Section 2: Motor recovery after stroke

Stroke is a leading cause of disability, commonly involving deficits of motor function (Bonita and Beaglehole 1988). Some degree of motor recovery typically occurs in patients who survive and this can be enhanced by rehabilitation therapy (Stroke Unit Trialists' Collaboration 1997). The neural processes contributing to spontaneous or rehabilitation-mediated recovery remain poorly understood (Cramer and Bastings 2000). One of the main aims of this thesis is to explore the degree to which reorganisation of cortical networks contributes to recovery after stroke. This section describes some new observations relevant to our understanding of the processes that drive recovery.

2.1 Pathophysiology of ischemic stroke

There are three main categories of stroke: ischemic stroke (80% of cases), intracerebral haemorrhage (15%) and subarachnoid haemorrhage (5%). Ischemic stroke (or cerebral infarction) occurs after the occlusion of a blood vessel in the brain and is characterised by rapidly developing clinical symptoms and/or signs of focal loss of cerebral function, with symptoms lasting more than 24 hours or resulting in death, with no apparent cause other than a vascular event (Warlow *et al.* 1996). If symptoms last less than 24 hours the event is classified as a transient ischemic attack (TIA). Stroke most commonly occurs in late middle and old age, usually in patients with vascular risk factors including hypertension, atrial fibrillation, smoking and diabetes mellitus. About 50% of ischemic strokes and TIAs are due to atherothromboembolism, 25% to intracranial small vessel disease, 20% to embolism from the heart and 5% to rare causes (Warlow *et al.* 1996).

Distal to occlusion of a large artery there is a fall in cerebral perfusion pressure (CPP) that leads to a series of haemodynamic and metabolic changes of increasing severity depending on the extent and duration of occlusion. First, there is an

autoregulatory stage of 'haemodynamic reserve' in which vasodilation causes an increase in cerebral blood volume (CBV). When CPP falls below the lower threshold of autoregulation there is a stage of 'misery perfusion' in which cerebral blood flow (CBF) declines but cerebral metabolic rate of oxygen ($CMRO_2$) remains the same. This uncoupling between flow and metabolism is possible because of an increase in oxygen extraction fraction (Baron *et al.* 1981). However, once oxygen extraction fraction is maximal, if CPP continues to fall there will be a decrease in $CMRO_2$ which is associated with ischemic neuronal damage. The severity and duration of reduced flow and metabolism determine whether the damage is reversible (the ischemic 'penumbra') or irreversible (the ischemic 'core') (Ackerman *et al.* 1981). Neurons in the penumbra are defined as being functionally inactive but structurally intact (Astrup *et al.* 1977; Astrup *et al.* 1981). Limiting neuronal loss in the surrounding penumbra is a major target for acute therapeutic interventions (see Section 2.4.1).

Functional impairments in remote regions that are connected to the infarcted area can occur hours or days after stroke (Von Monakow 1914). For example, a common finding (occurring in about 50% of stroke patients) is crossed cerebellar diaschisis, in which perfusion and metabolism are reduced by up to 50% in the cerebellar hemisphere contralateral to a stroke (Baron *et al.* 1980). Remote hypoexcitability can be a direct result of decreased excitatory synaptic input from the infarct or other disconnected regions. As some of these effects are purely functional (i.e. do not involve neuronal damage or death), their reversal could contribute to recovery (see Section 2.4.1).

2.2 Motor impairments and recovery after stroke

The idea that brain injury can produce motor impairments has a long history. As early as the 4th century BC, followers of Hippocrates noted that head injury could lead to contralateral movement disorders or seizures. This was partly explained in 1709 when Domencio Mistichelli produced the first diagram of the crossing of the pyramidal tracts. A year later Pourfour du Petit, a military surgeon, reported that unilateral hemiplegias in humans resulted from damage to the contralateral cerebral hemisphere (Finger 1994).

The degree to which recovery of movement occurred after brain damage was debated. In 1886 Sir David Ferrier reported that lesions to the precentral region in monkeys resulted in hemiplegia with no recovery. However, while Ferrier's animals were kept alive for only a few days, Italian scientists Luigi Luciani and Arturo Tamburini, who were carrying out similar experiments at the time, observed their animals for a number of months. In contrast to Ferrier's reports, they found substantial improvements in limb function over time (Finger 1994). Through the 20th century it has become increasingly clear that at least some recovery can occur after brain injury. Sherrington and colleagues lesioned motor areas of the monkey brain and found that the initial contralesional paralysis recovered over time (Leyton and Sherrington 1917; Grunbaum and Sherrington 1908). Luria's extensive work on head-injured soldiers in the second world war also documents recovery of motor, sensory and cognitive abilities (Luria 1963).

Clinical experience has shown that while motor impairments are common after stroke, some degree of recovery typically occurs in patients who survive. One prospective study found a hemiparesis in 88% of patients at stroke onset, with equal

numbers graded mild, moderate or severe (Bonita and Beaglehole 1988). However, by one month post-stroke, 26% had no impairment and 39% were graded as mild. At six months post-stroke 39% had no impairment and 36% had mild impairment. Most recovery occurs relatively soon after stroke. A study of upper extremity function after stroke found that maximum recovery was achieved by 95% of patients within 9 weeks (Nakayama *et al.* 1994). The extent of recovery is highly dependent on the severity of the initial deficit. 79% of patients with initial mild paresis regained full recovery, compared to only 18% of patients with initial severe paresis (Nakayama *et al.* 1994).

