Reorganisation and modulation of the human sensorimotor system: implications for recovery of motor function after stroke

Heidi Johansen-Berg

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Oxford

Linacre College Michaelmas Term 2001

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Short Abstract

In order to test the extent and functional significance of brain plasticity after stroke, experiments were conducted using functional magnetic resonance imaging (FMRI) and transcranial magnetic stimulation (TMS) to assess the neural representation of movements of an affected limb.

A cross-sectional study comparing movement-related activity in patients and controls found that movement of the affected hand in patients was associated with a more bilateral pattern of activity in the motor cortex and cerebellum. Laterality in the dentate nucleus of the cerebellum was correlated with laterality in the primary motor cortex. Dentate laterality was also correlated with hand impairment. These differences suggest that reorganisation of movement representations are related to recovery. Alternative explanations were tested specifically.

Studies on normal subjects explored the potential confounds of effort and attention. A study of movement parameters that influence effort found that increasing the complexity of movement was associated with greater and more bilateral motor cortical activity. Further studies found that attention to sensory stimulation or to movement modulates activity in sensorimotor cortical areas.

The relationship between changes in motor activity and changes in arm function were tested in a longitudinal study involving serial FMRI scans before and after rehabilitative therapy. Behavioural improvements in arm function after therapy correlated with increased FMRI activity in the premotor cortex, cerebellum and secondary somatosensory cortex.

The functional relevance of ipsilateral motor cortical activity was tested by temporarily interfering with cortical processing using TMS. This showed that TMS of motor or premotor cortex slows movements of the ipsilateral hand in controls and stroke patients. There was a significant correlation between FMRI and TMS measures in patients. Patients who showed a more bilateral pattern of premotor cortical activity also showed an enhanced effect of ipsilateral premotor cortex TMS.

This thesis contains approximately 70,000 words

Table of Contents

i. Long abstract

This thesis aims to investigate the extent and significance of brain reorganisation in recovery of movement after stroke. The experiments presented here use functional magnetic resonance imaging (FMRI) and transcranial magnetic stimulation (TMS) to address this question in stroke patients and normal controls. Sections 1 to 3 are introductory, Sections 4 to 9 present experimental results.

Section 1 is an introduction to the anatomy of the sensorimotor system in humans. It provides an overview of cortical and subcortical subdivisions within the motor and somatosensory systems. It demonstrates that both systems are organised as distributed networks of specialised areas but are also characterised by functional and anatomical overlap. This presence of functional overlap and parallel pathways could provide a substrate for brain plasticity.

Section 2 presents a review of recovery and rehabilitation of motor function after stroke. The possibility that brain plasticity contributes to recovery is discussed and examples of different patterns of brain plasticity are given. Potential mechanisms underlying brain plasticity are also discussed.

Section 3 gives an overview of the methods that will be used to investigate the modulation and reorganisation of the human sensorimotor system. The physical and physiological principles of FMRI are summarised. The nature and interpretation of the BOLD (blood oxygen level dependent) signal, and the spatial and temporal resolution of the signal are discussed. A brief overview of analysis of FMRI images is given. Principles of TMS are also described in this section. This section focuses on the use of TMS as a 'virtual lesion' technique for temporarily and locally inactivating regions of the brain.

Section 4 presents results from a cross-sectional study comparing movement-related brain activation in stroke patients and controls. This study was designed to characterise more fully patterns of reorganisation after stroke and to assess the degree to which activation changes were related to behavioural impairments. The study found that movement of the affected hand in patients was associated with increased activity in the dentate nucleus of the cerebellum and with a more bilateral pattern of FMRI activity in the primary motor cortex and cerebellum. The study also explored interactions between different elements of the motor system and found that laterality in the dentate nucleus of the cerebellum correlated with laterality in the primary motor cortex in patients but not in controls, suggesting a tighter coupling of cerebro-cerebellar circuits for recovered movement. This importance of the dentate was also demonstrated by the fact that it was the only region in which laterality correlated with a measure of hand impairment.

