CAN FUNCTIONAL MAGNETIC RESONANCE IMAGING (MRI) STUDIES HELP TO DEVELOP EFFECTIVE THERAPY INTERVENTIONS FOR STROKE PATIENTS?

Background to the Research:

Stroke affects over 100,000 people in Britain every year and is the commonest cause of adult physical disability. At present, there are no widely available medical interventions which will consistently reduce the extent of neuronal damage following the acute episode, and rehabilitation remains the mainstay of improving outcome in these patients. Despite its importance in improving outcome, very little research has been undertaken on understanding how therapy input influences the process of neuronal recovery from stroke. Hence, although several studies have shown that rehabilitation packages improve outcome, specific therapy interventions themselves may not be rooted in the physiology of recovery.

Recent advances in neuroimaging have made it possible to study the “in vivo” activity of the brain in awake subjects, especially during the performance of various tasks. We now know that the adult brain has considerable potential for plasticity in task performance, both in health and following injury. Mechanisms involved in recovery from brain injury include restoration of function of partially damaged pathways or strengthening of existing pathways (restitution) and development of new pathways in the unaffected areas of brain which take over the lost function (substitution). It is now believed that there are multiple motor circuits in the brain which serve similar functions. Conventional pathways dominate in healthy subjects and inhibit the activity of alternate pathways in other areas of the brain. Disruption of traditional pathways in cerebral ischaemia reduces or eliminates the inhibition normally exerted by these pathways and allows activation of alternate pathways in the pre-motor areas of the affected side and primary motor areas on the unaffected side. Hence, the paradigm for function has shifted from strict cerebral localisation to that of interactive functioning of diverse cortical areas activated by the constantly changing balance of inhibitory and excitatory impulses.

The process of reorganisation of neural activity has been demonstrated in human subjects who have suffered a stroke. However, the results from various studies have been inconsistent, and with some studies showing an increase and others a decrease in the areas of activation with recovery. The relationship between reorganisation and clinical recovery as well as the involvement of other areas in the brain remains a matter of controversy. Few studies have been undertaken on the temporal profile of reactivation after an acute stroke or the role that areas such as the pre-frontal lobe or cerebellum may play in new learning. Finally, the relationship between therapy interventions, clinical measures of functional improvement and patterns of neurological activation in the acute phases of stroke has not been systematically investigated.

The concept of reorganisation of cerebral activity and its susceptibility to external influences is the cornerstone of rehabilitation. Although most therapy regimens claim to modulate neuronal plasticity, there is little direct evidence that this is indeed the case. Most studies on therapy interventions have been undertaken in chronic stroke patients, with stable patterns of activation at baseline. The evaluation of the effects of therapy on plasticity after an acute stroke presents a different set of problems because changes in brain activation associated with natural recovery will confound those due to therapy input. Hence, the understanding of the temporal profile of changes in brain activation following an acute stroke is fundamental to designing future studies to evaluate the effect of therapy on neuronal plasticity.

Studying the patterns of brain reactivation using serial fMRI after an acute stroke presents methodological challenges, which need to be overcome prior to undertaking definitive studies. It is important to define the exact nature, location and size of infarction as well as exclude any old infarcts or subclinical ischaemic damage, which may confound patterns of recovery. The issue of neuroimaging in acute stroke is complex because of the diversity of structural and functional damage, alterations in cerebral blood flow in the acute phase, the ability of subjects to undertake certain tests and technical considerations such as movement. The recovery of vascular autoregulation following an ischaemic episode may be slow and variable; it is possible to have fully restored neuronal activity without measurable changes in...
blood flow or even a negative BOLD effect due to alterations of blood flow in the non-affected hemisphere in the acute phase. Finally it is possible that there may be no consistent relationship between neuroimaging findings and clinical improvements, thus questioning the clinical relevance of such expensive and time consuming techniques to study the impact of rehabilitation in stroke patients.