2.3 Movement Rehabilitation after stroke

Physicians of ancient Greece had a variety of strategies for improving outcome following "apoplexy", including hot baths, purgatives, scalp incisions, drinking soup and avoiding alcohol (Clarke 1963). The 15th century saw developments in the use of heat, hydrotherapy, weights, pulleys and walking machines. In the 18th century, electrical stimulation of the paretic limb became a common treatment (Finger 1994).

In more recent times there have been major developments in models of motor control that can be used to guide physiotherapeutic approaches (Plant 1998). Conventional physiotherapy is often based on the work of Bobath (Bobath 1978). A survey of UK-based senior physiotherapists found that 67% use this approach (Lennon *et al.* 2001). The Bobath concept emphasises the reduction of enhanced muscle tone in the affected limb. Active movement of the affected limb is discouraged while there is a risk of reinforcing abnormal tone through practice. However, there is little experimental evidence to support this approach. Recently, there have been challenges to the Bobath method and techniques that encourage active training of the affected

limb have received more attention (Sunderland *et al.* 1992; Taub *et al.* 1993; Butefisch *et al.* 1995; Carr and Shepherd 1982).

There is evidence that rehabilitation therapy after stroke can improve outcome (Ernst 1990), and reduce long-term disability (Stroke Unit Trialists' Collaboration 1997; Indredavik *et al.* 1997). There is a dose-dependent effect of rehabilitation, with more time spent in training leading to greater recovery (Kwakkel *et al.* 1999). However, there are surprisingly few controlled studies to compare the efficacy of different strategies. One of the few such studies compared the traditional Bobath approach to the Motor Relearning Programme (MRP) for acute stroke (Langhammer and Stanghelle 2000). The MRP is a task-oriented approach that encourages repetitive active and/or passive practice of motor skills (Carr and Shepherd 1982). Patients treated with the MRP had improved motor outcome (as measured by the Motor Assessment Scale and the Sødring Motor Evaluation Scale) and stayed fewer days in hospital than those treated according to the Bobath approach (Langhammer and Stanghelle 2000).

One active training technique that has made claims of success in rehabilitation of motor dysfunction after stroke is "constraint-induced therapy" (CIT). This approach has been championed by Taub and is based on his previous work with animals after deafferentation (Taub *et al.* 1993). Taub developed a theory of "learned non-use" to explain long lasting movement deficits in deafferented monkeys. He demonstrated that learned non-use could be overcome if the animals were forced to use the affected arm by restraining their unimpaired limb (Taub *et al.* 1994). These concepts have been successfully introduced to the clinic in the rehabilitation of limb movement after stroke and other brain injuries by restraint of the less impaired limb accompanied by a programme of exercise for the affected limb (Taub *et al.* 1993; Taub

et al. 1999). Improved function after CIT has been associated with altered patterns of movement-related cortical activity (Liepert *et al.* 1998; Liepert *et al.* 2000; Kopp *et al.* 1999).

2.4 Processes mediating motor recovery

There are a number of processes that may contribute to recovery of motor function after stroke. Firstly, resolution of pathological changes may allow for recovery at the cellular level. Second, development of compensatory movement strategies may enable 'recovery' of certain motor functions, although subtle differences in movement kinematics would then exist. Third, undamaged regions in the sensori-motor network may take over the function of damaged or disconnected areas. These possibilities are discussed in more detail below.

2.4.1 Resolution of pathology

In the acute stages after stroke recanalisation of occluded vessels, establishment of collateral flow and reduction in inflammation all contribute to salvaging partially spared tissue. Potentially resolvable pathological results of stroke are particularly relevant to the ischemic penumbra. Limiting neuronal damage in the surrounding penumbra is a major goal for acute therapeutic interventions as neurons there are initially structurally intact (Ginsberg *et al.* 1999; Procter 1990).

There are also suggestions that resolution of remote hypometabolism ('diaschisis' see Section 2.1) contributes to recovery (Feeney and Baron 1986) and that the extent of diaschisis determines functional impairments (Donnan *et al.* 1991). However, studies looking at the time scale of recovery and pathological change have found that extent and resolution of diaschisis does not independently predict recovery:

serial SPECT measurements have found that clinical recovery is not accompanied by resolution of remote effects (Bowler *et al.* 1995). Also, although the initial severity of crossed cerebellar diaschisis correlates with clinical outcome, it does not predict outcome independently of acute hypoperfusion volume, and persists even after extensive recovery of movement has taken place (Infeld *et al.* 1995).

2.4.2 Behavioural compensation

Depending on the measure used to assess outcome, a certain amount of recovery can be achieved through behavioural compensation, rather than genuine recovery of normal motor strategies. Detailed kinematic analysis of humans (Cirstea and Levin 2000) and animals (Whishaw *et al.* 1991; Whishaw 2000; Friel and Nudo 1998) shows that compensatory movement strategies can be employed after an infarct. For example, stroke patients tend to compensate for deficiencies in distal muscle control by increased use of the trunk to perform multi-joint pointing movements (Cirstea and Levin 2000). Similarly, a measure of motor performance suggested that rats with large lesions to the entire forelimb area of motor cortex perform as well as rats with much smaller lesions (Whishaw *et al.* 1991). However, kinematic analysis demonstrated that the rats with large lesions accomplished the movement with compensatory strategies such as increased body rotation.

2.4.3 Brain plasticity

Since Broca described localisation of language in the left frontal cortex in 1861, the concept of functional localisation has dominated systems-level neuroscience. Until relatively recently it was thought that functions were 'hardwired' in the adult brain.

Experiments on animals suggested that reorganisation or plasticity of neural networks was possible only during critical periods of early development (Blakemore 1991).

