Brain Plasticity and Upper Limb Function After Stroke: Some Implications for Rehabilitation

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Abstract

Neuroimaging and neurophysiology techniques were used to study some aspects of cortical sensory and motor system reorganisation in patients in the chronic phase after stroke. Using Diffusion Tensor Imaging, we found that the degree of white matter integrity of the corticofugal tracts (CFT) was positively related to grip strength. Structural changes of the CFT were also associated with functional changes in the corticospinal pathways, measured using Transcranial Magnetic Stimulation. This suggests that structural and functional integrity of the CFT is essential for upper limb function after stroke.

Using functional magnetic resonance imaging (fMRI), to measure brain activity during slow and fast passive hand movements, we found that velocity-dependent brain activity correlated positively with neural contribution to passive movement resistance in the hand in ipsilateral primary sensory (S1) and motor (M1) cortex in both patients and controls. This suggests a cortical involvement in the hyperactive reflex response of flexor muscles upon fast passive stretch.

Effects of a four week passive-active movement training programme were evaluated in chronic stroke patients. The group improved in range of motion and upper limb function after the training. The patients also reported improvements in a variety of daily tasks requiring the use of the affected upper limb.

Finally, we used fMRI to explore if brain activity during passive hand movement is related to time after stroke, and if such activity can be affected with intense training. In patients, reduced activity over time was found in supplementary motor area (SMA), contralateral M1 and prefrontal and parietal association areas along with ipsilateral cerebellum. After training, brain activity increased in SMA, ipsilateral S1 and intraparietal sulcus, and contralateral cerebellum in parallel with functional improvements of the upper limb. The findings suggest a use-dependent modification of cortical activation patterns in the affected hand after stroke.

Keywords: Stroke, Upper Limb, Brain Plasticity, Functional MRI, Diffusion Tensor Imaging, Transcranial Magnetic Stimulation

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To Véronique and Ruben
List of included studies


CONTENTS

1.0 INTRODUCTION
   1.10 Rehabilitation and upper limb function after stroke
      1.11 What is stroke?
      1.12 What is stroke rehabilitation?
      1.13 Upper limb function after stroke
      1.14 Clinical course and prognostic factors
      1.15 Rehabilitation interventions
      1.16 Recovery strategies
   1.20 Brain plasticity
      1.21 Sensory and motor system organisation
      1.22 Plasticity in the uninjured brain
      1.23 Brain plasticity after stroke

2.0 AIMS

3.0 SUBJECTS AND METHODS
   3.10 Subjects
   3.20 Clinical measurement of upper limb function
   3.30 Estimation of neural contribution to passive movement resistance
   3.40 Neuroimaging and neurophysiological techniques
      3.41 Functional magnetic resonance imaging (fMRI)
      3.42 Diffusion tensor imaging (DTI)
      3.42 Transcranial magnetic stimulation (TMS)
   3.50 Training programme

4.0 RESULTS AND DISCUSSION
   4.10 Degeneration and plasticity in the sensory and motor system and hand function
      4.11 Wallerian degeneration of the corticofugal tracts and hand function
      4.12 Cortical activity in ipsilateral primary sensory and motor cortex in relation to the neural contribution to passive movement resistance in the flexor muscles of the hand
   4.20 Use-dependent plasticity after stroke
      4.21 Effects of passive-active movement training
      4.22 Cortical activity changes in relation to time after stroke
      4.23 Training-induced cortical activity changes

5.0 CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

6.0 ACKNOWLEDGEMENTS

7.0 REFERENCES
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOLD</td>
<td>blood oxygen level dependent</td>
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<tr>
<td>CFT</td>
<td>corticofugal tracts</td>
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<td>CMA</td>
<td>cingulate motor area</td>
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<td>CP</td>
<td>cerebral peduncle</td>
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<td>DTI</td>
<td>diffusion tensor imaging</td>
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<td>EMG</td>
<td>electromyography</td>
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<td>FA</td>
<td>fractional anisotropy</td>
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<td>M1</td>
<td>primary motor cortex</td>
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<td>M1EMG</td>
<td>short latency EMG response</td>
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<td>M2EMG</td>
<td>long latency EMG response</td>
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<td>MAS</td>
<td>motor assessment score</td>
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<td>MEG</td>
<td>magnetoencephalography</td>
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<td>MEP</td>
<td>motor evoked potential</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>PMC</td>
<td>premotor cortex</td>
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<td>RC</td>
<td>recruitment curve</td>
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<td>S1</td>
<td>primary sensory cortex</td>
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<td>S2</td>
<td>secondary sensory cortex</td>
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<td>SMA</td>
<td>supplementary motor area</td>
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<td>SP</td>
<td>silent period</td>
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<td>TMS</td>
<td>transcranial magnetic stimulation</td>
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<td>WD</td>
<td>Wallerian degeneration</td>
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1.0 INTRODUCTION

1.10 Rehabilitation and upper limb function after stroke

1.11 What is stroke?
Stroke is defined by the World Health Organization (WHO) as “a condition characterised by rapidly developing symptoms and signs of a focal brain lesion, with symptoms lasting for more than 24 hours or leading to death, with no apparent cause other than that of vascular origin” (WHO, 1989). Stroke is a leading cause of morbidity and mortality with incidence rates around 200 per 100,000 inhabitants and year (Sarti et al, 2000; Riks-stroke, 2006). A majority of surviving patients exhibit a persisting motor disorder (Hendricks et al, 2002a). Weakness, caused by damage of cortical networks for movement and their projections and disuse-related mechanisms, is considered a major cause of disability (Twitchell 1951; McComas et al, 1973). Up to two thirds of stroke survivors experience impaired function in the upper limb (Jorgensen et al, 1995).

1.12 What is stroke rehabilitation?
Stroke rehabilitation can be considered as a process composed of medical, physical, psychological, social, educational and vocational interventions. The interventions are tailor-suited to match the goals of each individual. Most often the goal is to achieve a level of physical and psychological functioning that allows return home and performance of everyday activities. If the patient has severe limitations and it is believed that recovery is unlikely the alternative goal may be to aid the patient in modifying his/her desires to match his/her capacities (Pörn, 1984). Helping the patient to define reasonable goals for treatment is thus an important part of contemporary stroke rehabilitation. The final outcome depends on a complex interaction of multiple factors such as lesion characteristics, pre-stroke status of the person, comorbidities, interventions, etc.

Understanding how pathophysiological and brain plasticity mechanisms are related to functional outcome and recovery of the upper limb should help to improve rehabilitation interventions in the future. A general aim of this thesis was thus to examine the relation between upper limb function and reorganisation in the sensory and motor system using in vivo neuroimaging techniques.

1.13 Upper limb function after stroke

Weakness
In the upper limb a lesion of the sensory and motor circuits typically causes greater weakness of the wrist and fingers muscles compared to proximal shoulder muscles (Colebtach and Gandevia, 1989). Together with abnormal movement synergies (Twitchell, 1951; Brunnström, 1970; Welmer et al, 2006)
and impaired coordination in multiple joint movements (Levin, 1996; Beer et al, 2000) the resulting weakness may impair movement production and control which leads to limitations in goal oriented activities, independence in every day living and work capacity.

It seems likely that the degree of weakness is crucial in determining degree of movement deficit (Kamper et al, 2006; Ada et al, 2006a) but other motor disorders, such as spasticity, as well as other factors may also contribute. These include degree of sensory impairment, visual and perceptual problems (e.g., neglect), cognitive, emotional and speech-related difficulties. Environmental factors are also important as movements occur as interactions between the individual, the task, and the environment where the task is being performed (Shumway-Cook and Woollacott, 1995).

**Spasticity**

Spasticity is defined as “a motor disorder characterised by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex” according to Lance (1980). Spasticity also contributes to the movement deficit after stroke. When assessed by use of the modified Ashworth scale, spasticity is observed in about one fifth or more of all stroke patients (Sommerfeld et al, 2004; Watkins et al, 2002). There are both (i) non-neural and (ii) neural components which contribute to the increased resistance to passive movement in spasticity. The non-neural components include: spastic muscle cell atrophy and fibre type transformation (Dietz et al, 1986); reduced sarcomere length and changed muscle and extracellular viscoelastic properties (O’Dwyer et al, 1996; Singer et al, 2003; Friden and Lieber, 2003; Olsson et al, 2006). Neural components include: reduced stretch reflex thresholds and increased gain of the stretch reflex (Thilmann et al, 1991; Ibrahim et al, 1993; Pierrot-Deseilligny and Burke, 2005; Nielsen et al, 2007).

Hyperactive spinal stretch reflexes are associated with spasticity (Lance, 1980; Ibrahim et al, 1993). At present there is only some indirect evidence suggesting the possibility of supraspinal involvement in these reflex responses:

(i) Previous studies of electromyography (EMG) activity upon passive muscle stretch have shown a long-latency stretch reflex component with a duration that would allow for processing via a supraspinal loop (Kamper and Rymer, 2000; Ibrahim et al, 1993)

(ii) Animal studies have shown that passive stretch of a hand muscle results in neural activity in contralateral primary motor cortex (M1) (Cheney and Fetz, 1984)

(iii) Transcranial magnetic stimulation (TMS) studies in healthy humans have shown that stimulation over the contralateral M1 during an active task (to reduce the function of M1) can perturb corrective reflex
responses in active hand muscles (Palmer and Ashby, 1992; Lewis et al, 2004; Taylor et al, 1995)

(iv) Inhibition of contralateral M1, induced by transcallosal inhibition from ipsilateral M1, can also lead to reduced corrective reflex responses in active hand muscles (Tsuji and Rothwell, 2002)

(v) Subcutaneous nerve stimulation at the wrist can result in prolonged suppression of spinal reflexes in the ankle, which was considered to reflect supraspinal modulation of spasticity (Walker, 1982).

Studies showing a direct involvement of transcortical pathways in passive movement resistance after stroke are lacking (Brown, 1994; Sheean, 2002). This question is addressed in Study II.

1.14 Clinical course and prognostic factors

Recovery after stroke is highly variable, but most patients who survive show some degree of recovery. Meaningful assessment of final outcome and disability after stroke should encompass (i) body function and structure and (ii) activities domains of health according to the World Health Organization classification of functioning, disability and health (WHO, 2001). Measurements which are sensitive also to minor disabilities in patients with mild symptoms should be used. For example, mild paresis may cause limitations observable when performing a precision grasp but not hand grasp.

Most recovery of motor function occurs within 3-6 months post-stroke (Jorgensen et al, 1997) and recovery is assumed to plateau after 6 months (Jorgensen et al, 1995; Page et al, 2004). Only about 50% of the stroke patients with initial arm paresis regain useful function (Wade et al, 1983; Sunderland et al, 1989). Recovery is dependent on the severity of the initial symptoms: 79% of patients with mild paresis show full recovery of arm function whereas only 18% of patients with severe paresis show full recovery (Nakayama et al, 1994).

