



● *Original Contribution*

AN fMRI STUDY OF THE HUMAN CORTICAL MOTOR SYSTEM RESPONSE TO INCREASING FUNCTIONAL DEMANDS

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Functional magnetic resonance imaging (fMRI) was used to study activation changes in the human primary motor-sensory areas (MAs), supplementary motor areas (SMAs), premotor areas (PMAs) and the superior and inferior parietal areas (SPAs, IPAs) during right hand finger movements as the rate, force and complexity of movement were varied. A preliminary reproducibility study of a single subject doing the same repetitive index finger movements in nine different sessions over a six week period demonstrated highly consistent and highly localized activation in the contralateral MA. ANOVAs demonstrated highly significant main effects of increasing the force and complexity of movement, thereby illustrating the distributed and integrated systemic character of the cortical motor system. Interactions between brain region and the rate and complexity of movements suggested functional specialization of some components of the system. Increasing the rate of movement led to increased activity only in the contralateral MA; increasing complexity led to greater increases in activity in the left and right SPAs and the left IPA than in other areas. Although activation was evident in varying degree throughout the multiple motor areas, only the MAs showed consistent lateralization of activation. © 1997 Elsevier Science Inc.

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INTRODUCTION

The human cortical motor system has both highly localized and widely distributed features. Among the cortical motor areas, only lesions of the primary motor-sensory area (MA) along the central sulcus produce complete and lasting paralysis. However, even relatively simple appendicular movements are associated with activation of additional centers in the frontal, parietal and cingulate lobes, with recent studies indicating the presence of as many as eight different motor areas within the frontal cortex alone of the monkey (Kurata, 1994). This combination of localized and distributed properties invites study of the cortical motor system as an exemplar of important principles basic to cerebral functional organization. Toward this end, the present study used functional magnetic resonance imaging (fMRI) to quantitatively compare task related activity in different components of the cortical motor system as the rate, force and complexity of movement were independently varied. The study aimed to identify both

functional differences among components of the system, and functional properties of the system as a whole.

Among the cortical motor areas, those studied most completely have been the MAs, the premotor areas (PMA) running dorsoventrally along the lateral aspect of the frontal lobes immediately anterior and parallel to the MAs, the supplementary motor areas (SMA) located on the medial surfaces of the frontal lobes rostral to the MAs, and areas within the superior and inferior parietal areas (SPA and IPA). Previous studies have clearly established that the MAs are the primary origin of neurons that connect via the spinal cord with the motor endplates in peripheral muscle. It is less clear whether the MAs are simple relay stations, or have more complex functional characteristics. Functional imaging studies have been inconsistent in this regard with some finding changes in contralateral MA activity after practice of complex finger tapping tasks (Grafton et al, 1992a; Schlaug et al, 1994; Karni et al, 1995), and others failing to find differences with complex as compared to simple tasks (Shibasaki et al,

1993) or after practice of simple tasks (Friston et al, 1992; Rao et al, 1994). Activity in the ipsilateral MA, however, was greater with complex as compared to simple tasks, indicating potential variability of function in different functional contexts (Shibasaki et al, 1993). Since the MA receives extensive input from the SMA and PMA, areas in which activity clearly changes with practice or increased task difficulty, it may be more appropriate to attribute observed changes in MA activity to change in other components of the motor system or to the system as a whole.

Multiple studies have shown increased activity in the SMA and PMA as task difficulty increases (e.g., Roland et al, 1982; Colebatch et al, 1991; Rao et al, 1993; Bandettini et al, 1993). Differences between the connections of SMA and PMA to other brain regions supports the notion that their functions are different (Schell & Strick, 1984; Goldberg, 1985). Based in part on the behavioral effects of brain lesions (e.g., Halsband, 1982; Halsband et al, 1993), it has been proposed that the SMA has a specialized role in initiating movement, and in internally directed movement sequences, while the PMA plays a specialized role in movements triggered or guided by external sensory cues (see Goldberg 1985 and Tanji 1994 for fuller discussion). A number of studies have reported data consistent with this view (Ikeda et al, 1992; Lang et al, 1991; Playford et al, 1992; Roland et al, 1980; Fox et al, 1985; Dieber et al, 1991; Grafton et al, 1992a; Friston et al, 1992; Paus et al, 1993; Rao et al, 1994). Other studies, however, are clearly inconsistent with this proposed differentiation of SMA and PMA function. PMA activity has been shown to change with learning in parallel with SMA changes (Rao et al, 1994), and to increase during internally cued movement relative to externally cued movement to an extent similar to or greater than the change in SMA (Dieber et al, 1991; Playford et al, 1992). Significant increases in SMA activity but not PMA activity have been reported in tasks where movement direction was dependent on changing visual information (Grafton et al, 1992a, b) or movement rate was paced by external auditory cues (Remy et al, 1994), leading to the suggestion "that the SMA is involved in initiating movements triggered by sensory cues" (Grafton, 1994).