In recent years, however, it has become increasingly clear that representational networks in the adult brain are capable of extensive reorganisation. For example, in normal humans and animals, cortical reorganisation occurs with learning new motor skills (Karni *et al.* 1995), as well as learning of auditory (Recanzone *et al.* 1993) and visual (Walsh *et al.* 1999) tasks. Recovery of motor function after stroke is also associated with changes in motor cortical representations (Cramer and Bastings 2000). It is thought that undamaged areas and pathways in the brain 'take over' the functions of damaged regions.

Motor plasticity is possible as the motor system is organised as a distributed network (Section 1.1). Although different motor areas are functionally specialised there is nevertheless substantial functional overlap between them (Section 1.1.2). In addition, the dense interconnections between motor areas (Figure 1.7), and the presence of parallel descending motor pathways (see Section 1.1.4) allow for the possibility of intact regions of the network compensating for the loss of damaged or disconnected areas, in the same way that a distributed neural network model can show 'graceful degradation' after damage to some of its units (Rolls and Treves 1998).

Reorganisation can occur in regions adjacent to the lesion, in undamaged areas of the lesioned hemisphere, or in areas in the intact hemisphere. Examples of reorganisation at these different spatial scales are dealt with below. Potential mechanisms for reorganisation that operate at different spatial and temporal scales are described in Section 2.5.

2.4.3.1 Local remapping: areas adjacent to the lesion

The primary sensory and motor cortices are organised somatotopically and can be conceptualised as containing representational 'maps' of the sensory-motor apparatus of the body (see Figures 1.4, 1.15). Brain plasticity can involve local reorganisation of these representational maps.

The ability for local cortical reorganisation to occur as a result of altered input has been extensively investigated in the somatosensory cortex after peripheral damage in monkeys (Kaas 1991; Merzenich and Jenkins 1993). Amputation or deafferentation of a digit or a limb results in immediate silencing of the area of somatosensory cortex that previously represented the affected body part. Over time, however, the cortical region begins to respond to sensory inputs from body parts represented by adjacent areas of cortex (see Figure 1.15). Similar phenomena occur in humans after amputation (Kew *et al.* 1994) and may provide an explanation for some features of phantom limb sensations whereby touch to the face, for example, evokes the perception that the amputated limb is being stimulated (Flor *et al.* 1995; Knecht *et al.* 1995). The representation of the face is adjacent to the hand on the somatosensory homunculus (see Figure 1.15) suggesting that adjacent cortical representations invade silent areas after peripheral damage.

Local cortical reorganisation can also occur after central damage. After lesions to the representation of a single digit in the somatosensory cortex of monkeys, adjacent areas of cortex begin responding to sensory stimulation of the affected digit (Doetsch *et al.* 1990).

Recovery of movement after damage to the motor system is also paralleled by local cortical reorganisation in some cases. As early as 1950 Glees and Cole

demonstrated with surface stimulation that after a lesion to the thumb area of M1 in monkeys, the motor representation of the thumb shifted to the adjacent intact cortex (Glees and Cole 1950). Nearly 50 years later Nudo et al made small lesions of the digit representation in monkey motor cortex. After 3-4 months of spontaneous recovery intracortical microstimulation of M1 revealed that local remapping had occurred (Nudo and Milliken 1996). Stimulation of areas adjacent to the lesion, which had previously evoked elbow or shoulder movements, now produced movement of the digits. A second study demonstrated that this local remapping could be enhanced by rehabilitative training (Nudo *et al.* 1996; Figure 2.1).

There is also some evidence for local remapping in human sensorimotor cortex. A PET study found a ventral extension of activation during hand movement into the face area of motor cortex in some patients after capsular stroke (Weiller *et al.* 1993). FMRI studies have found a posterior shift in the location of motor cortical activity in both stroke (Pineiro *et al.* 2001) and multiple sclerosis (MS) (Lee *et al.* 2000).

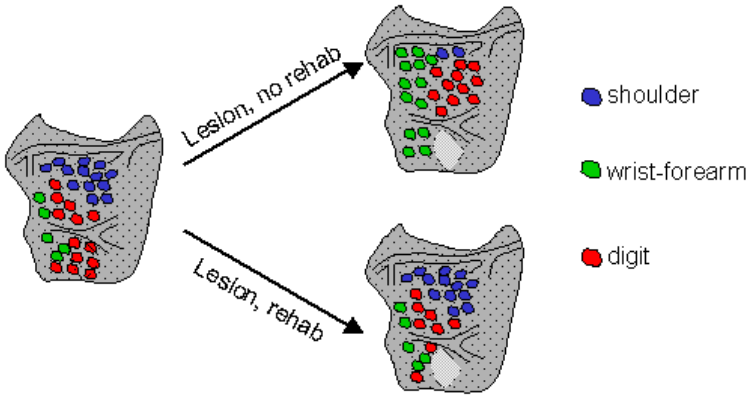

Figure 2.1: Example of local remapping revealed by intracortical microstimulation. Schematic showing an area of motor cortex and sites where electrical stimulation produced movement of shoulder (blue), wrist-forearm (green) or digits (red). After a lesion (pale grey area) stimulation of the infarcted region does not produce any movement. However, there is reorganisation of the surrounding representations, with the digit representation invading regions previously involved in representing the shoulder. This local remapping is enhanced with rehabilitative therapy. Based on Nudo et al (1996).

A posterior shift could reflect increased recruitment of corticospinal projections from somatosensory areas (see Section 1.1.3). A study using retrograde transport of fluorescent tracers from the spinal cord of the monkey found that although nearly 70% of corticospinal projections originated in frontal and cingulate cortex, there were also projections from primary and posterior parietal somatosensory areas, with 2.2% of the corticospinal projection arising in area 3a, 9% in 3b/1 and 13% in area 2/5 (Galea and Darian-Smith 1994). Alternatively the shift towards the postcentral gyrus could reflect increased attention to sensory information to guide movement of an affected limb (see Section 6).

There is some suggestion that local remapping in sensorimotor cortex is tightly coupled to injury burden as the size of the posterior shift in MS is correlated with injury burden (Lee *et al.* 2000). However, the fact that no correlation was found with clinical impairment in this study questions either the functional relevance of the shift, or the sensitivity of the technique. In the FMRI study of patients after subcortical stroke there was no correlation found between the size of the posterior shift and clinical impairment or lesion volume (Pineiro *et al.* 2001). However, the number of patients was small and the structural scans acquired did not allow for very accurate lesion volume quantitation. Also, in both the stroke and the MS study the FMRI voxel size was 4x4x6mm (in order to achieve whole brain coverage) and 5x5x5mm spatial smoothing was applied. The mean size of the posterior shift in the peak of lateral motor activity for the patient group relative to controls was 9mm in the MS study and 12mm in the stroke study. The smoothed voxel size is therefore large relative to the size of the shift and this might result in a loss of sensitivity in any correlation with the magnitude of the shift. In addition, FMRI is sensitive to haemodynamic changes in

large vessels (see Section 3.1.3.1) which can skew localisation of peak activations away from the small vessels close to the site of neuronal activation. Strategies for minimising these effects include use of high field scanners and surface coils (see Section 3.1.3.3). Future human imaging studies using such strategies and limited to coverage of motor cortex with small voxels could provide valuable further insight into the precise relationship between local remapping and functional recovery.

2.4.3.2 Intact regions in the damaged hemisphere

Plasticity can also occur over a wider spatial scale, with distinct intact brain regions taking over the function of the damaged cortex. This is made possible by the existence of functional overlap within the sensorimotor network. For example, although the majority of corticospinal projections arise from the primary motor cortex there are also direct projections from premotor and supplementary motor regions (see Section 1.1.4.1).

The importance of regions outside the primary motor cortex for recovery of movement has been demonstrated in both human and animal studies. The altered role of the SMA after primary motor cortex damage was demonstrated by a single cell recording study which recorded neuronal responses during a key pressing task before and after an M1 lesion in a monkey (Aizawa *et al.* 1991). Before an M1 lesion SMA neurons were active during task learning but this activity disappeared once the task became overlearnt. However, after a lesion to M1 the SMA became active during task performance again. This is consistent with the finding from some brain imaging studies of differentially increased activation in the SMA in recovered stroke patients (Cramer *et al.* 1997; Weiller *et al.* 1993). Altered SMA activity could reflect increased

recruitment of non-primary motor corticospinal projections, or it could reflect the need to 'relearn' previously automatic or effortless movements after damage.

There is also a potential role for the lateral premotor cortex in recovered movement. A PET study of recovered stroke patients showed that movement of the recovered hand did not activate the primary sensorimotor cortex in either hemisphere but did activate dorsolateral premotor cortex and SMA in both hemispheres (Seitz *et al.* 1998). This is also seen in a study of motor recovery after sensorimotor cortex lesions in monkeys (Liu and Rouiller 1999). After motor recovery had taken place primary and premotor regions in both hemispheres were inactivated by the GABA agonist, muscimol. The only area where inactivation produced a loss of recovered movement was the PMC in the damaged hemisphere suggesting that integrity of this region was crucial to recovery.

Increased recruitment of intact areas of the damaged hemisphere is not limited to classical motor regions. There have also been reports of increased activity in prefrontal cortex (Marshall *et al.* 2000) and posterior parietal cortex (Nelles *et al.* 1999a) associated with recovered movements.

The role of the cingulate in recovered movement has rarely been investigated. There are some reports of increased motor-related cingulate activity in stroke patients compared to controls (Weiller *et al.* 1992; Nelles *et al.* 1999b) and this typically has been interpreted as evidence for increased use of attentional mechanisms in recovered movement (Weiller *et al.* 1992). However, there are corticospinal projections from cingulate motor areas that are at least as dense as those from lateral premotor and supplementary motor areas according to some reports (Dum and Strick 1991; Galea and Darian-Smith 1994; Section 1.1.4.1). So cingulate motor areas could potentially

play a direct role in the execution of recovered movement. There are also dense projections from rostral and caudal cingulate motor areas to M1 and SMA (Wang *et al.* 2001). One reason for the lack of evidence for cingulate involvement in recovered movement may be the tendency for many studies to use a restricted volumes of interest approach which rarely includes cingulate motor areas. Future imaging studies should focus on activation patterns in human homologues of macaque cingulate areas with proven spinal projections in order to determine the role of cingulate areas in motor recovery after stroke.

Even after complete removal of the corticospinal tract in primates a great deal of recovery of motor function is possible and is probably mediated by the remaining descending motor tracts (Bucy *et al.* 1964; see Section 1.4). However, the corticospinal tract *is* necessary for normal distal movements. Individuated finger movements do not recover after complete transection of the corticospinal tract (Lawrence and Kuypers 1968), suggesting that non-pyramidal routes to the spinal cord are unable to compensate fully for the loss of the corticospinal tract.