Studies of clinical markers of outcome suggest that the final motor outcome might be defined within the first month after stroke (Duncan et al, 1992). Arm function at six months can be predicted by use of the Fugl-Meyer motor evaluation of the arm measured at four weeks (Kwakkel et al, 2003). This suggests that the potential for motor recovery is defined early after stroke. However, functional gains are possible without measurable improvements in motor function, e.g., improved self care and mobility by use of technical aids and through learning of compensatory movement patterns (Shelton et al, 2001a). Thus many other learning-related factors (e.g., behavioural, psychological) are probably involved in determining the final outcome.
Does the lesion relate to functional outcome of the upper limb after stroke?
To investigate how the lesion relates to functional outcome in patients with stroke, studies have also been performed using a variety of brain imaging techniques. In humans, a number of imaging studies have investigated whether lesion size (Pendlebury et al., 1999; Saver et al., 1999; Feys et al., 2000) or location (Binkofski et al., 2001; Fries et al., 1993; Shelton and Reding, 2001; Chen et al., 2000) correlate with motor outcome. Several of these studies indicate that lesions which damage the descending corticofugal projections have most impact on motor function.

The descending corticofugal tracts (CFT) connect cortical areas important for movement with the spinal cord. Part of the CFT is composed of the corticospinal tract (synonymous with “pyramidal tract”). Early studies in monkeys suggested that lesions of the corticospinal tract caused impaired independent movements of the fingers without impairing hand grasp or other functions (Bucy et al., 1966; Hepp-Reymond et al., 1974; Lawrence and Kuypers, 1968). The corticospinal tracts are thus thought to play a key role in complex voluntary selective hand movements such as independent finger movements and the precision grip (Davidoff, 1990; Wise and Evarts, 1981; Lawrence and Kuypers, 1968). Such corticospinal projections originate both from the primary motor cortex and from the more frontally located motor areas (Dum and Strick, 2002) and connect directly to inteneurones and motoneurones in the cervical spinal cord. The CFT also includes corticobulbar projections likely important for hand motor control.

Studies using transcranial magnetic stimulation (TMS) early after stroke have also shown that lack of motor evoked potentials (MEPs) in hand muscles is associated with poor functional outcome (Heald et al., 1993; Binkofski et al., 1996; Pennisi et al., 1999). Conversely, the presence of MEPs in the hand muscles is associated with good functional outcome (Hendricks et al., 2002b). Novel imaging techniques which allow quantification of white matter structure in the brain (Diffusion Tensor Imaging) can now be used in studying the relationship between lesion and outcome. This is addressed in study I of this thesis.

1.15 Rehabilitation interventions
Better outcome has been shown in patients managed in stroke units with a multidisciplinary staff where they are mobilised early (Jorgensen, 1996; Indredavik et al., 1999). Rehabilitation interventions likely affect functional outcome and recovery in the upper limb after stroke. However, there is a lack of evidence supporting that rehabilitation interventions after stroke are beneficial for upper limb function (Kwakkel et al., 1999a). Most studies performed have been underpowered and of low methodological quality (Wood-Dauphinee and Kwakkel, 2005; Woldag and Hummelshiem, 2002). Therapeutic approaches
(e.g., Bobath or motor relearning approach) can vary between clinicians with no
evidence that one approach is better than another in improving upper limb
function (Luke et al, 2004). Despite these considerations there is growing
support that some specific interventions may be beneficial for patients with
limited upper limb function, e.g., constraint-induced movement therapy (CIMT)
(Wolf et al, 2006), strength training (Ada et al, 2006b), and bilateral arm
training (Stewart et al, 2006). Studies also support that intense training
programmes are more beneficial than less intense ones (Kwakkel et al, 1999b;
Kwakkel et al, 2004). Training of tasks that are functionally relevant is also
considered important (Carr and Shepherd, 1998). There is increasing evidence
supporting that training induces reorganisation in the sensory and motor system
in the brain in association with improved motor function (for review see Nelles,
2004; Hodics et al, 2006). How training, focussed on use of passive movements,
effects upper limb function and cortical reorganisation is addressed in Study III
and IV of this thesis.

1.16 Recovery strategies
Dobkin and Carmichael have suggested that recovery strategies are categorised
as follows: i) Restitution; ii) Substitution; iii) and Compensation (Dobkin and
Carmichael, 2005).

i) **Restitution** refers to functional improvements that are relatively independent
from external events. Restitution includes processes often labelled under
“spontaneous recovery mechanisms” such as reperfusion through recanalisation
of occluded vessels and establishment of collateral blood flow. Together with
resolution of brain oedema these mechanisms are considered intrinsic and
minimally affected by rehabilitation intervention. However, neuroprotective
therapy may be beneficial early restoring function to hypoperfused cells
neighbouring the lesion (Davis and Donnan, 2004).

ii) **Substitution** refers to functional improvements that are more dependent on
external events (e.g., interventions) and personal factors (e.g., attention,
motivation). Substitution involves relearning of movements so that undamaged
areas in the brain can substitute for the damaged areas. This process is likely
related to learning and use-dependent plasticity (Fig. 1) (Weiller, 1998;
Butefisch et al, 2000; Chen et al, 2002; Calautti and Baron 2003; Cramer, 2004;
Dobkin, 1998; Nudo et al. 2001; Rijntjes and Weiller, 2002; Rossini et al, 2003;
Ward and Frackowiak, 2006). Rehabilitation interventions are considered to
utilise the plastic potential to promote functional recovery (Dobkin and
Carmichael, 2005). Brain plasticity as a theory for recovery after stroke has
likely influenced how clinicians think about rehabilitation of persons suffering
from stroke (Table 1).

iii) **Compensation** refers to functional improvements that are achieved by
modification of the movement pattern used in a task or by changing the
environmental constraints of a task.
Fig. 1 Motor function improvements are mediated by different mechanisms in the early and late phases of recovery. Substitution of damaged brain areas involves structural and functional reorganisation of sensory and motor brain areas. Improvements due to relearning of movements or compensatory movement strategies may also occur in the chronic phase. There is evidence suggesting that such improvements are also mediated by brain plasticity.
Theories on the causes of stroke and recovery

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<tr>
<th>Theories on the causes of stroke and recovery</th>
<th>Methods</th>
<th>Rehabilitation intervention</th>
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<tr>
<td>~400 B.C. to ~200 A.D. Hippocratic-Galenic doctrine. <em>Humoral imbalance</em> as mechanism of apoplexy, e.g., Galen attributed stroke-symptoms to accumulated phlegm or black bile in the ventricles (Karenberg and Hort, 1998a)</td>
<td>Animal dissections</td>
<td>Hippocrates: &quot;to cure a vehement apoplexy is impossible; and a weak one not very easy&quot;</td>
</tr>
<tr>
<td>~300 B.C. Plato and others attributed <em>higher functions</em> to head and brain. Later, about 400 A.D., Nemesius located different mental functions in the ventricles. The <em>ventricular localisation</em> of mental functions became well established in the Middle Ages (Green, 2003). Haly Abbas, in 1523 A.D., related apoplexy (Greek word for stroke meaning &quot;struck with violence as if by a thunderbolt&quot; (Quest, 1990)) to congestion of the ventricles (Karenberg and Hort, 1998b)</td>
<td>Case studies of behaviour</td>
<td>~500 A.D. Caelius Aurelianus that one could treat paresis by active and assisted motion in and out of water (Licht, 1973)</td>
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<td>Around 1300 A.D., paralleling establishment of university medical education around Europe (e.g., Salerno, Montpellier), advancements were made in the description of aetiology and prognosis of apoplexy (Karenberg and Hort, 1998c)</td>
<td>Renaissance of empirical experimentation</td>
<td></td>
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<td>1400-1600 A.D. Leonardo da Vinci’s and Andreas Vesalius’ anatomical drawings and William Harvey’s development of the theory of circulation advanced the understanding of cerebrovascular system (Karenberg and Hort, 1998b)</td>
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<td>Johan Wepfer (1658) showed that apoplexy results from perturbation of the cerebral circulation and described cases caused by cerebral haemorrhage (Karenberg, 2004)</td>
<td><em>In vivo</em> symptoms compared with post-mortem brain autopsy findings</td>
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<td>In the end of the 18th century Galvani showed that electricity was conducted and could be generated in the nerve and muscle itself: “animal spirits had become electricity” (Bennett, 1999)</td>
<td></td>
<td>In the 18th century blood-letting became popular for the treatment of apoplexy (Licht, 1973)</td>
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<td>Gall (1758-1828) described the location of 37 different cognitive functions in different parts of the brain, based on skull shape (“phrenology”) (Tizard, 1959)</td>
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<td>Flourens (1794-1867) believed that the brain was a homogenous organ with all parts having similar functions, i.e., “equipotentiality”. The amount and not the location of brain damage was the decisive factor. Thus, small lesions could always be compensated for as intact brain areas would take over (Tizard, 1959)</td>
<td>Lesion studies in animals (excitation and stimulation)</td>
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<td>Findings of specific perceptive and motor language regions in the brain by Broca (1861) and Wernicke (1874) lead to the localisation theory of brain functions (i.e., that functions are represented in specific areas in the brain) (Lacour, 2004)</td>
<td>Post-mortem lesion studies in humans</td>
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<tr>
<td>Franz (1874-1933): “It is apparent that some possibility of functional adaptation”</td>
<td>Detailed study of</td>
<td>First account, by Franz (1874-1933), of use of restraint on</td>
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exists in the brain for certain types of movements so that when a certain ‘centre’ and its connected muscles cannot be utilised, other ‘centres’ and their connecting muscles may be brought into play to bring about desired result” (Colotla and Bach-y-Rita, 2002)

learned behaviours after cortical ablations in animals

unaffected arm and intense therapy for affected arm after motor cortex ablation in monkey (Colotla and Bach-y-Rita, 2002). Oden (1918) also used a restraint on the unaffected arm in monkeys recovering from lesions. “Stimulating exercises” are recommended to enhance recovery after stroke

Table 1. Theories of brain function likely influenced how clinicians viewed the causes of stroke and how persons suffering from stroke were rehabilitated. These theories were in turn likely affected by the experimental methods available and by prevailing theories of brain function (Tizard, 1959) and motor control (Shumway-Cook and Woollacott, 1995). Perhaps, brain plasticity may be considered a theoretical bridge between earlier theories of equipotentiality and localisation of function.

Sherrington and colleagues mapped out motor responses in non-human primates elicited by stimulating the precentral gyrus. Evidence was accumulating that lesions in the precentral region produced movement abnormalities (Leyton and Sherrington, 1917). Later, Penfield and Rasmussen (1950) performed similar mapping in humans undergoing surgery for epilepsy. They described cortical localisation of sensory and motor functions (the sensory and motor homunculus)

Electrophysiological stimulation studies

In 1896 Fulgence Raymond created the first hospital gym for rehabilitation (rééducation des mouvements), and in 1903, Brissaud advised that the hemiplegic patient should exercise regularly: “walk the patient and make him use his hand purposefully”. This was followed by a drought period where exercise after brain injury was commonly cautioned against and the world literature was almost silent on the need for rehabilitation (Licht, 1973)

Hebb (1947) found that rats allowed to run freely around his house (enriched environment) were better learners and had better memory capacity than rats in a less stimulating environment. He later postulated that cortical neural connections are dependent on our experience.