Objectives:

The objectives of the project were to:

1) Develop functional neuroimaging protocols that allowed accurate and reliable serial assessment of brain activation patterns following an acute stroke.
2) Design clinically relevant motor task paradigms that were suited to the changing abilities of patients recovering from an acute stroke.
3) Study longitudinal patterns of brain activation for motor task performance in subjects with different types of stroke.
4) Develop therapy techniques that will provide consistent, measurable interventions for future controlled studies using FMRI.

Study Progress

Objective 1: Development of functional neuroimaging techniques:

This was undertaken in 5 control and 5 stroke subjects. All subjects had a “pre study” MRI scan to characterise the infarct in stroke patients, exclude silent or multiple lesions and significant leukoaraiosis.

A 1.5T GE neuro-optimised MR system was used and each session took approximately 2 hours. Subjects underwent structural (axial DE and FLAIR, DTI) and functional (blood oxygen level dependent [BOLD]- based) imaging as well as perfusion studies at each session. Perfusion was measured using a small bolus of gadolinium-DTPA (Magnevist or Omniscan) contrast. The axial T2 and FLAIR images provided information on the anatomical location of infarction. DTI gave information on white matter tracks that connect different cortical areas.

Fig 1: T2 MRI scan showing a lacunar Infarct.  
Fig 2: Fractional anisotropy index map of the same patient showing disrupted white matter tracts.
Technical issues such as head movement were resolved by using post processing methods that spatially realign each volume of data that is acquired every 3 seconds over the course of a 5 minute study.\textsuperscript{14} We also unravelled the confound of motion correlated to the stimulus.\textsuperscript{15} In order to address potential problems with altered vascular autoregulation after stroke, we performed a quantitative perfusion measurement, which involved the administration of a small bolus of gadolinium-DTPA (Magnevist or Omniscan) for probing blood brain barrier disruption. We outlined the methodology to correct for any differential haemodynamics both between subjects and within subjects between the 2 hemispheres.\textsuperscript{16} As BOLD contrast does not produce a quantitative measure of brain activity, we used the information from the quantitative perfusion maps to normalise for intra and intersubject variations in cerebral physiology.

There was increased activation associated with increased movement in some patients, especially in the early stages of recovery. Hence, in addition to graded tasks with a variable “load” to probe recovery related improvements in performance, we performed further analyses using each subject as their own control. This allowed more reliable evaluation of longitudinal changes in individual subjects.

Objective 2: Development of the motor paradigm:

A graded paradigm using choice reaction time was developed to assess recovery in motor processes. Motor performance was measured by a paced random joystick which could be moved up, down, left or right in response to visual cues on a screen (Fig 3). The test was staged for the severity of deficit and could measure a graduated response from crude arm movements seen in early recovery to fine movements resulting from greater hand and finger recovery. All controls and patients were given practice sessions for these tasks prior to FMRI tests till their performance reaches a plateau. The motor paradigm lasted for five minutes and was of A/B design. None of the subjects (control or stroke patients) reported difficulties in understanding the tasks or fatigue in their performance.

![Fig 3: The choice reaction task for motor performance showing the passive and active state](image).

We focused on fine motor tasks, performed a range of left versus right experiments and tailored the test design to work over a range of task difficulties. Some subjects had difficulties with fine hand and finger movements at the first measurement point. We compared a task done badly at the early stage of recovery with a task done well at the later stage of recovery by using a graded (variable block periodic) design where initially one can compare the task performance versus a crude resting condition to produce a crass contrast. Within the active component of the functional imaging study we then had a range of different task difficulties to ensure that the subject was not working at ceiling during the course of the whole study at each time point. We repeated motor paradigms within each session, so that any differences between the sessions could be ascribed correctly as true effects.
Objective 3: Patterns of brain activation in different stroke types

The preliminary study highlighted the technical and data handling complexities of undertaking serial studies on neuronal activation following an acute stroke. The information gained in these experiments was used to develop a rigorous design which controlled for variations in cerebral perfusion, movement and position artefacts on repeated scanning, effects of graded motor response and involuntary activity of the unaffected side to investigate reactivation patterns following large vessel (cortical) and small vessel (lacunar) stroke. The study also provided information on the patterns of activation in healthy subjects, with which stroke patients could be compared.

