Section 10: General conclusions and future directions

The aim of this thesis was to investigate the activation, modulation and reorganisation of the human sensorimotor cortex. This was largely motivated by the need to better understand the extent and significance of cortical reorganisation with recovery of motor function after stroke. Evidence is accumulating that patterns of brain activation associated with movement of an affected limb after stroke differ from control patterns. However, the correct interpretation and functional significance of these differences remains unclear. It is tempting to conclude that the different patterns of activation reflect adaptive reorganisation that underlies recovery of movement. However, other possible interpretations exist. The experiments in this thesis were therefore designed with the following specific aims:

- *To more fully characterise the differences in movement-related brain activation seen after stroke (Section 4)*
- *To explore potential confounding factors in normal populations (Sections 5-7)*
- *To assess the degree to which changes in activation patterns relate to rehabilitation-mediated changes in function (Section 8)*
- *To test the functional significance of activation in the undamaged hemisphere by temporary interference with motor cortical processing (Section 9)*

The conclusions of these investigations, and suggestions for future research, are discussed below.

10.1 Patterns of movement-related activation after stroke

Section 4 gave the results from a cross-sectional study designed to characterise patterns of movement-related FMRI activation in patients after a first ischaemic stroke. Movement of the affected hand in patients was associated with different patterns of FMRI activation from control hand movement. Specifically, affected hand movements were associated with a more bilateral pattern of activity in the motor cortex and cerebellum.

A number of functional imaging studies have reported a relative increase in activity in the ipsilateral motor cortex after stroke (Cramer *et al.* 1997; Cao *et al.* 1998; Chollet *et al.*

1991; Weiller *et al.* 1992; Cuadrado *et al.* 1999). Although a small number of studies have reported increased bilateral cerebellar activity with affected limb movements (Weiller *et al.* 1993), the majority of studies have focussed on cortical motor processing.

In addition to a change in overall laterality of movements, there was also evidence for a change in interactions between different elements of the motor system. Interactions were tested by correlating changes in laterality measures between different areas. In patients (but not controls) there was a correlation between laterality in the dentate nucleus of the cerebellum and the primary motor cortex. The importance of the dentate nucleus was further demonstrated by the finding that it was the only region where laterality correlated with affected hand impairment. These results provide preliminary evidence of increased correlation between cerebellar and cortical motor centres after stroke that may reflect increased reliance on cortical-cerebellar circuits.

Cortico-cerebellar circuits are known to be important in motor learning in normal subjects (Ramnani *et al.* 2000; Jenkins *et al.* 1994). Recovery of movement after stroke can be seen as a form of 'relearning' affected limb movements. Movements that are learnt can be executed automatically whereas unlearnt movements are attentionally-demanding. The automaticity of movements can be tested by dual task paradigms (Section 7). These have been used to assess the degree of attention required to perform movements after stroke. The finding that previously automatic movements, such as walking, require increased attentional resources after stroke ((Bowen *et al.* 2001) and Section 7.4.5), is analogous to the increased demands of normal motor learning. When normal subjects are learning a new motor task performance of a cognitively demanding concurrent task can substantially slow motor performance (Passingham 1996). However, once the task is learnt this interference effect is greatly reduced (Passingham 1996). Together, these results emphasise that recovery of movement after stroke may share behavioural features with new motor learning and may therefore depend on similar brain mechanisms.

There have been developments in techniques for investigating connections and interactions between brain regions with functional imaging (Friston 1994). Functional connectivity analyses look for correlations between signal timecourses of different brain regions. The results from Section 4 suggest a correlation between laterality in the dentate nucleus and the motor cortex in patients but not controls. In addition, activation in the motor cortex and whole cerebellum was more bilateral in patients. It would therefore be interesting to test whether the signal timecourse in the dentate was more highly correlated with the motor cortex in patients than controls.

It is clearly impossible to infer the direction of influence or the cause of correlation from a functional connectivity analysis. A correlation between the dentate and the motor cortex for example, could reflect a functional connection from either region to the other, or from a third region to or from both, or simply that activity in both areas is correlated with the task paradigm.