Evidence from the study of head-injured patients during the second world war supported that recovery of motor, sensory or cognitive abilities could occur (Luria, 1968)

Stemming from the theory of hierarchical CNS organisation Bobath (1978) proposed that motor recovery following stroke could be guided by enhancing inhibition within the CNS (reducing muscle tone) in order to improve postural control, which is key for voluntary movement control (Luke et al, 2004)

Beginning with the seminal work from the Frackowiak group (e.g., Chollet et al, 1991) many groups have studied how reorganisation of sensorimotor networks is related to recovery after stroke (Butefisch et al, 2000; Chen et al, 2002; Calcutti and Baron 2003; Cramer, 2004; Nudo et al. 2001; Rijntjes and Weiller, 2002; Rosini et al, 2003; Ward and Frackowiak, 2006; Weiller, 1998)

Neuroimaging and quantitative movement analysis

Movement science approach to rehabilitation after stroke (Carr and Shepherd, 1998). Establishment of plasticity-related principles for motor recovery after stroke (e.g., need for intense repetition and functionally meaningful training; maintenance of function through active use; effects of lesion, age, and time on recovery)
**1.20 Brain plasticity**

The term plasticity refers to the ongoing changes of a biological organism throughout life in response to normal and abnormal experience (Rioult-Pedotti and Donoghue, 2003). Brain plasticity means that the structure and function of the brain has a “capacity for being moulded” (Oxford English Dictionary) and implies that the brain is continually reorganising (Pascual-Leone et al, 2005). This capacity of the nervous system to be moulded through interaction with the environment, during development and learning, allows us to adapt to the requirements and situations we find ourselves in. In other words: “behaviour will lead to changes in brain circuitry, just as changes in brain circuitry will lead to behavioural modifications” (Pascual-Leone et al, 2005).

Brain plasticity has important consequences for rehabilitation after stroke. If the individual can somehow substitute for the damage in the brain by altered utilisation of remaining undamaged tissue, for example by recruiting neighbouring undamaged cells (Buonomano and Merzenich, 1998), movement patterns important for every day activities may be achieved. However, plasticity is not necessarily always positive for the individual. Adaptations may occur which lead to impaired behaviour (so called maladaptive plasticity). Maladaptive plasticity in the brain has been reported in conditions such as dystonia, phantom limb pain after amputation, and allodynia (Pujol et al, 2000; Flor, 2003; Maihofner et al, 2006). The development of pain and spasticity after stroke may also be related to such maladaptive processes. Given that plasticity in itself is not always beneficial better understanding of these processes may allow clinicians to harness plasticity in rehabilitation.

An important point when discussing brain plasticity in relation to substitution after brain damage is that the brain only represents part of the movement apparatus. Structural and functional changes also occur in spinal cord (Edgerton et al, 2004), alpha motoneuron (McComas, 1973), and in the muscle (O’Dwyer et al, 1996; Friden and Lieber, 2003; Olsson et al, 2006; Jakobsson et al, 1991) and changes at these multiple levels are most likely interdependent (Wolpaw and Carp, 2006). Thus, consideration should be given the whole neuro-muscular axis of movement production.

Another consideration is that plasticity may also occur without observable changes in behaviour (Kaas, 1991). This is often considered to be due to lack of sensitivity in behavioural measures used (i.e., that subtle behavioural changes occur but are not measurable). Pascual-Leone et al (2005) reported early plastic changes during motor and visual learning occurring without behavioural correlates. It is only during later phases of learning that the coupling between plastic and behavioural changes become observable. This suggests that subtle plastic changes are ongoing in every task we perform, every experience we
perceive, and every situation we find ourselves in. It is only through repetition that these changes become more robust and long lasting.

1.21 Sensory and motor system organisation
How the sensory and motor system is organised is of importance when considering plasticity of this system. Many brain areas are important for producing voluntary hand movements in humans. The main cortical motor areas include the primary motor cortex (M1), the premotor cortex divided into dorsal and ventral premotor cortex (PMd and PMv), the supplementary motor area (SMA) divided into SMA-proper and pre-SMA, and the cingulate motor area divided into caudal and rostral cingulate motor areas (CMAc and CMar) (Roland and Zilles, 1996; Rouiller, 1996). These areas have direct projections to the spinal motor neurons and networks (Dum and Strick, 2002). Other cortical areas are also highly important for adequate motor control. These areas include primary and secondary sensory areas (S1 and S2) for sensory feedback and prefrontal areas for planning and attending to actions. Subcortical structures involved in motor control include thalamus, basal ganglia and cerebellum (Ghez and Krakauer, 1991).

The sensory motor system is organised in a distributed manner with many cortical areas involved during hand movements (e.g., Ehrsson et al, 2000). The sensory motor system is hierarchically organised with three levels of control: the spinal cord, brainstem and forebrain. Processing of movements occurs both serially and in parallel across these levels (Ghez and Krakauer, 1991). Within M1 different parts of the arm show a distributed representation with extensive overlap (Schieber, 2001). This allows greater flexibility than suggested by the discrete somatotopic representations. Together this organisational flexibility in the motor system suggests potential for plasticity (Schieber, 2001). The organisation of the sensory motor system has important consequences for recovery after stroke as it suggests that different brain areas may have similar functional capacities. Thus damage to one area may be compensated for by recruitment of an undamaged area with the same function.

1.22 Plasticity in the uninjured brain
Use-dependent plasticity and mechanisms normally involved in learning and compensation for degenerative effects in ageing may be engaged in the relearning of movements after stroke (Krakauer, 2006; Dobkin, 1998; Butefisch et al, 2004). These topics are introduced below.

Use-dependent plasticity
The representation of a body part in the sensory or motor cortex is often termed the sensory or motor map. These representations are continuously remodelled in a use-dependent manner (Butefisch et al, 2000; Dobkin, 1998). Animal studies
have shown that sensory and motor maps in the brain reorganise in response to afferent input (for review see Kaas, 1991). In rats, limb immobilisation, reducing tactile input, leads to reduced somatosensory maps (Coq and Xerri, 1999). In humans, temporary deafferentation of fingers results in increased somatosensory-evoked cortical fields (measured with magnetoencephalography (MEG)) for neighbouring non-deafferented body parts (Rossini et al, 1994). Amputation of a body part also results in reorganisation of the sensory maps so that non-amputated body parts become represented in the amputated areas (for review see Kaas, 1991).

Reduced sensory input also leads to reorganisation of motor maps (Angel et al, 2003). Immobilisation of the ankle results in reduced excitability in the M1 representation of the tibialis anterior muscle (Liepert et al, 1995). Temporary forearm deafferentation results in increased corticomotor excitability in biceps muscle (Brasil-Neto et al, 1992). Amputation of a body part also results in increased corticomotor excitability of body parts proximal to the amputation (Cohen et al, 1991).

The reverse pattern of reorganisation occurs with increased input. Rats housed in an enriched environment have larger sensory maps for the forepaw (Coq and Xerri, 1998). Sensory training also leads to increased cortical representation of the trained body part (Recanzone et al, 1992). In humans, increased tactile discrimination sense after training occurs in parallel with reorganisation in S1 (Godde et al, 1993). Substantial evidence also exists for a similar relationship between reorganisation in M1 and training-induced improvements in motor performance (for reviews see Nudo et al, 2001; Monfils et al, 2005). These studies indicate that the degree of use is important for how body parts and movements are represented in the brain. Of potential interest is that such modified motor maps seem to occur only during skill learning and not strength training (Remple et al, 2001; Plautz et al, 2000).

**Motor learning**

Two main types of motor learning include learning a new skill (*motor skill acquisition*) and adapting an already learned skill to different environmental contexts (*motor adaptation*) (Shadmehr and Wise, 2005; Ungerleider et al, 2002). Doyon and Benali (2005) defined five phases of motor learning: 1) an early fast phase in which considerable improvement in performance occurs in the first session; 2) a later slow phase of improvement in performance over many sessions; 3) a consolidation phase in which improvements occur after a period of rest without additional practice; 4) an automatic phase when performance requires minimal cognitive resources and performance doesn’t deteriorate over time; and 5) a retention phase when the skill can be performed after long delays without further practice on the task.
The primary motor cortex (M1) is fundamental in the control of voluntary movements and is involved in motor learning (Sanes and Donoghue, 2000). During the early phase of motor learning rapid plastic changes occur in M1 (Robertson et al, 2003). Even 15-30 minutes of training of new thumb movements can lead to changed TMS-invoked movement direction in the trained thumb (Classen et al, 1998). After five days with two hours of practice per day the threshold for TMS activation of the trained hand flexors and extensors decreases and the size of the cortical representation increases (Pascual-Leone et al, 1995). These changes occurred in parallel with performance improvements. Karni et al (1995), using functional magnetic resonance imaging (fMRI), have shown that M1 is involved in both fast learning (i.e., within first measurement session) and in slow learning (i.e., after 4 weeks of training). Together these studies show that motor skill acquisition is associated with plasticity in M1 and that these changes occur as early as in the first practice session.

Studies of brain function in individuals with highly developed motor skills have also shown reorganisation of M1 and its projections associated with the learning and retention of complex motor skills. Increased cortical representation of the left hand muscles, as tested with TMS, has been found in violin players (Elbert et al, 1995) and increased corticomotor excitability (i.e., increased muscle response upon TMS stimulation of M1) has been found in highly trained badminton players (Pearce et al, 2000). Structural changes in both white and grey matter have also been reported in subjects with highly developed motor skills (Bengtsson et al, 2005; Draganski et al, 2004).

Neuroimaging studies examining brain areas involved in motor skill acquisition (using different tasks) have shown that many other cortical and subcortical areas are also involved in learning (Halsband and Lange, 2006). Different neural circuits may be involved depending on whether the learning is implicit or explicit (Grafton et al, 1995: Halsband and Lange, 2006). It has been proposed that two separate networks are involved in motor learning: cortex-basal ganglia and cortex-cerebellum (Hikosaka et al, 2002). A model has been put forward explaining how these cortico-striatal and cortico-cerebellar networks are differentially involved in various phases and in different types of motor learning (motor adaptation or motor skill acquisition) (Ungerleider et al, 2002). Both networks are considered to be involved in the early phase of learning. Later, when significant learning has occurred there is a differential involvement of these networks in consolidating and maintaining the long-term memory. The cortico-striatal network is more involved in motor skill acquisition and the cortico-cerebellar network is more involved in motor adaptation. This model has shown good correspondence with recent behavioural and neuroimaging data.
from motor learning studies along with results from lesion studies (Doyon and Benali, 2005).