The results of this study suggest that the altered patterns of FMRI activity observed may reflect processes of adaptive reorganisation that underlie behavioural recovery. However, alternative interpretations exist and were explored in the following sections.

Interpretation of functional imaging studies of recovered movement can be difficult if patients find movements more effortful, or require more attention to perform movements of the affected limb. The extent to which effort and attention modulate sensorimotor activity in normal subjects was investigated in Sections 5 to 7.

In Section 5 the effect of factors that influence the 'effortfulness' of a movement were quantified. Increasing the rate or complexity of movement was associated with increased and more bilateral patterns of motor cortical FMRI activity. The implications of this finding for the design of studies of motor recovery are discussed.

Section 6 demonstrates that directing attention to sensory stimulation produces an increase in FMRI activity in primary somatosensory cortex, secondary somatosensory cortex and the insula. Section 7 presents results showing that distracting subjects from movements by concurrent performance of a counting task led to decreases in movement-related activity in sensorimotor areas. There was some overlap between areas modulated by attention and areas that have been implicated in recovery of movement after stroke (e.g., primary motor cortex, SMA). However, other areas that may play a role in recovery were not modulated by attention (e.g. premotor cortex). Furthermore, despite the fact that this experiment used a very demanding distractor task, the modulatory effects of attention were relatively subtle. Therefore, attentional factors are unlikely to explain all of the altered patterns seen in motor representations after stroke. Nevertheless, there is need for further study on the extent to which attentional factors differ in stroke patients, and the degree to which attentional changes could explain FMRI changes. Possible approaches to this are discussed in Section 10.

Given the potential confounds in the interpretation of cross-sectional differences between patients and controls in movement-related FMRI activity, subsequent sections in the thesis were designed to test the strength of the relationship between altered activation patterns and motor recovery. This was done by assessing the extent to which changes in motor function were reflected by changes in motor cortical activity (Section 8) and by testing whether relative increases in ipsilateral FMRI signal reflected activity that was crucial to recovered movement (Section 9).

In Section 8 serial FMRI scans were performed on patients before and after a two week period of rehabilitative therapy. Behavioural improvements were assessed with a number of tests including grip strength. The correlation between behavioural changes and

FMRI changes was tested. Improvements in grip strength correlated with increased FMRI activity in the cerebellum, premotor cortex and secondary somatosensory cortex.

In Section 9 the importance of motor and premotor areas for movement of the ipsilateral hand was tested by transiently interfering with cortical processing with TMS. Stimulation of motor and premotor cortex slowed ipsilateral hand movements in control subjects. This effect was significantly greater for TMS of the left hemisphere, suggesting a left hemisphere dominance for control of ipsilateral hand movements. TMS of the undamaged hemisphere also slowed movements of the ipsilateral (affected) hand in patients after stroke in a manner distinct from the control pattern. Early (100ms) TMS of ipsilateral PMC slowed simple movements in patients and not controls. There was a correlation between the size of this slowing effect and the laterality of PMC FMRI activation in patients. This demonstrated that patients who showed a more bilateral pattern of FMRI activation also showed an enhanced effect of ipsilateral TMS. This suggests that the relatively increased FMRI signal in ipsilateral motor areas does reflect activity that is crucial to recovered movement.

Finally, Section 10 presents a summary of the results and suggestions for future research. These include further investigation of the influence of attentional factors in stroke patients, and the degree to which these are reflected in movement-related patterns of FMRI activity. Application of connectivity analyses to assess interactions between brain regions in active and resting data are discussed.

