a well-known property of reflex transmission (Marsden *et al.*, 1976). Actual increases in the *gain* would require increases in the *ratios* of reflex to pre-stretch components (i.e. increases in the constants of proportionality). These were not seen after denervation (Figures 2-6 and 2-7). The long latency EMG components also increased after denervation in proportion to pre-stretch EMG, but as just mentioned, the peripheral contribution to these components is hard to estimate. However, if Ib reflexes were involved, these were scaled up with pre-stretch activity too, so again there was no reason to invoke reflex gain changes after denervation.

Some important differences between our experiments and those of Pearson *et al.* (1999) should be noted. First, our cats were walking on pegs rather than on a treadmill. It has been suggested that peg-walking is more demanding and that this might have led to a different mode of locomotor control. We doubt this, because the cats negotiated the pegs with ease after just one or two trials and ran back and forth across them for food

rewards. A second difference was that the largest adaptive increases in EMG components occurred on the first day after denervation, compared to control trials on the three days prior to denervation. However there is a problem in comparing these values directly. Denervation of LG, SOL and PL abolishes afferent input from these muscles and therefore some of the heteronymous synaptic input to MG motoneurons. About 20% of total Ia monosynaptic input to MG can be assumed to be absent after the denervation (Burke & Rymer, 1976). This is why Pearson *et al.* (1999) only considered adaptive changes from baseline measurements commencing a few hours *after* denervation. However, even if we exclude our pre-denervation data, our conclusions regarding parallel and proportional increases in pre-stretch and reflex components after denervation still hold. In fact in Fig. 2-6A, right panel, the ratios of short-latency responses to pre-stretch activity *dropped* immediately after denervation in 200mm/s stretches, consistent with the 20% estimated drop in Ia synaptic input. Third, the hypothesis of Pearson *et al.* (1999) regarding a rapid increase in reflex gain followed by a more gradual re-scaling of central locomotor drive was based on changes in late components of EMG, by which the authors meant components of EMG occurring within a 100ms period centered on the peak of EMG activity in the step cycle. This is an important distinction: as we were specifically testing the reflex gain hypothesis, we defined long-latency components as those occurring within the interval 65 to 165ms after the abrupt perturbations coinciding with foot contact. In contrast, the late component of Pearson *et al.* (1999) had no fixed latency with respect to foot contact, as the peak of MG EMG occurred at different times in the step cycle. Thus our conclusions regarding responses to known test inputs do not

contradict the *observations* of Pearson et al., though they are at variance with the hypothesis drawn from them.

Carrier et al. (1997) compared patterns of treadmill locomotion of intact and spinal cats before and after denervation of ankle flexors. Cats with intact spinal cords adapted to denervation within a few days and achieved symmetrical gait by increasing hip and knee flexion. After spinalization knee hyperflexion persisted and gait was asymmetrical. Yet a cat first spinalized and *then* partially denervated regained symmetrical gait. The results suggested that there were gradual changes in both supraspinal and intraspinal connections after partial denervation. Because pre-contact EMG in MG is largely centrally generated (Engberg & Lundberg, 1969; Gorassini *et al.*, 1994) adaptive increases in descending drive after denervation of synergists was probably responsible for the immediate increases in pre-contact EMG in our cats. We did not find convincing evidence for a change in reflex gain independent of the changes in pre-stretch activity, i.e. there was no evidence of a reorganization of spinal reflex transmission in MG after denervation of its synergists.

Cutaneous receptors in and around the footpads signal ground contact with high-frequency bursts of discharge (Trend, 1987). In perturbation trials, the sudden upward force of the pegs on the footpads presumably caused very rapid bursts of firing in many of these receptors. Synchronous activation of cutaneous nerves by electrical stimulation during locomotion evokes short-latency responses in ankle muscles in normal cats (Abraham *et al.*, 1985). Mechanical stimuli applied to the dorsum of the foot can also evoke EMG responses, particularly during the swing phase (Wand *et al.*, 1980). Short and long latency cutaneous excitatory and inhibitory reflexes have also been recorded

during fictive locomotion in cats (Schmidt *et al.*, 1989; LaBella *et al.*, 1992; Degtyarenko *et al.*, 1996). In humans it has been argued that medium-latency responses are mediated purely by skin input (Corden *et al.*, 2000). Yet it has also been shown in intact cats that the abolition of skin input does not seem to have a major effect on locomotor control (Engberg, 1964; Bouyer & Rossignol, 1998). In two cats we used local anaesthesia to abolish input from footpad skin receptors (Figures 2-8 and 2-9). This had no detectable effect on any of the components of EMG response to peg pops. It is true that other skin receptors of the foot and lower leg probably continued to respond to the perturbations and it is quite possible that these receptors contributed to the short and medium latency EMG responses before and during footpad anaesthesia. On balance however, the evidence favours muscle receptor input as being the dominant influence. Note that our test of the hypothesis of adaptive changes in stretch reflex gain does not depend on the type of receptors involved, nor indeed did the original paper insist on the responses being mediated by muscle receptors (Pearson *et al.*, 1999).

Could any of the components of response have been auditory startle reactions to the peg pops? To address this, we used a sensitive Eletret microphone placed in the walkway at a position corresponding to the cat's head to record the sound caused by one of the pegs popping at its fastest velocity. This showed that though there was very little sound at the onset of peg movement, a sharp sound was generated when the peg reached its stop about 25 ms after release. This second sound was of a similar intensity to a sharp handclap about 30cm from the microphone. This could have resulted in startle responses, at least in the first few trials. The latency of auditory startle responses in cat hindlimbs is 18-20 ms (Gruner, 1989) giving an expected net latency of startle responses of 43-45ms

in our trials, which would correspond to component c. As mentioned above, long-latency component d was unaltered in trials with peg-popping compared to no-peg-pop trials, so neither startle nor stretch reflexes need to be invoked for these components. Components a and b precede the sound pulse so a startle response contribution can be ruled out for these components too. Auditory startle responses generally show rapid adaptation whereas response component c showed little adaptation after many repetitions in our experiments. Therefore, although we cannot rule out a contribution of auditory startle responses to component c in the fastest perturbations, proprioceptive inputs seem the more likely source.

Could displacements about joints other than the ankle have contributed? The video films and the stick-figures in Fig. 2-1 show that in the first 30 ms the displacement of the peg caused dorsiflexion about the ankle but very little change in the other joints. The final frame shows that on day 1 the leg yielded and by 120ms the hip joint had been displaced. In principle this might have affected long-latency component d but in fact this component remained constant whether there were perturbations or not. Admittedly the large responses in VL in Figure 2-3 do suggest that the knee extensors were transiently stretched, though the responses could also have been mediated by ankle extensor afferents with synaptic connections to knee extensor motoneurons. We did not attempt a full analysis of the changes in VL after the partial denervation because these were not of direct relevance to the hypothesis being tested. The large delayed responses in TA, which were reciprocally timed with peaks of activity in MG (Figure 2-3), might have been caused by a small transient re-stretch of TA at the end of the step perturbation. It is interesting that these responses became much smaller in the days after partial

denervation. Because we cannot be certain of the sensory origin of the TA responses and because their longer latency allowed time for more complex processing, we have not attempted to explain this decline. It therefore remains an open question whether descending inputs and/or spinal reflex transmission to TA motoneurons change in the days after partial denervation of triceps surae muscles.

We conclude that the centrally generated pre-contact MG EMG activity increases in an adaptive manner after denervation of synergistic muscles and this is associated with an increased amplitude of stretch reflexes. Both mechanisms serve to increase the force produced by medial gastrocnemius to counteract the loss of force from the denervated muscles. There was no compelling evidence of a change in the gain of reflex transmission after denervation.

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CHAPTER 3

A FES-Assisted Exercise Therapy System for Hemiplegic Hand Function

Adapted from Gritsenko, V. and Prochazka, A. (2004) A FES-Assisted Exercise Therapy System for Hemiplegic Hand Function. *Arch Phys Med Rehabil*, in press.

3.1 Introduction

According to statistical data from the Heart and Stroke Foundation of Canada (HSFC, 2002), about 40% of all the people who have had a stroke are forced to live with a moderate to severe impairment. The most widely used rehabilitative techniques aimed at restoration of motor control after stroke are neurodevelopmental treatment (Bobath, 1977) (NDT) and proprioceptive neuromuscular facilitation (Voss, 1967) (PNF). Although both techniques are forms of exercise therapy, they rely on different principles to facilitate recovery of movement. The main principles of NDT are to inhibit unwanted muscle patterns, such as flexion synergies, and to facilitate automatic reactions, such as protective extension. The main principle of PNF is to strengthen functional movement patterns with sensory stimuli - for example, by increasing resistance to movement or by using traction to stimulate proprioceptors. Both therapeutic techniques are equally effective in restoring movement after 6 weeks of treatment (Dickstein *et al.*, 1986).

Another technique, constraint-induced movement therapy (CIMT), was more recently developed specifically for rehabilitation of upper-extremity function (Taub &

Wolf, 1997). Reports have appeared of large gains in function of the hemiplegic extremity in activities of daily living (Taub & Wolf, 1997) (ADLs). However, only a small percentage of people with hemiplegia have enough voluntary hand opening to qualify for CIMT. Another approach is based on using functional electric stimulation (FES) of muscles to augment hand function (Baker *et al.*, 1979). Although reports show improved hand function when FES has been used as an exercise program, the functional gains were modest and of limited duration (Baker *et al.*, 1979). Combining the last 2 approaches into 1 FES-assisted exercise therapy may allow a larger group of stroke patients to benefit from both types of therapy. A recent study by Popovic et al. (Popovic *et al.*, 2002) tested this idea in a group of subacute stroke subjects. Popovic reported better performance of everyday tasks by subjects, who practiced tasks with FES assistance, as compared with control subjects, who exercised without FES.

The first goal of our study was to build and test an exercise workstation for implementation of FES-assisted exercise therapy, which would permit us objectively to assess improvement in upper-extremity function on an everyday basis. The second goal was to make an initial assessment of the effectiveness of the therapy in improving hemiplegic upper-extremity function in a group of people whose level of motor function would have ruled them out for CIMT. We hypothesized that FES-assisted exercise therapy would result in measurable improvements in upper-extremity function.

3.2 Methods

3.2.1 System

The therapeutic system consisted of a workstation and a FES stimulator. The workstation included a desk with a number of instrumented objects (Fig. 3-1). The objects were chosen to represent household items, manipulation of which would require movements of the whole upper-extremity in various configurations. A spring-loaded doorknob and a handle attached via a cord and pulley to an adjustable set of weights were instrumented with potentiometers, which allowed us to monitor their displacement and velocity. The other objects consisted of 3 rectangular blocks and a cylinder, which were transferred by the subjects between 2 docking bays. These were instrumented with internal infrared sensors, which generated an electric signal when an object entered the bay. This allowed us to time movements of the objects between the 2 bays. The sensor signals were processed with a custom-built control circuit and then digitized (200 samples/s) by a CED Power 1401 laboratory interface (Cambridge Electronic Design, UK). The data were stored on a desktop computer and later analyzed by using Matlab, version 6.1 (MathWorks, USA), and SigmaStat, version 2.03 (Softek Inc, USA), software.

To assist subjects with hand opening, we used a modified Impact Cuff stimulator (Prochazka *et al.*, 1997) with a pair of surface electrodes to stimulate wrist and finger extensor muscles. The subjects triggered the Impact Cuff by pushing one of the buttons on the workstation (Fig. 3-1) just before grasping an object and when they wanted to release it.