2.4.3.3 The role of the undamaged hemisphere

Recovery can also be mediated by changes in the undamaged hemisphere, possibly reflecting increased recruitment of uncrossed spinal projections (see Section 1.4).

Evidence that the undamaged hemisphere becomes crucial for recovered movement can be found in a small number of reports of patients who have had a second stroke (Fisher 1992; Lee and van Donkelaar 1995). In these cases patients had recovered movement of the initially affected limb. However, a second stroke in the previously undamaged hemisphere resulted not only in a new contralateral hemiparesis,

but also in a reappearance of the original motor deficit in the limb ipsilateral to the second stroke. This suggests that the original recovery was mediated by the initially undamaged hemisphere.

Many functional imaging studies have shown increased activation of the ipsilateral motor areas during movement of the affected limb after stroke (Cramer *et al.* 1997; Cuadrado *et al.* 1999; Weiller *et al.* 1992; Chollet *et al.* 1991; Cao *et al.* 1998; Caramia *et al.* 1996; Honda *et al.* 1997; Caramia *et al.* 1996; Netz *et al.* 1997). Many of these studies have focussed on the importance of the undamaged primary motor cortex (Chollet *et al.* 1991; Cramer *et al.* 1997). Studies using transcranial magnetic stimulation (TMS) have reported increased incidence of ipsilateral motor evoked potentials (MEPs) to primary motor cortex stimulation after stroke (Turton *et al.* 1996).

Temporal as well as spatial information about the role of ipsilateral motor areas in recovered movement can be gained by combining PET with recordings of movement-related cortical potentials (MRCPs) (Honda *et al.* 1997). PET scans of two patients revealed increased motor-related ipsilateral motor cortical activity compared to controls. MRCP recording measured two premovement potentials, the *bereitschaftspotential* (BP, which reaches maximum 1100-750ms before movement onset) and the negative slope (NS, which reaches maximum 400-0ms before movement onset). In both patients the peak of the NS, which was strongly lateralised in controls, was shifted towards the ipsilateral hemisphere. However, there was less difference in the location of the BP (although this was only detectable in one of the two patients). Although the study involved very small numbers of heterogeneous patients performing different movement tasks, it does provide preliminary evidence that involvement of the undamaged hemisphere may vary at different stages of movement processing.

Specifically, it suggests that the ipsilateral hemisphere is particularly involved in a time window a few hundred milliseconds before movement onset. This hypothesis should be further tested with electrical recording in larger patient groups and could also be investigated with transcranial magnetic stimulation (Section 3.2, Section 9) or event-related FMRI (Section 3.1.8.4).

The assumption that increased involvement of the ipsilateral primary motor cortex represents an adaptive response to disease is challenged by the report that the incidence of ipsilateral MEPs is either unrelated to recovery (Netz *et al.* 1997) or more common in patients with poor motor recovery (Turton *et al.* 1996). However, the conclusion of the latter study that involvement of the undamaged hemisphere is therefore *maladaptive* (Turton *et al.* 1996) may not be warranted. There was no quantitative assessment of lesion volume in this study but 5 out of 13 patients in the poorly recovered group were classified as having large lesions and all poorly recovered patients had visible lesions. By contrast none of the 8 patients in the well recovered group were classified as having large lesions, and two did not have any visible lesion. It therefore seems likely that poorly recovered patients would have had more extensive damage than well recovered patients. In this case recruitment of uncrossed corticospinal projections may be adaptive, as the range of possible reorganisational strategies may be smaller. It is important to determine whether increased ipsilateral muscle responses are a predictor of recovery outcome independently of lesion load or initial stroke severity.

Nevertheless, there remains some compelling evidence to suggest that plasticity in the undamaged hemisphere can correlate with improved motor recovery. For example, a recent study found that rehabilitative training after experimental stroke

improved motor function and led to dendritic growth in the undamaged motor cortex in rats (Biernaskie and Corbett 2001).

There is also evidence that sites in the undamaged hemisphere important for recovery might not be limited to the primary motor cortex. Some imaging studies have reported increased activation in ipsilateral premotor cortex during movement of the affected limb (Weiller *et al.* 1992; Seitz *et al.* 1998). This activation seems to be tightly coupled to recovery as a longitudinal study found that increased ipsilateral PMC activity did not occur acutely but only after some recovery had taken place (Nelles *et al.* 1999b).

Similarly, there is debate over the role of the right hemisphere in recovery from aphasia. A cross-sectional study comparing activation patterns in Wernicke's aphasics and normal controls during verb generation and word repetition tasks found that patients had relatively increased activity in right hemisphere homologues of language areas. Longitudinal studies have suggested that the involvement of the right hemisphere increases over the course of recovery (Thulborn *et al.* 1999; Musso *et al.* 1999). Two patients (one with Broca's and one with Wernicke's aphasia) studied serially with FMRI showed increasingly right lateralised language-related activity during comprehension tasks (Thulborn *et al.* 1999). In a group of Wernicke's aphasics, consecutive PET scans were taken before and after a brief language training procedure. After the training comprehension tasks were associated with an increase in right superior temporal gyrus activity that correlated with the improvement in language function (Musso *et al.* 1999).