Ageing

Hand function decreases with age, especially after the age of 65 years. This is considered to be due to a combination degenerative changes in the hand (joints, muscle, nerves, etc.) and in neural control (Carmeli et al, 2003). Age-related increases in brain activity during gripping have been found suggesting compensation of cortical networks for task-related degenerative changes (Ward and Frackowiak, 2003). Such age-related increases in brain activity were reported in areas known to be involved in grasping, i.e., in primary sensory and motor cortex, premotor cortex, cingulate cortex, intraparietal sulcus, insula, frontal operculum and cerebellar vermis (Ward and Frackowiak, 2003). Despite these age–related changes in performance and cortical activation patterns, learning of new motor skills may be relatively intact in the elderly (Seidler, 2006). However, findings of reduced training-related plasticity in M1 in older subjects, with the same level of performance improvement as younger individuals, suggest that other brain areas may be involved in motor learning in older individuals (Sawaki et al, 2003). Indeed, older individuals activate sensory areas more during simple hand and foot movements and cognitive areas more during coordinated hand and foot movements than do younger individuals (Heuninckx et al, 2005). Thus an up-regulation of sensory monitoring and attention may help to compensate for age-related degeneration of movement capacity.

As brain reorganisation is likely being utilised to compensate for age-related degenerative changes it seems probable that the ageing brain has reduced capacity to compensate for damage caused by stroke. This would imply that older stroke patients would have reduced capacity for functional improvements and limited rehabilitation potential. However, studies examining the effects of age on outcome have shown minimal importance of age as a predictor of functional independence at time of discharge from hospital (only 3% of FIM score predicted by age) (Bagg et al, 2002) and small differences between young and old patients (> 55 years) in maximal improvement in performance of daily activities (Kugler et al, 2003). Considering that older individuals can improve both strength (Hunter et al, 2004) and aerobic fitness (Malbut et al, 2002) when trained there seems to be no evidence supporting that age is a limiting factor for stroke rehabilitation (Kugler et al, 2003).

Mechanisms of brain plasticity

Several molecular and cellular mechanisms at the synapse are considered to underlie these use-dependent changes in sensory and motor maps (for review see Buonomano and Merzenich, 1998). One of the main sites of synaptic plasticity
is the dendritic spine (Johansson, 2004). The lifetime of the dendritic spine can be highly variable. Up to 50% of the spines in mouse barrel cortex are present for only a few days or less (Trachtenberg et al, 2002). Importantly, the sensory experience is associated with the formation and elimination of these spines (Trachtenberg et al 2002). Such changes in the dendritic spines together with reweighting of synaptic strengths (Buonomano and Merzenich, 1998; Witte, 1998), metabolic neuronal changes (Mattson and Liu 2002), unmasking of existing inactive horizontal connections (Sanes and Donoghue, 2000), and perhaps axonal regeneration (Chen et al, 2002) are some of the underlying mechanisms involved in mediating functional changes in cortex. Astrocytes, important for neurovascular coupling and regulation of synaptic environment, may also be involved in brain plasticity (Johansson, 2005). Modified neurotransmitter function, e.g., in excitatory glutamatergic or inhibitory GABA-ergic synapses, may also contribute (Witte, 1998). Long term potentiation and long term depression have also been shown to occur in sensory and motor cortex (Castro-Alamancos et al, 1995).

Similar mechanisms likely underlie plastic changes after stroke. For a comprehensive review of likely mechanisms see Nudo et al (2001) and Johansson (2004, 2005).

1.23 Brain plasticity after stroke

*Substitution by undamaged areas in primary sensory and motor cortex*

Recovery of movement after stroke is sometimes associated with reorganisation in primary motor cortex (M1). Glees and Cole (1950) showed in monkeys, by use of electrical stimulation, that intact areas of M1 after lesion can be recruited into the hand motor map. This occurred together with recovery of hand gripping. More recently, Nudo and Milliken (1996) also found evidence in monkeys for local remodelling in M1 after 3-4 months of spontaneous recovery after M1 lesions using intracortical microstimulation. In a pioneering follow-up study they also showed that this remodelling could be enhanced by rehabilitative training (Nudo et al, 1996). Interestingly, inactivation of the recruited areas in M1, by injection of lidocaine, has also been shown to affect hand function negatively (Rouiller et al, 1998).

Similarly, in humans *in vivo* neuroimaging has shown that performance of an active motor task after stroke is associated with a lateral and posterior displacement of activity in M1, probably into S1 (Weiller et al, 1993; Calautti et al, 2003; Pineiro et al, 2001). In a study using multiple neuroimaging methods (TMS, MEG and fMRI) Rossini et al (1998) also showed a posterior shift of activity in the sensory and motor areas in the affected hemisphere. Recently, Jaillard et al (2005) showed in patients with M1 infarcts that the displacement of task-related activity in M1 occurs progressively over time in association with
recovery of hand function. Together, the above results support that remodelling of hand motor maps in M1 occurs in relation to recovery after stroke. The increased activity in M1 (and into S1) areas not normally activated has been interpreted as reflecting recruitment of corticospinal connections (Galea and Darian-Smith, 1994; Dum and Strick, 2002) in order to compensate for the damaged connections. Whether these new motor maps in M1 and S1 are involved in producing and controlling movements in the same way as did the damaged area remains to be elucidated.

**Substitution by other undamaged cortical areas**

Early cross-sectional studies have reported increased task-related activity occurring in bilateral sensorimotor areas, SMA, premotor, insular, prefrontal, and parietal sensory areas as compared to controls (Brion et al, 1989; Chollet et al, 1991; Weiller et al, 1992; Weiller et al, 1993; Cramer et al, 1997; Cao et al, 1998; Pineiro et al, 2001; Seitz et al, 1998; Neltes et al, 1999a). More recently, increased movement-related activation of ipsilateral primary and secondary motor areas has been shown to occur in patients showing poor functional outcome in the chronic phase post-stroke (Ward et al, 2003a). Studies in which patients were followed longitudinally during recovery have shown that motor recovery is associated with increased movement-related activity in contralateral S1 and M1 (Marshall et al, 2000; Calautti et al, 2001; Feydy et al, 2002), ipsilateral premotor cortex (Neltes et al, 1999b; Calautti et al, 2001), and ipsilateral cerebellum (Small et al, 2002). These studies show that the early increased bilateral sensorimotor activity patterns normalise into predominantly contralateral activity patterns as the patient recovers motor function (Calautti et al. 2001; Feydy et al. 2002; Marshall et al. 2000). Patients demonstrating poor motor recovery continue to activate ipsilesional M1 (Johansen-Berg et al, 2002a; Carey et al, 2005) and secondary motor areas (Ward et al. 2003b) more than those demonstrating good recovery.

Mirror movements have been found to occur together with increased ipsilateral activation (Weiller et al, 1993; Kim et al, 2003) and might thus explain the increased ipsilateral activation pattern observed after stroke. Few of the neuroimaging studies have controlled for mirror movements using EMG. However, in a study with simultaneous fMRI and EMG measurement ipsilateral activity during paretic hand movements was found in patients without any mirror movement activity (Butefisch et al, 2005). Also, case studies in recovered stroke patients in which a second stroke in the ipsilateral hemisphere leads to impairment of motor function in the recovered hand suggest involvement of the ipsilateral hemisphere in recovery of hand function (Fisher CM, 1992).

The increased activity in sensory and motor areas in patients with poor recovery may rather reflect substitution of areas with corticospinal projections (Galea and
Such substitution may not be as efficient as using the original corticospinal connections (Maier et al, 2002) and thus this strategy is only utilised in patients with poor recovery (Ward et al, 2003a). Indeed, Ward et al (2006) later confirmed that severe functional impairment of corticospinal pathways from contralateral M1 after stroke was related to increased movement-related activity in bilateral secondary motor areas.

Whether recruitment of widespread secondary motor areas is of functional relevance to performance of motor tasks with the paretic hand can be tested using TMS. TMS can be used to interrupt normal cortical function during the performance of motor tasks with the paretic hand in stroke patients. Such studies indicate a role of bilateral premotor, ipsilateral M1 and superior parietal cortex in timing and accuracy of movements performed using the paretic hand (Johansen-Berg, 2002b; Lotze et al, 2006; Fridman et al, 2004). Recently, a study using multimodal techniques in subcortical stroke patients demonstrated (i) greater ipsilateral activation in sensorimotor, premotor and parietal areas (using PET), (ii) greater cortico-cortical connection strength between motor areas in the ipsilateral hemisphere (using EEG coherence analysis), and (iii) the occurrence of TMS-induced corticospinal responses in the contralateral hemisphere only (i.e., no ipsilateral responses found) (Gerloff et al, 2006). The authors interpreted these findings as evidence for involvement of the ipsilateral motor areas in higher-order aspects of motor control (such as planning, monitoring etc.) rather than being involved in execution of movements.

Another interesting consideration is that complex motor tasks in healthy subjects have been shown to involve bilateral sensory and motor networks more than simple motor tasks (Ehrsson et al, 2000; Carey et al, 2006). This suggests that extended sensory motor networks are engaged during more demanding tasks, perhaps for performance monitoring and increased attention (to improve accuracy). As activation patterns after stroke are similar to those in healthy subjects performing complex motor tasks (Lotze and Cohen, 2006) it may be that: i) movements are more difficult for them to perform than for controls, or that ii) areas previously used in complex tasks may substitute for damage in areas involved in simple tasks after stroke. To rule out the first explanation careful monitoring of perceived task difficulty is indicated in neuroimaging studies of stroke patients (Ward et al, 2003a). Another possibility is the use of a passive task that does not engage patients and healthy controls differently.

Passive hand movements activate similar brain areas as active movements due to movement-related sensory feedback from proprioceptive and cutaneous receptors (Weiller et al, 1996). In longitudinal neuroimaging studies using a passive task, enabling the inclusion of patients with complete paresis, a
normalisation of contralateral S1 and M1 activity has also been reported (Tombari et al, 2004). Use of a passive hand task also revealed recovery-related recruitment of SMA and bilateral secondary sensory (S2) areas (Loubinoux et al, 2003; Tombari et al, 2004). Together with findings of reduced metabolic activity in the contralateral thalamus in patients with poor motor recovery (Binkofski et al, 1996) these studies suggest the importance of normal sensory processing for recovery of motor function. Increased activity in S1 and S2 also has been shown to occur in parallel with recovery of sensory function in the hand post-stroke (Carey et al, 2002a; Staines et al, 2002).

Diaschisis

Diaschisis means reduced function of a non-injured brain area due to damaged connections from the injured area (von Monakow, 1914). After stroke, hypometabolic areas remote from the lesion have been observed at rest (Feeney and Baron, 1986; Baron et al, 1992), indicating presence of diaschisis after stroke. However, its relation to functional recovery remains unknown. Nonetheless, findings of similar brain areas involved in lesion-related and task-related brain activity patterns occurring after stroke (Seitz et al, 1999) suggest that diaschisis does have functional consequences for stroke patients.

Movement compensation and brain plasticity

Multi-joint movement patterns (synergies) may be impaired after stroke (Dewald et al, 1995). The occurrence of abnormal movement synergies after stroke (Twitchell, 1951), e.g., the flexor synergy including shoulder flexion and abduction, elbow flexion, and forearm supination (Brunnström, 1970), may be considered a compensatory strategy developed when attempting to move the arm with an impaired sensory motor system (Latash and Anson, 2006). In other words, after stroke the reduced repertoire of possible movement patterns makes compensation by a less efficient movement pattern a potentially meaningful strategy to improve function. Stroke patients may for example compensate poor reaching ability by greater bending of the trunk to achieve the task (Cristea and Levin, 2000; Roby-Brami et al, 2003). Such behavioural strategies are also likely to cause remodelling of the brain’s structure and function. Similarly, reduced use of the weak limb after stroke (Laplane and Degos, 1983; Andre et al, 2004; Sterr et al, 2002) may also have neural correlates in the brain. This is explored in Study IV.
2.0 AIMS
A general aim of this thesis was to investigate some aspects of brain plasticity in the cortical sensory and motor system in relation to upper limb function after stroke.

Specific aims of the studies included:

- to explore if the degeneration of the corticofugal tracts is related to functional outcome of the upper limb after stroke (Study I)
- to explore whether cortical activity is related to the neural contribution to passive movement resistance in the flexor muscles of the hand after stroke (Study II)
- to explore the effects of repetitive, passive-active movement training on upper limb motor function and ability in patients with chronic stroke with arm paresis (Study III)
- to explore the effects of intense training on cortical activation in a pilot functional magnetic resonance imaging study (Study III)
- to explore if brain activity during passive movements is related to time after stroke, and if such activity can be affected with intense training (Study IV)
3.0 SUBJECTS AND METHODS

3.10 Subjects
Stroke patients in the chronic phase (> 6 months) were recruited from the Department of Rehabilitation Medicine, Danderyd Hospital and Uppsala University Hospital to participate in the studies.

The following inclusion criteria were used:

i) left subcortical infarction in the middle cerebral artery territory (Study I, II, and IV); left and right subcortical and cortical infarction or haemorrhage (Study III)

ii) ability to communicate and understand information of the study (Study I-IV)

iii) right handedness according to the Handedness Inventory (Oldfield, 1971) (Study I, II, and IV)

iv) age 40-65 (Study III)

v) intact proprioception at wrist (Study III and IV)

Exclusion criteria included:

i) usual contraindications to MRI (Study I, II, and IV)

ii) epilepsy (Study I-IV)

iii) previous history of neurological disorder (Study I-IV)

In studies I, II and IV healthy right handed subjects without a history of neurological disorder were recruited as controls. All subjects gave written informed consent, according to the Declaration of Helsinki, before participating in the study. The studies were approved by the Ethics Committee at the Karolinska Hospital, Stockholm.

3.20 Clinical measurement of upper limb function
Clinical measurement of upper limb function included assessment of:

i) Sensory function by assessing 2-point discrimination in the digits, light touch in hand (using Semmes-Weinstein Monofilament test), proprioception (elbow, wrist and thumb position sense (Fugl-Meyer et al, 1975)), and stereognosis (recognition of 8 items) (all assessed in Study I and III; proprioception at the wrist assessed in Study II and IV)

ii) Active range of motion measurement of the wrist and finger (metacarpophalangeal joints) movements with a goniometer (Gajdosik and Bohannon, 1987) (Study I-III)

iii) Muscle tone assessment of finger and wrist flexors according to the modified Ashworth scale (Bohannon and Smith, 1987) (Study I-IV)

iv) Upper limb function using arm, hand and fine motor sections of Motor Assessment Scale (MAS) (Poole and Whitney, 1988) (Study I-III)
v) Hand and finger dexterity with the Box and Blocks test (Mathiowetz et al. 1985) (Study I) and the Nine Hole Peg Test (NHPT) (Heller et al, 1987) (Study I-III)

vi) Maximal grip strength using Grippit (Lagerström and Nordgren, 1998) (Study I and IV)

vii) Amount of paretic hand use was assessed according to the Motor Activity Log (MAL) (Uswatte et al, 2005) (Study I)

3.30 Estimation of neural contribution to passive movement resistance
Clinical measurement of spasticity is usually performed by manually moving the limb passively while assessing the resistance. The examiner then rates the perceived resistance according to a 6-point ordinal scale, the modified Ashworth scale (Bohannon and Smith, 1987). This subjective assessment does not allow differentiation of the non-reflex from the reflex components of the passive movement resistance. We have developed a clinical spasticity measurement tool which allows separate quantification of non-neural and neural components to passive movement resistance. This method consists of passive ramp-hold movements at controlled velocities (slow and fast) while the patient is relaxed. The resistance is continuously recorded during the passive movement. Stretch reflexes do not contribute to the resistance measured in the beginning of the movement (earliest contribution at about 35 ms). Mechanical properties such as viscosity and inertia do however contribute early to the resistance. By using a velocity which induces stretch reflexes in the majority of patients (e.g., 236º/s) we can obtain an estimate of the neural contribution to the passive movement resistance by subtracting the resistance generated early during the movement (P1 in Fig. 2) from the resistance generated late in the movement (P2 in Fig. 2). This method was used in Study II to estimate degree of neural contribution to passive movement resistance at the wrist in chronic stroke patients.

In a separate group of 15 chronic stroke patients (unpublished data) we found that such an estimation of the neural contribution to the passive movement resistance showed good correlation with EMG recordings. $M1_{EMG}$ and $M2_{EMG}$ amplitude correlated positively with the estimated neural contribution to passive movement resistance ($r = 0.73$, $p = 0.004$ and $r = 0.78$, $p = 0.001$, respectively). In these patients, the neural resistance also correlated positively with clinically rated muscle tone ($r = 0.64$, $p = 0.01$) and negatively with maximal grip strength ($r = -0.83$, $p < 0.001$).
Fig. 2 (A) A custom built device was used to examine the resistance to passive wrist extension (40º) at constant velocity produced by a computer controlled step motor. Hand, fingers and forearm were fastened to allow movement only at the wrist joint. A force sensor was attached to the device under the hand to measure resistance to passive movement. Resistance traces and EMG recordings shown for a patient with large (B) and small (C) neural contribution to passive movement resistance. M1_{EMG} = short latency stretch reflex occurring at about 32 ms and M2_{EMG} = long latency stretch reflex occurring at about 130 ms. For estimation of neural contribution two resistance measures (points) were extracted from the raw force trace: (i) P1 = the highest resistance early after movement onset. This point occurs before 35 ms (i.e. before onset of earliest EMG activity + electromechanical delay). This point consists of force generated by moved structures i.e. muscle- and non muscle tissue acceleration, inertia and viscosity. (ii) P2 = the highest resistance after possible contribution to resistance from stretch reflexes (after 35 ms) and before the end of movement. This point reflects a sum of muscle length-dependent and velocity-dependent muscle resistance together with velocity-dependent neural resistance. (mV = millivolts; N = Newton; ms = milliseconds).
P1 is composed not only of viscosity but also of inertia, acceleration effects on viscosity, and short-range stiffness (Rack and Westbury, 1974). This may explain why our method resulted in negative values of neural contribution to passive movement resistance in some subjects (i.e., this occurred when P1 was larger than P2). It was conceivable that our estimated neural contribution to passive movement resistance may have been effected by these other mechanical parameters. In order to check whether such non-neural contributions could be effecting our estimation of neural contribution to passive movement resistance we used mathematical modelling of the neuro-biomechanics of the human wrist to estimate the passive muscle components and the active neuronal component during passive movement of the hand in stroke patients. The modelled parameters were tuned to make model output (resistance trace) fit measured data (for parameters see Table 2). Other parameters, e.g., hand weight and size, inertia, series element (tendons), motoneuron pool activation and deactivation dynamics and initial viscosity are held constant and are the same for all subjects. The model components and its parameters are described by Winters and Stark (1985, 1987) and Schuind et al (1994). The results from the model confirmed that reflex gain was the only parameter which correlated with our estimation of neural contribution to passive movement resistance (Table 2).

<table>
<thead>
<tr>
<th>Non-neural parameters</th>
<th>Definition</th>
<th>Relation to estimated neural contribution to PMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance due to stiffness of muscle and other tissues (torque-angle), Kp</td>
<td>FKp = Kp*L</td>
<td>r = 0.09 , p = 0.74</td>
</tr>
<tr>
<td>Exponential resistance related to maximal muscle length, Pos0</td>
<td>FPos0 = e(L-Pos0)-1</td>
<td>r =-0.21, p = 0.44</td>
</tr>
<tr>
<td>The viscous component of the resistance which increases with speed (torque-velocity), Bp</td>
<td>FBp = Bp*v.</td>
<td>r =-0.47, p = 0.08</td>
</tr>
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**Neural parameters**

- Reflex gain, Rg
  
  Rg is modelled as a simple closed loop feedback proportional to muscle length and with a 34 ms delay. The feedback signal acts as a neural input to the muscle. The input increases proportionally to muscle length. 
  
  r = 0.77, p < 0.001

Table 2. Non-neural and neural parameters modelled. PMR = passive movement resistance; F = force; L = muscle length; v = velocity.
3.40 Neuroimaging and neurophysiological techniques

3.41 Functional magnetic resonance imaging (fMRI)
We used fMRI and the BOLD contrast (Ogawa et al, 1990) to study neural activity during hand movements in Studies II-IV. Simultaneous fMRI imaging and cell recording studies in monkeys have shown that the BOLD signal reflects input and intracortical processing in an area rather than its output (Logothetis et al, 2001). The BOLD signal likely represents activation of excitatory rather than inhibitory synapses (Waldvogel et al, 2000). This implies that the negative BOLD signal (e.g., found in multiple brain areas Study II) is more likely reflecting a reduced activation rather than inhibition.

The preprocessing and statistical analysis of fMRI images was performed using statistical parametric mapping (versions SPM99 and SPM2) software from Wellcome Department of Cognitive Neurology, UCL, London (www.fil.ion.ucl.ac.uk/spm). For the fMRI studies our preprocessing steps involved: (i) Realignment: during scanning it is very likely that the subject moves the head. Small movements (just a few millimetres) can be compensated for by realigning the images; (ii) Normalisation: brains have different dimensions and normalising the images to a template brain (Talaraich and Tournoux, 1988) allows comparison of different brains. However, in patients with brain lesions normalising the images in the normal way may lead to distortions. We therefore masked the lesions from this normalisation step in all our fMRI experiments (Brett et al, 2001); (iii) Spatial smoothing: there is remaining anatomical variability after normalisation. Smoothing the data from fMRI images with a Gaussian smoothing kernel (e.g., 8 mm) increases the overlap of functional activations between subjects, and this facilitates group analyses. Statistical analysis of fMRI images included fitting a general linear model to the data from each voxel (time series). Parameter estimates and error from the model fitting were used to calculate activation maps. The statistical parameters of each voxel are associated with probability (p-value) which is used for setting significance threshold. As the brain images are made up of many thousand voxels (typical dimensions = 3 x 3 x 5 mm) correction for multiple comparisons, as implemented in SPM2, was used to rule out obtaining false positives.

3.42 Diffusion tensor imaging (DTI)
Diffusion of water is affected by the presence and orientation of existing boundaries, such as neural fibres and myelin sheaths in well organized neural tracts. Due to these barriers water typically diffuses more in one than in any other direction. This is termed anisotropic water diffusion. The extent of anisotropic diffusion can be quantified by a measure, called fractional anisotropy (FA) (Basser and Pierpaoli, 1996). Importantly, FA is independent of
actual orientation of diffusion (Sotak, 2002) and reflects microstructural properties of tissues with well oriented boundaries (e.g., white matter fibres). Specifically, FA values range from zero (i.e. isotropic diffusion) to one (i.e. completely one dimensional diffusion) and the value is directly related to cross sectional density and diameter of fibres as well as the extent of myelination. It also indicates the organization of the boundaries because crossing arrangements manifest a lower FA value (Le Bihan, 2003). By using MRI to acquire diffusion-weighted images in at least 6 non-collinear directions, it is possible to estimate a diffusion tensor in each voxel, which describes the variability of the diffusion process. From the diffusion tensor specific FA can be calculated (Basser et al, 1994). We used DTI, in Study I, to investigate white matter integrity in the corticofugal tracts after stroke.

3.43 Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a non-invasive technique in which a focussed magnetic field pulse is used to evoke electric discharge of cortical neurons (Rothwell, 2003). When the coil is placed on the scalp over the motor cortex and a discharge of sufficient magnitude is given a motor evoked potential (MEP) is measurable with electromyography (EMG) in the hand muscles. The size of the MEP depends on the stimulation intensity, the excitability and the integrity of the corticospinal pathways. We used TMS to study the functional integrity of the corticospinal pathway in patients after stroke (Study I). We collected recruitment curves (Devanne et al, 1997; Siebner and Rothwell, 2003) as they are considered more reliable than maximal amplitude in MEP responses (Carroll, et al 2001). We also used TMS to examine the duration of the silent period (SP) which is a silent period in the EMG occurring after stimulation of an active target muscle. The SP has been attributed to TMS activation of spinal and cortical interneuronal circuits (Cantello et al, 1992) and thus changes in SP duration can indicate whether any intracortical processing changes have occurred in M1 after stroke.

3.50 Training programme

Training programmes used in previous studies often require a certain level of intact upper limb motor function to partake. The use of passive movements in patients with lower levels of residual function may be an alternative approach when active movement production is limited. The rationale for the use of passive movement training is also supported indirectly by findings from various studies showing:

(i) that retained sensory function is considered a positive prognostic indicator of motor functional outcome (Winward et al, 1999)

(ii) that intact central processing of sensory information after stroke, indicated by somatosensory evoked potentials, is related to favourable
functional outcome in the chronic phase (Kusoffsky et al, 1982; Fierro et al, 1999)

(iii) that brain areas are activated similarly during active and passive movements (Weiller et al, 1996), even if to a lesser extent (Mima et al, 1999)

(iv) that passive movement training in healthy subjects can lead to increased activity in contralateral primary sensory and motor cortex and SMA (Carel et al, 2000)

(v) excitability of the cortical projection to hand muscles can be increased after peripheral sensory stimulation (Ridding et al, 2000; Kaelin-Lang, et al 2001)

(vi) that sensory stimulation may have beneficial effects on motor function in chronic stroke patients (Conforto et al, 2002)

The training programme used in Study III and IV thus consisted of repetitive passive reaching and grasping movements of the paretic arm and hand guided by a therapist. The training consisted of a 5-10 minute warm up of upper limb active movements (for shoulder, elbow, wrist and hand) which the patient was capable of carrying out independently. Stretching of muscles (hand and finger flexors and forearm pronators) was also performed for up to 5 min for subjects with increased muscle tone. Thereafter the patient received passive movement training of the upper limb. The passive movement pattern chosen for each individual depended on his/her functional capacity. Meaningful movements which the patient could not execute were trained (e.g., reaching or grasping and letting go movements of wrist and hand, or a combination of both). The movement was repeated 200 - 400 times per session. During the passive training the patients were instructed to “feel and observe” the movement. It was hoped that this would engage the patient’s volitional drive (Lotze et al, 2003). The passive training was followed by attempts to voluntarily reproduce the same movement sequence with support by a therapist, so called assisted active movements (lasting 5 min). Training lasted half an hour and was performed five days/week during four weeks.
4.0 RESULTS AND DISCUSSION

4.10 Degeneration and plasticity in the sensory and motor system and hand function

4.11 Wallerian degeneration of the corticofugal tracts and hand function
(Study I)

It is believed that the degree of damage to the CFT after stroke is important for the functional outcome of the upper limb (Davidoff, 1990; Binkofski et al, 1996; Feydy et al, 2002). We used DTI to quantify white matter organization of the CFT at the level of the cerebral peduncle (CP), as most descending fibres run in parallel at that level, making it an optimal region of interest to examine white matter organization (Virta et al, 1999). Fractional anisotropy (FA), indicating white matter organisation, was calculated for the CFT of both sides (affected and unaffected sides in patients) in the patients in the chronic phase after stroke and in a group of healthy controls (Fig 3 A). The functional integrity of the corticospinal pathway was examined using TMS. Slope of recruitment curves (RC) and silent period (SP) duration were measured (Fig 4).

A positive relation was found between DTI (FA) and TMS (RC) results indicating a correspondence between structure and function of the descending CFT (Fig 3 B). FA also correlated positively with maximal grip strength further suggesting relevance of structural integrity of the CFT. According to FA values, the patients were also classified into groups with minimal or extensive Wallerian degeneration (WD). Patients with more extensive WD had poorer grip strength, dexterity and range of movement (Fig 4).
Fig. 3 Wallerian degeneration of the CFT and upper limb function. (A) The $FA_{AHUH}$ values for the control subjects ($n = 9$) and the stroke patients ($n = 7$). Note that four patients demonstrate $FA_{AHUH}$ values distinctly lower than the range of values for control subjects (i.e., extensive WD). (B) How white matter organization in the CFT relates to corticospinal excitability ($RC_{AHUH}$) in patients. Correlation between $FA_{AHUH}$ and $RC_{AHUH}$ remained significant even if Patient 4 (with no MEPs on affected side) was excluded ($r = 0.89, p = 0.02$). Correlation also remained significant if Patient 6 (outlier value) was excluded ($r = 0.89, p = 0.02$). (C) How white matter organization in the CFT relates to intracortical inhibition ($SP_{AHUH}$). Patient 4 is excluded from analysis of $SP_{AHUH}$. (D) The relation between $FA_{AHUH}$ values and grip strength.
Fig. 4 Corticospinal excitability and upper limb function in patients with or without extensive WD. (A) Patients with extensive WD had lower $\text{RC}_{\text{AH/UH}}$ than patients with minimal WD ($p = 0.03$) and controls ($p = 0.008$). (B) Patients with extensive WD had higher $\text{SP}_{\text{AH/UH}}$ values than patients with minimal WD ($p = 0.05$) and controls ($p = 0.01$). (C) Differences between patients with extensive WD and those with minimal WD were found in upper limb function (MAS), grip strength, wrist extension, and dexterity (BBT and NHPT) scores. All clinical measures were normalized so that a score of 1 signified a similar level of function as the non-affected side.
Damage to the CFT a major determinant of upper limb function after stroke

We found a correlation between the degree of WD in the CFT, measured by DTI, and upper limb function, using TMS and behavioral measures. Our findings of reduced FA in the CFT (using DTI) suggest that the ipsilesionally projecting CFT fibres have undergone extensive Wallerian degeneration (Thomalla et al, 2004). The patients who had extensive Wallerian degeneration also had showed minimal increase of EMG responses in the paretic hand upon TMS stimulation of increasing intensities. As the slope of the recruitment curve should reflect the amount of remaining excitable elements (under the TMS coil), which project from primary motor cortex (M1) to the ventral horn of the cervical spinal cord after stroke (Carroll et al, 2001; Devanne et al, 1997) these findings suggest a close relationship between the degeneration of the white matter in the CFT and the functioning of the corticospinal pathway. We also found a relationship between degree of WD and intracortical inhibition in M1, as indicated by the silent period (Cantello et al, 1992). The negative relationship between degree of degeneration of the CFT (DTI) and SP duration in patients may be caused by damaged afferent connections projecting to M1, as the sensory projections from the ventral thalamus pass close to the descending corticofugal fibres in the posterior limb of the internal capsule (van Kuijk et al, 2005; Liepert et al, 2005). Changes in SP duration may contribute to motor recovery after stroke (Liepert et al, 2000a; Classen et al, 1997) but further studies are indicated.

DTI and TMS results both correlated strongly with grip strength in the patients. Strength in the wrist and finger flexors after stroke is considered a good indicator of upper limb function (Sunderland et al, 1989; Boissy et al, 1999). We also found that patients with FA_{AIUH} above 0.60 (i.e., 60 % of the values obtained for the “non affected” side) recovered some ability to perform fine motor tasks. This is similar to previous studies in stroke showing that recovery of dexterity occurred if more than 60 % of CP size was spared (Warabi et al, 1990) and findings, in cortical stroke patients, that damage to more than 37 % of the cortical areas involved in hand movements resulted in total loss of hand dexterity (Crafton et al, 2003). Together with our results these findings suggest that there may be a critical threshold of intact fibres of the CFT that are needed for recovery of dexterity after stroke.

Our findings support that the amount of remaining intact nerve fibres in the CFT seems to be a major determinant for the outcome after stroke. A previous DTI study in stroke patients examined early after stroke (2-16 days), also reported a correlation between FA in the CP and general motor outcome (Thomalla et al, 2004), which indicates that DTI could be used early for later prediction. Preliminary findings suggest that FA reductions along the CFT increase over time (Buffon et al, 2005; Thomalla et al, 2005). There is a need for more
longitudinal DTI studies together with detailed assessment of motor function to evaluate the best time-point to perform DTI to predict outcome. Recently, Stinear et al (2007) showed that in patients with no MEPs the integrity of the descending tracts in the posterior limb of the internal capsule (measured with DTI) was important in determining degree of functional improvement with four weeks training. This supports that the degree of integrity of descending tracts from non-primary motor areas is important in patients with damaged projections from M1 (no MEPs) (Ward et al, 2006a). This is in line with previous fMRI findings of better recovery in patients with ipsilesional activation during paretic hand movements (Loubinoux et al, 2003; Ward et al, 2003 b). This suggests that DTI could also be used to predict which patients will benefit from rehabilitation intervention.

4.12 Cortical activity in ipsilateral primary sensory and motor cortex in relation to the neural contribution to passive movement resistance in the flexor muscles of the hand (Study II)

We used fMRI to study brain activity during fast and slow passive movements of the wrist in chronic stroke patients and healthy controls. The subject’s hand was positioned in the hand device shown in Fig. 2 allowing measurement of the resistance to passive movement. An estimation of the neural contribution to passive movement resistance was calculated as detailed in section 3.3. This allowed us to test whether the BOLD signal during passive hand movement was associated with the neural component of the enhanced muscle resistance to stretch. By contrasting cortical activity at two velocities we were also able to identify areas showing a velocity-dependent modification of activity. Since the muscle resistance in spastic muscles is velocity dependant (Lance, 1980), we also related the BOLD signal during the velocity-dependent contrast to the neural contribution to passive movement resistance.

