

Section 7: Effect of cognitive factors on sensorimotor activation: Attention to movement

The previous section demonstrated that attention to sensory stimulation modulates activity in somatosensory areas including primary motor cortex. The current section describes an experiment designed to assess whether attention to movement modulates activity in motor cortex.

7.1 Introduction and rationale

7.1.1 Sensory attention and motor attention

Directing attention to sensory stimulation can increase perceptual sensitivity and modulate neuronal activity (Giard *et al.* 2000; Johansen-Berg and Lloyd 2000; Mangun 1995). Just as we can direct our attention towards or away from sensory stimulation, we can also attend to movements to differing degrees (Broadbent 1970; LaBerge *et al.* 1969; James 1890; Passingham 1996; Rosenbaum 1985).

Brain areas modulated by selective sensory attention can include multi-modal association areas involved in the direction and focus of attention, as well as modality-specific regions involved in stimulus perception. In the visual system for example, there is now a broad consensus that direction and focus of visuospatial attention depends on an interconnected set of frontal and parietal areas (Bushnell *et al.* 1981; Corbetta *et al.* 1993; Gitelman *et al.* 1999; Nobre *et al.* 1997; Posner *et al.* 1984; Robinson *et al.* 1995; Steinmetz and Constantinidis 1995; Walsh *et al.* 1999). In addition, it is now clear that attentional modulation also occurs in the modality-specific occipital cortex including primary visual cortex (V1). Recording studies in the monkey have shown that single cell activity in V1 is modulated when attention is directed to a stimulus in the cell's receptive field (Motter 1993). Neuroimaging studies in human subjects have confirmed that the primary visual cortical BOLD signal is modulated with attention (Brefczynski and DeYoe 1999; Gandhi *et al.* 1999; Martinez *et al.* 1999; Somers *et al.* 1999; Watanabe *et al.* 1998).

Attending to movements to different degrees can also affect behavioural responses. If subjects are distracted from their actions it is more likely that they will make a mistake or perform the action more slowly (Passingham 1996). The question this raises is: in what areas of the motor cortex is activity modulated to account for this behavioural change?

The systems for visual and motor attention are similar in organisation but there are some important differences between them. Primary mechanisms for motor attention depend on a distributed set of parietal and frontal regions (Jueptner *et al.* 1997). The particular parts of the parietal and frontal lobes that are important for motor attention however are different from the visuospatial areas. The left hemisphere rather than the right hemisphere appears to play the dominant role (Rushworth *et al.* 1997; Rushworth *et al.* 2001). Within the parietal cortex, different regions are concerned with visuospatial and motor attention; within the left hemisphere it is the more anterior supramarginal region, rather than the posterior intraparietal region near the angular gyrus, that is involved with motor attention (Deiber *et al.* 1996; Krams *et al.* 1998; Rushworth *et al.* 2001).

7.1.2 How early does attentional modulation occur in the motor system?

If visual attention can modulate activity in the primary visual cortex, then by analogy a specific question arises as to whether motor attention modulates activity in the primary motor cortex (M1). Changes in M1 activity reflect dynamic processes throughout the network of brain regions involved in motor planning and movement control. For example, it is now established that even imagining movements activates the primary motor cortex (Decety *et al.* 1994). That this activity is a necessary part of the process is suggested by a transcranial magnetic stimulation (TMS) study in which TMS over M1 impaired the motor imagery (mental rotation) (Ganis *et al.* 2000). Further, motor evoked potentials elicited by

M1 TMS are modulated by observation of movements (Fadiga *et al.* 1999; Fadiga *et al.* 1995) and motor learning produces plastic changes in M1 (Karni *et al.* 1995).

There is some evidence suggesting that M1 itself might be segregated functionally so any attentional modulation may differentially affect distinct subregions. The human motor cortex is known to be divided into cytoarchitecturally and neurochemically distinct anterior and posterior regions (4a and 4p respectively (Geyer *et al.* 1996)) and it is not clear in which division motor attentional effects might be found. For example, it is possible that the TMS experiments primarily affected the more anterior parts of the motor cortex (Ganis *et al.* 2000; Fadiga *et al.* 1999; Fadiga *et al.* 1995). It is known that the motor hotspot lies over the posterior precentral gyrus, just anterior to the central sulcus (Wassermann *et al.* 1996). However, with TMS it is difficult to stimulate the deeper situated area 4p. With fMRI it is possible in principle to quantify separately the magnitude of change in putative 4a and 4p.

Variations in attention to movement can be achieved in a number of ways. One approach is to vary the automaticity of a movement sequence (Jueptner *et al.* 1997). Another approach is to direct attention away from a movement by use of a competing distractor task which can slow motor performance, particularly during motor learning (Passingham 1996).

The experiment reported in this section uses functional magnetic resonance imaging (fMRI) to address specifically the question of whether modulation of activity by attention could be detected in primary and premotor areas. The attentional manipulation used was distraction from the motor task by concurrent performance of a distractor task (counting back in threes). Subjects were cued to perform a sequential button press sequence, to count back in threes, or to perform both tasks simultaneously (Figure 7.1). Motor and counting performance was paced by a flashing visual stimulus. In order to match the difficulty of the task across subjects, the rate of the cue was set individually according to each subject's

counting speed (see methods). FMRI images were analysed with two methods. First, a random effects group analysis was used and second a volumes of interest (VOI) approach was applied. With a VOI approach it was possible to determine the effects of attention on individual subjects and to define more accurately changes in the motor cortex and the medial and lateral components thought to correspond to areas 4a and 4p.

7.2 Methods

Subjects: 12 healthy right-handed subjects participated (aged 23-35, 4 men, 8 women). All agreed to the protocol according to guidelines approved by the local research ethics committee.

FMRI scanning: A 3T Varian/Siemens MRI system was used. Axial echo-planar volumes were acquired (21x6 mm slices, TE=30ms, TR=3000ms, FOV=256x256, matrix = 64x64, flip angle = 90°). A T1-weighted anatomical image was also acquired for each subject to define individual regions of interest (IR 3D Turbo Flash, 64x3mm axial slices, TR=30ms, TE=5ms, TI=500ms, flip angle=15°, FOV=256x256, matrix=256x256).