However, other studies have questioned the interpretation of increased right hemisphere activity in language recovery. In one PET study patients were scanned

after successful melodic intonation therapy (MIT) for nonfluent aphasia (Belin *et al.* 1996). Listening to words without MIT produced activation of right hemisphere homologues of language, whereas listening to words with MIT produced activation of Broca's area in the left hemisphere. The authors interpret this as showing that right hemisphere activation patterns are maladaptive and reflect persistence of aphasia, whereas MIT produced a normalisation of language-related activation, with reactivation of Broca's area. However, if MIT produces generalised language recovery as reported, then it is unclear why right hemisphere activation, if it reflects persistence of aphasia should still be present after recovery has occurred. An FMRI study of lexical-semantic processing in recovered aphasics found that while the group as a whole showed increased right hemisphere activation relative to controls, individual patients with predominantly right-hemisphere activity tended to be more poorly recovered than patients with bilateral activation (Cao *et al.* 1999). Therefore, reactivation of left hemisphere language areas was seen as crucial for full recovery to occur. Similarly, a serial PET study of word repetition in aphasic patients found that well-recovered patients showed increased metabolic activity in left hemisphere language areas at follow-up, whereas poorly-recovered patients were only able to activate the right hemisphere homologues (Heiss *et al.* 1997).

2.4.3.4 Conclusions on patterns of brain plasticity in motor recovery

There is little consensus on which areas are crucial to motor recovery and it is possible to find evidence to implicate most motor cortical areas in recovery after stroke. This might reflect the heterogeneity of stroke patients and recovery processes and the flexibility of the motor network to adapt differently in response to different patterns of

damage. Alternatively the lack of consensus could reflect the methodological limitations of the studies so far.

As well as identifying areas where changes occur after stroke it is crucial to determine the degree to which those changes are functionally relevant. This could be addressed by serial imaging studies looking at activity changes coupled to functional recovery (see Section 8). Another potentially informative approach is to explore the consequences of disrupting activity in candidate areas (see Section 9). This approach has been successfully applied in the study of expanded somatosensory representations in Braille readers (Pascual-Leone and Torres 1993). Single pulse transcranial magnetic stimulation (TMS) was applied to the somatosensory cortex to transiently disrupt processing during a tactile discrimination task. If TMS of a specific region slows responses on the task it is assumed that the underlying cortex is necessary for normal performance (see Section 3.2.2). This approach allows mapping of the area of somatosensory cortex recruited to perform the task. The area of somatosensory cortex where TMS affected performance was three times greater in blind Braille readers compared to sighted controls. Also, TMS was effective at twice as many sites over the somatosensory cortex for the dominant hand compared to the non-dominant hand in Braille readers. Together, these results suggest that the increased specific sensory-motor skill of the Braille readers was associated with an expanded representation of the dominant hand in the somatosensory cortex and that activation of the expanded representation was functionally necessary for normal performance of a tactile task. This approach has not yet been used in the study of motor recovery after stroke (see Section 9).

2.5 Potential mechanisms of brain plasticity

Although evidence demonstrating brain plasticity in response to learning, damage or experience has grown exponentially in recent years, the idea that the adult brain is capable of reorganisation is not new. The suggestion that brain plasticity could occur as a result of changes in network architecture and growth of new fibres was made by Cajal (1904) in reference to skill acquisition:

> "The work of a pianist, speaker, mathematician, thinker etc., is inaccessible for the untrained human, as the acquisition of new abilities requires many years of mental and physical practice. In order to fully understand this complicated phenomenon, it is necessary to admit, in addition to the strengthening of pre-established organic pathways, the establishment of new ones, through ramification and progressive growth of dendritic arborizations and nervous terminals."

Such mechanisms are now thought also to play a role in adaptive reorganisation after brain damage. Potential mechanisms for cortical reorganisation after stroke include removal of inhibition from areas connected to the lesion site, sprouting of new fibres and synapses in intact cortex and increased recruitment of previously existing pathways. These are dealt with in detail below.

2.5.1 Removal of inhibition

Removal of local inhibition could provide a mechanism for cortical reorganisation by unmasking latent excitatory horizontal connections (Jacobs and Donoghue 1991). There is increasing evidence that inhibitory activity is reduced following a lesion. There is a decreased density of $GABA_A$ receptors around experimentally induced lesions in the rat for the first few days following a lesion (Schiene *et al.* 1996). The reduced density of $GABA_A$ receptors extends to remote regions connected to the infarcted region (Qu *et al.* 1998b; Qu *et al.* 1998a). This decrease in GABA receptor

density is accompanied by an increase in the density of NMDA receptors (Qu *et al.* 1998b) resulting in local hyperexcitability (Mittmann *et al.* 1998). These effects probably contribute to the enhanced long-term potentiation (LTP) observed around a lesion site (see Section 2.5.3)

In addition to changes in the overall density of $GABA_A$ receptors there have also been reports of change in the receptor sub-unit composition (Redecker *et al.* 2000). Specific subunits are downregulated at different locations within and surrounding a lesion site and in interconnected areas. Changes in subunit composition can influence receptor pharmacology and electrophysiology and are thought to contribute to hyperexcitability in patients with focal epilepsy associated with cortical malformations (Redecker *et al.* 2000). Such changes could also encourage excitability after a lesion such as a stroke and thereby facilitate synaptic strengthening.

Changes in inhibitory activity seem to be tightly coupled to functional recovery. Injection of diazepam, a GABA agonist, delays sensory recovery if given acutely after frontal lesions in rats (Schallert *et al.* 1986), whereas the GABA antagonist, pentelenetetrazol accelerates sensory (though not motor) recovery after sensorimotor lesions in rats (Hernandez and Schallert 1988).