ii. Abbreviations

AC	anterior commisure
BOLD	blood oxygen level dependent
CNR	contrast to noise ratio
EEG	electroencephalography
EMG	electromyography
ERP	event-related potential
FEAT	FMRIB's easy analysis tool
FILM	FMRIB's improved linear model
FLIRT	FMRIB's linear image registration system
FMRI	functional magnetic resonance imaging
FMRIB	Oxford Centre for FMRI of the Brain
FOV	field of view
FWHM	full width at half maximum
HRF	haemodynamic response function
HWHM	half width at half maximum
GABA	gamma-aminobutyric acid
GLM	general linear model
IPSP	inhibitory post synaptic potential
IR	inversion recovery
LFP	local field potential
LSF	least squares fitting
M1	primary motor cortex
MCA	middle cerebral artery
MEG	magnetoencephalography
MEP	motor evoked potential
MRI	magnetic resonance imaging
MS	Multiple Sclerosis
PC	posterior commisure
PET	positron emission tomography
PMC	premotor cortex
S1	primary somatosensory cortex
S2	secondary somatosensory cortex
SEP	somatosensory evoked potential
SMA	supplementary motor area
SNR	signal to noise ratio
SPM	statistical parametric mapping
RF	radio frequency
TE	echo time
TI	inversion time
TMS	transcranial magnetic stimulation
TR	repetition time
V1	primary visual cortex
VAC	vertical plane extending from the AC and perpendicular to the AC-PC line
VOI	volume of interest
VPC	vertical plane extending from the PC and perpendicular to the AC-PC line

iii. List of figures

iv. List of tables

v. Publications arising from work in this thesis

Papers published or in press:

Pineiro R, Pendlebury ST, **Johansen-Berg H** and Matthews PM. Altered haemodynamic response in patients after subcortical stroke measured by FMRI. *Stroke*. 33, 103-9

Johansen-Berg H and Matthews PM (2001) Attention to movement modulates activity in sensorimotor areas including primary motor cortex. *Experimental Brain Research*. 142, 13-24

Johansen-Berg H, Christensen V, Woolrich M and Matthews PM (2000) Attention to touch modulates activity in both primary and secondary somatosensory areas. *NeuroReport* 11(6) 1-5

Pineiro, R., Pendlebury, S. T., **Johansen-Berg, H**., & Matthews, P. M. (2001). FMRI detects posterior shifts in primary sensorimotor cortex activation after stroke: evidence for local adaptive reorganisation? *Stroke*. 32 1134-1139

Johansen-Berg H and Lloyd DM (2000) The physiology and psychology of selective attention to touch *Front Biosci* 5, D894-904 (review) (www.bioscience.org/current/special/attentio.htm)

Papers submitted:

Johansen-Berg H, Dawes H, Guy C, Wade D and Matthews PM. Correlation between motor improvements and altered FMRI activity after rehabilitative therapy. Submitted.

Johansen-Berg H, Rushworth MFS, Bogdanovich M, Kischka U, Wimilaratna S and Matthews PM. The role of ipsilateral premotor cortex in hand movement after stroke. Submitted.

Abstracts:

Johansen-Berg H, Rushworth MFS and Matthews PM. A TMS and FMRI study of the functional of ipsilateral motor cortical activation in stroke. 8th International conference for Functional Mapping of the Human Brain, Sendai, Japan

Johansen-Berg H, Dawes H, Guy C, Wade D and Matthews PM. An fMRI study of the neurobiological basis for motor rehabilitation after stroke. Annual meeting of the Society for Research in Rehabilitation. Manchester, UK

Johansen-Berg H, Matthews PM (2001) Attention to movement modulates activity in motor cortical areas. 7th International conference for Functional Mapping of the Human Brain, Brighton, UK

Johansen-Berg H, Christensen V, Woolrich M and Matthews PM (2000) Attention to touch modulates activity in both primary and secondary somatosensory areas. 6th International Conference for Functional Mapping of the Human Brain, Texas, USA

Johansen-Berg H, Pendlebury ST and Matthews PM (1999) Interactions between rate, complexity and handedness in a finger tapping task using the dominant and non-dominant hand. 5th International Conference for Functional Mapping of the Human Brain, Dusseldorf

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