Subjects were given full verbal and written instructions on the task before entering the scanning room. Once the instructions were clearly understood, subjects were given only enough practice (2 minutes) to ensure that they were able to carry out the protocol as pilot studies had shown that the behavioural effects of distraction on reaction times drop off with practice. The two tasks were:

Count back in threes (silently) from a given three digit number (e.g., 125, “125, 122, 119, 116.....”).

Press one of 4 buttons in sequence (1,2,3,4,3,2,1,2 etc) in response to each visual cue

Four different experimental conditions required subjects to perform a single task, dual tasks or to rest without movement or counting. The conditions were:

- A. Single task, counting only
- B. Single task, button press only
- C. Rest
- D. Dual task, counting and button press, simultaneously

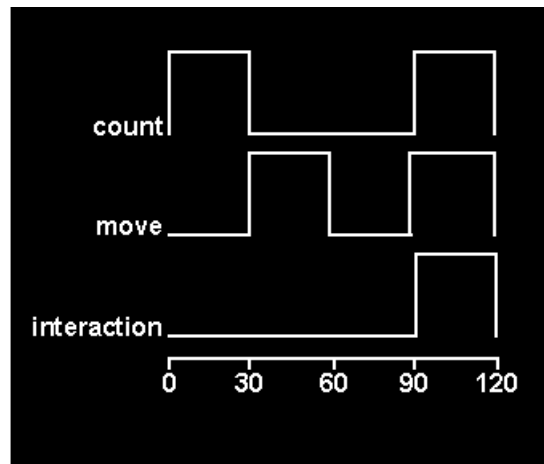


Figure 7.1: Paradigm design: One ABCD cycle. This cycle was repeated 3 times giving a total experiment length of six minutes. The top row indicates when subjects engaged in the counting task, the second row indicates when subjects were moving and the third row indicates the interaction between the two – i.e. periods when the two tasks were performed simultaneously.

The fMRI paradigm consisted of 30 second blocks of the tasks in an ABCD cycle (Figure 7.1). The cycle was repeated 3 times, giving a total paradigm length of 6 minutes. Task performance was paced by a flashing symbol projected onto a screen at the foot of the scanner tube. A different symbol was used for each of the four conditions. So, subjects were instructed to count back one digit (condition A), press one button (condition B), or do both (condition D), each time a symbol flashed on the screen. Each 30 second block was preceded by an instruction screen (eg: A: “count back from 78”, B: “focus on movement”, C: “rest”, D: “count back from 89 and move”). For each counting block a different number was given to subjects as the starting point.

As counting rates were highly variable between subjects, the rate of the counting cue presentation was set individually for each subject. First, the number of digits a subject was able to count back when counting aloud and self-paced in a 30 second period was determined. A cueing rate for use in the scanner was then chosen that presented 5-7 fewer counting cues than this in each 30 second counting period (mean number of counting cues per A block = 16; range 10 to 25). Inter-cue intervals were varied pseudo-randomly by \pm 50% of mean, to prevent anticipatory responses.

To assess whether or not subjects were counting accurately in the dual task condition (condition D), subjects were told not to make a button press when they reached a multiple of ten in the counting. A record of stimulus presentation and button press timing was collected and analysed off line to detect omitted button presses in response to cue stimuli during the dual task. If these omissions occurred at the correct point relative to the start counting number during a dual task this was taken as evidence of correct counting. The numbers of movements made in the single and dual task conditions were matched by equating the number of movement cues presented in B blocks to the number of movements a subject should make in the following D block (mean number of movements cued in blocks B/D = 13.18, range 8 to 19). In this way any differences seen between activation in single and dual tasks could not be attributed to differences in the total number of movements made.

Button press reaction time data was collected to assess how well subjects had performed this complex task. Subjects were excluded from further analysis if their behavioural data had any of the following features:

- i). Button presses during any A or C blocks
- ii). Failure to press buttons during any B or D blocks

- iii). Button presses withheld on fewer than 60% of the multiples of 10 reached during D blocks.

Image analysis: Image analysis was carried out using tools from the FMRIB Source Library (FMRIB, Oxford, UK, www.fmrib.ox.ac.uk/fsl).

The following pre-statistics processing was applied: motion correction using MCFLIRT (Jenkinson and Smith 2001); spatial smoothing using a Gaussian kernel of full width half maximum 5.0mm; mean-based intensity normalisation of all volumes by the same factor; nonlinear highpass temporal filtering (Gaussian-weighted least squares straight line fitting, with $\sigma=90.0s$).

Statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich *et al.* 2001). Two models were used. The first model (used for the group analyses) modelled the main effects of counting and button pressing versus rest and the positive and negative interactions between the two tasks. The second model (used for the VOI analysis) modelled the single tasks of counting or moving alone, and the dual task of counting and moving together as three separate event types. This allowed measurement of the difference in signal change between attended and distracted movement. The Z (Gaussianised T) statistic images for the individual subjects were thresholded using clusters determined by $Z>3.1$ and a cluster significance threshold of $p=0.05$ (Forman *et al.* 1995; Friston *et al.* 1992; Worsley *et al.* 1992).

Registration of EPI images to high-resolution images and into standard space (Talairach & Tournoux, 1988) was carried out using FLIRT (FMRIBs Linear Image Registration Tool (Jenkinson and Smith 2001)).

Group Analysis was carried out using a random effects analysis. The group Z statistic images were thresholded using clusters determined by $Z > 3.1$ and a cluster significance threshold of $P = 0.05$ (Forman *et al.* 1995; Friston *et al.* 1992; Worsley *et al.* 1992).

This resulted in Z statistic images for the main effects of counting and of movement and for the interaction between the two tasks. Areas showing a positive interaction were more active in the dual task condition than the sum of the two single task conditions. Areas showing a negative interaction were less active in the dual task condition than the sum of the two single tasks conditions. The negative interaction was of prime interest as this should include areas that are modulated by attention to movement, i.e. areas that are less active when subjects are distracted from their movement.