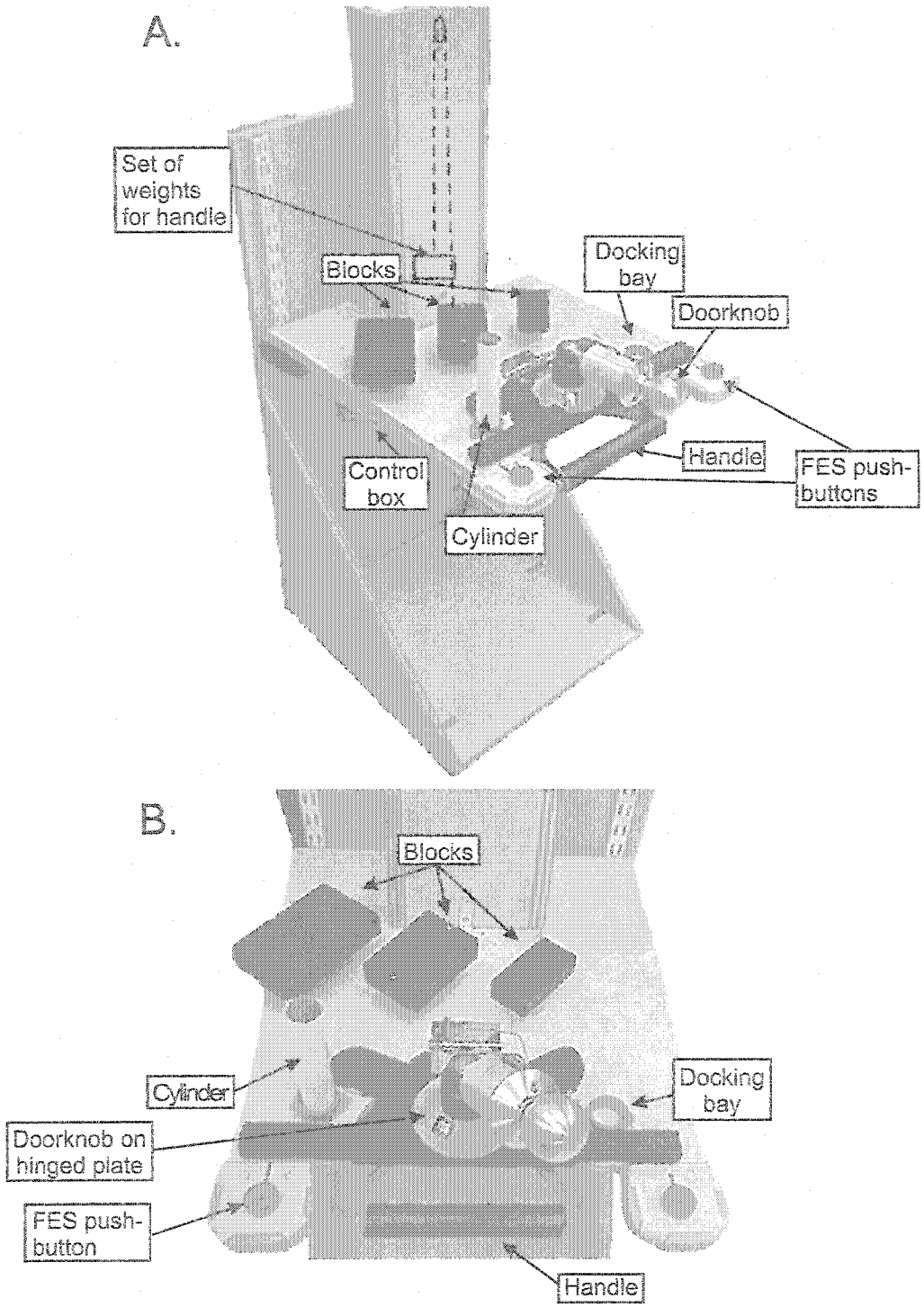

Figure 3-1. Exercise workstation. A. Side view. B. Close up of the objects. The handle and the doorknob were instrumented with rotational potentiometers to measure displacement. Docking bays were instrumented with photoelectric sensors to detect time of insertion of the cylinder or one of the blocks.

3.2.2 Participants

To test the system, we recruited a convenience sample of 6 subjects with hemiplegia, whose characteristics are summarized in Table 3-1. All subjects were more than a year poststroke, by which time the recovery of upper-extremity function is thought to reach a plateau (Nakayama *et al.*, 1994). The subjects served as their own controls. The following inclusion criteria were used during subject enrollment: stroke having occurred more than a year before the study and inability to voluntarily grasp and release any 3 objects on the workstation. The following exclusion criteria were also used: (1) inability of FES to open the impaired hand or intolerance of FES by the subject; (2) no voluntary movements of the shoulder and elbow; (3) serious cognitive deficit (Mini-Mental State Examination, score <16) (Folstein *et al.*, 1975), visual hemineglect (letter cancellation test, >2 letter difference) (Albert, 1973), or severe depression (Center for Epidemiological Studies Depression Scale score >16) (Hautzinger & Bailer, 1993); (4) other serious medical conditions; or (5) injuries to arms or hands. The procedure was approved by the local hospital ethics committee, and all subjects signed a letter of informed consent after receiving a description of the project.

3.2.3 Intervention

Therapeutic intervention consisted of daily 1-hour sessions for 12 consecutive workdays, during which subjects performed 3 tasks for about 20 minutes each. The tasks consisted of reaching, grasping, moving (e.g., pulling, rotating), and releasing an object on the workstation with the hemiplegic upper extremity. The objects were chosen on the basis of the subject's ability to grasp them with FES assistance at the beginning of

Characteristics	Values ± STD
Number of subjects:	
Males	3
Females	3
Mean age	53.5±14.8
Side of stroke:	
Dominant hemisphere	4
Non-dominant hemisphere	2
Mean number of years post-stroke:	5.6 ± 4.4

Table 3-1. Subject's Characteristics.

the training period. If a subject was able to grasp more than 3 objects, the 3 most difficult tasks were chosen. If a subject was not able to grasp 3 objects because of inability of FES to adequately open the hand, this subject was excluded from the study. Once chosen, objects were not varied during the therapeutic intervention. During an exercise session, each task was repeated as often as possible for 20 minutes, which resulted in the number of repetitions being between 5 and 15 in 1 session. Only successful trials were saved for further analysis; hence, if an object was dropped or mishandled in any other way, the trial was disregarded.

3.2.4 Assessment and statistical analysis

Two types of outcome measure were used to assess functional improvement in upper-extremity function: kinematic measures and clinical tests. Kinematic measures were obtained from sensors fitted to the manipulated objects. These measures were the time taken to reach and grasp the object, mean velocity of the handle, and maximum amplitude of rotation of the doorknob. Rather than analyzing these values separately, we combined them in a performance score by using the following analysis. We normalized the kinematic measures and their standard deviation (SD) in relation to their maxima over all exercise sessions for each subject, which made them vary between 0 and 1. Then we calculated the mean score for each task by averaging normalized kinematic measures and normalized SD. Values of variables, such as the time to reach an object and the SD, decreased with improvement in performance, whereas the rest increased. Therefore, the normalized values of the time taken to reach and grasp an object and the SD were subtracted from 1, so that the maximum value of the cumulative score represented

maximum improvement. For each subject, these task scores were then averaged into a final score that represented each subject's performance during each exercise session. The final performance (FP) scores for all subjects were pooled and analyzed with the 1-way repeated-measures analysis of variance (ANOVA), followed by Dunnett multiple comparisons, treating FP score values recorded on the first day of exercise as control measures.

Clinical measures included assessment of impairment by using the upper-extremity portion of the Fugl-Meyer Assessment (FMA) (Fugl-Meyer *et al.*, 1975) and the Wolf Motor Function Test (WMFT) (Wolf *et al.*, 1989). Subjects' performance during these 2 tests was videotaped by a researcher and later rated by a volunteer clinician, who was unaware of the time the assessment was made (pre-treatment, post-treatment, follow-up). The Motor Activity Log (MAL) (Taub & Wolf, 1997) was used to estimate involvement of the hemiplegic extremity in subjects' daily lives. Statistical analysis of the clinical measures from 4 subjects was performed by using the 1-way repeated-measures ANOVA, followed by Dunnett multiple comparisons. Two subjects who declined to undergo the follow-up assessment were excluded from statistical analysis of clinical scores. The study was performed in 2001–2002.

3.3 Results

Figure 3-2 shows the FP scores of 6 subjects using the workstation for 12 days and the FP scores of 4 subjects using the workstation on a follow-up session (day 72). Figure 3-2A shows individual FP scores, whereas Figure 3-2B shows the FP scores

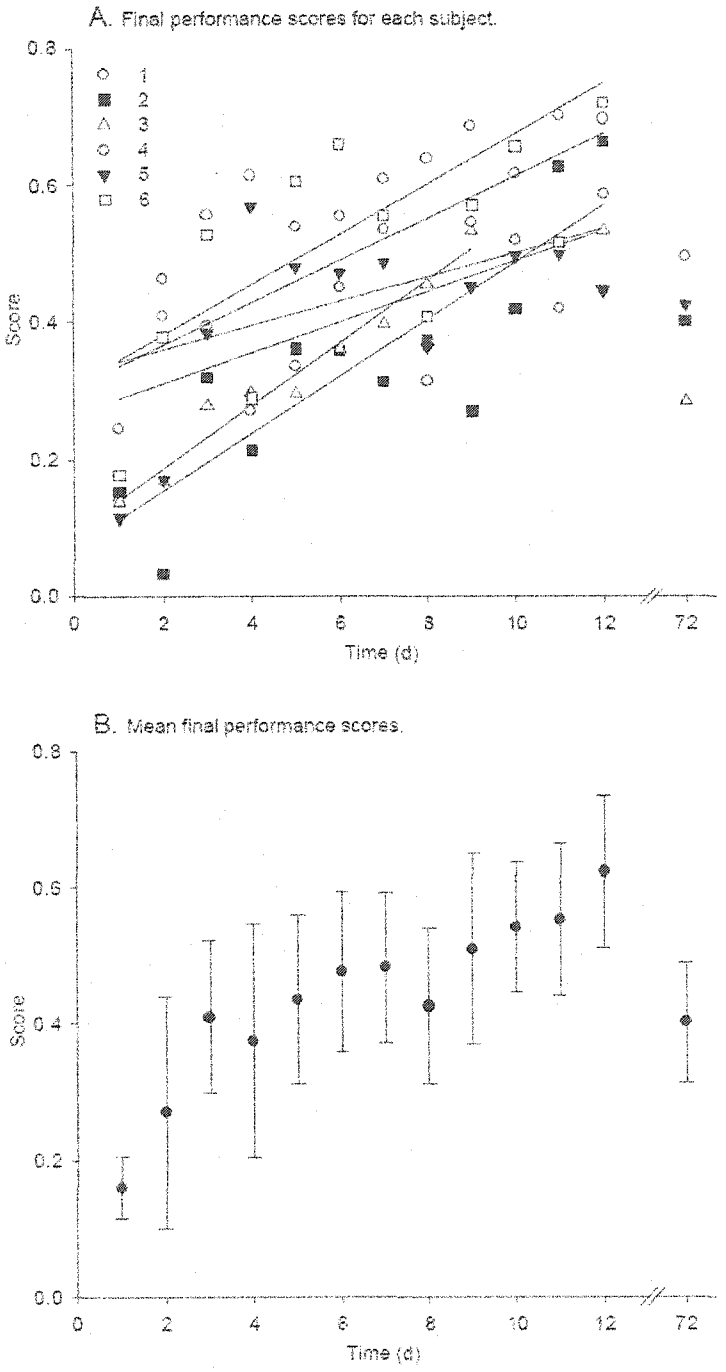

Figure 3-2. Final performance score. A. Each bullet represents the FP score per day per subject. Regression lines were fitted to the data to indicate trends in subjects' performance during the exercise period. B. Values of the FP scores averaged over all subjects ± standard deviation.

averaged over all subjects. The data show gradual improvement in subjects' performance with continued use of the workstation. The maximum change in the mean FP scores between the first and the last day of exercises was 287% (pre-/post-treatment effect size [pre/post ES] of the mean FP scores = 5.46). Statistical analysis of the FP scores showed that improvement of subjects' performance was statistically significant ($F = 8.210$, $P < .001$). Dunnett multiple comparison (q) analysis showed that the FP scores starting from the third day of exercises differed significantly from the FP scores on the first day of exercises (q for columns 3–12 = 4.242, 3.651, 4.686, 5.371, 5.481, 4.508, 5.942, 5.841, 6.023, 7.136, respectively; $P < .05$ in all cases). At the 2-month follow-up (FU), the improvement in performance was still present, although somewhat reduced (pre/FU ES of the mean FP scores = 3.44). Dunnett multiple comparison analysis showed that the follow-up FP scores differed significantly from the control scores ($q = 3.795$, $P < .05$).