Eleven acute stroke subjects and 5 controls were studied. Inclusion criteria for stroke patients were: 1) under 75 years of age; 2) previously fit stroke with no significant disability; 3) first ever stroke confirmed on clinical and MRI assessment at baseline; 4) Moderate stroke defined as Barthel score between 10-14 at 1 week; 5) Good prognosis for arm recovery defined as a score of 2 or more on Rivermead Motor Assessment Scale.17

Stroke subjects were categorised as those with small vessel disease (infarcts affecting the deeper structures and more likely to involve connections rather that primary areas) and those due to large vessel disease (infarcts in which primary motor areas as well as connections were involved). Following baseline scanning, all patients received intensive therapy and further imaging studies were undertaken at 4 weeks and 3-4 months.

Results in control subjects showed that several parts of the brain were activated whilst undertaking the choice reaction task. Performance of the task with the right hand activated both visual areas (perception of the stimuli) and the left primary motor cortex (to affect the task) as well as the right cerebellum (possible role in planning and coordination) and the supplementary motor areas, premotor cortex and prefrontal cortex (possible role in planning, sequencing, task execution). These observations are consistent with the theory that motor function in human subjects does not have strict cerebral localisation but is controlled by interactive functioning of diverse cortical areas. This also supports the concept that undamaged cortical areas may have the capacity to take over the function of damaged areas following injury.

Fig 4: Group brain activation, matched controls
The next series of studies was undertaken in acute stroke patients. That the brain has a capacity for neuroplasticity is not a new observation; reorganisation of brain activity has been reported in previous studies.\textsuperscript{7,12} The novel aspect of our study is that we charted the course of reorganisation over a period of time in acute stroke patients and grouped these into stroke patients with predominantly cortical strokes (where the grey matter and the motor neurons were affected) and those with subcortical stroke (where the white matter connections rather than the neurons were affected predominantly).

In patients with cortical stroke, use of the affected limb was associated with significant cerebellar activity on the opposite side to the injury but no activity in the primary or supplementary motor cortex on any side in the acute phase (Fig 5). This activation was opposite to that seen in controls suggesting that parts of the unaffected half of the brain may be involved very early on in the recovery process. This was followed by increased activation of the frontal areas and both hemispheres, again very different from patterns seen in healthy controls and suggestive of the unaffected side making considerable contributions to return of activity, even when no clinical improvement was visible (Fig 6).

At 3 months FMRI showed activation of the motor areas in the unaffected side of the brain on moving the affected limb, suggesting that new centres in the unaffected part of the brain had taken over the function of damaged areas in the brain (fig 7). There were also changes in the activation patterns on movement of the unaffected limb, both during the acute and recovery phase, suggesting functional interconnectivity between hemispheres. To summarise, recovery in these patients was associated with the development of new pathways in the unaffected areas of brain, suggesting substitution or diachesis as the mode of recovery.

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\caption{Fig 5: Cortical stroke 2 weeks \quad Fig 6: cortical stroke 4 weeks \quad Fig 7: Cortical stroke 3 months}
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\caption{4 weeks \quad 3 months}
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\caption{Fig 8. Large vessel stroke: activation in left cerebellum and motor areas increases steadily and proportionately with improvement in left limb function}
\end{figure}
In patients with lacunar strokes, where the white matter was predominantly affected, a different pattern of reactivation was seen. Use of the affected limb was associated with significant activity in opposite cerebellum but no activity in the motor areas of either side in the acute phase, a pattern similar to that observed in cortical stroke (Fig 9). In contrast to cortical stroke, return of limb activity was associated with increased activation in this cerebellum only with no bilateral involvement and a significant increase in the activation of the motor and premotor areas on the affected, rather than the unaffected side. The pattern of activation at 3 months in this type of stroke resembled the pattern seen in control subjects (Fig 10). Use of the unaffected limb was associated with activation patterns similar to those seen in control subjects. These data suggest that recovery in patients with lacunar stroke may occur due to the repair of previously damaged pathways rather than the development of new centres in the unaffected part of the brain (restitution).

Regardless of the type of stroke, cerebellar activation soon after acute injury appears to be an important pre-requisite for recovery and may be of prognostic significance.