Areas showing a negative interaction could include counting-related activation that is decreased as a result of distraction (due to the motor task), motor-related activation that is decreased as a result of distraction (due to the counting task) or other effects of performing a demanding dual task. In order to separate out these contributions an image calculator within Medx (Sensor Systems, Inc, VA, USA) was used to mask the thresholded negative interaction Z score in four different ways. The thresholded main effect Z scores of counting and button pressing were binarised to produce a counting mask and a movement mask. Four further masks were created, based on:

- i) Areas activated by counting only (counting mask minus movement mask)
- ii) Areas activated by movement only (movement mask minus counting mask)
- iii) Areas of overlap between counting and movement (counting plus moving)
- iv) Areas not activated by counting or moving (i.e. areas outside the main effect masks) (the inverse of counting mask plus movement mask)

These four masks were then multiplied with the thresholded negative interaction Z scores. The individual subjects' registered high-resolution T1-weighted anatomical scans were averaged to produce mean high-resolution images onto which the thresholded statistical images were overlaid. This allowed assessment of activation in terms of anatomical landmarks as well as reporting the Talairach co-ordinates of peak activations within each anatomically defined region (Talairach and Tournoux 1988).

In order to test whether repetition of the dual task affected the results (e.g. due to task practice) a second analysis of the group data was performed. A time-dependent linear trend was added to the model. The linear trend was modelled in two separate ways. Firstly as a linear increase per dual task block (i.e. first block has value of 0, second block 0.5, third block 1) and secondly as an increase per volume within each dual task block (i.e. first block has values increasing from 0 to 0.33 (increment of 0.033 per volume), second block from 0.33 to 0.66 and third block from 0.66 to 0.99).

Volumes of Interest Analysis: In order to explore further the behaviour of motor cortical areas when performing dual tasks versus single tasks the following volumes of interest were defined for each subject based on their high-resolution T1-weighted anatomical scans. Lateral regions (Primary motor, premotor and primary sensory cortex) were all drawn from the level of the top of the lateral ventricles to the most dorsal slice of the brain (Figure 7.2):

1. *Primary motor cortex (4a):* Lateral half of anterior bank of central sulcus (Geyer *et al.* 1996)
2. *Primary motor cortex (4p):* Medial half of anterior bank of central sulcus (Geyer *et al.* 1996).
3. *Premotor cortex:* Precentral gyrus and sulcus
4. *Primary somatosensory cortex:* Cortex lying within the posterior bank of the central sulcus and anterior to the postcentral sulcus.

5. *Supplementary motor area (SMA)*: Cortex lying on the medial surface above the cingulate sulcus posterior to the vertical plane above the anterior commissure (VCA line) and anterior to the vertical plane above the posterior commissure (VCP line) (Fink *et al.* 1997).

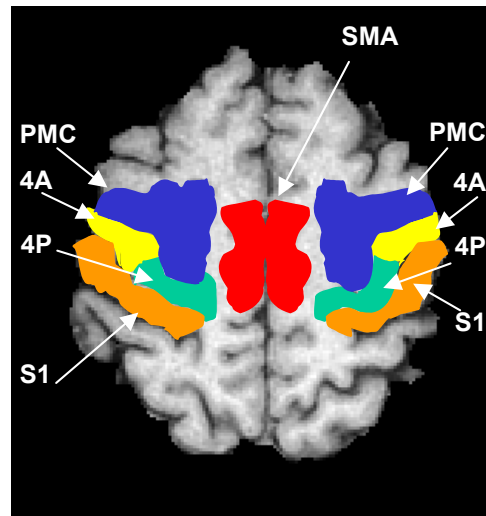


Figure 7.2: Illustrative example of volumes of interest drawn on a single subject's high-resolution T1-weighted image. **Blue:** premotor cortex, **red:** supplementary motor area (SMA), **yellow:** primary motor cortex (putative 4a), **green:** primary motor cortex (putative 4p), **orange:** primary somatosensory cortex.

FLIRT was used to derive a linear transformation for each subject from anatomical space to EPI space. This transformation was applied to binary masks covering the VOIs. For each subject the thresholded Z statistic images for moving (single task plus dual task) versus rest were added together and binarised. The binarised thresholded Z statistic image for counting versus rest was subtracted from the combined movement image to give a movement only mask for each individual subject. The movement only mask was multiplied by each VOI. The masked VOIs were then multiplied with the parameter estimates for moving alone versus rest (attended movement) and with dual task versus rest (unattended movement). The mean parameter estimate over the VOI was found and divided by the mean signal over time to give the percent signal change for that VOI. One-tailed paired t-tests

were performed to test whether the mean percent signal change in movement areas was greater for the single task than the dual task. As ten VOIs were used, these tests used a corrected probability threshold of 0.005.

As described above, movement rate was set individually for each subject in order to match difficulty levels. However, this obviously introduces between-subject variability in movement rate. In order to assess whether or not this influenced activation levels in the motor cortices, or the change in activation levels between single and dual task conditions, the correlation between movement rate and fMRI activity within the 10 VOIs was tested using Pearson's correlation co-efficient with a corrected probability threshold of 0.005.

In order to assess effects of task repetition specifically in motor cortex the mean percent signal change within the motor cortical VOIs was found for each block of the dual task.

7.3 Results

Behavioural data showed that one subject failed to perform the task correctly (by pressing buttons in non-movement blocks), so data from this subject were excluded from further analyses.

The speed of the tasks was determined individually for each subject based on their counting speed, so subjects varied in the number of movements cued per block (Table 7.1). As there was no significant difference in the mean total number of button presses made between the two movement conditions (single task and dual task), any differences seen between the two tasks are unlikely to be explained by a difference in the number of movements made.

	Mean	range
Number of movements cued per block	13.18	8 – 18
Number of button presses incorrectly made on multiples of 10	0.36	0 - 2
Number of cued movements not made per subject	4.00	0 - 7
Total movements made per subject		
Single task	37.73	24 - 49
Dual task	37.36	24 - 48
Reaction time (msec)		
Single task	394	Sd = 125
Dual task	553*	Sd = 254

Table 7.1: Behavioural results. Asterisks indicates significant difference between single and dual task mean reaction time.