One way of avoiding some of the problems associated with interpreting correlations in the presence of a task is to look for interactions between brain regions in resting state data. Studies looking at cross correlations in 'resting' data in normal subjects have identified correlations between signals from different brain regions in the absence of an explicit task (Biswal *et al.* 1995). These are predominantly based on low frequency fluctuations in signal and are thought to reflect phase-locked neuronal activity in functionally related regions (Cordes *et al.* 2001). On a single subject level strong correlations may simply reflect ongoing cognitive or sensory activity as the brain is not really in a state of rest. However, averaging across subjects may remove these elements and reveal more subtle patterns of resting interactions between brain regions. It would be of particular interest to see whether these patterns differ in a clinical population. Current cross correlation methods for testing such hypothesis are highly dependent on the choice of 'seed' voxels. If this bias is avoided by testing numerous seeds then the techniques become extremely computationally-demanding. A potential solution to this problem could be found in the use of a data-driven technique such as independent components analysis which could be used to extract spatially or temporally independent patterns of activity without the need to specify a starting point for the analysis (McKeown *et al.* 1998).

10.2 Potential confounds: the effects of movement factors and attention in normal subjects

It is tempting to conclude from Section 4 that the altered patterns of motor activation after stroke are related to recovery. However, potential confounds exist if the movement task differs between patients and controls. For example, patients may require more effort or more attention to perform the motor task.

10.2.1 Effects of movement factors

Attempts were made to control for effort in Section 4 by normalising movement rate to a proportion of each subject's maximum tapping rate. However, other less controlled features of the movement (such as force, amplitude, complexity) may have influenced the 'effortfulness' of the movements differentially between patients and controls. The effects of various movement factors that may influence effortfulness was investigated in normal subjects in Section 5. It was shown that increasing the rate or complexity of movements led to increases in activation volume and a more bilateral pattern of motor cortical activity. However, interpretation of these changes may differ for the two movement factors.

Increasing movement rate results in an increase in the proportion of the sampling time that is occupied by the task. This would result in increased signal to noise which might be expected to have a greater effect on ipsilateral motor cortical activation as the signal there is typically smaller. Increasing movement complexity does not change the duty cycle of the task and therefore the observed changes in FMRI activation are likely to be related to the increased effort required. However, the explanation of the rate effect in terms of changes in duty cycle may not apply across a clinical population. In a group of normal control subjects the range of maximal achievable rates is likely to be limited. Therefore performance of a given absolute rate will require a similar degree of effort across the group. In a clinical population the range of maximum rates is likely to be much greater and therefore performing movements at a fixed absolute rate will require different degrees of effort for different subjects. For this reason, movement rate was normalised relative to each subject's maximum performance in some of the patient studies (Section 4, Section 8). In Section 4 where comparisons were made between patients and controls it was appropriate to attempt to match for effort across subjects by normalising rate. In Section 8, where patients were assessed longitudinally, a within-subject design was used such that each patient effectively acted as his or her own control and the focus was on changes over time. In this case movement features were individually set at a fraction of each subject's maximum force or rate at the start of the study and then kept constant throughout. This enabled assessment of whether activation patterns changed over time to produce the same absolute movement output.

10.2.2 Effects of attention

Movement of an affected limb can be variably attentionally-demanding. The modulatory effects of attention on cortical processing have been extensively studied in the visual system (Posner *et al.* 1982) and to a lesser extent in the auditory (Jancke *et al.* 1999) and somatosensory systems (Mima *et al.* 1998; Roland *et al.* 1982; Hyvarinen *et al.* 1980). There is general consensus that in various sensory modalities directing selective attention to a sensory stimulus causes an increase in stimulus-related brain activity (Posner *et al.* 1982; Jancke *et al.* 1999; Mima *et al.* 1998). If similar processes occur when patients direct attention to a moving limb, then we might expect increases in movement-related activation that reflect attentional processes rather than adaptive reorganisaton. Whether attention to sensory stimulation or to movement modulates FMRI activity was addressed in Sections 6 and 7.

In Section 6 the modulatory effects of attention were assessed in the somatosensory system. Selective attention to tactile stimulation resulted in increased FMRI activity in a network of somatosensory processing areas including primary somatosensory cortex. Touch is only one element of somatosensation, and it would be particularly interesting to extend these investigations to proprioceptive inputs. It may be that movement of a recovered limb requires increased attention to proprioceptive feedback.