Parietal lobe contributions to human motor function have been less extensively studied. SPA but not IPA activity has been shown to increase during tasks that require hand movement in specific directions, cued either by ongoing visual targets (Grafton et al, 1992b) or by auditory signals to move in one of four pre-specified directions (Dieber et al, 1991). Such activation was absent with repetitive finger tapping (Remy et al, 1994), and when eye movements were made back and forth between two fixed targets in response

to either visual or auditory cues (Fox et al, 1985), suggesting that the extent of SPA activity may depend upon the complexity of the required movement selections. Decreases in SPA activity after subjects practiced and became more adept at a complex finger movement sequence are consistent with this possibility (Seitz and Roland, 1992; Schlaug et al, 1994).

Two methodological factors have probably contributed to the inconsistencies evident in existing findings. First has been incomplete control of important aspects of the motor tasks themselves. For example, only a few studies comparing simple and complex finger movements have standardized the rate of movement, and to our knowledge none have standardized the range or force of movement. Variation in these basic aspects of motor activity could alter observed patterns of motor system activation. Second has been lack of statistical analyses necessary to evaluate the significance of differences in activation among different components of the motor system. It is not sufficient, for example, to determine in separate analyses that the SMA is more active in complex than simple tasks while the PMA is not. The complex-simple difference could be significant in the SMA at $p = .04$ and non-significant in the PMA at $p = .12$, but such a difference in the apparent significances would not itself be a reliable finding. We are not aware of any functional imaging study that used analysis of variance (ANOVA), or other comparable statistical methods, to support conclusions of selective alteration in activity of some but not other components of the motor system.

fMRI provides quantitative data on individual subjects that lend themselves naturally to the required ANOVAs. These data also permit correlation analysis to identify associated changes in different component areas, thereby providing information about system level properties. For the present study, we built a tapping device that enabled us to control and vary the rate, force and range of movement of the fingers of one hand. With these methods, we evaluated the effects of changes in the rate, force and complexity of finger movements on activation in cortical motor areas. Preliminary to this, we evaluated the reproducibility of our methods by measuring MR signal changes associated with simple finger tapping in the same individual on nine different occasions.

EXPERIMENTAL METHODS

Subjects:

Three different groups of subjects participated: one to study reproducibility; one to study effects of rate and force of movement; and one to study effects of complexity of movements. One man (age 43 years) participated in the reproducibility study, and was stud-

ied in nine test sessions over a six week period. Eleven subjects (7 men, 4 women; mean age 29 years, range 21–32) participated in the comparison of movements at different rates and against different resistances. Six subjects (4 men, 2 women, mean age 32 years, range 25–43) participated in the comparison of simple and complex movements. All were right handed, defined as writing and doing at least 5 of 7 everyday tasks with that hand (Wexler et al, 1979). None had history of neurologic or psychiatric illness. None were taking medications with central nervous system effects. None were regular users of alcohol or illicit substances with CNS effects and none had used any such agents within 48 hours of study. Two subjects were members of the research staff. All others were paid volunteers who responded to local advertisements. All gave informed, written consent following procedures approved by the Human Investigations Committee of Yale University School of Medicine.

Finger Movement Motor Activation Tasks

In order to standardize and quantify finger movement activity, we designed finger tapping devices. These devices consist of wooden levers or paddles that pivot about a central fulcrum. The end that is tapped has a flattened area slightly broader than a finger. Rubber bands are attached between the other end of the paddle and the base of the structure. The distance between the fulcrum and the rubber band is varied in order to change the resistance against which the subject taps. At the end of each tap, the rubber band returns the paddle to the starting position. When tapping, the subject pushes the tapper until it makes contact with a stop-pad, ensuring a constant range of motion for all taps. The sound created by the paddle contacting the stop-pad is audible in the control room, and the end of the paddle is clearly visible protruding from the magnet opening, allowing both auditory and visual confirmation of the range and rate of subject tapping. For studies involving only movement of the index finger, a tapper with one paddle is used. For studies involving movement of all fingers, a tapper with four paddles is used. The base of the tapper is attached to a padded arm rest.

The hand, wrist, and forearm were secured to the base of the tapper in order to minimize the likelihood of additional muscles being engaged in different experimental conditions. A pad was placed under the palm of the hand, propping up the hand at a 30° angle relative to the wrist. A velcro strap was placed snugly across the back of the hand to keep it resting securely on the pad. This served to limit or prevent rocking movements of the whole hand at the wrist joint, thus isolating movement to the index finger itself. Straps were also placed around the wrist and the forearm (about two-

thirds of the way to the elbow), securing the arm to the base of the tapper and preventing lifting movements of the arm as part of the effort to move the tapper.

The task in the reproducibility study was simple repetitive tapping with the right index finger at 90 taps/minute paced by the sound (also 90/minute) of the oscillating field gradients used for imaging. Resistance was set at the minimum level necessary to return the tapping paddle to the start position at the end of each tap, and was subjectively experienced as very easy.

Simple right index finger tapping was also used in studying the effects of rate and force, but at two different rates and at two different force levels (i.e., four different conditions in all). At the fast rate, subjects tapped with every machine sound (each slice acquisition, 90/minute). At the slow rate they tapped with every other sound (45/minute). The low resistance condition was the same as in the reproducibility study. Resistance for the high resistance condition was determined individually for each subject so as to produce a force requirement that was experienced as moderately difficult and substantially greater than the easy condition. Prior to imaging we observed each subject tap against their individually set high resistance, so as to ensure that the force required did not lead to additional arm and wrist movement, especially with sustained tapping. We chose not to use a constant high resistance setting across all subjects, because to do so would likely either create conditions too easy for some subjects or so difficult for others that they would also make wrist and arm movements. To provide additional assurance on this point, each subject was observed tapping at their individually selected high resistance setting prior to the study in order to ensure that there were no visible movements of the wrist or arm.

In order to evaluate the effects of increasing complexity of movement, we compared repetitive movement of the same fingers to sequential movements of different fingers. There were two sequential movement patterns: 1) index, middle, ring and little finger taps; and 2) index, index, ring, middle, middle, and little taps. Both required memory of previous, different finger movements in order to make most current movements. There were also two simple repetitive movements: 1) tapping with the index finger; and 2) tapping with all four fingers in unison. Neither of the simple movements precisely matched the physical demands of the complex movements; the single index tapping did not involve all fingers as did the complex patterns, while repetitive movement of all four fingers together involved more total muscle activity than the sequential movement of one finger and then another. The two together however act as a composite reference condition for major aspects of the complex tasks. Using two different sequential patterns allowed for more total

complex trials while limiting practice effects, and also matched the use of two different repetitive tasks. All taps were made with the right hand on the 4-finger tapper described above, with range and force of motion constant across conditions and rate paced by the machine noise at 90 taps/minute.

Image Acquisition Protocol

Imaging was performed on a 1.5 Tesla magnet (Signa, General Electric, Milwaukee, WI) modified for echo-planar imaging by Advanced NMR Inc. (Wilmington, MA). A circularly polarized head coil was used. Each subject lay supine in the scanner. A Velcro strap around each subject's head, and a cushion that molded to cranial contour when inflated were used to minimize head motion. Following a sagittal anatomic sequence (repetition time [TR] 500 milliseconds, echo time [TE] 11 milliseconds, in plane resolution 0.9×0.9 millimeters, 5 millimeter sections with 2.5 millimeter intervals), three axial-oblique anatomic images were obtained using conventional spin echo techniques (TR 500 milliseconds, TE 13 milliseconds, in-plane resolution of 1.6×1.6 millimeters, 7 millimeter contiguous sections). These were acquired through the frontal and parietal lobes in a plane parallel to the intercommissural line. In 8 subjects (3 in the complexity study and 5 in the rate and resistance study), the 3 slice locations were centered at Talairach z levels of 39, 46, and 53. In 9 subjects (3 in the complexity study and 6 in the rate and resistance study), the 3 slice locations were centered at Talairach z levels of 44, 51, 58. For functional imaging, 60 images were acquired at each of the same three locations with a gradient recalled echo-planar technique (TR 2000 milliseconds, TE 45 milliseconds, 60° radio frequency pulse, in-plane resolution of 1.6×1.6 millimeters, 7 millimeter contiguous sections, 1 shot, imaging time of 2 minutes, 9 seconds). This sequence is particularly sensitive to changes in local magnetic field homogeneity that may arise, for example, secondary to changes in tissue deoxyhemoglobin concentration. While increases in cerebral metabolic activity increase oxygen demand, local increases in blood flow associated with increases in local cerebral metabolic activity more than compensate for this need and consequently lead to a net local decrease in deoxyhemoglobin concentration (Fox et al., 1988). Changes in the echo-planar fMRI signal reflect this net change in deoxyhemoglobin concentration, and thereby provide a measure of localized changes in brain activity (Ogawa et al., 1990; Shulman et al., 1993). Previous work has established that such procedures are sensitive enough to detect changes in cortical activity associated with small motor movements (e.g., Kim et al., 1993).

For the reproducibility study, external landmarks were carefully aligned each session with marks on the coil and scanner table. The matching of each session's scanning

planes to previous images was judged by an experienced neuroradiologist. In all three studies subjects tapped for 40 seconds, preceded and followed by 40 second rest periods, with instructions to start and stop tapping given verbally. Sixty images were acquired for each slice, 20 during the activation and two rest periods respectively. Two such trials were performed for each motor task during each session. All tasks were done once before any were repeated, with serial position of the different tasks counterbalanced within subjects. In the rate and force study this was done by reversing the original task sequence during the repetitions. In the complexity study this was done by presenting a simple condition in the first, fourth, fifth and eighth positions, and presenting complex tasks in the second, third, sixth and seventh positions. Much larger sample sizes would be necessary in order to counterbalance the positions of each condition relative to each other across subjects, and task order was therefore held constant across subjects (Easy 45/min, Easy 90/min, Hard 45/min, Hard 90/min, Hard 90/min, Hard 45/min, Easy 90/min, Easy 45/min; and Repetitive 1, Sequential 1, Sequential 2, Repetitive 2, Repetitive 1, Sequential 1, Sequential 2, Repetitive 2). This counterbalancing thus controls linear effects of factors such as practice, increasing or decreasing comfort in the magnet, or fatigue. It does not control for the effects of a particular task on the task that immediately follows. Subjects were instructed not to move any body parts other than their tapping fingers during imaging.

Data Analysis

Anatomic and functional images were transferred to a Sun Sparc II work station for analysis. The image data were analyzed using programs written in Matlab (The Mathworks, Natick, MA). The first three functional images from each period were excluded from quantitative and statistical analyses in order to achieve steady state conditions in the pretask baseline period and to avoid the transient hemodynamic response delay in task-related activation at the start and end of tapping. The extent of motion in each image data set was evaluated by studying the center of mass position over time. All trials (e.g., one baseline - activation - baseline period) during which the center of mass moved more than 0.4 voxels from its initial position were excluded. One male subject from the rate and resistance study showed excessive movement in multiple trials and was consequently dropped from the data set, leaving a sample of ten subjects. One trial each was excluded from three additional subjects in this data set. Task-related percent mean signal changes and student t-values were calculated voxel by voxel by comparing signal intensity in the 17 images during task activity to that during the 34 images in the pre and post activity periods. Maps of t-values were inspected to rule out rims of

high or low values along the borders of the brain that would be indicative of motion artifact. Values from the repetitions of the task were averaged to determine percent signal change. Individual voxels were considered activated during the task if their t-values for *both* repetitions of the task were above a prescribed threshold (set as described below).