In the dual task condition subjects were instructed to omit the button press when they reached a multiple of 10 in the counting task. This allowed verification that subjects were counting backwards as instructed. Subjects performed the dual task well: on average they failed to miss the button presses on multiples of ten less than once (mean 0.4 times) over the course of the whole experiment (Table 7.1). Although subjects made a similar number of movements in the single and dual task conditions, slowed reaction times (Table 7.1, paired t-test: $t=-3.565$, $df=10$, $p=0.005$) in the dual task condition demonstrated that the counting task effectively distracted subjects from the motor task.

We tested the behavioural data for evidence of a learning effect. Repetition of the dual task did lead to decreases in the reaction time during the dual task condition (mean RTs \pm s.d: block 1: 774 ± 490 ms; block 2: 545 ± 215 ms; block 3: 536 ± 219 ms) but these decreases were not significant using a repeated measures GLM to compare the effect of block across the whole experiment or using a paired t test to compare the first and the last blocks.

FMRI data:

Random effects group analysis: Figure 7.3 shows thresholded Z statistic group images for the counting task (7.3a), the button-pressing task (7.3b) and the negative interaction between the two tasks (7.3c). Tables 7.2 to 7.4 give Talairach co-ordinates of the voxel with the maximum Z score within each anatomical region.

Main effect of counting backwards (Figure 7.3a, Table 7.2). Counting backwards in threes (versus rest) produced bilateral activation in the precentral gyrus, intraparietal sulcus, medial superior frontal gyrus, anterior cingulate cortex and anterior insula. The medial frontal activation was thought to be in the pre-supplementary motor area (pre-SMA) as it was positioned anterior to the vertical plane above the anterior commissure (VCA line). The cingulate activation was all anterior to the VCA line. Activation was seen only in the left hemisphere in the putamen, thalamus and inferior frontal gyrus. Activation also was seen in the right superior frontal sulcus.

Main effect of button pressing (Figure 7.3b, Table 7.3). Button pressing with the left hand (versus rest) produced bilateral activation in pre- and post-central gyri, the superior bank of the sylvian fissure (secondary somatosensory cortex, S2), medial superior frontal gyrus (SMA), cingulate sulcus, posterior insula, putamen and thalamus. Activation was seen unilaterally in right central sulcus, left inferior frontal gyrus and left cerebellum. The cingulate activation for button pressing was located posterior to that for counting and largely posterior to the VCA line.

Interactions between counting and button pressing (Figure 7.3c, Table 7.4). In addition to the main effects of counting and button pressing, positive and negative interactions between the two tasks were also examined. A positive interaction indicates increased activity during the

dual task performance over and above the linear sum of activations in the two single task conditions. No areas showed a significant positive interaction. A negative interaction indicates lower activation in the dual task condition than the sum of activations in the single tasks. Areas showing a significant negative interaction included bilateral cingulate (posterior to the VCA line), medial superior frontal gyrus (SMA), posterior insula and superior temporal gyrus, left pre- and post-central gyri and left putamen (Figure 7.3c).

Anatomical region	Talairach co-ordinates of max Z score			Max Z
	X	y	z	
Precentral gyrus L	-44	-2	44	4.8
Precentral gyrus R	40	-2	32	4.3
Inferior frontal gyrus L (BA 44/45)	-46	18	22	4.0
Anterior cingulate R	10	8	40	3.5
Anterior cingulate midline	0	20	38	4.3
Anterior insula L	-32	22	0	4.6
Anterior insula R	36	24	-4	7.3
Intraparietal sulcus R	32	0	50	4.5
Intraparietal sulcus L	-54	-38	40	4.0
Putamen L	-26	2	4	4.3
Pre SMA R	2	12	54	4.1
Pre SMA L	-4	8	68	4.1
Middle frontal gyrus L	-28	48	14	4.0
Superior frontal sulcus R	32	0	50	4.5
Superior temporal L	-56	8	6	4.2
Thalamus L	-14	-14	-2	4.0