Removal of inhibition could play a role in apparent reorganisation not only locally but also across the corpus callosum. Studies using transcranial magnetic stimulation (TMS) over both hemispheres have shown that stimulation of one motor cortex suppresses subsequent muscle activity evoked by TMS of the opposite motor cortex in normal subjects (Ferbert *et al.* 1992), but not in subjects with agenesis or lesions of the corpus callosum (Meyer *et al.* 1995). This suggests excitation of one motor cortex results in transcallosal inhibition of the opposite motor cortex. After a

unilateral lesion reductions in transcallosal inhibition might be expected. This could provide an explanation for the increased ipsilateral motor cortical activity seen after stroke (see Section 2.4.3).

However, there are a number of reasons for dismissing this as a full explanation. First, the timescale of increased involvement of the ipsilateral motor cortex suggests that it cannot be mediated entirely by the immediate removal of transcallosal inhibition. Caramia et al used TMS to demonstrate that ipsilateral muscle responses were more commonly evoked in patients after stroke. However, ipsilateral responses were not present in any of the subgroup of 3 patients they tested in the first 24 hours after stroke (Caramia *et al.* 1996), suggesting that disinhibition of the intact hemisphere does not immediately lead to increased recruitment of uncrossed motor pathways. Also, an FMRI study found no difference between chronically acallosal patients and controls in the localization or extent of ipsilateral motor cortical activation with simple unilateral hand movement (Reddy *et al.* 2000).

2.5.2 Sprouting of new connections

Local growth of axons and synapses could provide a mechanism for intracortical remapping of sensorimotor representations (see Section 2.4.3.1). Evidence for sprouting of new fibres and synapses can be found from studies detecting the presence of molecular and cellular correlates of growth. For example, the GAP-43 protein is associated with neuronal growth cones. There is increased expression of the GAP-43 gene around the rim of a stroke post-mortem in humans (Ng *et al.* 1988) and increased expression of the GAP-43 protein adjacent to infarcts in the rat 3 to 14 days after experimental stroke (Stroemer *et al.* 1995). Synaptophysin, a calcium-binding protein found on synaptic vesicles, is enhanced adjacent to experimental ischemic lesions

slightly later (14-60 days) suggesting that synaptogenesis follows dendritic sprouting (Stroemer *et al.* 1995).

The functional importance of sprouting in mediating recovery is demonstrated by two animal studies showing correlations between behavioural recovery and neuronal growth or growth-associated proteins (Rowntree and Kolb 1997; Stroemer *et al.* 1998). Following motor cortex lesions in the rat, blocking expression of basic fibroblast growth factor by neutralizing antibodies resulted in a substantial decrease in motor recovery and dendritic growth compared to control rats (Rowntree and Kolb 1997). This suggests that dendritic sprouting or survival, stimulated by the presence of growth factors, normally mediates recovery. Administration of D-amphetamine to rats after middle cerebral artery occlusion led to enhanced behavioural recovery and was associated with increased expression of GAP-43 and synaptophysin (Stroemer *et al.* 1998).

The time course of growth is complex. There appears to be a two-stage process of structural change after injury with an initial period of dendritic overgrowth followed by a later period of pruning (Jones and Schallert 1992).

Sprouting can also occur remote from the site of damage. As well as being found around the lesion rim, increased expression of synaptophysin has been detected in the contralesional hemisphere 14 to 60 days after experimental stroke (Stroemer *et al.* 1995) and dendritic sprouting has been found in pyramidal cells in the intact hemisphere after cortical lesions in rats (Jones and Schallert 1992). Dendritic sprouting in the intact hemisphere depends both on the presence of the lesion and on resulting asymmetrical limb use (Jones and Schallert 1994). Therefore, sprouting does not occur

only in response to a lesion, or only as a result of a behavioural experience, but rather depends on lesion-behaviour interactions (Jones and Schallert 1994).

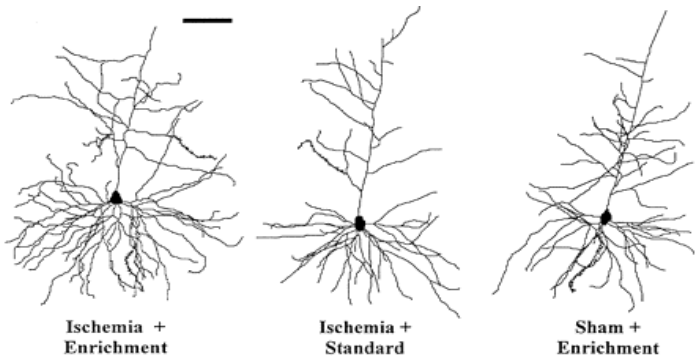

Figure 2.2: The influence of enrichment on dendritic growth and complexity following an ischemic infarct. Ischemia plus enrichment (left) leads to enhanced dendritic branching compared to either ischmia alone (centre) or enrinchment alone (right). Figure taken from (Biernaskie and Corbett 2001), Scale bar 100um.

Evidence that sprouting in the undamaged hemisphere is tightly coupled to recovery comes from the finding that rehabilitative training and environmental enrichment after ischemic lesions in rats leads to improved forelimb function and enhanced dendritic complexity and length in the undamaged hemisphere (Biernaskie and Corbett 2001; Figure 2.2). Furthermore, intracisternal injection of basic fibroblast growth factors enhances functional recovery after experimental lesions in rats and the enhanced recovery is probably mediated by processes in the intact hemisphere as immunostaining for GAP-43 shows a selective increase in the contralesional sensorimotor cortex (Kawamata *et al.* 1997).

2.5.3 Altered synaptic strength in existing local networks

Local remapping could occur as a result of changes in synaptic strength. Possible mechanisms for such changes included long term potentiation (LTP) and long term depression (LTD). These mechanisms have been extensively studied in the rat hippocampus, where they are thought to mediate learning and memory (Bliss and

Lomo 1973). It is now apparent that these processes are not limited to the hippocampus. In vitro studies of slices of rat motor cortex have demonstrated LTP and LTD in layer II/III horizontal connections (Hess and Donoghue 1994; Hess and Donoghue 1996). Even in vivo, LTP and LTD can be induced in the neocortex of freely moving adult rats after prolonged and repeated stimulation trains (Froc *et al.* 2000; Trepel and Racine 1998).

There is also evidence that increased synaptic efficacy occurs in response to behavioural training. In post mortem studies of slices of rat motor cortex, larger amplitude field potentials were found contralateral to a trained forelimb, suggestive of increased synaptic efficacy. This appeared to depend on a mechanism similar to LTP as the amount of further potentiation that could be induced by electrical stimulation was reduced in the trained motor cortex (Rioult-Pedotti *et al.* 1998).

As well as increasing synaptic efficiency, induction of LTP is associated with structural changes including increased spine density (Ivanco *et al.* 2000), similar to changes that are seen to occur after experimental motor cortex lesions and rehabilitation or environmental enrichment (e.g. Figure 2.2). The possibility that LTP plays a role in plasticity after stroke is strengthened by the finding of increased LTP in the area surrounding an experimental lesion in the rat (Hagemann *et al.* 1998). However, unlike the structural changes that occur after lesions and are found in homotopic regions of the undamaged hemisphere (see Section 2.5.2), there was no evidence of increased LTP in the contralesional hemisphere (Hagemann *et al.* 1998).

2.5.4 Altered recruitment of existing pathways

The motor system comprises a distributed network of functionally specialised subunits (see Section 1.1.2). However, despite the specialisation of different components of the

motor system there is nevertheless a high degree of functional overlap between them. Functional overlap and parallel pathways enable flexibility in the normal brain and allow the possibility of plasticity in the damaged brain.

Changes in pathway recruitment

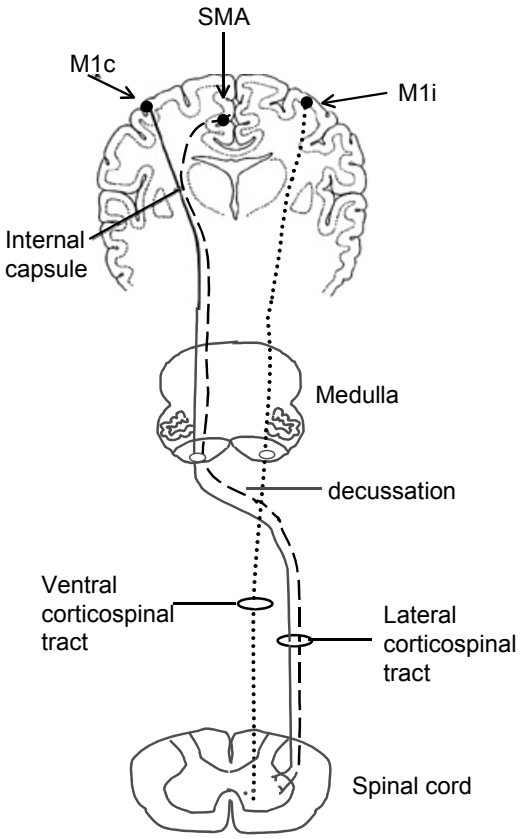

Figure 2.3: Schematic of corticospinal tract pathways. Solid line represents lateral corticospinal tract from M1. After injury alternative pathways could be recruited including the uncrossed ventral corticospinal tract from the undamaged hemisphere (dotted line) or fibres from the lateral corticospinal tract originating from non-primary motor areas in the damaged hemisphere (dashed line). C=contralateral to affected limb, I=ipsilateral to affected limb

Increased involvement of the undamaged hemisphere after stroke (see Section 2.4.3) could reflect recruitment of uncrossed spinal projections (Figure 2.3, see also Section 1.1.4 and table 1.1). For example, while 70-90% of pyramidal fibres decussate into the lateral corticospinal tract, 10-30% are uncrossed and form the ventral corticospinal tract (Nathan and Smith 1973). However, the majority of the uncrossed fibres project to motorneurons of proximal muscles (Armand 1982), whereas motor tasks used in imaging studies of stroke recovery typically involve distal muscle movements (Cramer and Bastings 2000). An alternative explanation for increased

ipsilateral activation is disinhibition due to reduced transcallosal input (see Section 2.5.1).

Increased activity of non-primary motor areas in the damaged hemisphere (see Section 2.4.3.2) may reflect increased recruitment of corticospinal projections from these areas (Figure 2.3). Although the majority of corticospinal projections originate in the primary motor cortex a substantial proportion come from other motor areas of the frontal lobe (Dum and Strick 1991; see Section 1.1.4 and tables 1.2 and 1.3). Therefore increased activity in lateral premotor, supplementary motor or cingulate motor areas after stroke could reflect increased recruitment of corticospinal projections from these regions.

2.6 Conclusions

Although stroke often produces severe initial motor deficits there can be great potential for recovery. This section has described candidate neural processes that may contribute to functional recovery. Reorganisation of cortical networks may accompany recovery although it is unclear which brain areas are crucial. Reorganisation at this level can be studied by non-invasive human brain imaging techniques.

The following section discusses the methodology used in experiments in this thesis. Human brain imaging techniques are relatively new and meaningful interpretation of the results generated depends on understanding what is being measured. The next section describes some of the physical and physiological principles of functional magnetic resonance imaging and discusses some of the methodological issues in experimental design.

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