Section 7 investigated the effects of attention to movements using a dual task paradigm. Normal subjects performed a motor task with and without a concurrent distractor task. Sensorimotor areas where activity was reduced with distraction were identified as being modulated by attention to movement. These areas included the supplementary motor area (SMA), insula and cingulate cortex. A volumes of interest analysis additionally detected attentional modulation in the contralateral primary motor cortex (area 4p).

Together these results demonstrate that directing attention to movements or to sensory stimulation results in increased activity in sensorimotor areas, some of which have been implicated in recovery of motor function after stroke (primary motor cortex, SMA). However, despite the strong attentional distractor used in section 7, the modulatory effects of attention were subtle. Furthermore, other brain areas that have been shown here to play a role in recovery (e.g. premotor cortex, Section 8) were not modulated by attention. Therefore it is unlikely that attentional factors could fully explain the changes in movement-related activation seen after stroke.

Nevertheless, given that attention to movement has subtle effect on the magnitude of movement-related activation, it is important to assess the degree to which attentional factors are altered after stroke. There is mixed evidence over the extent to which stroke patients have to pay more attention to their movements. Dual task paradigms suggest that increased attention is required for recovered walking (Haggard *et al.* 2000; Bowen *et al.* 2001). However, a similar study on recovered upper limb movement found no evidence for increased attentional demand (Platz *et al.* 2001). It would be particularly interesting to run a dual task paradigm in parallel with a simple FMRI movement study in patients. This would allow one to test whether patients who show increased areas of activity during affected hand movements are those who show increased interference effects during dual task paradigms. If this were found to be the case it would raise questions over the interpretation of brain imaging studies of movement recovery.

Later sections in the thesis attempted to test the assertion that the altered activation patterns associated with movement of an affected limb were related to recovery and had functional relevance.

10.3 The neurobiological basis of rehabilitation-mediated recovery of motor function

One way of assessing the functional relevance of the different patterns of movement-related activation observed in stroke patients is to quantify the degree to which changes in activation are associated with changes in arm function. Section 8 addressed this issue by serial FMRI scanning of chronic stroke patients before and after a two week rehabilitation procedure. Patients who were at least six months post stroke were chosen for study as the majority of recovery occurs in the first few months post stroke (Nakayama *et al.* 1994) so it was hoped that the patients would have reached a relatively stable functional state.

As expected, there was a wide variation in recovery of arm function in response to rehabilitation. The amount of behavioural recovery was compared to the change in FMRI activity over time. In a voxel-based correlation analysis across the whole sensorimotor system there was a significant correlation between improvement in grip strength and increase in FMRI activity in the contralateral premotor cortex, contralateral secondary somatosensory cortex and bilateral cerebellum (lobule V1 and crus 1). A volumes of interest analysis focussing on cortical motor areas found a correlation between improvement and increased FMRI activity in both contralateral and ipsilateral premotor cortices.

This study therefore suggests that rehabilitation-mediated improvements in motor ability are tightly coupled to reorganisation in motor representations. The changes in affected hand representation that correlated with improvement were all *increases* in FMRI signal, suggesting that there is an increase in extent or magnitude of activity with training. Decreases in activation after therapy that correlated with improvement were only found during movement of the unaffected hand. This decrease in primary motor cortical activity was hypothesised to be related to the non-use of the unaffected hand.

The study also identified specific regions of the motor system where such changes occurred. The evidence for involvement of the cerebellum in recovery of movement was interesting given the findings from Section 4 of a tight relationship between cerebellar laterality and level of motor impairments. However, the regions of the cerebellum implicated differed between the two studies. In Section 4 the dentate nucleus was shown to be more active in patients than controls. In Section 8 increased activity in the superior posterior regions of the cerebellar hemispheres (lobule V1 and Crus 1) correlated with improvements in motor ability. However, these two observations may reflect adaptation of the same cerebellar motor circuit as there are reciprocal connections between the ventrolateral regions of the dentate nucleus and the lateral cerebellar hemispheres in macaque (Tolbert and Bantli 1979).