In controls, a normal pattern of brain activity was observed during passive movement compared to rest (Fig. 5 A) (Weiller et al, 1996). Widespread functional deactivations (i.e., negative passive movement-related BOLD signal) also occurred in controls (Fig. 5 A). Patients activated similar areas but to a lesser degree (uncorrected threshold p<0.001) and showed no functional deactivations (Fig. 5 B). When contrasting the brain activity occurring during fast and slow movements (i.e., a velocity-dependent contrast) controls showed activity the contralateral S1 and M1, ipsilateral temporal gyrus, primary and secondary visual areas, and ipsilateral S1 and premotor cortex (PMC) (Fig. 5 C). Patients had minimal velocity-dependent activity (Fig. 5 D).
Patients activated a number of areas more than the controls during passive
movement and in the velocity-dependent contrast (p<0.05, corrected) (Fig. 6). These areas included bilateral S1 and M1 (deeper and more anterior in contralateral hemisphere), contralateral inferior frontal gyrus, medial prefrontal and occipital visual areas. Plotting the parameter estimates (i.e., differences in effect sizes) in these areas revealed that controls demonstrated negative mean values (i.e., functional deactivations) and patients showed positive mean values in the same areas. In other words, patients were activating areas normally deactivated by controls.

In patients, velocity-dependent brain activity correlated positively with neural contribution to passive movement resistance in a number of areas (p<0.05, corrected) (Fig. 7). Correlations occurred in ipsilateral S1 (area 3b) extending into M1 (area 4a), contralateral inferior frontal gyrus (BA 45), precuneus, middle cingulate cortex, SMA, cerebellum and primary and secondary visual areas. Plotting the parameter estimates in these areas revealed that controls had negative mean values whereas patients had positive mean values in these areas. Plotting the parameter estimates also revealed that velocity-dependent brain activity in controls correlated with neural contribution to passive movement resistance in bilateral S1/M1.
Fig. 6 Group differences in brain activity during passive movement of the wrist. (A) Patients > Controls during MOVT - REST. (B) Patients > Controls during FAST - SLOW. Patients activated bilateral S1 and M1 (deeper and more anterior in contralateral hemisphere) more than controls during passive movement and in the velocity-dependent contrasts. Patients also had increased activity in contralateral inferior frontal gyrus, medial prefual and occipital visual areas. Controls demonstrated negative mean parameter estimates in all these areas whereas patients had a positive mean. Colour bars show areas more active in red-yellow and areas less active in blue-green (based on F values). S1 = primary sensory cortex; M1 = primary motor cortex; V1 = primary visual cortex; Crb = cerebellum; CC = cingulate cortex; SMA = supplementary motor area; L = left.

Fig. 7 Velocity-dependent brain activity correlating positively with neural contribution to passive movement resistance during condition in stroke patients (corrected, p<0.05). Colour
Cortical involvement in hyperactive stretch reflexes after stroke

We found that the velocity-dependent brain activity in ipsilateral primary sensory (area 3b) and motor cortex (area 4p) correlated positively with neural contribution to passive movement resistance in both stroke patients and controls. In the controls we also found a positive correlation between activity in contralateral S1 and M1 and neural contribution to passive hand resistance. This latter finding is in agreement with studies in healthy individuals showing contralateral cortical involvement in the long latency stretch reflexes arising when voluntarily contracting hand muscles are perturbed stretch reflexes in response to perturbation during voluntary contraction (Palmer and Ashby, 1992; Lewis et al, 2004; Tsuji and Rothwell, 2002; Taylor et al, 1995). Early studies in stroke patients reported reduced long latency stretch reflexes in voluntarily contracting hand muscles (Marsden et al, 1977; Dick et al, 1987). The discrepancy with our findings is likely due to task differences. In our experiment optimal performance was complete relaxation of the muscle during stretch whereas in the other studies investigating stretch reflex responses in voluntarily contracting muscles the optimal performance was a rapid correction of the required isometric force of the hand muscle tested.

In controls it is most conceivable that the passive movement leads to deactivation of the ipsilateral hemisphere through transcallosal projections from the contralateral hemisphere. The passive muscle stretch results in Ia sensory input which is transmitted through the dorsal columns to the sensory thalamus. The sensory thalamus sends projections to both area 3b and area 2 (Friedman and Jones, 1981). From contralateral area 2 there are dense connections with the motor cortex (Yumiya and Ghez, 1984). From contralateral area 2 there are dense transcallosal connections to area 2 in the opposite hemisphere (Jenny, 1979; Rouiller et al, 1994). It is therefore likely that it is through transcallosal connections with the contralateral S1 and M1 that the ipsilateral S1 and M1 respectively are deactivated, as we found during passive movement in controls. This is in line with recent fMRI and TMS reports of ipsilateral S1 and M1 inhibition occurring during sensory stimulation of the hand (Hlushchuk and Hari, 2006; Swayne et al, 2006). In the stroke patients, with lesions damaging sensory pathways, this normal processing sequence is disturbed. Whether the increased ipsilateral activation is due to disturbed interhemispheric communication (Calautti et al, 2007), up-regulation of ipsilateral projecting sensory pathways (Lipton et al, 2006; Noachtar et al, 1997), impaired gating of sensory input (Staines et al, 2002a), or disturbed subcortical processing is not clear. The exact way in which disturbed sensory processing results in ipsilateral
hyberactivity remains to be clarified but the importance of intact sensory processing is in line with findings that thalamic infarcts disturb intracortical inhibitory and excitatory processing in M1 (Liepert et al, 2005), that reduced metabolism in the sensory thalamus is related to poor motor recovery after stroke (Binkofski et al, 1996), and that increased somatosensory-evoked potentials is associated with reduced spasticity in children with cerebral palsy (Park et al, 2002).

In the patients, the increased ipsilateral activation may lead to increased neural contribution to passive movement resistance by influencing ipsilaterally descending pathways, such as the corticoreticulospinal, corticovestibulospinal (Nathan et al, 1996), or the corticopropriospinal (Pierrot-Deseilligny, 1996). Activation of these pathways would alter spinal network activity which in turn would lead to increased firing of the alpha motoneuron. Alternatively, the increased ipsilateral activity may only reflect disturbed sensory processing and may thus not be directly involved in the increased long latency reflex response. However, given that long-latency components occur after muscle stretch in patients (unpublished data) and previous evidence for a transcortical loop in passive hand muscle reflexes in monkey (Cheney and Fetz, 1984) it seems likely that the increased isplilateral activity rather reflects a transcortical involvement in the regulation of neural contribution to passive movement resistance. This may have implications for the understanding of the pathophysiology of spasticity after stroke.

4.20 Use-dependent plasticity after stroke

4.21 Effects of passive-active movement training (Study III)

Given the rationale for passive training we studied whether such training, together with active components, could be beneficial for a group of chronic stroke patients (Study III). Patient’s upper limb function was measured on three occasions during a baseline period before and once after training. All patients trained as described in section 3.5.0. After training, the group improved in active range of motion at the wrist and MAS scores for the arm (p<0.05). Interestingly, two patients who had no voluntary wrist extension during the baseline measurement phase showed active wrist extension of 8° and 22° after training. The patients also reported improvements in a variety of daily tasks requiring the use of the affected upper limb, which suggested that the improved motor function was functionally relevant.

Passive-active movement training: a useful alternative in rehabilitation

The training study showed that repetitive, passive-active movement training can improve upper limb motor function and ability in patients with chronic stroke with all degrees of upper extremity paresis. The training effects found are
supported by the reported functional improvements. The passive-active movement training in this study successfully incorporated the use of enhanced somatosensory input which has previously been shown to improve corticomotor output (Ridding et al, 2000; Kaelin-Lang et al, 2002; Carel et al, 2000) and muscle strength post stroke (Glanz et al, 1996). Such training also enables the inclusion of more severely affected patients with stroke than other training regimens (Taub et al, 2002) and can therefore be regarded as a useful alternative in rehabilitation. However, we did not perform any follow-up measures of hand function after the training. A one-month follow-up measurement would have supplied valuable information about how the positive effects of training were maintained or not.

4.22 Cortical activity changes in relation to time after stroke (Study IV)

In the present fMRI study we used a passive wrist flexion-extension movement in the scanner to examine whether the sensorimotor representation of the passive movement is reduced with time after stroke. In the same patients, we also investigated the effects of training on brain activity (see 4.23). Control subjects activated contralateral S1 and M1, PMC, thalamus and prefrontal cortex during passive wrist movement. Activations also occurred in ipsilateral cerebellum and bilateral S2 areas (p<0.05, corrected) (Fig 8 A). The patients, all with intact proprioception at the wrist, activated contralateral S1, M1 and thalamus (Fig. 8 B) during passive wrist movement. However, the patients showed reduced activity in ipsilateral cerebellum and a tendency for reduced activity in contralateral M1 and S1, PMC and cingulate cortex (p<0.05, uncorrected) (Fig. 8 C).

In patients, reduced passive movement-related activity over time was found in SMA, prefrontal and parietal association areas (p<0.05, corrected). Activity in contralateral primary motor cortex, ipsilateral supramarginal gyrus and ipsilateral cerebellum showed tendency for correlation (p<0.05, uncorrected) (Fig. 9 A). The parameter estimates during passive movement versus rest in the above areas correlated strongly with time poststroke (i.e., more than 80% of the variation in brain activity in the areas reported was explained by the variation in time poststroke) (Table 3). When plotted against other variables (i.e., age, lesion volume and upper limb sensorimotor function measures) the parameter estimates only correlated with wrist extension (i.e., in the contralateral intraparietal sulcus).
Fig. 8 Brain activity during passive wrist movement (contrasted with rest) for control subjects is illustrated in (A) and for patients in (B). Activations are illustrated on glass brain images. Group difference (Controls>Patients) is illustrated in (C). Controls activate contralateral sensorimotor areas (axial section, Z = 69) and ipsilateral cerebellum (coronal section, Y = -48) more than patients. Activations are superimposed on mean control T1-weighted anatomical image (p < 0.001, uncorrected). Colour bar depicts t-values (L = left).

Fig. 9 In (A) passive movement-related brain activity which correlates negatively with time
poststroke, superimposed on patients' mean T1-weighted anatomical image in. Color bar depicts t-values (L = left). In (B) passive movement-related brain activity which increased after training. Note that the coordinates of the sections are identical for both axial (Z = 54) and coronal (Y = 36 and -63) sections in (A) and (B) (p < 0.001, uncorrected).