Table 7.2: Areas of activation for main effect of counting backwards

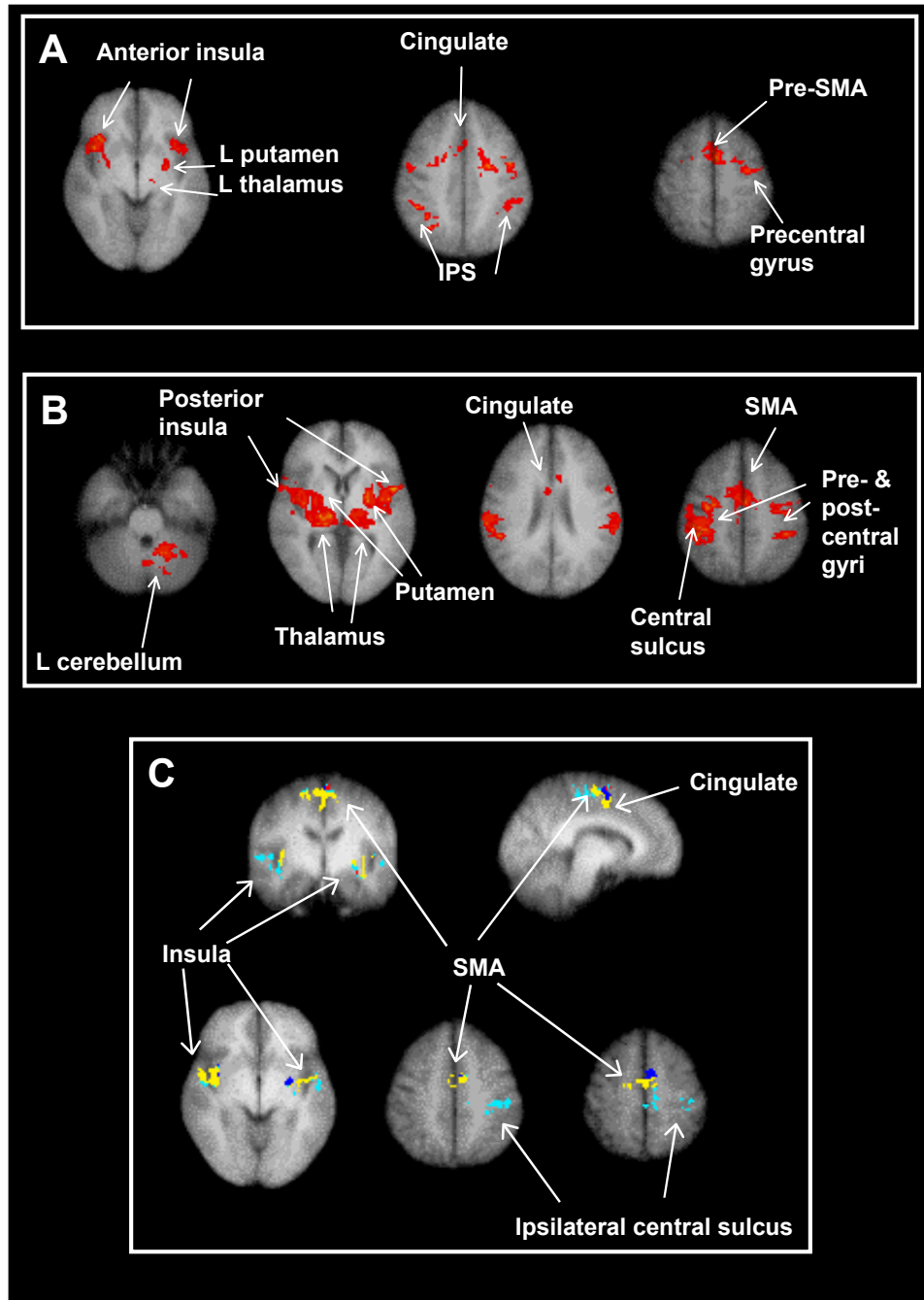


Figure 7.3: Group Z statistic maps superimposed onto average high-resolution scan for 11 subjects for the following three contrasts: **A:** Main effect of counting backwards versus rest. **B:** Main effect of button pressing versus rest. **C:** Negative interaction between the two tasks (i.e. areas showing reduced activity in the dual task compared to the single tasks). C is colour coded by the following masks based on the main effects conditions: **Yellow:** activated by movement and not counting, **red:** activated by counting and not moving, **blue:** activated by both moving and counting, **turquoise:** activated by neither moving nor counting.

Anatomical region	Talairach co-ordinates of max Z score			Max Z
	x	y	z	
Postcentral gyrus R	62	-26	34	5.2
Postcentral sulcus L	-44	-34	40	6.1
Postcentral gyrus L (superior bank of sylvian fissure)	-54	-24	12	5.0
Postcentral gyrus R (superior bank of sylvian fissure)	66	-22	28	5.2
Central Sulcus R	34	-12	48	4.9
Precentral gyrus L	-28	-8	54	4.0
Precentral gyrus R	30	-10	56	4.9
Medial frontal gyrus L (SMA)	-6	4	58	4.7
Medial frontal gyrus R	4	-4	58	4.6
Cingulate cortex R	4	0	44	5.1
Cingulate cortex L	-2	-4	48	4.6
Inferior frontal gyrus L	-48	8	2	5.2
Posterior Insula R	28	-22	16	4.8
Posterior Insula L	-42	2	-2	4.8
Putamen L	-36	-4	-4	4.9
Putamen R	32	10	-6	4.6
Thalamus R	14	-20	4	5.2
Thalamus L	-16	-18	-6	4.9
Cerebellum L	-28	-28	-40	4.5

Table 7.3: Areas of activation for main effect of button pressing

Anatomical region	Talairach co-ordinates of max Z' score			Max Z
	X	Y	Z	
Precentral Gyrus L	-28	-22	64	4.0
Central sulcus/ Postcentral gyrus L	-40	-24	52	4.4
Cingulate R	6	-10	46	3.9
Cingulate L	-6	-4	48	4.0
Medial frontal gyrus L	-2	-12	64	4.7
Medial frontal gyrus R	10	-4	64	4.0
Insula /claustrum R	44	-4	-10	4.5
Insula/claustrum L	-36	-8	-16	4.3
Superior temporal gyrus L	-56	-14	0	4.0
Superior temporal gyrus R	52	0	-8	4.3
Putamen L	-28	-6	-8	4.6

Table 7.4: Brain regions showing a negative interaction between the dual task and individual tasks of counting and button pressing

Regions showing a negative interaction were subdivided into those regions that were activated by movement alone, regions activated by counting alone, regions activated by both movement and counting and regions activated by neither task. This analysis revealed differences in the number of voxels and the anatomical structures showing a negative interaction within each functional mask (Figure 7.3c). Almost half of the voxels (999/2098 voxels) showing a negative interaction were in regions activated by movement alone, including the SMA, posterior insula and cingulate. The next largest contribution (844/2098 voxels) was in regions activated by neither main task, including posterior regions of medial frontal cortex, bilateral superior temporal gyrus and a cluster covering left central sulcus, precentral and postcentral gyri. A small proportion of voxels (234/2098 voxels) were in regions

activated by both tasks, including the anterior portion of the medial frontal lobe, the left putamen and the right insula. Very few voxels (21/2098 voxels) were in regions activated by counting alone, including left putamen, left postcentral gyrus and the most superior and anterior parts of the activation in medial frontal cortex.

In order to assess practice or learning effects with repetition of the dual task a linear trend was added to the model during the dual task blocks. The main effects activation maps of counting and button pressing with this model were the same as those produced in the original group analysis (data not shown). The model identified no clusters showing a linear increase in activation with task repetition but did identify 3 clusters (in left and right middle temporal gyri and cerebellum) showing a linear decrease in activation with task repetition. Modelling the linear trend did have some effect on the contrast of most interest, the negative interaction term. The model identified two clusters for the negative interaction term – one in the contralateral insula (590 voxels) and one in the SMA (497 voxels).

Volumes of interest analysis: The group analysis required not only that a large proportion of subjects showed a significant negative interaction between the two tasks, but also that the location of the voxels showing the interaction overlapped in standard brain space. In contrast, VOI analysis allows comparisons even if there is modest individual local variation in functional anatomy and enables one to see how many of the subjects show a reduction of signal in the dual task condition. An additional analysis was therefore performed based on signal change within individual volumes of interest defined by anatomical landmarks on the individual brains.