There have been some other suggestions that the specific regions of the cerebellum found here may be important for recovery of movement, at least in the case of early brain damage. Although cortical damage in adults is associated with resting hypometabolism in the contralesional cerebellum (Baron *et al.* 1980), there have been reports of symmetrical metabolism or paradoxically increased contralesional cerebellar metabolism in brain damaged children (Shamoto and Chugani 1997) specifically in lobules VI and Crus I (Niimura *et al.* 1999). Increases in contralesional lobule VI and Crus I metabolism were also detected in adults with temporal hypometabolism compared to adults with frontal hypometabolism (Niimura *et al.* 1999). These specific regions have also been implicated in normal motor learning (Ramnani *et al.* 2000).

The findings from Section 8 raise a number of interesting questions. Firstly, it would be interesting to assess whether the changes observed in patients are a specific response to training in the context of disease, or whether the same patterns would be observed in normal subjects undergoing a similar training procedure. This would also help address the issue of whether motor recovery after stroke is similar to normal motor learning. Tackling this issue would require a training procedure which could elicit strong behavioural changes in both patients and controls so that a similar range of behavioural outcomes was achievable in both subject groups.

Secondly, the training procedure used in Section 8 incorporated many different principles, loosely based on the technique of constraint-induced therapy. It is therefore unclear which elements of the procedure drove behavioural changes or neural changes or both. It would therefore be informative to run future studies isolating particular elements of the intervention (e.g., restraint only, strength training only, dexterity training only) to test whether particular elements are crucial to the behavioural or neural response.

Thirdly, the small numbers in the study presented here did not allow any assessment of the type of patients who are likely to improve after therapy, or to show FMRI changes after therapy. Factors which are likely to influence the extent of behavioural improvement and brain reorganisation include time post stroke, stroke side, type and location, age, initial impairment level and initial movement-related FMRI pattern.

10.4 The functional relevance of ipsilateral motor cortical activity assessed with transient interference by TMS

The results from Sections 4 and 8 provided evidence that certain patterns or changes in activity were related to motor impairment or recovery. In Section 4 laterality of FMRI response in the dentate nucleus of the cerebellum was shown to correlate with upper limb impairment. In Section 8 improvements in grip strength after therapy correlated with increased activity in bilateral cerebellum, premotor cortex and contralateral S2. However, these results cannot tell us whether activity in these sensorimotor regions is essential for movement of a recovered limb. To do this requires an interference technique. In animal studies it is possible to test whether a brain area is necessary for a task by permanent selective lesion, or by temporary inactivation by cooling or application of GABA agonists. Such approaches are not possible when studying the human brain. However, the technique of TMS can be used to locally and temporarily interfere with cortical processing and therefore test the importance of a specific area to task performance. This approach was employed in Section 9 to test the role of the primary and premotor cortices in simple and complex movements of the ipsilateral hand in normal controls and patients after stroke.

First, normal subjects performed simple and complex motor tasks in the scanner. Both tasks were associated with activation of ipsilateral motor and premotor areas and the amount of activation was significantly greater for the complex task. To test the functional significance of these ipsilateral motor activations, these areas were targeted with single pulse TMS. Application of TMS pulses at specific time points after a cue to move slowed simple and complex movements of the ipsilateral hand. This effect was significantly greater with TMS of the left hemisphere, suggesting a left hemisphere dominance for control of ipsilateral hand movements, as has previously been reported (Schluter *et al.* 1998; Schluter *et al.* 2001). The times at which TMS was effective depended on the site of stimulation and the complexity of the movement task. Stimulation of primary motor cortex (MC) or premotor cortex (PMC) slowed simple and complex movements when applied late after the cue to move. However, stimulation of left premotor cortex also had an effect when applied early but only with complex movements. This suggests that motor and premotor cortex are involved in execution of ipsilateral hand movements and that left premotor cortex plays an additional early role in complex ipsilateral movements, possibly reflecting its involvement in movement selection. There were consistencies between the FMRI and TMS results –

specifically, both approaches demonstrated increased involvement of premotor cortex in complex movements. However, there were also discrepancies between results from the two approaches. For example, while the TMS results showed a clear left dominance for the control of ipsilateral movement, there was no clear difference in the magnitude of ipsilateral motor cortical FMRI activation associated with movements of the left or right hand.