**Table 3. Correlation coefficients (r values) between clinical variables and brain activity in areas found to be related to time poststroke. Significant correlations are marked with * = p <0.05 and ** = p <0.01. CL = contralateral; IL = ipsilateral; Sup = superior; Inf = inferior; Mid = middle; Crb = cerebellum.**

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Reduced cortical activity over time due to lack of use?
The correlation analysis in Study IV showed that patients in the later phase after stroke had reduced activity during passive movement in a number of sensory and motor brain areas. Given that training enhanced brain activity in similar areas (Fig. 9), that the cortical maps are highly use-dependent (see section 1.22), and previous reports that stroke patients in the chronic phase use their affected hands less even if capable (Laplane and Degos, 1983; Andre et al, 2004; Sterr et al, 2002) it seems likely that the reduced brain occurring later after stroke is due to reduced use of the paretic hand. It may be that this reduced cortical activity is reflecting behavioural changes similar to the “learned non-use” phenomenon (Taub et al, 2002). Another possibility is that the patients have reduced attention to sensory stimuli of the affected hand without this being observed clinically (no patients had any clinical signs of neglect). Such reduced attention to the hand could lead to reduced activity in primary and secondary sensory areas (Drevets et al, 1995; Rushworth et al, 2003). Over time this reduced attention would lead to reduced synaptic efficiency in the attention networks. Indeed, it seems likely that the cortical networks involved in attention to sensory stimuli of a body part and the networks involved in movement of the same body part would undergo similar use-dependent changes over time after stroke.

4.23 Training-induced cortical activity changes (Study III+IV)
In study III we also described training effects on cortical activation in two patients using fMRI. Cortical activation in both patients increased after training during active wrist extension in contralateral M1, ipsilateral S1/M1 and dorsal premotor cortex as well as in cingulate cortex, cerebellum and prefrontal areas.
(for more details see Study III). These changes occurred in parallel with improvements in motor function.

Another investigation of training effects on cortical activity was carried out in five of the patients who participated in the cross-sectional study (section 4.22/Study IV). Training in these patients resulted in behavioural improvements, although there was a large variation among subjects. MAS scores were improved in three patients, range of active wrist extension increased in two, and two exhibited reduced muscle tone in the wrist and finger flexor muscles (see Study IV for more details). All patients also reported increased use of the paretic arm and hand in one or more everyday functions.

In this fMRI study we used a passive hand movement task in the scanner. After training, single-subject analysis showed that activity significantly increased in SMA and pre-SMA in four of five trained patients. All patients also showed increased activity in primary sensory and motor areas and cerebellum (Fig 10 C). Group analysis of the training effect revealed increased activity in pre-SMA and SMA, ipsilateral primary sensory cortex and intraparietal sulcus, and contralateral cerebellum (Fig 9 B).

Several areas that increased activity with training were similar to those that showed i) reduced activity in the patient group when compared with the control group, and ii) reduced activity with time after the stroke. These areas included the SMA and ipsilateral cerebellum. Other areas in which the training induced increased activity, exhibited only ii) reduced activity with time. These areas included pre-SMA, ipsilateral S1 and intraparietal sulcus, and contralateral cerebellum.
Fig. 10 Brain activity in stroke group (A) before training and (B) after training ($p < 0.001$, uncorrected). Visual comparison reveals apparent increases in neuronal activity in
supplementary motor area (SMA), primary sensory cortex (S1), prefrontal cortex (PFC) and cerebellum (Crb) similar to findings in group analysis of training effect. (C) Single-subject fixed effects analysis of training effect showing that activity increased in cerebellum and primary sensory and motor areas in all patients. Increased activity in SMA and pre-SMA was found in four patients (L = left).

Up-regulation of areas with corticospinal projections
Increased brain activity occurred in S1, M1, and SMA bilaterally after training. This occurred in parallel with improved upper limb function. Increased activity in sensorimotor areas after training have previously been associated with recovered motor function (Luft et al, 2004; Johansen-Berg et al, 2002b; Ward et al, 2006b). These areas have corticospinal projections (Dum and Strick, 2002; Galea and Darian-Smith, 1994) and thus increased activity may relate to increased corticospinal excitability (Koski et al, 2004) which may help substitute for the damaged hand projections.

In healthy subjects, with intact corticospinal projections, demanding hand movements have been shown to engage a more widespread network of brain areas than less demanding tasks (Dettmers et al, 1995; Ehrsson et al, 2000). This pattern of activity is similar to the increased activity pattern found in stroke patients after training suggesting that areas normally involved in demanding tasks, including ipsilateral sensory and motor areas, may be recruited after stroke (Lotze and Cohen, 2006). Our findings of increased ipsilateral S1 and M1 activation after training support that the unaffected hemisphere is involved in the training-mediated improvement and suggest that sensorimotor areas in the spared hemisphere may play a role in training mediated improvements after stroke (Gerloff et al, 2006).

Up-regulation of areas involved in motor learning and attention
Increased brain activity after training also occurred in areas without corticomotor projections (e.g., cerebellum). This may reflect an up-regulation of sensorimotor areas related to motor learning and not just to enhanced corticomotor excitability. Indeed, the above areas are known to be involved in the automatization phase of motor learning (for review see Doyon and Benali (2005)). Reorganization related to learning would be in line with the idea that learning mechanisms are important for mediating poststroke recovery and training-induced functional improvements (Krakauer, 2006; Monfils et al, 2005). Another possibility is that training increases the attention to passive movements of the paretic hand. This may explain increased activity in sensory and attention related brain areas, such as S1 and parietal and prefrontal areas (Rushworth et al, 2003). The increased activity may be related to altered gating of sensory stimuli through prefrontal cortex (Staines et al, 2002b). Future studies
incorporating behavioural measures of attention may help to elucidate the role of attention during training.

*Reorganisation likely influenced by degree of function and lesion location*

Previous training studies of patients with mild motor deficits have predominantly shown an increase in contralateral sensory and motor activity (i.e., in S1, M1, and premotor areas) occurring in association with improved motor function (Johansen-Berg et al, 2002a; Liepert et al, 2004; Nelles et al, 2001; Carey et al, 2002b; Liepert et al, 2000b). Training in patients with poorer motor function at baseline seems to result in a more bilateral increase of activation (Schaechter et al, 2002) with increased ipsilateral S1 and M1 activity (Luft et al, 2004). This is in line with our findings of increased ipsilateral S1/M1 activation in three out of five patients (Fig. 10 C) with moderate to severe impairment prior to training.

Lesion location may also affect the movement-related activity pattern in the brain. Patients with subcortical damage activate more widespread areas than patients with cortical damage (Luft et al, 2004). It has also been shown that lesions damaging sensory input to S1 may lead to decreased intracortical inhibition on the affected side (Liepert et al, 2004). Hamzei et al (2006) recently reported reduced activity after training (CI-therapy) during passive hand movement in contralateral S1 and M1 in patients with intact hand projections from M1 (i.e., not affected on anatomical MR images and with normal MEPs). In these patients, paired-pulse TMS stimulation revealed a decrease in intracortical inhibition after training. The opposite pattern was found in patients with damaged hand projections from M1. In these patients the activity during passive hand movement increased in extent after training and intracortical inhibition increased. The authors interpret the first pattern as reflecting an increase in synaptic efficiency which was not possible in the patients with damaged projections from M1. These studies show that lesion location is of likely importance when investigating training effects and indicates further investigation.
5.0 CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

Neuroimaging studies have been critical for our understanding of the pathophysiology and brain plasticity after stroke. New imaging sequences, like diffusion tensor imaging (DTI) allow sensitive quantification of white matter integrity in the brain. Using DTI early after stroke to identify degree of damage of the corticofugal tracts (CFT) may prove useful in the future for predicting functional outcome after stroke. Incorporating new methods for probabilistic tractography (Johansen-Berg and Behrens, 2006) to distinguish degree of damage to different descending projections (Newton et al, 2006) may also be valuable. Together with DTI, transcranial magnetic stimulation (TMS), to test the integrity of the direct corticospinal projections after stroke, may add valuable information when predicting outcome and which patients will benefit from rehabilitation interventions (Stinear et al, 2007). However, future studies on how best to predict outcome using costly neuroimaging techniques should be compared to prediction based on use of sensitive and reliable sensory and motor function measures at various time points after stroke (Hendricks et al, 2002a; Kwakkel et al, 2003).

Our findings of cortical involvement in the neural response in the hand flexor muscles during fast passive movement after stroke may have implications for the pathophysiology of spasticity. Spasticity can take many months to appear (Gracies, 2005) suggesting that maladaptive plasticity at the spinal level is the main determinant of its development. Indeed, the strong correlations between the neural component and cortical activity observed in study II may only be secondary to changed spinal processing of passive movement (i.e., input from spinal cord affects cortical activity). Alternatively, it may be that these cortical areas are contributing to the altered activity in the spinal circuits (i.e., output from cortex affects spinal cord activity). Future studies using repetitive TMS (Rothwell, 2003) to perturb the cortical activity in the areas found to correlate with neural contribution to passive movement resistance will shed light on nature of this involvement.

Our Passive-Active movement training programme successfully incorporated components shown to be important for improving motor function in the chronic phase after stroke, even in patients with severe deficits. The training focused on meaningful movements and was sufficiently intense to improve upper limb function and to drive reorganisation of brain circuits involved in hand movement. Training in the chronic phase may also prevent down-regulation of movement-related cortical activity which likely occurs due to reduced use of the paretic hand (Sterr et al, 2002). Further investigation of the relation between ability to move, perception of movement, and actual use of the hand may help explain why some patients late after stroke do not use the hand to their full
capacity. Use of intense training programmes in the early phase after stroke, also require further study.

Today many innovative treatments are being suggested based on findings from neuroimaging studies. Examples of such treatments include:

(i) use of bilateral arm training to reduce inhibition in brain areas that may substitute for damaged areas (Caraugh and Summers, 2005)
(ii) using a mirror to create the illusion of movement in the paretic hand can increase excitability in ipsilateral motor projections which may be important for substitution (Garry et al, 2005)
(iii) combination of hand training with blockade of sensory stimuli from the upper arm can result in better motor function improvement in the hand and lead to increased corticospinal excitability to hand muscles than just training alone (Muellbacher et al, 2002)
(iv) use of motor imagery to activate brain areas important for movement in patients who are not eligible for active movement training (Sharma et al, 2006)
(v) use of robots and virtual reality interfaces in training may help to create intense training of tasks in meaningful settings for the patient (Ferraro et al, 2003; Deutsch et al, 2004)
(vi) repetitive transcranial magnetic stimulation (rTMS) over the motor cortex ipsilateral to the paretic hand (thus reducing the interhemispheric inhibition of the damaged hemisphere) can result in improved motor function and dexterity in stroke patients (Mansur et al, 2005)
(vii) use of transcranial direct current stimulation (Hummel et al, 2005) and theta burst stimulation (with TMS) (Talelli et al, 2007) to modify cortical excitability can also lead to improved hand function after stroke
(viii) pharmaceutical interventions, such as amphetamines (Martinsson et al, 2007) or anti-depressants (fluoxetine) (Pariente et al, 2001), may be used to modulate cortical excitability and improve motor function after stroke

It is hoped that use of neuroimaging methods will continue to improve our knowledge of the neurobiology of outcome and recovery after stroke. This should lead to new interventions based on what we know on how lesion, brain function, and behaviour of the individual interact. It is believed that such insights will lead to the establishment of training principles based on scientific findings rather than on “schools of thought”, predominantly based on clinical experience. However, even today in our search for the optimal way to treat individuals with stroke it must be considered that we too, just like our predecessors, are perhaps constrained by our contemporary theories of motor control and what we know about how the brain works. Only more research can answer if this is the case.
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69


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