Figure 3-3 summarizes the clinical assessments of upper-extremity function in the same subjects. At the end of treatment, functional ability scores of the WMFT increased on average to 111% of pretreatment values (Fig. 3-3A) (mean pre/ post ES = .57). At the 2-month follow-up, the WMFT scores further increased on average to 119% of corresponding pretreatment values (mean pre/FU ES = .54). ANOVA of the functional ability scores from 4 subjects showed that changes in the values were statistically significant ($F = 6.112$, P=.036). Mean time to perform tasks in the WMFT decreased by the end of treatment on average to 90% of pretreatment values (mean pre/post ES = .28) (Fig.3-3A) and at the follow-up to 74% of corresponding pretreatment values (mean pre/FU ES = 1.02). ANOVA of the mean time values showed that the changes in the values were not statistically significant ($F = 1.805$, $P = .243$) because of larger variability

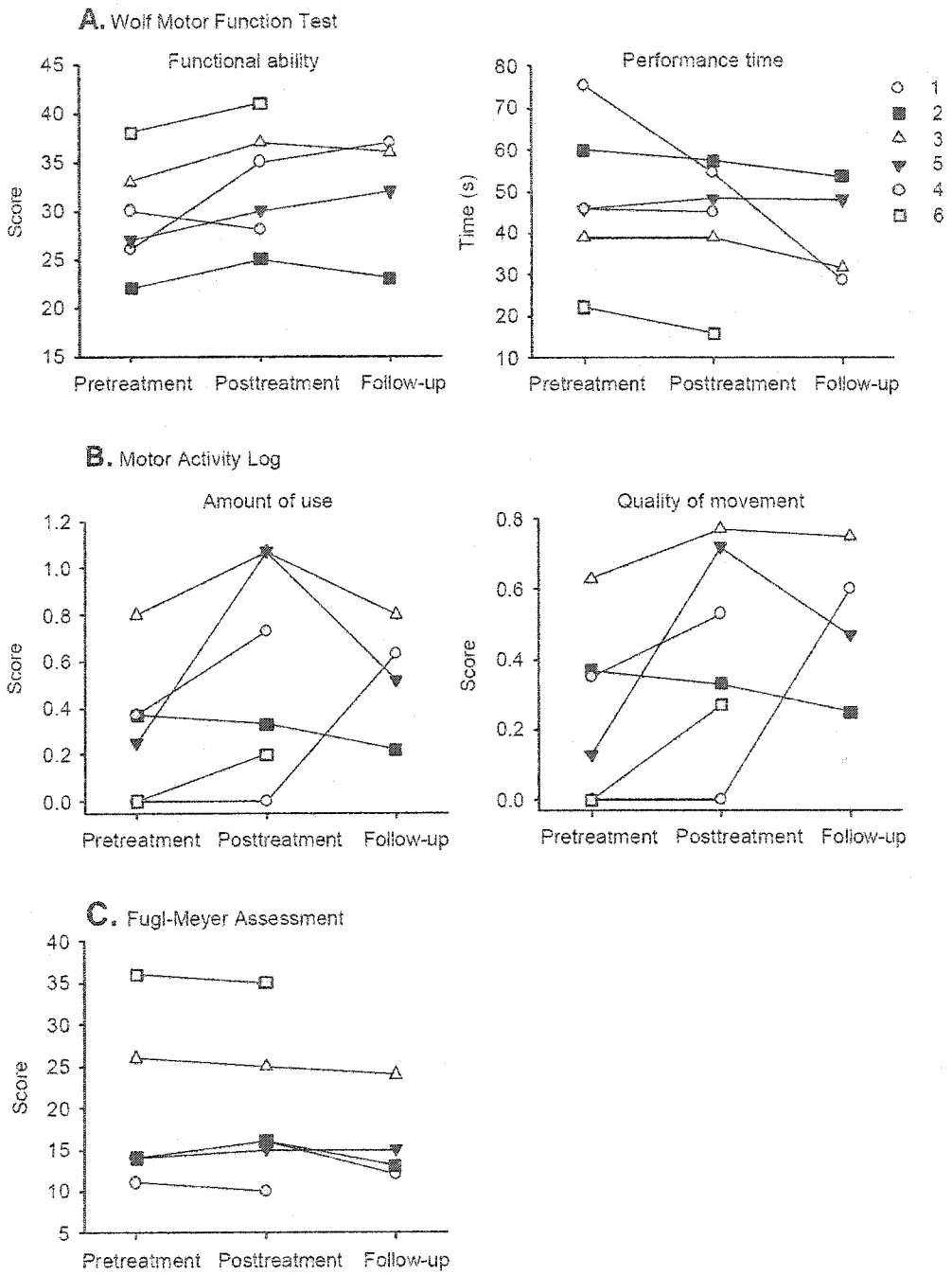

Figure 3-3. Clinical assessment data. Results from the WMFT are plotted in row A, results from the MAL in row B and results from the FMA in row C for all subjects. Two-month follow-up was done for four out of six subjects.

of data. The changes in the MAL scores were rather variable from subject to subject. The amount of use (AOU) scores increased post-treatment on average to 187% of pretreatment values (Fig. 3-3B) (mean pre/post ES = .61). At the follow-up, AOU scores had declined on average to 153% of corresponding pretreatment values (mean pre/FU ES = .64). The pattern for the quality of movement (QOM) scores of the MAL was very similar to the AOU scores (mean pre/post ES = .60; mean pre/FU ES = .24) (Fig. 3-3B). ANOVA of both QOM and AOU scores of the MAL did not show statistically significant effects of the treatment (QOM: F = 1.121, P = .386; AOU: F = .831, P = .480). There were no significant changes in the FMA scores (mean pre/post ES = .13; mean pre/FU ES = -.17; F = 3.273, P = .109).

3.4 Discussion

This pilot study indicated that 12 hours of exercise on the workstation was associated with modest improvements in upper- extremity function in 6 subjects with chronic hemiplegia. Workstation sensors recorded statistically significant improvement in hand function in all 6 subjects. All subjects included in the study were more than a year poststroke, at which time no spontaneous recovery is expected (Nakayama *et al.*, 1994). Therefore, we believe that the quantitative results represent genuine improvements in hemiplegic hand function resulting from the exercises using the workstation. Because changes in subjects' performance were also shown to be present with the WMFT, we believe that some improvement in hand function carried over to unpractised tasks.

Two months after the intervention, hand function was still augmented in comparison with the first day of treatment, according to the workstation sensors and the

WMFT. This shows the possible long-term benefit of exercise therapy using the workstation, in accordance with results reported in other exercise therapy studies (Kraft *et al.*, 1992; Sunderland *et al.*, 1992; Taub *et al.*, 1993). However, because only 4 of 6 subjects were available for the follow-up, the long-term benefits of the therapy may be under- or overestimated and will need further study.

MAL scores failed to show a statistically significant carryover effect of the improvement in hand function into the patients' ADLs. This may be because the improvements in hand function, which occurred after using the workstation for 2 weeks, were not large enough to make a significant impact on the subjects' daily activities.

The FMA results support this conclusion. We believe that the FMA, being a measure of overall motor impairment, is relatively insensitive to modest changes in hand function. Failure of the MAL to measure statistically significant carry over of functional improvements to the patients' ADLs may also be because of the limited selection of tasks in the log. Subjects included in our study had very limited hand function. It is possible that if more simple ADL tasks, which more likely would be attempted by severely affected subjects, were included in the MAL, the carry over of improvements would be more apparent. To summarize, because neither the MAL nor the FMA showed statistically significant changes in the scores, the clinical relevance of documented improvements in hand function have not been shown and merit further study.

The functional gains in hemiplegic hand function resulting from the use of the workstation were lower than gains reported for CIMT (Taub & Wolf, 1997). Factors such as fewer hours of therapeutic intervention in our study (Taub & Wolf, 1997) and less intensive daily exercise protocol (Sivenius *et al.*, 1985) may account for this difference.

Also, the subjects in our study were at a lower level of sensorimotor function than those in the CIMT studies. The inclusion criteria in those studies specified a minimum of 10° of extension at the metacarpophalangeal and interphalangeal joints and 20° of extension at the wrist (Taub *et al.*, 1993). It has been reported that stroke survivors with lower sensorimotor function have a decreased potential for recovery than those who are less severely affected (Chen *et al.*, 2000). Because of the absence of a control group, we cannot completely rule out the possibility that other forms of exercise therapy of similar duration would be as effective as using the workstation. However, the goal of our study was to make an initial evaluation of the efficacy of a workstation in delivering goal-directed exercise therapy with quantified outcomes to a group of stroke patients who usually receive no therapy at all. In this regard, the workstation approach proved to be viable and useful not only in formalizing exercise sessions but also in providing quantitative evaluation data. A controlled, blinded study, using an improved system and longer training period, is now under way.

3.4.1 Conclusion

Our study showed that the use of FES-assisted exercise therapy in conjunction with an instrumented workstation was associated with improvements in hand function in a group of hemiplegic people whose level of motor function would have excluded them from CIMT. The eventual goal of this research is to provide workstations for home use that will allow people with hemiplegia to engage in regular teletherapy sessions to improve upper-extremity function.

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CHAPTER 4

Effectiveness of FES-assisted exercise therapy for hemiplegic hand function during the subacute phase of recovery

4.1 Introduction

Previously we described a new therapeutic approach, FES (functional electrical stimulation) -assisted exercise therapy, designed for people with severe hemiparesis of their hand (Gritsenko & Prochazka, 2003). Severe hemiparesis restricts the ability of stroke patients to perform functional tasks and therefore often prevents successful reintegration of the impaired arm in daily activities, affect termed learned non-use (Taub, 1994). The FES-assisted exercise therapy combines exercise techniques derived from constraint induced movement therapy (CIMT) (Taub *et al.*, 1998), which was developed to overcome learned nonuse, with FES-assisted hand opening. Successful application of a combined (FES plus exercise) therapy for the hemiplegic upper extremity has been recently reported (Cauraugh *et al.*, 2000; Popovic *et al.*, 2002).

Several studies have addressed applicability of exercise therapies during the subacute period following stroke (Blanton & Wolf, 1999; Page *et al.*, 2002b). Certain preliminary and case studies have reported successful application of modified CIMT in subacute stroke patients (Blanton & Wolf, 1999; Page *et al.*, 2002a; Page *et al.*, 2002b). Combined FES with training therapy has also been reported to be effective during the subacute stage of recovery (Popovic *et al.*, 2002). Our study evaluates the effectiveness

of an instrumented workstation to deliver FES-assisted exercise therapy and improve hemiplegic hand function in subacute stroke patients.

Recovery of hand function after stroke has been shown to coincide with cortical reorganization in both impaired and unimpaired hemispheres (Brion *et al.*, 1989; Cicinelli *et al.*, 1997; Rossini *et al.*, 1998; Vang *et al.*, 1999; Byrnes *et al.*, 2001). The therapeutic interventions have also been shown to induce functional improvements accompanied by cortical reorganization (Traversa *et al.*, 1997; Liepert *et al.*, 1998). In this study we will measure the amount of cortical reorganization induced by the FES-assisted therapy and how well does this reorganization correlate with the functional improvements.