The effect of TMS of motor cortical areas was also tested in patients after stroke. This group was chosen for study for two reasons. Firstly, by choosing a group of patients with a range of recovery values it was thought that they would display a range of FMRI laterality measures and TMS disruption effects. This wide variation could help define the relationship between the TMS and FMRI measures. Secondly, comparing the magnitude of TMS-induced slowing effects in patients relative to controls could provide a strict test of the hypothesis that there is increased recruitment of ipsilateral motor areas after stroke.

The effects of ipsilateral TMS on reaction times differed between patients and controls in a manner that was dependent on the time and target of the TMS pulse. Early (100ms) TMS over ipsilateral PMC slowed simple movements in patients and not controls. This suggests that the premotor cortex has a specific early role in even in simple movements of an impaired hand. This is interesting as this temporal pattern of early PMC involvement was observed for only for complex movements in the control group. Slowing effects of 100ms were greatest in more impaired patients.

The study found significant correlations between the slowing effects of premotor cortex stimulation (at 100ms) and the laterality of FMRI activation in the premotor cortex during the simple task. This demonstrates that those patients who show more bilateral PMC FMRI activation also show greater slowing effects of PMC TMS. This suggests that the ipsilateral movement-related activation detected after stroke is functionally-relevant.

The small numbers in the study in Section 9 make the conclusions preliminary. The study could also be simplified by use of repetitive rather than single pulse TMS. There were a number of attractions to using single pulse TMS originally. Firstly, it allows testing not only of which areas are necessary for a task but also when their involvement is crucial. This allowed separation of different components of a task such as movement selection (early stimulation of premotor cortex) and movement execution (late stimulation of motor or premotor cortex) in the control study. It was originally hoped that this could provide a powerful approach for the investigation of adaptive reorganisation after stroke. It could be used to assess whether an area has 'taken over' the function of an affected region not only in terms of the tasks that the novel area is now involved in, but also the temporal pattern of involvement. Secondly, there are fewer safety and discomfort issues with single pulse TMS (see Section 3.2.3.2).

Despite the attractions of single pulse TMS, the study could perhaps be made more powerful by use of dual-pulse or rTMS. A train of pulses would probably produce a greater behavioural effect and so may provide a more sensitive test. Also, the number of trials (and therefore tiredness and discomfort) could be reduced as there would no longer be the need to test numerous timepoints. Given these time savings, the number of trials contributing to a single data point could be increased, which would reduce noise.

Further experiments are also required to test the route via which the effects of ipsilateral PMC TMS are mediated. For example, it would be interesting to directly compare the effects of contralateral and ipsilateral PMC TMS in patients, as some of the results found here could be due to transcallosal effects on the opposite hemisphere.

10.5 Final conclusions

The experiments presented in this thesis attempted to investigate the extent and significance of brain reorganisation in recovery of motor function after stroke. Although previous studies have demonstrated different patterns of movement-related brain activity in recovered stroke patients the significance of these patterns is unclear. Studies on normal subjects were used to investigate potential confounds in the interpretation of altered patterns of brain activity. Studies on patients further characterised the nature of the activation changes, and the extent to which they were related to recovery.

Experiments on the effect of attention in normal subjects showed that directing attention to sensory inputs or to movement modulates activity in sensorimotor cortical areas. These results suggest that further investigation is needed to assess whether this is an important factor in studies of motor recovery. Dual task paradigms could be used to clarify the degree to which increased attention to movement is required for movement of an affected limb, and looking for correlations between interference effects and brain imaging measures could test whether increased activation can be explained by increased attention.

The studies of stroke patients presented here have strengthened the argument that changes in activation patterns are related to recovery. Section 4 presented a cross sectional study showing that patients have more bilateral patterns of motor-related activity in motor cortex and cerebellum. Laterality in the dentate nucleus of the cerebellum was related to impairment. Section 8 related changes in motor representation to changes in function after therapy. Improvements in grip strength correlated with increased FMRI activity in the premotor cortex and cerebellum. Section 9 demonstrated the functional significance of ipsilateral premotor cortex for recovered movement by temporarily inactivating these areas with TMS. Patients who showed relatively increased ipsilateral premotor cortical FMRI activity also showed enhanced slowing effects of PMC TMS, suggesting that the FMRI pattern reflects functionally relevant changes.

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