The VOI approach also allowed quantification of attention-related changes in fMRI activation in subregions of M1. The motor activation maps from some subjects demonstrated distinct regions of activity within the central sulcus (Figure 7.4). The locations

of these subregions correspond to the reported cytoarchitectonic maps of areas 4a and 4p – i.e one more inferior and posterior region in the depths of the sulcus, and one more superior and anterior region in the lateral portion of the sulcus (Geyer *et al.* 1996). However, as two clearly distinct regions were not visible in all subjects the motor activation maps could not be used to generate functionally-defined volumes of interest. Anatomical landmarks were therefore used to define areas as described in the methods.

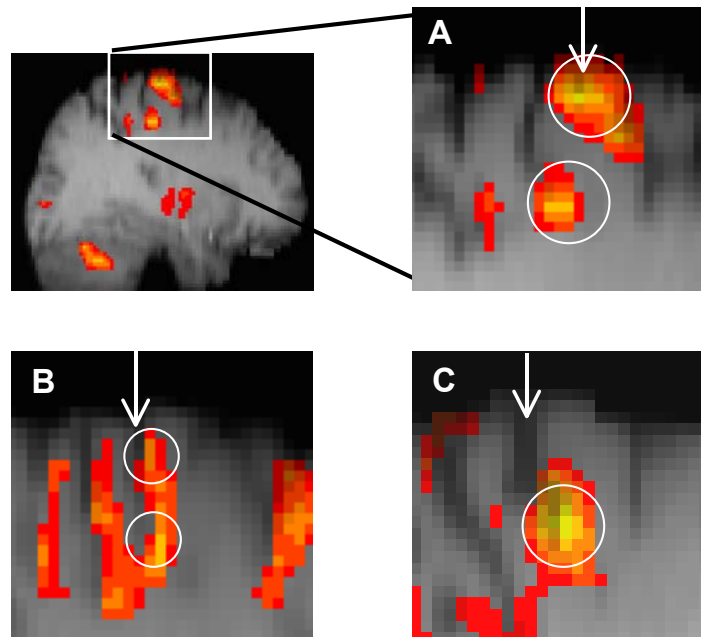


Figure 7.4: Example of primary motor cortex activation clusters in individual subjects. In 6/11 subjects (e.g. **A**) two distinct clusters were clearly visible and thought to correspond to areas 4a and 4p. In 2/11 subjects there were two distinct peaks visible in a single cluster (e.g. **B**) and in the remaining 3/11 subjects only a single cluster of activation was visible, thought to correspond to area 4a in 2 subjects and area 4p in one subject (e.g. **C**). Saggital slices at level of Talairach X=32 showing individual subject activation for button pressing versus rest thresholded at 50% of that subjects maximum Z score. The position of the central sulcus is shown by the white arrow. Activation clusters proposed to correspond to functional subregions within primary motor cortex are outlined by white circles.

The mean signal change between rest and movement was significantly reduced during the dual task in the depths of the right central sulcus (area 4p) and left SMA (at $p < 0.005$, corrected for 10 comparisons, Table 7.5, Figure 7.5). 10/11 subjects showed a decreased in signal change in the dual task in right 4p and 9/11 subjects showed this pattern

in the left SMA (Figure 7.5). A large number of subjects also showed a decrease with distraction in right 4a (9/11 subjects, $p=0.03$) and right SMA (8/11 subjects, $p=0.03$) but these differences did not reach significance with a Bonferroni correction for multiple comparisons.

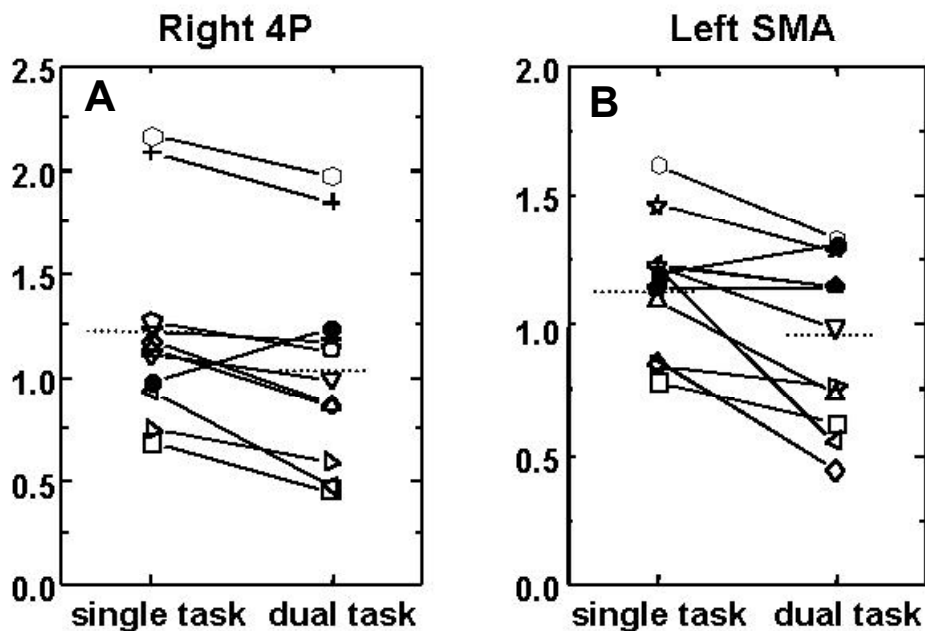


Figure 7.5: Mean percent signal change from rest to task for single (move only) and dual (move and count) tasks. Each symbol represents a different subject. Horizontal dotted lines represent mean of all 11 subjects. Open symbols represent subjects who showed a decrease in signal in the dual task. **A:** 10/11 subjects showed a decrease in signal in right 4p ($t=3.18$, $p=0.0049$). **B:** 9/11 subjects showed a decrease in signal in left SMA ($t=3.20$, $p=0.047$).

In order to test whether any effects found could be due to between-subject differences in movement rate, correlations between movement rate and FMRI activation were tested within the 10 VOIs. No significant correlations were found at the corrected p-threshold of 0.005 (for 10 VOIs). At an uncorrected p-threshold of 0.05 there was a significant correlation between movement rate and FMRI signal change in right 4a during the dual task ($r=0.654$, $p=0.029$) but no significant correlations between movement rate and the *difference* in signal change between the single and dual task conditions.

ROI	Mean % change (\pm sd)		t	p (1 tail)
	Single task	Dual task		
Central Sulcus 4p R	1.22 (0.48)	1.05 (0.50)	3.18	0.0049*
Central Sulcus 4p L	1.00 (0.36)	0.91 (0.13)	0.88	0.20
Central Sulcus 4a R	1.52 (0.46)	1.31 (0.44)	2.14	0.029
Central Sulcus 4a L	1.27 (0.49)	1.26 (0.52)	0.05	0.48
Precentral sulcus R	1.00 (0.29)	1.07 (0.30)	-1.07	0.16
Precentral sulcus L	1.09 (0.45)	1.27 (0.42)	-1.78	0.053
Post central sulcus R	1.29 (0.31)	1.17 (0.38)	1.86	0.047
Postcentral sulcus L	1.24 (0.36)	1.09 (0.46)	1.16	0.14
SMA R	1.12 (0.31)	0.99 (0.31)	2.19	0.027
SMA L	1.54 (0.26)	0.94 (0.33)	3.20	0.0047*

Table 7.5: Results from VOI analysis with standard deviation (sd) in parentheses, demonstrating that certain sensorimotor area show lower activation during the dual task than the single task of button pressing alone.

To assess the effects of dual task repetition specifically in motor cortex the mean percent signal change was found with the motor cortex VOIs for each block of dual task performance. There was no change in the mean percent signal change from block to block for any of the motor cortex VOIs nor were there any trends for change in the pattern of individual subject percent change.

7.4 Discussion

This experiment shows that reducing attention to finger movement by asking subjects to perform a concurrent counting task is associated with decreased BOLD signal in motor cortical regions, compared to the signal evoked by performing the movement without distraction.

7.4.1 Attentional modulation by distraction – effects in sensorimotor cortex

In a random effects group analysis positive and negative interactions between a moving task and a counting task were modelled. This identified changes in fMRI activation associated with dual as opposed to single task performance. The main question for this experiment was specifically whether attention to movement modulates activity in sensorimotor areas. Areas showing a negative interaction therefore were subdivided into areas activated during movement, areas activated during counting, areas of overlap between the two and areas not activated by either task. A large proportion of voxels showing a negative interaction were within regions classed as sensorimotor areas. Thus, diverting attention from movement causes a decrease in activation in sensorimotor areas including SMA, cingulate motor areas and insula. However, this analysis did not reveal attentional modulation of the contralateral primary somatosensory or motor cortex.

One possible explanation for the lack of an effect in these areas is that they were masked out by the technique used. With the masking technique ‘motor areas’ were defined as those activated by movement but not by counting. Therefore areas activated by both tasks would not be identified as sensorimotor areas. However, this possibility can be dismissed as the contribution of overlap to areas showing a negative interaction was slight (less than 10%) and did not include primary sensorimotor cortex.

An alternative explanation for the absence of attentional modulation in the primary motor cortex is slight inter-subject variations in the exact positions of the primary motor cortex activation associated with finger movement. The group analysis is a strict test, as it requires not only that many subjects show an effect, but also that the locations of the effects overlap in standard space. This may be over-restrictive if only a small and potentially anatomically variable region shows selective modulation; registration of individual brains in a standard space inevitably introduces averaging of signal change between small, adjacent structures. Therefore, a second analysis looked at signal change within anatomically defined volumes of interest. This approach has previously been shown to be sensitive to attentional modulation in primary sensory cortical regions, possibly because it allows for slight variations in individual anatomy (Johansen-Berg *et al.* 2000; Jancke *et al.* 1999).

Comparison of signal changes within the individually defined volumes of interest (Table 7.5, Figure 7.5) found that the majority of subjects showed a smaller response in contralateral primary motor cortex in the dual task compared to the single task. This is consistent with a trend for increased primary motor activation with attention reported in a previous PET study (Jueptner *et al.* 1997). Attentional modulation of the response was significant in right (contralateral) putative 4p. Note that this does not clearly demonstrate that modulation of primary motor cortex occurs *only* in right 4p; the attentional effect in 4p could not be shown to be significantly greater than the effect in 4a (in fact 9/11 subjects showed a decrease in right 4a activation with distraction, though this effect did not reach the corrected significance level). Although these results do suggest regional variability in the strength of the attentional effect on the motor system they do not allow firm conclusions about the precise localisation of modulatory effects. The voxel size (4x4x6mm) and smoothing (5x5x5mm) used mean that the boundaries between functionally distinct regions

may be blurred. Future studies with smaller voxels focussed only on the motor cortical areas could help in confirming this finding. Also, the known variability between cytoarchitecture and sulcal landmarks makes it difficult to say for certain that the medial central sulcal volume of interest lies wholly within putative area 4p.

Both the group analysis and the VOI analysis in the current study also demonstrated significant differences between single and dual task signal change in the SMA, particularly on the left.

Although the group level analysis did not demonstrate a negative interaction effect in contralateral primary motor cortex, there was a cluster including parts of the *ipsilateral* central sulcus and pre- and post-central gyri that was deactivated in the dual task relative to the single tasks. This cluster fell into the ‘neither task mask’, i.e., although this ipsilateral sensorimotor region was not significantly activated by button pressing (or counting), it was significantly deactivated in the dual task relative to the single tasks. This region has previously been shown to be active during motor preparation (Deiber *et al.* 1996; Schluter *et al.* 1999; Krams *et al.* 1998).

The strong attentional effect seen in the posterior insula in the current experiment is consistent with the bilateral modulation of insula activity with attention to tactile stimulation reported in Section 6.

7.4.2 Common mechanisms for directing or focussing attention

The present study suggests that attention to movement involves medial frontal cortex, as does attention to sensory stimulation. The group analysis demonstrated involvement of bilateral anterior cingulate cortex and SMA in attention to movement. This is consistent with previous work. For example, Jueptner *et al.* (1997) reported strong attentional effects in right anterior cingulate (for right hand movements) and left prefrontal cortex and trends in

areas including right anterior SMA. However, the effects in cingulate cortex in the experiment presented in this section appear to be superior to those reported by this group. There was no evidence of involvement of the prefrontal cortex in attention to movement, perhaps because of the relatively undemanding nature of the motor task and the fact that movements were externally instructed and so subjects did not have to decide of their own accord which movements to make and when (thus the movement lacked what has been termed “willed action”) (Deiber *et al.* 1991; Frith *et al.* 1991; Hadland *et al.* 2001; Jahanshahi *et al.* 1995).

The term ‘motor attention’ (or ‘intention’, or ‘attention to action’) is used in a number of different contexts. In the current study it refers to the difference between single and dual task conditions. In the single task condition subjects are able to focus attention on their movements whereas in the dual task condition subjects have to pay less attention to their movements as they are distracted by the counting task. Attention in this case refers to ‘thinking about’ each movement as it is being made (Jueptner *et al.* 1997). Another very different context in which attention to movement is required is in motor learning. In this context subjects must generate new responses, monitor movement outcome, rehearse mentally and keep track of previous moves (Passingham 1996). None of these elements are required by the movement task in the current study, which is less attentionally demanding than learning a novel movement sequence. However, the attentional manipulation in the current study depended more on reducing attention in the dual task condition than on placing high demands on the motor attention system in the single task condition.

7.4.3 Does dual task performance require activation of executive areas?

The positive interaction term in the group analysis identified areas that were active in the dual task over and above the sum of activation for the two single tasks. No areas were

found to show a significant positive interaction. This suggests that this dual task does not require substantial recruitment of additional cortical areas, or extra activation of task-related cortical areas. In contrast, D'Esposito et al (1995) found that dual performance of a verbal and a spatial working memory task was associated with prefrontal and cingulate cortex activity that was not seen in the single task conditions (D'Esposito *et al.* 1995). Activation in these executive areas may reflect involvement of a hypothetical supervisory attentional system (Norman and Shallice 1986) or central executive (Baddeley and Hitch 1974). However, a recent fMRI study failed to find any activity exclusive to dual task performance of auditory and visual tasks (Adcock *et al.* 2000). In line with the current investigation a number of other studies have found that dual task performance tends to be associated with decreases in task-related activity rather than increases or recruitment of additional areas (Goldberg *et al.* 1998; Klingberg 1998)

7.4.4 Mental calculation

The neural correlates of mental calculation have been the subject of a number of recent imaging studies. The present investigation adds to this growing body of data. Counting backwards activated a network of regions including bilateral pre-SMA, intraparietal sulcus, precentral sulcus, cingulate cortex and anterior insula, the left putamen, thalamus and inferior frontal gyrus and the right superior frontal sulcus. These results are broadly consistent with previous neuroimaging and TMS findings in which the areas most commonly involved in serial subtraction tasks have been in bilateral (but often predominantly left hemisphere) posterior parietal (predominantly inferior parietal cortex) and inferior frontal cortices (Burbaud *et al.* 1999; Cowell *et al.* 2000; Dehaene *et al.* 1999; Göbel *et al.* 2001; Roland and Friberg 1985; Rueckert *et al.* 1996). A role for the putamen in mental calculation

is supported by case studies of patients with subcortical infarcts resulting in acalculia (Corbett *et al.* 1986; Hittmair-Delazer *et al.* 1994).

7.4.5 Conclusions

This section has demonstrated that attention to movement modulates activity in motor cortical areas including SMA and primary motor cortex. The primary motivation for carrying out this experiment was to aid the interpretation of functional imaging results from patients with brain injury.

In Section 4 of this thesis it was shown that movement of a previously paretic hand is associated with more bilateral patterns of motor cortical activation. Previous studies have shown that movement of an affected hand produces increased activation in motor cortical areas including the SMA and primary motor cortex (Cramer *et al.* 1997; Lee *et al.* 2000; Pineiro *et al.* 2001; Reddy *et al.* 2000; Rossini *et al.* 1998; Weiller *et al.* 1992; Weiller *et al.* 1993; Cao *et al.* 1998; Cramer *et al.* 1997; Lee *et al.* 2000; Reddy *et al.* 2000; Weiller *et al.* 1993). While one interpretation of these activation differences is in terms of cortical “reorganisation” in response to disease, a potential confound is differences in attention to movement as it might be expected that recovering patient subjects would pay more attention to movement of their affected hand.

Together with the results from the previous section, the findings presented here suggest that attention to movement or to sensory stimulation can modulate activity in sensorimotor cortical areas. Some of these areas are similar to those implicated in recovery of movement after stroke (i.e. primary motor cortex and SMA). However, although the attentional modulation in this study was a demanding distractor task, the modulatory effects found were subtle. In addition, other areas that have been shown to play a role in recovery

(e.g. premotor cortex (Seitz *et al.* 1998)) did not appear to be modulated to attention to movement. Therefore it is unlikely that attentional factors could fully explain the magnitude and spatial distribution of changes in movement representations seen after stroke.

Nevertheless, it is important to assess the degree to which attentional factors alter after stroke. Behavioural studies have used dual task paradigms to assess whether patients require increased attention to perform movements with affected limbs. If a movement is attentionally demanding then performance of a concurrent distractor task, which competes for attentional resources, should disrupt motor performance. Studies of walking after stroke have found that performing concurrent cognitive or verbal tasks disrupts gait in recovering patients (Bowen *et al.* 2001; Haggard *et al.* 2000). The degree of interference (reduction in stride duration) correlates with disability, suggesting that more disabled patients have to pay greater attention to walking (Haggard *et al.* 2000). However, one study of upper limb movements found no evidence for an increased dual task effect in patients after stroke relative to controls and therefore concluded that affected arm movements were not more attentionally demanding (Platz *et al.* 2001).

In conclusion, although there may be alterations in attention to movement after stroke, it is not clear that such changes apply to upper limb movements. Furthermore, although distraction from movement does modulate activity in motor cortical areas, the magnitude and spatial distribution of effects suggest that attentional factors are unlikely to explain altered patterns of motor cortical activity after stroke. The argument that the altered patterns represent adaptive reorganisation could be strengthened by two approaches that are explored in the remaining sections of this thesis. The first approach tests whether changes in brain activation patterns are related to therapy-mediated changes in function (Section 8). The second approach tests whether the increased areas of activation in patients are

functionally relevant, i.e. whether interference with those areas of activation impairs movement of a recovered hand (Section 9).

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