4.1.1 Study hypotheses:

1. Subjects receiving FES-assisted exercise therapy will have larger gains in their hand function and more pronounced cortical reorganization compared to controls.
2. Improvements in hand function will correspond to changes in cortical excitability of both control and treatment groups of subjects.

4.2 Methods

4.2.1 System

The therapeutic system comprised a workstation and a FES device. The device was a modified Impact Cuff (Prochazka *et al.*, 1997) and it was used for assistance with hand opening. Following the study described in Chapter 3 (Gritsenko & Prochazka, 2003) the workstation was redesigned to accommodate a larger number of instrumented objects and a placement section with instrumented shelves, where any unaltered objects with

light base could be used (Fig. 4-1). In addition to the objects used in the previous workstation, such as the spring-loaded doorknob and the weighted handle, a new set of objects included a door-handle, a dead-bolt, a hand exerciser and two jars of different sizes with screw-on lids. These objects were instrumented with potentiometers, except for the jars, which had infrared proximity sensors for the detection of lid attachment. The shelves in the placement section were also instrumented with the proximity sensors (Fig. 4-1). This section of the workstation was used to practice transfer of objects between shelves. The objects used in the placement section comprised blocks, cylinders and cones of various sizes. The sensors allowed us to record time and amplitude of object movement. The sensor signals were digitized (200 samples/sec) by a custom built control circuit and stored on a desktop computer. The data were later analyzed using Matlab 6.1 (Mathworks®, USA) and Excel 2003 (Microsoft®, USA) software.

4.2.2 Subjects

13 subjects with stroke-induced hemiparesis were recruited for this study among inpatients of the Glenrose Rehabilitation hospital. The subject characteristics are summarized in Table 4-1. The subjects were randomized into control and treatment groups, 7 and 6 subjects respectively. The following inclusion criteria were used during subject enrolment: 1) stroke occurred less then 3 months before the study; 2) the Brunnstrom stage for the hand was less then 4 and the subject was unable to voluntarily grasp and release any three objects on the workstation. The exclusion criteria were as following: 1) inability of FES to open the impaired hand or intolerance of FES by the

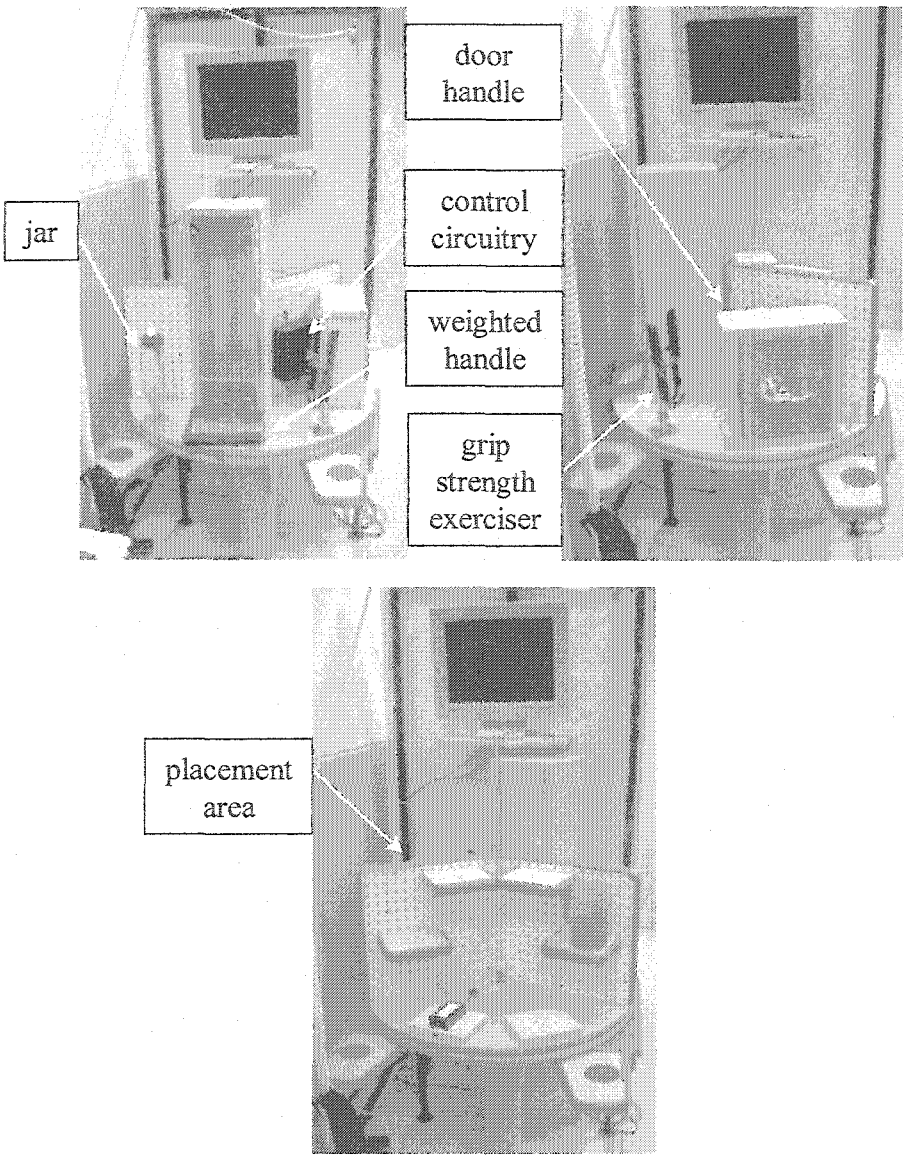


Figure 4-1. The workstation. The top of the workstation rotates 360 deg. The objects on the workstation and the shelves in the placement area are instrumented with sensors to detect various parameters of tasks performed by the subjects.

Treatment group	**SJ**	**EC**	**HF**	**WB**	**CB**	**LD**	**MB**	**Means**	**STD**
Sex	F	F	M	M	F	M	F		
Age	40	83	66	49	32	53	75	56.86	18.60
Months after stroke	1	2	1.5	2	1.5	1.5	2	1.64	0.38
Stroke hemisphere	RN	RN	LD	RN	RD	RN	LD		
Type of infarct	isch	isch	hem	hem	isch	isch	isch		
Treatment (weeks)	4	3	4	4	4	4	3	3.71	0.49
Brunnstrom, adm.	2/2	2/2	2/2	2/3	2/2	1/2	3/2	2/2.1	0.6/0.4
Control group	**WM**	**RH**	**SC**	**CF**	**MM**	**PA**		**Means**	**STD**
Sex	F	M	F	F	M	F			
Age	79	63	43	70	59	63		62.83	12.01
Months after stroke	2	2.5	2.5	2.5	1.5	1		2.00	0.63
Stroke hemisphere	RN	RN	RN	RN	LN	LD			
Type of infarct	hem	hem	isch	isch	isch	isch			
Sham treatm.(weeks)	4	4	4	3	3	3		3.50	0.55
Brunnstrom, adm.	1/1	2/2	2/2	2/1	2/2	2/2		1.8/1.7	0.4/0.5

Table 4-1. Subject characteristics. Brunnstrom values are arm / hand scores on admission. Hemispheres RN - right non-dominant, LD - left dominant, etc. Hem - hemorrhagic stroke, isch - ischemic stroke. Means - averages of group characteristics, STD - standart deviation of group characteristics.

subject; 2) serious cognitive deficit (Mini-Mental Test, score <16) (Folstein *et al.*, 1975), sensory deficits (Ontario Society of Occupational Therapy Perceptual Evaluation, score<30) (Fisher *et al.*, 1991) or severe depression (CES-D Scale, score >16) (Hautzinger & Bailer, 1993); 3) other serious medical conditions; 4) injuries to arms or hands. Three healthy control subjects who were not age matched to hemiparetic subjects were assessed by transcranial magnetic stimulation (TMS). The procedure was approved by the local hospital ethics committee and all subjects signed a letter of informed consent after receiving a description of the project.

4.2.3 Intervention

Subjects in the treatment group attended one-hour exercise sessions every workday for 3-4 weeks (15-20 sessions) in addition to their regular therapy. The subjects used their affected hand to manipulate three objects on a workstation for the duration of the session. The tasks consisted of reaching, grasping, moving (pulling, rotating, etc) and releasing an object on the workstation with the hemiplegic upper extremity. The movements were assisted by a weighted sling system when unassisted voluntary effort to move the shoulder or the elbow was insufficient for the successful accomplishment of the task. The objects were chosen as described in Gritsenko et al. (Gritsenko & Prochazka, 2003). The subjects in the control group received sham treatment for the same period of time as the treatment group. The sham treatment consisted of weak electrical stimulation of arm muscles for 15 minutes daily. The control subjects attended exercise sessions once weekly so that their performance on the workstation could be monitored and compared to performance of the treatment subjects.

4.2.4 Assessment and statistical analysis

Two types of outcome measures, kinematic scores and clinical tests, were used to assess improvement in upper extremity function. Kinematic scores were obtained from the sensors fitted to the manipulated objects. The sensor recordings were combined into performance scores for each object (OS) using the following formula:

$$OS1 = (nRT1/mRt1+nMT1/mMt1+mA1/nA1)/3,$$

where OS1 - performance score for object 1; mRt1, mMt1, mA1 - mean time to reach and grasp object 1, mean time taken to move object 1, mean amplitude of movement of object 1 respectively for each subject; nRt1, nMt1, nA1 – corresponding mean values for a normal control volunteer. The mean values were calculated by averaging timing and amplitude variables from all individual trials in one day for each object. To calculate OS for the task of transferring objects between shelves only the timing variables were averaged. Linear regression was fitted to the OS values for each subject to estimate trends in the data. The slopes of the regression lines fitted to the OS values were averaged separately for the treatment and the control groups across all tasks and for each task individually. Statistical analysis was performed using a 1-tailed t-test.

Clinical measures included the upper extremity portion of the Fugl-Meyer test (FMT) (Fugl-Meyer *et al.*, 1975), which assessed active range of motion, and the Wolf Motor Function Test (WMFT) (Wolf *et al.*, 1989), which measured motor impairment. Subjects' performance during these two tests was videotaped and rated by an occupational therapist, who was unaware of which subjects belonged to which group.

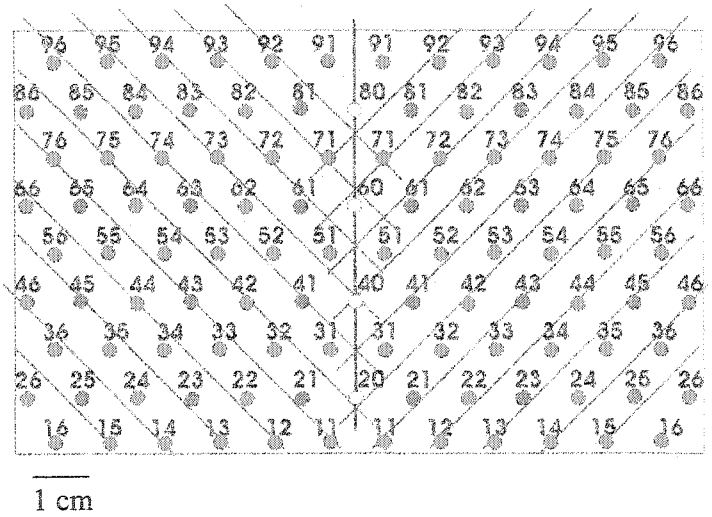
Other clinical measures included Brunnstrom scores for the upper extremity and the Functional Independence Measure (FIM), which were routinely administered to the inpatients in the hospital. During the course of the study we discovered that the Brunnstrom rating was not always consistently done on both admission and discharge, therefore pre- and post-treatment data are only available for 6 subjects. The results of these tests given on the closest dates to the start and the end of the therapy were used to further assess functional recovery. The Motor Activity Log (MAL) (Taub *et al.*, 1993) was used to estimate involvement of the hemiplegic extremity in the subjects' daily life. FMT, WMFT and MAL were administered pre-treatment, post-treatment and at 3-month and 6-month follow up. Statistical analysis was performed using a 1-tailed t-test.

4.2.5 Transcranial magnetic stimulation

In 9 out of 13 subjects TMS of motor cortex was carried out. 4 subjects were excluded from TMS assessment because of a history of seizures or unwillingness to undergo magnetic stimulation. TMS was used to map both affected and unaffected cortical representations of hand muscles. It was carried out pre-treatment, post-treatment and at 3-month and 6-month follow-up. Cortical representations of hand muscles of 3 healthy volunteers were also repeatedly mapped to establish background variability of the method.

A figure-of-eight coil was used to stimulate scalp locations over the motor cortex. The locations were determined by an equidistant grid placed over the scalp and centered on the midline of the subjects (Fig. 4-2a). Relative distance of the grid to the vertex (Cz) was recorded during each session. Before mapping commenced a hot-spot location was determined. It was defined as a scalp location where the simulation of smallest amplitude

A. Equidistant grid



B. Cortical map of the finger flexor muscle

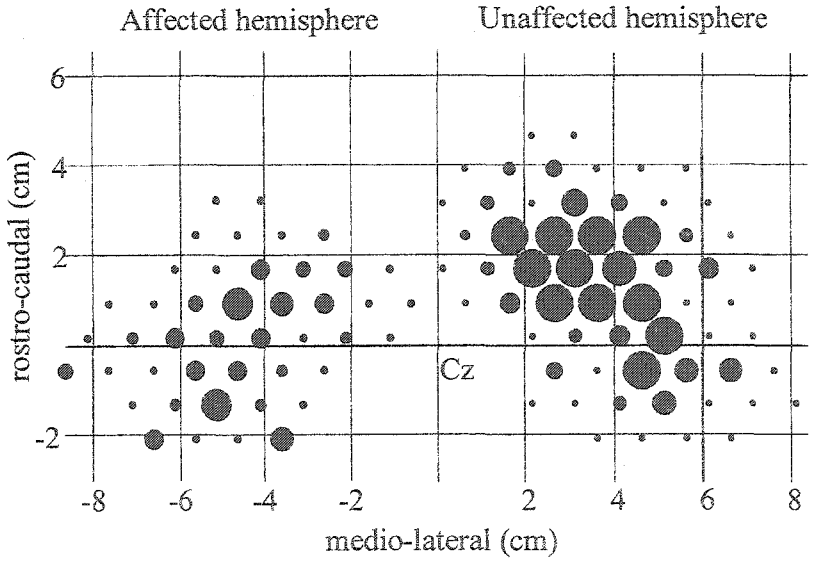


Figure 4-2. TMS methods. A. Equidistant grid, which determined the scalp locations for stimulation. The vertical line at the center of the grid was aligned with the midline. The lines at 45 deg. indicate the orientation of the coil. B. An example of a cortical map constructed from the mean amplitudes of MEPs. Cz marks the location of the vertex. The dots represent all stimulated locations with the smallest dots indicating zero response.

evoked the largest motor-evoked potential (MEP). Once the hot-spot was determined on the first session, motor threshold (MT) was measured at this location on all following sessions for each subject. MT was defined as a stimulator output value that evokes 5 MEPs larger than 10μV in response to 10 stimuli. The mapping was carried out at 110% of the motor threshold. The coil was oriented at a 45 deg angle to the midline with the handle pointing toward the back of the head. The mapping started at the hot-spot and followed outward along the grid until MEP amplitudes became less than 10μV. Four stimuli were applied to each location.

MEPs were recorded with the surface EMG electrodes over the thenar muscles (TH), the finger flexors (FF), flexor digitorum profundus, and the wrist extensors (WE), extensor carpi ulnaris, which were identified by palpation. The subjects were instructed to completely relax their muscles during stimulation, however complete relaxation of the affected hand was not always achieved. EMG was sampled at 1000Hz by a CED Power 1401 laboratory interface (Cambridge Electronic Design®, UK). The data were later analyzed using Matlab 6.1 (Mathworks®, USA). EMG was rectified and the 4 MEPs at each location were averaged. Then a portion of the mean EMG trace containing MEP was selected, the background EMG was subtracted and the resulting trace was integrated. Figure 4-2b shows an example of a motor map constructed from mean MEP amplitudes for one of the subjects. Each dot represents a stimulated scalp location. The size of the dots is proportional to the amplitude of the response to TMS at this location calculated as described above.

To compare changes in map sizes, map volume (MV) was calculated as a sum of all non-zero responses to TMS of each hemisphere. Zero response was defined as a mean

MEP less than 10μV in amplitude. MV and MT values were compared between groups using a 1-tailed t-test. The relationship between functional improvements measured by FMT and the changes in MV and MT values was estimated by calculating a correlation coefficient.

4.3 Results

Figure 4-3 shows mean performance scores for each object for all subjects with fitted linear regressions. Upward slopes of regression lines (RS) indicate improvement in performance of the corresponding task. The results show that in most instances both the treatment and the control subjects improved their performance on the workstation. For three out of four objects the mean of RS values of all the treatment subjects was slightly higher than those of the control subjects, 0.026 and 0.013 respectively. For the tasks shown in Fig. 4-3a, 4-3b and 4-3d the differences between the mean RS values for treatment and control subjects were 23%, 10% and 98% respectively. None of these differences were statistically significant. Figure 4-4 illustrates the mean RS values, averaged across all tasks for each subject. It is clear, that although there is a small difference in the group averages of the mean RS values, the data from the two groups largely overlap. The differences of the mean RS values were statistically significant. This indicates that there was no difference between improvements shown by the treatment and control subjects in their performance on the workstation.

The scores of all clinical tests indicate that most of the subjects improved in their hemiplegic hand function (Fig. 4-5 and Fig. 4-6). These tests failed to show a

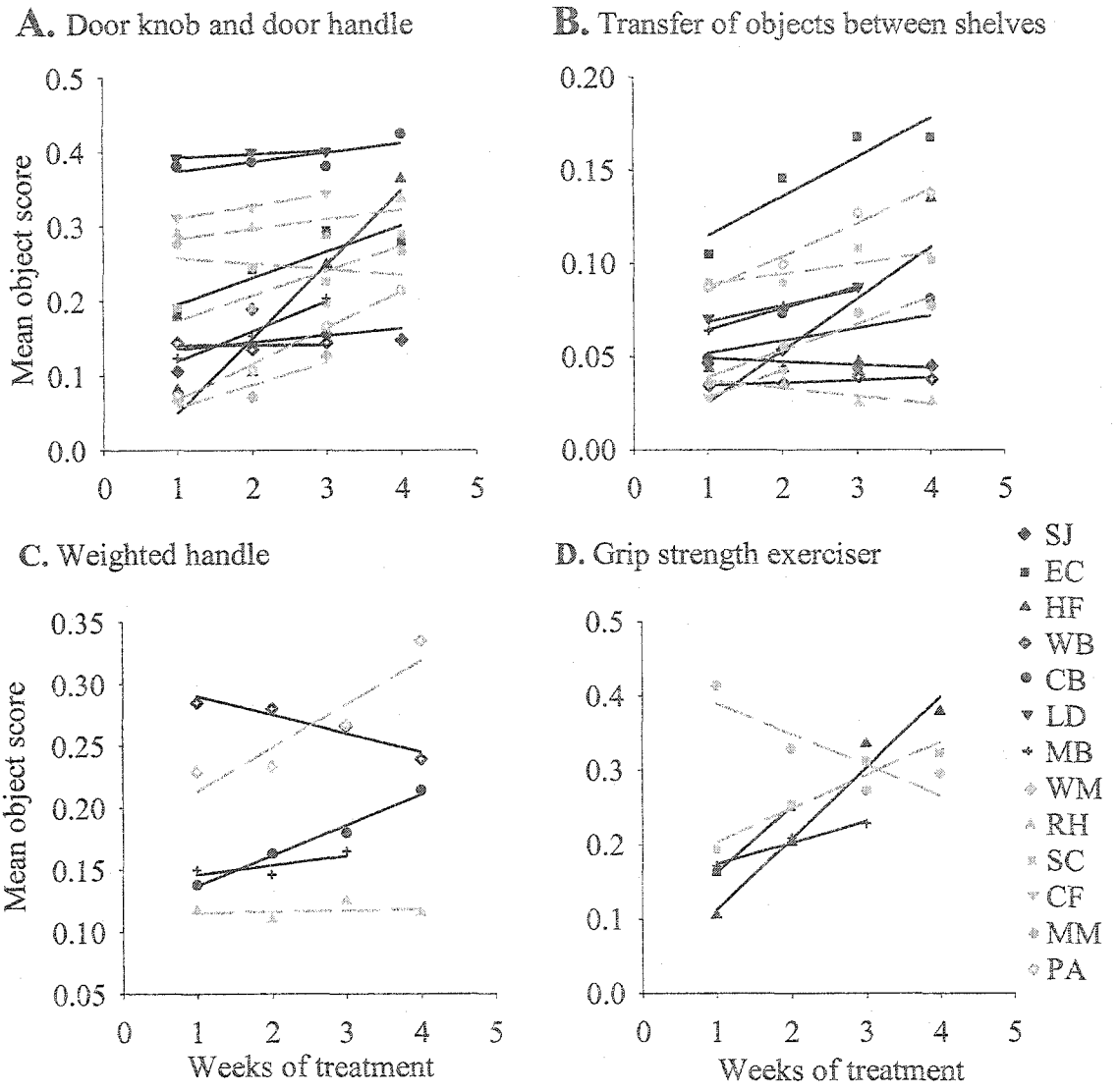


Figure 4-3. Mean performance scores for each object with linear regressions. Black symbols and solid lines - treatment group, grey symbols and dashed lines - control group. Upward slopes indicate improvement.

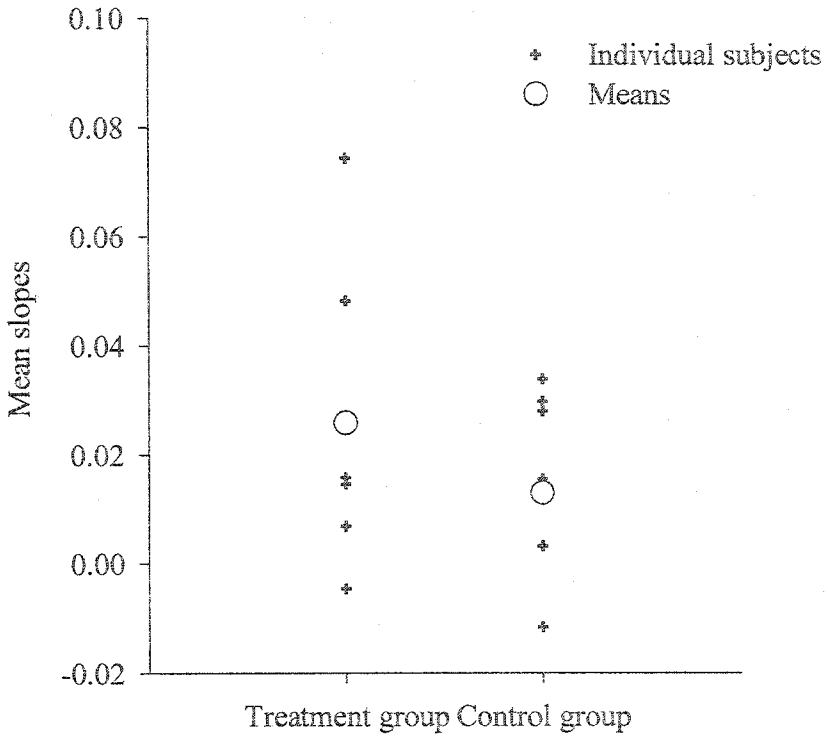


Figure 4-4. Averaged slopes of regression lines fitted to OS values. + - mean OS values per subjects; O - mean of the mean of OS values per group.

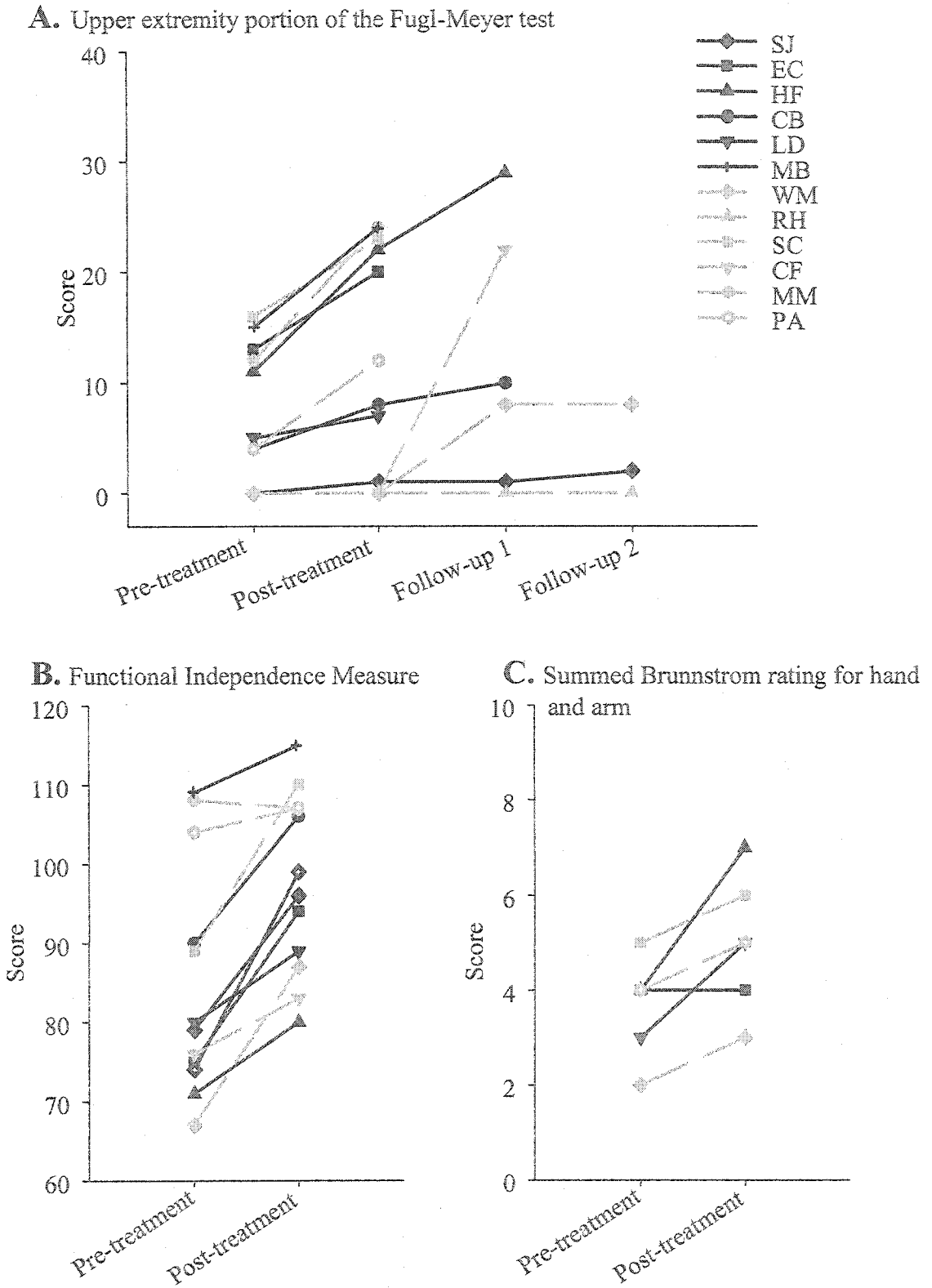


Figure 4-5. Results of FMT, FIM and the Brunnstrom rating. Black symbols and solid lines - treatment group, grey symbols and dashed lines - control group.

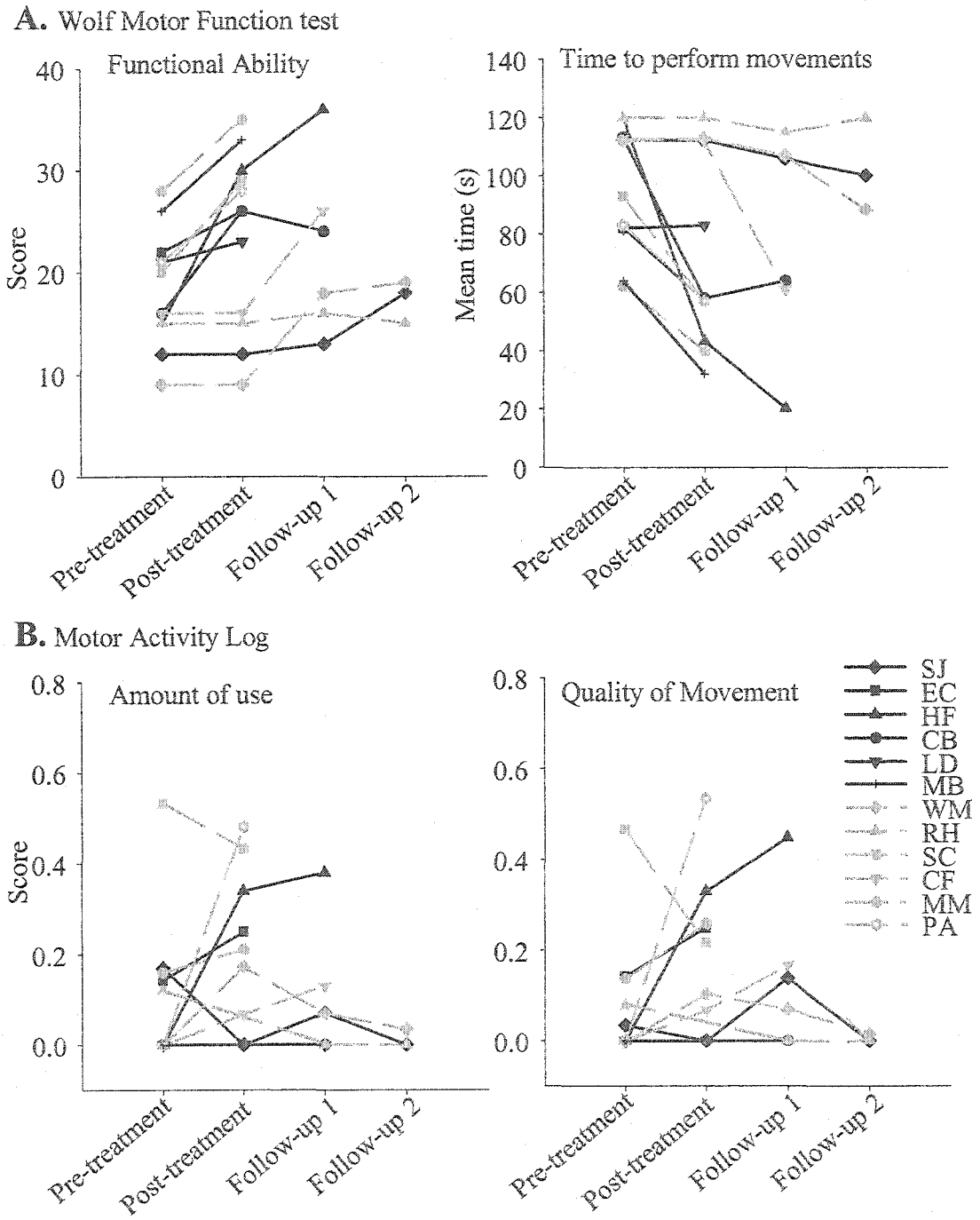


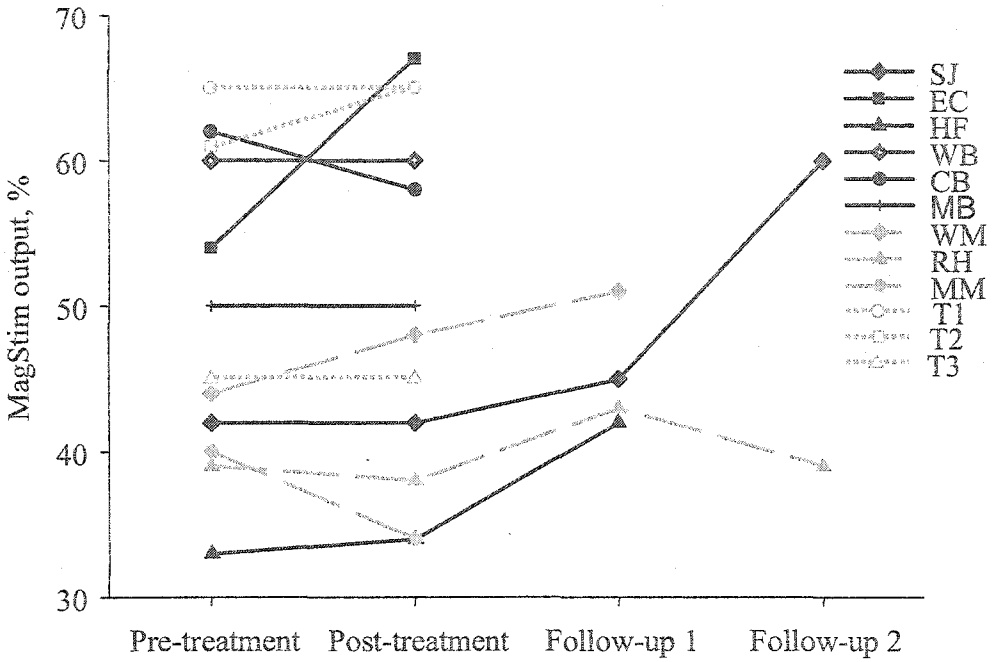
Figure 4-6. Results of WMFT and MAL. Black symbols and solid lines - treatment group, grey symbols and dashed lines - control group.

statistically significant difference between the treatment and the control group. Interestingly, the changes in the FIM scores neither correlated with the improvements in the voluntary range of motion measured by FMT (correlation coefficient, r = 0.1), nor with the improvements in the functional ability of the hemiplegic arm measured by WMFT (r = 0.05) (Fig. 4-5b). Correlation coefficient between the changes in WMFT and FMT scores was 0.5. This indicates that the functional improvements, which resulted from increased hand function, were not measured reliably by FIM.

Results of the TMS assessment are illustrated in Figures 4-7, 4-8 and 4-9. Figure 4-7a shows MT values for the unaffected hemisphere. Subjects T1, T2 and T3 are healthy volunteers, whose measurements were simply repeated twice to estimate the variability of the data. Only one subject showed a large increase in the motor threshold post-treatment. There was no difference between the change in MT of the treatment group and that of the control group. Three out of four subjects, assessed at the follow-up, showed a gradual increase in MT. The changes in FMT scores and the changes in MT for the unaffected hemisphere did not correlate (r = -0.06). The same comparison between the FMT scores and MT values for the affected hemisphere showed high negative correlation (r = -0.8). This indicates that changes in cortical excitability of the unaffected hemisphere did not underlie improvements in hand function, while small changes in excitability of the affected hemisphere in a small group of subjects seemed to correspond well with functional changes.