Fig 9: Lacunar stroke 2 weeks

Fig 10: Lacunar stroke 3 months

Fig 11. Small vessel stroke: Activation in right motor areas decreases steadily and inversely with improvement in left limb function
Objective 4: Development of therapy interventions

Standardisation of therapy input was difficult because of lack of consensus about the best treatment practice amongst therapists, variability in practice between therapists and between patients treated by the same therapist. A review of literature was inconclusive about the benefit from intensive therapy on arm function or general functional abilities. Treatments such as repetitive training or resistance strengthening exercises were associated with little benefit, the best results being reported with task-specific therapy interventions. Constraint therapy, in which use of the affected arm is encouraged by immobilising the unaffected arm, showed promise in patients with chronic stroke but the number of studies available for acute stroke patients was limited and there were concerns about patient adherence, safety and comfort.

A programme of constraint therapy for acute patients was developed and assessed for feasibility, patient comfort and safety, magnitude of effect and reproducibility. Preliminary data in 10 patients meeting the inclusion criteria for MRI studies showed that the approach was feasible, safe and acceptable in acute stroke patients. Based on these preliminary observations, a project is being developed to test effectiveness of this approach in acute (as opposed to chronic) stroke patients, using clinical outcome measures prior to undertaking small, well-characterised studies using functional imaging.

Dissemination:

The findings of the research have been discussed at several research and multidisciplinary research meetings. Formal presentations include:

1. European Society of Magnetic Resonance, Cannes, France 2002
2. Welsh Stroke Conference, Cardiff, November 2002
3. European Stroke Conference, Valencia, Spain 2003
4. South London Stroke Research Group, St George's Hospital, October 2003

Data from the project has also been published in:


Key outcomes of Remedi funding

Support from Remedi has enabled the successful completion of our research aimed at validating fMRI techniques for use in recovering stroke patients, which will minimise the various sources of bias and improve the scientific rigour of future studies. No two strokes are the same and although the challenges posed by heterogeneity in stroke recovery and methodological issues in accurate and reliable measurement of serial changes in brain activation are considerable, these can be overcome by the methodologies developed in this study. Major achievements are:

1) The ability to reliably assess cortical reorganisation longitudinally.

The issue of neuroimaging in acute stroke is complex because of the diversity of structural and functional damage, alterations in cerebral blood flow in the acute phase, the ability of subjects to undertake certain tests and technical considerations such as movement and
head position. We have achieved accurate and reliable serial fMRI measurement of brain activation in acute stroke patients, which allows comparative studies of changes in brain functioning in the first 3 months after stroke. Although Positron Emission Tomography scans have been used to study recovery previously, it has not been possible to undertake longitudinal studies because of radiation risks associated with repeat scanning. Cortical mapping after Transcranial Magnetic Stimulation has been used but the technique is limited because of poor resolution and susceptibility to bias because of differences in the position of coil and intensity of stimulus.

2) The ability to visualise intact and damaged white matter tracts.

We have developed the use of a novel technique (Diffusion Tensor Imaging) to actually visualise white matter tracts in the brain and to see how these are damaged in stroke. These tracts connect different cortical areas and also conduct cortical outflow to the periphery. We have been able to demonstrate loss of integrity of these tracts in acute stroke and restitution with recovery.

3) The development of a graded motor paradigm, which takes into account varying performance associated with recovery

Many subjects have difficulties with fine hand and finger movements soon after stroke, which may improve with time. We have developed paradigms which can compare tasks done badly at the early stage with a task done well at the later stage of recovery and ensure that the subject is not working at ceiling at any time point during the course of the study.

4) Identification of different patterns of activation associated with different stroke types

A novel finding of the research was the finding that recovery in function was associated with the activation of new pathways in the unaffected areas of brain (substitution or diachesis) in patients with cortical infarcts. On the other hand, activation of damaged pathways or recruitment of new pathways to the affected hemisphere (restitution) was associated with recovery in patients with lacunar infarcts. This may be of relevance in determining the effectiveness of specific therapy approaches in different types of stroke.

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References: