

Section 5: The influence of movement features on motor cortical activation in normal subjects

The previous section demonstrated that movement of the affected limb in stroke patients is associated with altered patterns of movement-related activity including relatively increased ipsilateral motor cortex activation. However, interpretation of such changes is difficult as patients may find the movement more effortful than control subjects. In this section the effects of factors which influence 'effortfulness' was tested in a group of normal subjects

5.1 Introduction and Rationale

There have been suggestions that the increased motor cortical activation associated with recovered movement reflects the degree of effort required to generate movement in a previously paretic limb rather than any reorganisation (Stephan and Frackowiak 1997). Although 'effortfulness' itself is difficult to define and quantify, there are clearly certain factors that influence the amount of effort required to produce a movement. For example, complex movements are more effortful than simple movements, greater effort is required to produce movements of greater force or speed, and movement of the non-dominant hand can require more effort than movement of the dominant hand.

The degree to which movement factors such as rate, force, complexity or direction influence the activity of motor cortical cells is debated. For example, Georgopoulos suggests that the firing of M1 cells reflects movement direction (Georgopoulos *et al.* 1986), while others suggest that movement force influences M1 activity (Mussa-Ivaldi 1988). Recently, human brain imaging studies have begun to address these issues by characterising the relationship between movement factors and brain activation (e.g. Wexler *et al.* 1997).

The current study quantified the effects of the movement factors of rate, complexity and dominance on motor cortical activation in normal subjects.

5.2 Methods

Subjects Six subjects (3 right handed, 1 female, 2 male; 3 left handed, all male; aged 22-31) participated. All subjects gave informed consent in accordance with ethical approval from the Central Oxford 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). A T1-weighted anatomical image was also acquired for each subject (IR 3D Turbo Flash, 64x3mm axial slices, TR=30ms, TE=5ms, TI=500ms, flip angle=15°, FOV=256x256, matrix=256x256).

Subjects performed a visually-cued finger tapping task using a 3 x ABAC design. The task blocks varied in movement complexity (A = sequential (1,2,3,4,3,2,1 etc), B = random). The visual cue was a schematic representation of the hand (e.g. .---- for the right hand) on which a star appeared to indicate which finger should be moved (e.g. .*--- for index finger; .---* for little finger). The task was performed first with the dominant then with the non-dominant hand, and was performed at two rates (1Hz, 2Hz).

Image analysis Image analysis was performed within MEDx (Sensor Systems Inc., VA, USA). For each subject and each session, automated image preprocessing and t-tests were carried out using FEAT 2 (FMRIB, Oxford, UK). This included 3D motion correction using AIR (Woods *et al.* 1999), spatial smoothing using a Gaussian kernel of FWHM 5mm, intensity renormalization of all volumes to the same mean value, Gaussian lowpass filtering of HWHM 2.8s, non-linear highpass filtering (Gaussian-weighted LSF straight line fitting, with sigma=72.0s). Z score statistic images were produced for the comparisons of interest (B vs A and C vs A) using the Student's t-test and thresholded using resel (corrected Bonferroni) thresholding with a corrected significance threshold of $p < 0.01$

Three broad volumes of interest were defined on each subject's high-resolution scan:

1. *Sensorimotor cortex plus premotor cortex (SMC/PMC) contralateral to hand moved*: The lateral cortex extending from postcentral sulcus to 1cm anterior to precentral sulcus, from the level of the lateral ventricles to the dorsal surface of the brain.
2. *SMC/PMC ipsilateral to hand moved*: as for 1.
3. *Supplementary motor area (SMA) (bilateral)*: The cortex on the medial brain surface above the cingulate sulcus posterior to the plane extending through the anterior commissure and perpendicular to the AC-PC line (VCA line) and anterior to a plane extending through the posterior commissure and perpendicular to the AC-PC line (VCP line) (Fink *et al.* 1997).

The number of activated voxels in the VOIs was compared between different conditions using Wilcoxon signed ranks tests. To test the hypotheses that increasing rate or complexity leads to increased activity and decreased laterality one-tailed p-values were used. For testing relationships between factors two-tailed p-values were used. The number of activated voxels within the SMC/PMC VOIs was used to calculate a laterality index (LI) ($(C-I)/(C+I)$ where C = contralateral and I= ipsilateral).

5.3 Results

Effect of movement rate Increasing the rate of movement (from 1Hz to 2Hz) produced an increase in the total number of activated voxels pooled across all VOIs (Figures 5.1, Table 5.1, $Z=1.782$, $p=0.04$). This tendency held for all three VOIs separately (contra SMC/PMC: $Z=-1.572$, $p=0.053$; ipsi SMC/PMC: $Z=-1.992$, $p=0.023$; SMA: $Z=-1.782$, $p=0.032$). There was also a trend for faster movements to have a lower LI (Figure 5.2 $Z=-1.572$, $p=0.058$).

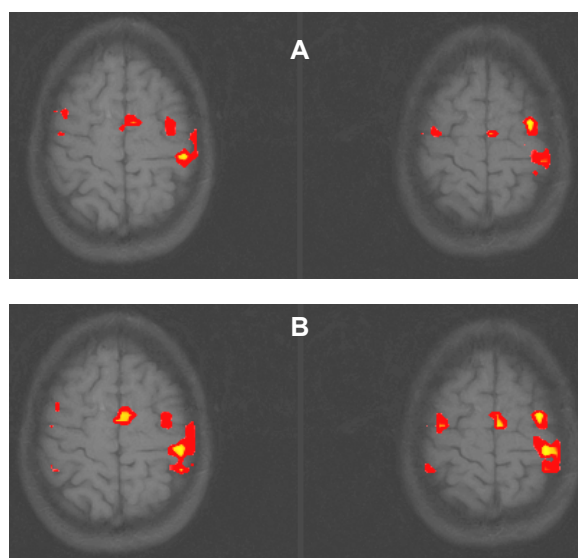


Figure 5.1: Increasing movement rate leads to increased and less lateralised motor cortical activation. Representative pattern of activation from 2 slices through the hand area of primary motor cortex for one subject. A. Simple movement of right (dominant) hand at 1Hz. B. Same movement at 2Hz.

Subject	Handedness	Contralateral			Ipsilateral		
		1Hz	2Hz	% change	1Hz	2Hz	% change
1	Right	47.50	23.13	-51.32	8.50	9.50	11.76
2	Right	75.50	118.13	56.46	18.38	35.13	91.16
3	Right	144.50	173.63	20.16	99.88	143.63	43.80
4	Left	109.25	121.25	10.98	74.63	74.00	-.84
5	Left	92.17	102.38	11.08	38.38	65.83	71.55
6	Left	48.13	74.63	55.06	34.63	51.25	48.01
Mean		86.17	102.19	17.07	45.73	63.22	44.24
s.d.		37.49	50.46	39.38	34.87	45.62	34.78

Table 5.1: Increasing movement rate leads to increase in the number of suprathreshold voxels for both contralateral and ipsilateral motor areas.

Right handed subjects

Left handed subjects

Figure 5.2: Increases in rate from 1Hz (grey bars) to 2Hz (white bars) also led to a decrease in laterality index in most subjects ($Z=-1.572$, $p=0.058$), indicating that faster movements were associated with a more bilateral pattern of activation. Each pair of grey and white bars represents data from a single subject.

Effect of movement complexity Increasing the complexity of movements (with random as opposed to sequential cues) also produced increases in the overall number of activated voxels (Figure 5.3, Table 5.2, $Z=2.201$, $p=0.014$). This tendency held for all three VOIs (contra SMC/PMC: $Z=-2.201$, $p=0.014$; ipsi SMC/PMC: $Z=-2.201$, $p=0.014$; SMA: $Z=-1.572$, $p=0.058$). Laterality index (LI) was lower in the complex task than in the simple task (Figure 5.4, $Z=-1.892$, $p=0.028$), suggesting that the randomly cued movements recruited a more bilateral motor network.

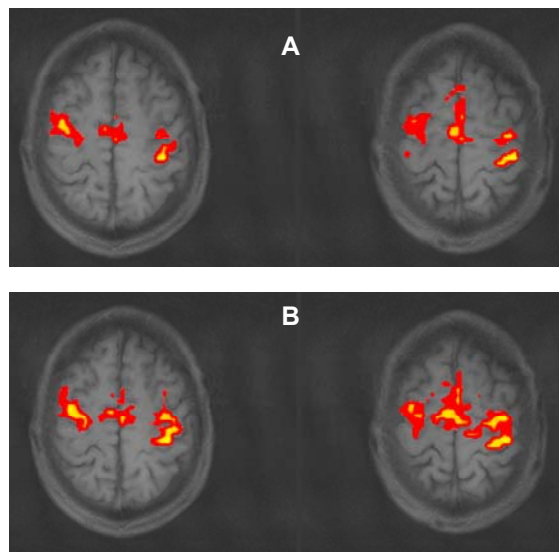


Figure 5.3: Increasing movement complexity leads to increased and less lateralised motor cortical activation. Representative pattern of activation from 2 slices through the hand area of primary motor cortex for one subject. A. Simple movement of right (dominant) hand at 1Hz. B. Complex movement at same rate.

Subject	Handedness	Contralateral			Ipsilateral		
		simple	complex	% change	simple	complex	% change
1	Right	34.88	35.75	2.51	4.63	13.38	189.19
2	Right	87.75	105.88	20.66	18.00	35.50	97.22
3	Right	153.75	164.38	6.91	114.75	128.75	12.20
4	Left	101.38	129.13	27.37	64.88	83.75	29.09
5	Left	90.00	106.00	17.78	45.14	55.14	22.15
6	Left	57.25	65.50	14.41	40.63	45.25	11.38
Mean		87.50	101.10	14.94	48.00	60.29	60.21
s.d.		40.68	45.55	9.11	38.95	40.76	70.87

Table 5.2: Increasing movement complexity leads to increase in the number of suprathreshold voxels for both contralateral and ipsilateral motor areas. However, the magnitude of the increase is greater for the ipsilateral motor area ($Z=-1.782$, one-tailed $p=0.047$)

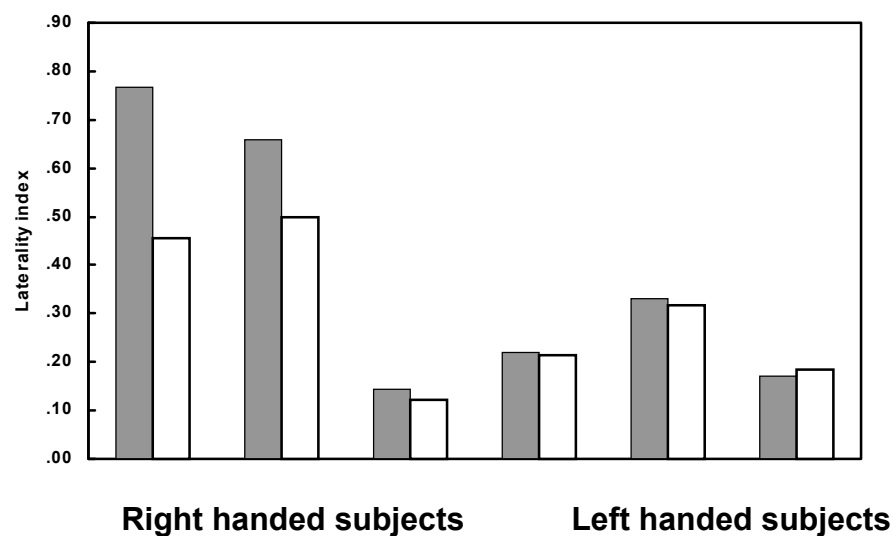


Figure 5.4: Increases in complexity from simple (grey bars) to complex (white bars) led to a decrease in laterality index in 5 out of 6 subjects ($Z=-1.892$, $p=0.028$). Each pair of grey and white bars represents data from a single subject.

Effect of dominance There was no clear effect of dominance of hand moved on the number of activated voxels (Figure 5.5) or the laterality index.

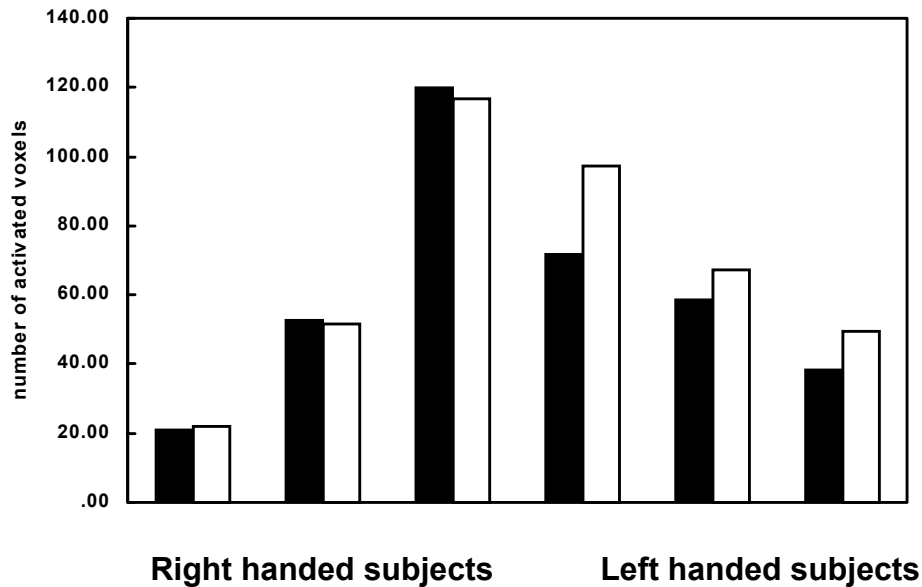


Figure 5.5: There was no clear effect of dominance on the number of activated voxels across the group. Black bars represent movements of the dominant hand and white bars represent movement of the non-dominant hand

Effect of handedness Right handers had a higher mean LI and lower mean overall voxel count than left handers (Table 5.3). However, these differences were not significant.

	Right handers		Left handers	
	mean	se	mean	se
Voxel count	63.0	28.1	70.5	13.2
LI	0.44	0.15	0.24	0.04

Table 5.3: Voxel count (across all 3 VOIs) and laterality index (LI) for left and right handed subjects. There were no significant differences between left and right handers

Interactions The small subject numbers in the current study did not allow for interactions to be assessed statistically. However, whether the effects of changing one movement factor (e.g rate), held equally with alterations in another factor (e.g. complexity), was tested.

Increases in rate produced similar increases in activation for simple and complex movements and increases in complexity led to similar increases for both slow and fast movements. Rate-related and complexity-related increases were observed for movements of the dominant and the non-dominant hand.

However, rate related increases did not hold for all combinations of dominance and complexity: Rate-related increases were clearly seen in the complex task with the dominant hand and the simple task with the non-dominant hand (Figure 5.6, simple, non-dominant: $Z=-1.738$, $p=0.037$; complex, dominant: $Z=-2.201$, $p=0.014$). However, the increases were not significant in the simple task with the dominant hand or the complex task with the non-dominant hand (Figure 5.6). This may reflect a genuine interaction between these factors, or may simply reflect the limited power of the current experiment, given the small numbers of subjects.

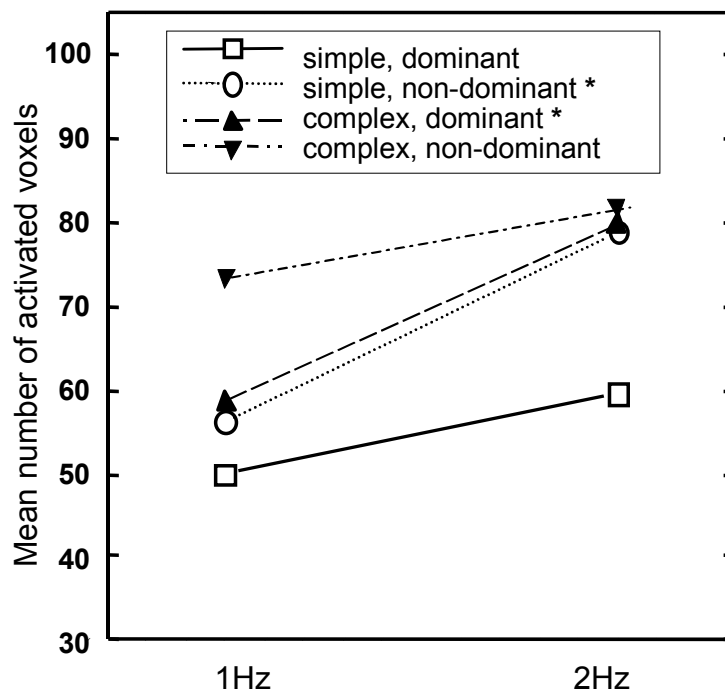


Figure 5.6: Rate-related increases were significant for simple movements of the non-dominant hand ($Z=-1.738$, $p=0.037$) and for complex movements of the dominant hand ($Z=-2.201$, $p=0.014$) but not significant for complex movements of the non-dominant or simple movements of the dominant hand. This may reflect interactions between movement factors.

5.4 Discussion

This study investigated the effects of movement rate, complexity and handedness on motor cortical activation. Increases in the rate and complexity of finger tapping movements resulted in an increased area of activation in motor cortical regions and a decreased laterality index in both right and left handed subjects. The influence of each of these movement factors is discussed in more detail below.

5.4.1 Effect of increasing rate

Increasing movement rate from 1Hz to 2Hz led to increased activity in all motor cortical VOIs and a decreased laterality index. This is broadly consistent with the results from previous brain imaging studies that have assessed the effects of increasing movement rate (Jenkins *et al.* 1997; Rao *et al.* 1996; Jancke *et al.* 1998b; Wexler *et al.* 1997; Sadato *et al.* 1996b; Sadato *et al.* 1997; Jancke *et al.* 1998a). Increases in the number of suprathreshold voxels with faster movements may simply reflect the increased signal to noise that would be expected as a greater proportion of the sampling time is occupied by the task (i.e. there is an increase in ‘duty cycle’). The increase in signal to noise may have a greater effect in the ipsilateral motor cortex, as the signal is typically lower. Therefore the decreased laterality index may reflect increased signal to noise rather than recruitment of bilateral motor networks.

There is a consensus that increasing rate can lead to increased activation in motor cortical areas. However, a linear relationship between rate and activation does not hold for all brain regions, for all frequencies or for all imaging modalities. For example, although some studies have reported a rate effect in all motor cortical regions tested (Jenkins *et al.* 1997), others have found the effect only in contralateral primary motor cortex (Wexler *et al.* 1997), which would argue against the duty cycle explanation presented above. In the very slow movement range (i.e. less than 1 Hz) a linear relationship is not observed (Jancke *et al.* 1998b) and at frequencies greater than 2Hz rCBF may not increase further but reach a

plateau (Sadato *et al.* 1996b). With fMRI, the rate effect at higher frequencies depends on the activation measure chosen: signal intensity change increases linearly with rate across a wide frequency range (1 to 4Hz), but the area of suprathreshold activation tends to decrease as rate increases beyond 2Hz (Sadato *et al.* 1997). The non-linear increase with increasing movement rate is probably related to non-linearities in the haemodynamic response that have been observed with closely spaced sensory stimuli (Glover 1999).

Most studies of the effects of rate have kept the duration of different movement tasks constant. Therefore, in addition to differing in the rate of movements, different task blocks would also differ in the number of movements produced, so this could provide an alternative explanation for the increases observed.

5.4.2 Effect of complexity

The experiment presented here demonstrated that a complex movement (randomly-cued finger tapping) produced more widespread and bilateral motor cortical activation than a simple movement (sequentially-cued finger tapping). Unlike the rate-related changes, the patterns observed with increasing complexity cannot be explained simply by an increase in duty cycle. Rather, performance of complex movements is associated with increased and more bilateral recruitment of motor cortical areas. Increasing movement complexity has been reported to increase activity in a variety of brain areas including contralateral M1 (Gerloff *et al.* 1998), ipsilateral M1 (Chen *et al.* 1997; Shibasaki *et al.* 1993), dorsal premotor cortex (Sadato *et al.* 1996a), precuneus (Sadato *et al.* 1996a), cerebellar vermis (Sadato *et al.* 1996a), thalamus (Sadato *et al.* 1996a), the superior and inferior parietal lobe (Wexler *et al.* 1997) and SMA (Gerloff *et al.* 1997; Shibasaki *et al.* 1993). Some of the variability in the different areas reported might stem from the lack of a clear definition of what constitutes movement complexity and the consequent variation in the ways it has been modified in the different studies. For example, some studies have compared activation during individual

versus sequential finger movements (Shibasaki *et al.* 1993), whereas others have compared scale (i.e. 1,2,3,4,3,2,1 etc) versus non-scale sequences (Gerloff *et al.* 1998; Chen *et al.* 1997), or sequences of different lengths (Sadato *et al.* 1996a).

5.4.3 Effect of hand dominance

This experiment did not find strong evidence for an effect of dominance of the hand moved. This may be due to the small subject numbers and the mixture of left and right handed subjects in the study. Some previous imaging studies have found that the degree of motor cortical activation depends on the dominance of the hand being moved. In right-handed subjects movement of the dominant hand is associated with greater contralateral motor cortex activity than movement of the non-dominant hand (Dassonville *et al.* 1997) and movement of the non-dominant hand is associated with increased activity in ipsilateral motor cortex in addition to contralateral motor cortex (Kawashima *et al.* 1993; Singh *et al.* 1998). These factors would combine to result in a decrease in the relative laterality of motor cortical activation for non-dominant hand movement

Effects of other movement factors are also dependent on the dominance of the hand being moved. For example, changes in activation with bimanual compared to unimanual movements are found in the left hemisphere but not the right hemisphere in right-handed subjects (Jancke *et al.* 1998a). Also, frequency effects in cerebellum depend on the dominance of the hand being moved: For movements of the dominant hand there is only a small increase in activation with increasing rate whereas for movements of the non-dominant hand there is a significant increase in activation with increasing rate (Jancke *et al.* 1999).

5.4.4 Effect of handedness

This experiment did not find any evidence for a difference between left and right handed subjects. However, the subject numbers in the current study were small. Other studies

suggest that brain structure and function differ according to handedness. There are handedness-dependent structural differences between the left and right hemispheres: the central sulcus contralateral to the dominant hand is deeper and has a greater neuropil volume (Amunts *et al.* 1996). In addition, the neural control of bimanual movements differs according to handedness, with the hemisphere contralateral to the dominant hand showing greater activation during bimanual movements (Viviani *et al.* 1998). Some functional imaging studies suggest that there are also handedness-dependent differences in movement-related brain activation. For example, the increased ipsilateral activation seen with non-dominant hand movements in right-handed subjects is not seen in left-handed subjects (Singh *et al.* 1998). However, one study found no effect of the *direction* of handedness but a significant effect of the *degree* of handedness on the laterality of motor cortical activation (Dassonville *et al.* 1997), with subjects with the strongest hand preference showing relatively less ipsilateral activation.

5.4.5 Conclusions

Increasing the rate and/or complexity of movement tasks was associated with increased activation across the motor cortical system in a group of normal subjects. However, the correct interpretation of these increases may differ for the two movement factors. Increasing movement rate results in movement execution occupying a greater proportion of the sampling time. The observed changes in fMRI signal might therefore be explained by the resultant increase in signal to noise rather than altered recruitment of motor areas. By contrast, increasing movement complexity should not alter the task ‘duty cycle’ and therefore observed changes are more likely to reflect increased and more bilateral recruitment of motor cortical areas.

However, the ‘duty cycle’ explanation of rate effects may only apply within subjects, or across subjects in normal populations where the range of maximum achievable rates

would be limited. In control groups, movement at a given rate would therefore require a similar degree of effort across subjects. By contrast, in a patient population, movement at a given absolute rate may require different degrees of effort for different subjects, and there is likely to be a wider range of maximum achievable rates in a patient group. For patient populations it may therefore be useful to normalise performance rate to individual maxima (e.g. Section 4).

These findings have implications for the interpretation of the additional and more bilateral activations seen in some stroke patients during movement of their recovering limb. Some of the movement factors investigated in the current study are likely to affect the amount of effort required to produce a movement. More effortful movements (e.g. more complex) were associated with larger and more bilateral activation volumes. It is probable that some stroke patients will find movements more effortful than controls, and this increase in effort could explain the altered activation patterns observed when factors affecting effort are not matched.

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