Only 4 out of 9 subjects showed any MEPs due to stimulation of the affected hemisphere and in one of these subjects MEPs only appeared post-treatment (Fig. 4-7b). Because the number of subjects with responses to stimulation of the affected side was

A. Threshold values for the unaffected hemisphere.



B. Threshold values for the affected hemisphere.

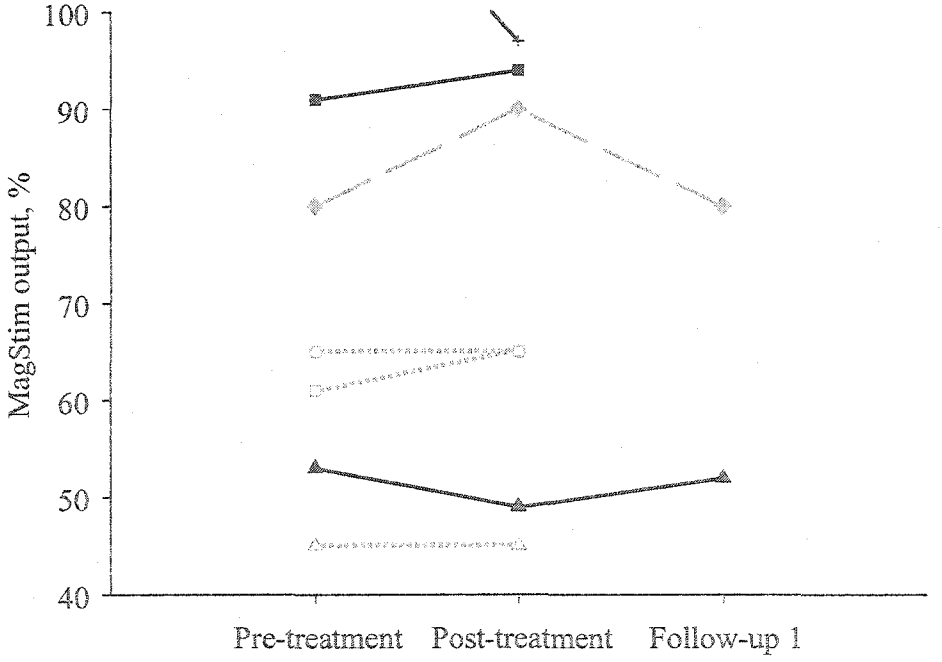


Figure 4-7. Motor threshold values. Black symbols and solid lines - treatment group, grey symbols and dashed lines - control group, open symbols and dotted line - normal controls.

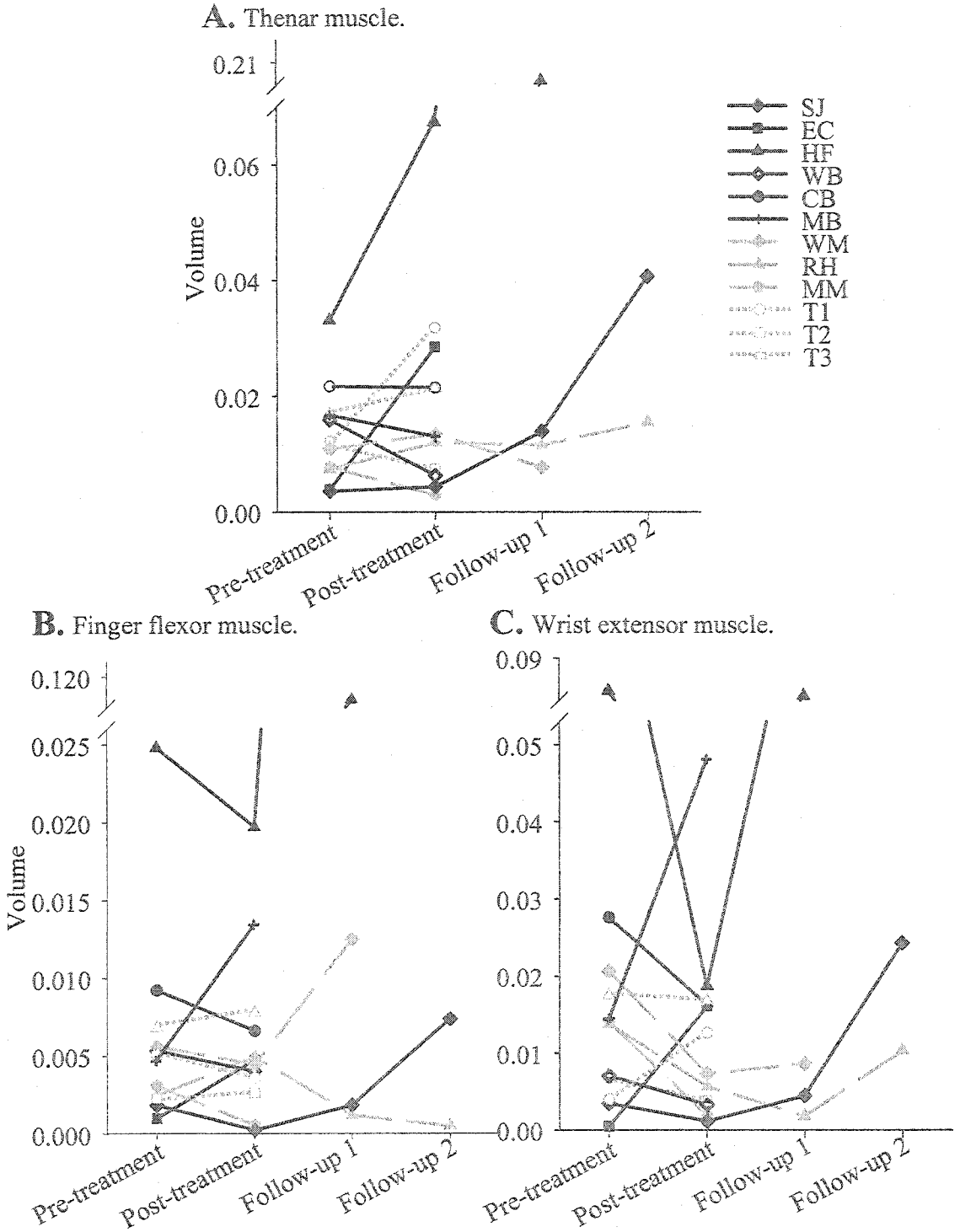


Figure 4-8. Motor map volumes of the unaffected hemisphere. Black symbols and solid lines - treatment group, grey symbols and dashed lines - control group, open symbols and dotted line - normal controls.

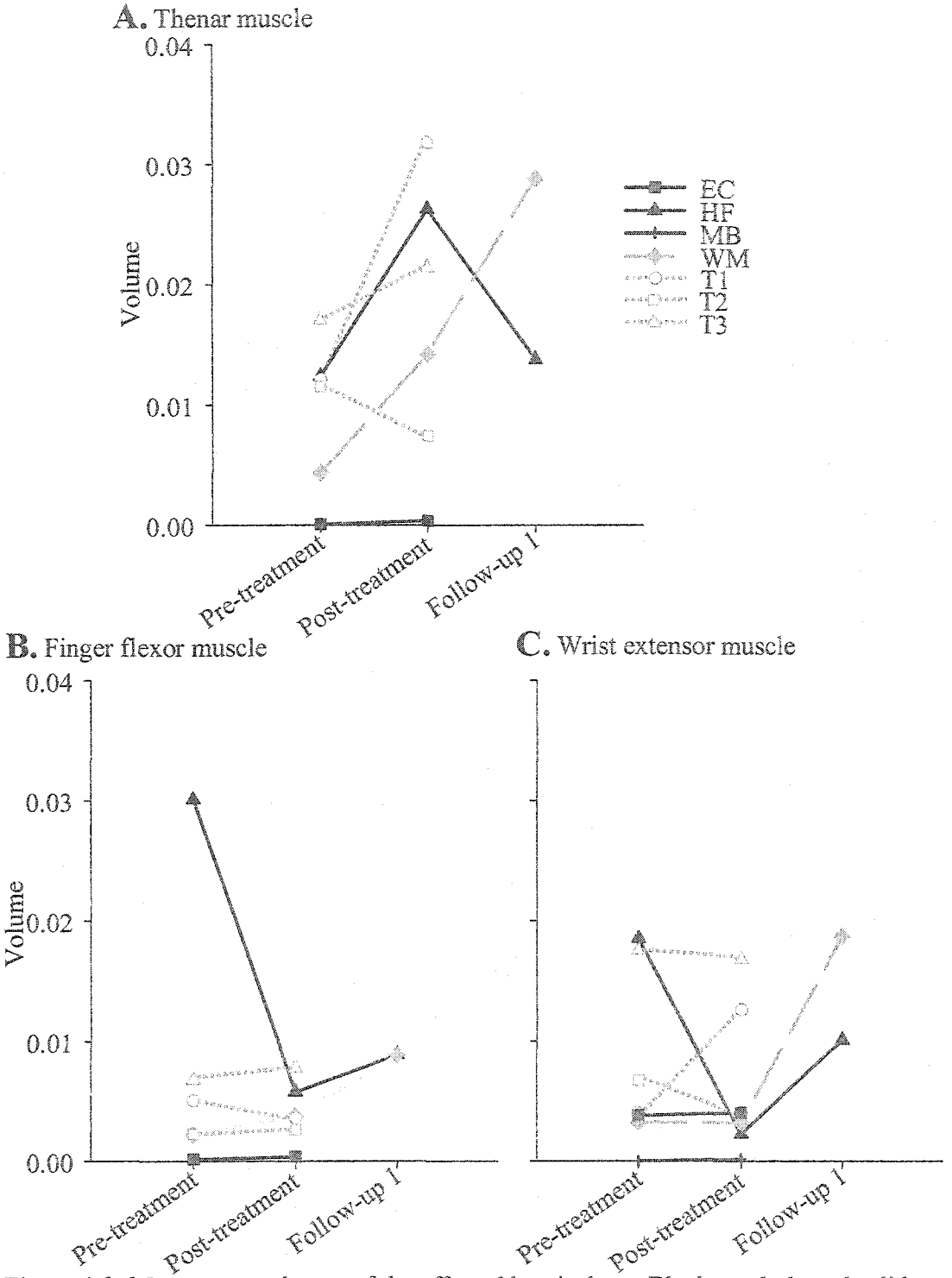


Figure 4-9. Motor map volumes of the affected hemisphere. Black symbols and solid lines - treatment group, grey symbols and dashed lines - control group, open symbols and dotted line - normal controls.

very low and only one of them was randomized into the control group, no comparisons of motor thresholds between groups can be made.

Figures 4-8 and 4-9 show MV values for TH, FF and WE muscles. The MV values were highly variable and correlated poorly with the changes in hand function as measured by FMT. The correlation coefficients between the difference in pre-/post-treatment scores of FMT and the changes in unaffected MV values for the TH, FF and WE muscles were 0.28, -0.03 and -0.2 respectively. Subject HF, who had the largest MEPs and showed very large changes in map volumes, sometimes in the opposite direction for different muscles, largely influenced the values of the correlation coefficients for the whole group. If he is excluded from the calculations, the correlation coefficients are -0.11, 0.24 and 0.41 for TH, FF and WE muscles respectively. There was no statistically significant difference in MV changes between the treatment and control groups. No clear trend is visible from the volume measurements of the affected maps (Fig. 4-9). This indicates that MV values are unreliable measures of cortical excitability.

4.4 Discussion

The first hypothesis, stating that subjects receiving FES-assisted exercise therapy will show larger gains in their hand function in comparison to controls, was not supported by the study. The results indicate that FES-assisted exercise therapy does not improve hemiplegic hand function of subacute stroke patients beyond that occurring spontaneously or due to existing clinical rehabilitation techniques. A number of factors may account for this result. It is possible that there are not enough subjects recruited for the study to detect a difference between the control and treatment groups. We conducted

a power analysis in order to estimate the sample size needed to obtain a statistically significant difference in the mean scores between the control and the treatment groups. The analysis has shown that, assuming the same variability of data, 50 more subjects are needed in each group in order to detect the 46% difference in RS means (Fig. 4-4) or the 65% difference between the changes of WMFT scores for different groups (Fig. 4-6a, Functional Ability) with statistical significance. Recruitment of so many subjects is beyond the scope of this study, because of a limited number of patients at the Glenrose Rehabilitation hospital who are eligible to participate in the study.

Another reason for the ineffectiveness of the therapy to improve hand function of the treatment subjects more than that of the control subjects may be that the amount of therapy already administered by the hospital saturates the ability of subacute stroke patients for recovery. In other words, the patients may already be recovering as fast as they can and the addition of another therapy has no benefit. Lowered endurance of subacute stroke patients due to the disruption of their circulatory system (Adams & Imms, 1983; Takeyasu *et al.*, 1989; Mori *et al.*, 1994) and other factors, such as medications, sensory disturbances or cognitive problems, may limit the amount of therapeutic intervention they can endure and, therefore, the speed of their recovery (Dobkin *et al.*, 2003).

The evidence for the benefits of early therapeutic intervention following a stroke is at times contradictory. Animal studies indicate that early intervention may exacerbate damage to the nervous tissue and worsen the outcome (Kozlowski *et al.*, 1996; Humm *et al.*, 1998). A recent human study investigating effectiveness of prolonged upper- and lower-extremity therapies has found no positive effects of both therapies on functional

recovery of subacute stroke patients beyond that exhibited by the control group subjects (Kwakkel *et al.*, 2002). On another hand, other studies have reported that modified CIMT, combined FES and training therapy and intensive conventional therapeutic exercise do induce gains in function (Page *et al.*, 2002a; Popovic *et al.*, 2002; Duncan *et al.*, 2003). However, the latter studies have also reported that the subjects with high hand function at the beginning of the treatment improve much more than the low functioning subgroups of subjects. In our study we have purposefully recruited stroke patients with severe hemiparesis of the arm and hand, some of whom were even lower in their hand function compared to the subjects recruited in the studies by Page *et al.*, Popovic *et al.* and Duncan *et al.* Other studies have reported that the lower functioning stroke patients have less potential for recovery (Chen *et al.*, 2000), which may help explain the lack of effect in our study.

Analysis of the responses to TMS of the affected hemisphere in 4 subjects showed no consistent differences between the changes in cortical excitability of the 3 treatment subjects and 1 control subject. The motor threshold values for the affected hemisphere seemed to correlate well with functional changes of individual subjects measured by FMT. Decreased motor threshold corresponded with increased functional recovery, which is consistent with the results of other studies (Heald *et al.*, 1993; Catano *et al.*, 1996; Pennisi *et al.*, 2002). This indicates that motor threshold measurements may be useful for estimation of cortical excitability. However, the number of subjects with responses to TMS of the affected hemisphere is not large enough to draw any definite conclusions. Interestingly, the subjects with responses in the affected hemisphere were not always the ones showing the largest functional gains. This contradicts other reports

stating that the absence of MEPs is a reliable predictor of poor recovery of function (Catano *et al.*, 1995; Escudero *et al.*, 1998; Pennisi *et al.*, 1999).

Changes in map volumes that were documented for the affected hemisphere were variable and poorly correlated with functional recovery measured by the clinical tests. Some of the variability in the volume measurements for the affected hemisphere may come from variable involuntary background activity of hand muscles in spastic subjects. Other studies have shown that MEP amplitudes and various other outcome measures calculated from them do vary between measurements in normal and brain damaged subjects (Catano *et al.*, 1995; Ellaway *et al.*, 1998; Uy *et al.*, 2002). This shows that large variability of map volume measurements precludes their successful usage as a measure of cortical excitability.

The responses to TMS of the unaffected hemisphere did not correlate with functional recovery and did not show any differences between the control and treatment groups despite existing reports of cortical reorganization in the unaffected hemisphere, which seem to underlie recovery of function following a stroke (Chollet *et al.*, 1991; Weiller *et al.*, 1992). In our study, 3 out of 4 subjects assessed at the follow-up showed consistent increases in the motor thresholds of their unaffected hemispheres. These subjects have improved in their functional abilities, which were measured by the clinical tests, despite a decrease in the excitability of their unaffected hemispheres (Fig. 4-7a). This result argues against involvement of the unaffected hemisphere in functional recovery. However, because more follow-up data is yet to be collected, no definite conclusion regarding this issue can be drawn.

In conclusion, the study results indicate that FES-assisted exercise therapy for hemiplegic hand function did not increase functional recovery of subacute stroke patients beyond that seen in control subjects. Map volume measurements using TMS were found to be unreliable for estimation of changes in cortical excitability of subacute stroke patients with severe hemiparesis.

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CHAPTER 5

General Discussion

Three separate studies are described in this thesis, all of which concern CNS plasticity following injury. Chapter 2 investigated plasticity following damage to peripheral nerves in cats, while Chapters 3 and 4 studied plastic changes following stroke in humans. Other studies have shown that damage to PNS can induce adaptive plasticity in neural pathways in the spinal cord (Goldberger, 1988; Whelan *et al.*, 1995) as well as in supraspinal centers (Donoghue & Sanes, 1988; Sanes *et al.*, 1990; Cohen *et al.*, 1991; Pons *et al.*, 1991; Carrier *et al.*, 1997). Specifically, it was hypothesized that changes in gain in the spinal oligosynaptic pathways from muscle afferents to motoneurons play a part in adaptive plasticity after damage to peripheral nerve (Whelan *et al.*, 1995; Pearson *et al.*, 1999). The study in Chapter 2 tested the existence of plasticity in the pathways underlying short- and medium-latency stretch reflexes. It found changes in these pathways, but they were proportional to the changes in the descending locomotor drive. This indicates that adaptive plasticity following PNS damage does not involve the oligosynaptic pathways from Ia, II and possibly Ib afferents to motoneurons, arguing against a change in gain independent of activation level.

Plasticity following CNS damage such as stroke has also been documented in a variety of brain structures. Plastic changes in motor cortical region M1 (Glees & Cole, 1950; Nudo & Milliken, 1996), premotor cortex (Liu & Rouiller, 1999), supplementary motor area (Aizawa *et al.*, 1991) and the cerebellum (Chollet *et al.*, 1991) in the

hemisphere affected by the damage have been implicated in driving recovery of motor function. Plastic changes in the undamaged hemisphere have also been documented; however, the debate about the role of these changes in functional recovery is still under way (Chollet *et al.*, 1991; Weiller *et al.*, 1992; Honda *et al.*, 1997; Seitz *et al.*, 1998). The study in Chapter 3 investigated plastic capabilities of the brain following a stroke, which took place more then a year before the study. The results of this study showed that adaptive plasticity can be induced by FES-assisted exercise therapy in people with severe chronic hemiplegia, who are generally believed to have reached a plateau in their recovery (Nakayama *et al.*, 1994; Chen *et al.*, 2000). Chapter 4 describes a study, which investigated adaptive plasticity during the subacute phase after a stroke in a group of people with severe hemiplegia. Although during the course of this study adaptive plasticity was documented in the form of functional improvements of all subjects, enhancement in functional recovery of the treatment group of subjects compared to controls did not reach statistical significance. This indicates that there may be an upper limit to the effectiveness of rehabilitation to increase functional plasticity of severely affected stroke patients during the subacute stage of their recovery (Dobkin *et al.*, 2003). The study in Chapter 4 also found that the map volume, a variable widely used in TMS studies, was unreliable in measuring changes in cortical excitability in the subacute group of stroke patients with severe hemiplegia.

The studies described in this thesis have deepened our understanding of damage induced changes in CNS by investigating the neural sites of adaptive plasticity and methods of its augmentation.

5.1 Future directions

The results of the thesis have shown that FES-assisted exercise therapy is effective during the chronic stage of recovery following stroke. However, during the course of the study questions were raised about the future application of the therapy in a clinical setting. The results of the study suggest that chronic stroke patients may benefit more from a prolonged intervention. However, the difficulties that people with severe hemiplegia experience with commuting can prevent a large proportion of patients from participating in future studies. Therefore, the next logical step in the development of the FES-assisted therapy is to deliver it in the homes of the patients. This would allow the therapy to reach more people, extend the duration of their therapy and broaden the range of questions which could be addressed by future studies.

During the course of the studies in Chapter 3 and 4 the workstation was redesigned twice in order to improve its user-friendliness and adaptability to each subject's unique impairments. The last workstation was found to be adequate for the delivery of the therapy provided that another person was present, e.g. an occupational therapist, to help with minor readjustments of the objects for each subject. In order to make the workstation more automated it is currently being redesigned so that the need for an assisting person is removed. The future workstation will be comprised of a motorized base with modular objects attached to it. The base will be outfitted with motors, which will move the objects in horizontal and vertical directions. The modules of each object will be designed to accommodate a variety of tasks and they will have the ability to move in the third dimension (toward and away from the subject). This will ensure effortless

adjustment of the workstation to the needs of each subject and broaden the variety of tasks that can be performed during the exercise sessions. The workstation will also be compact and easily transportable so that it can be put in a subject's home.

The new workstation will also be more automated in its delivery of the exercise therapy. Software will be written, which will analyze all the sensor signals from the workstation objects and provide on-line feedback and guidance to the subjects regarding their task performance. The software will contain personalized information on the choice of tasks for each subject and will be able to detect how well they are carried out. This will allow the program to display statistics on the performance of each subject and to detect any problems with the workstation components.

While complete automation of an exercise therapy is feasible, the value of expert opinion of a therapist and his/her personal interaction with a patient should not be underestimated. To take these issues into account one of the directions to pursue with the home based therapy is remote monitoring of the patients by the therapist over the Internet. The workstation computers in patients' homes will be connected to one of the computers in the laboratory with teleconferencing equipment. This will allow patients and the therapist to interact during exercise sessions. The role of the therapist will be to observe the progression of the therapy and to offer advice and encouragement to the subjects during their exercises.

Another issue arising from the studies described in this thesis is the type of outcome measures that are most reliable for the evaluation of functional improvements. The FIM is used widely to assess improvements following therapeutic interventions

(Chae *et al.*, 1995; Miyai *et al.*, 1997; Chen *et al.*, 2000; Shelton *et al.*, 2001). Results in Chapter 4 indicate that FIM does not adequately reflect the changes in function measured by other more direct tests, such as FMT and WMFT. FMT in its turn was found to be rather insensitive to small changes both in our study, described in Chapter 3, and in studies by other researchers (van der Lee *et al.*, 2001; Mao *et al.*, 2002). The workstation built for the delivery of FES-assisted exercise therapy offers quantitative measures of functional improvement. The tasks performed on the workstation can be adjusted to match the level of impairment in individual patients, all the parameters of the tasks can be reliably replicated and the sensor data can be analyzed to produce an objective performance score. A future study is in the planning stage that would test the reliability and sensitivity of the performance score for quantification of improvements in hemiplegic hand function during spontaneous recovery and after an injection of botulinom toxin prescribed for relief of spasticity.

In the studies included in this thesis no attempt was made to dissociate the effects of FES and training on functional improvements of stroke patients. The combination of FES with training has been shown to be more effective than the use of FES alone for restitution of walking (Ladouceur & Barbeau, 2000; Barbeau *et al.*, 2002). Similar comparisons can be made in one of the future studies pertaining to the augmentation of hemiplegic hand function. During the proposed study the FES device would be given for home use to one group of subjects, while the other group would receive both the FES device and exercise training on the workstation. Comparing the functional improvements between groups immediately following the treatment period and at a few follow-up dates

would provide a more definitive answer to the question of which approach is more beneficial. Based on the results from other studies, it is most likely that the combined FES and training therapeutic protocol will prove to be the most beneficial (Ladouceur & Barbeau, 2000; Barbeau *et al.*, 2002; Cauraugh & Kim, 2002; Chae, 2003).

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