Reproducibility was evaluated by creating t-value activation maps for each study session. Since the magnitudes of physiological and other noise sources varied from session to session, the t-threshold was set individually for each session at a level just low enough to reveal areas of activation within the contralateral MA. This enabled us to evaluate the constancy of location of activation within the contralateral MA, and the relation of its intensity to activation elsewhere in the brain. The number of voxels above the selected thresholds varied across the sessions from 0.5% to 2.0% of voxels within the brain. Voxels were eliminated that did not belong to a cluster of at least five voxels above the t-threshold, on the assumption that more isolated "activations" were more likely to be artifactual.

For quantitative comparisons of effects of rate, force and complexity on different component areas, data analysis proceeded by defining anatomic boundaries of SMA, PMA, MA, SPA and IPA in each hemisphere (Fig. 2A-C). This was done for each of the 3 axial-oblique T₁-weighted anatomic images obtained in each subject: (1) SMA (supplementary motor area, slices at z = 51, 53 and 58 only)—bordered posteriorly by paracentral sulcus, extending anteriorly to cover approximately the caudal half of medial aspect of superior frontal gyrus; (2) PMA (premotor area, all slices)—spanning precentral sulcus over the dorsolateral frontal lobe, incorporating anterior precentral gyrus; (3) MA (primary motor-sensory area, all slices)—anterior and posterior banks of central sulcus; (4) SPA (superior parietal area, all slices)—posterior aspect of postcentral gyrus extending posteriorly to intraparietal sulcus and medially to posterior interhemispheric fissure, including portions of superior parietal lobule and precuneus; and (5) IPA (inferior parietal area, all slices)—posterior and lateral to intraparietal sulcus, incorporating portions of supramarginal and angular gyri. Data from all three slices were combined, creating a single set of voxels for each of the 10 anatomically defined regions of interest for each subject. The mean numbers of voxels in each region averaged over all subjects were: RSMA 78, LSMA 86.5, RPMA 212, LPMA 212, RMA 274, LMA 266, RSPA 819, LSPA 906, RIPA 627 and LIPA 619. However, there was considerable variability among subjects in the relative sizes of different regions and/or in the extent to which different regions were represented in the three imaging planes.

Statistical comparisons of the different rate, force and complexity conditions were made using repeated

measures ANOVA, with activation intensity as the dependent variable (calculated as described below). Brain region (Region) was one factor in all analyses. It had 10 levels (right and left SMAs, PMAs, MAs, SPAs and IPAs). In analysis of the rate and force data set, there were two other factors: Rate (45 vs 90 taps/min) and Resistance (easy vs hard). In analysis of the complexity data set there was only one factor, Complexity (simple vs. complex), in addition to Region. The results of greatest apriori interest were possible interactions between Region and any of the other factors, since such interactions would provide statistical confirmation that different regions showed different responses to the increases in rate, force or complexity. When a significant interaction between Region and another factor was present, two types of follow-up analyses were done. *First*, analyses were conducted for each region individually. In the case of the rate and force study, these were two-way repeated measures ANOVAs with both Rate and Resistance as factors. In the case of the complexity study these were one-way repeated measures ANOVAs with complexity as the only factor. Since these analyses were not done to establish the overall significance of experimental effects, but rather to indicate which regions showed the greatest changes in association with the factor (Rate, Resistance or Complexity) that interacted significantly with Region, we have identified all regions with *p* values less than .10. *Second*, analyses were conducted to determine whether change in any particular region was reliably greater than the change in any other region. In order to determine this we conducted pairwise comparisons of two regions at a time, with the task manipulation as a second within subject factor.

Main effects of Rate, Resistance or Complexity were also of interest. Such effects would indicate a generalized increase or decrease on average for all 10 cortical motor areas in response to the increase in rate, force or complexity. Main effects of Region were not of interest.

In the study of the effects of complexity, data from the two repetitive and the two sequential tasks were combined (see rationale above) prior to calculation of any of the dependent variables (see below). Prior to this, two preliminary ANOVAs were done, one comparing the two repetitive tasks and one comparing the two sequential tasks, to ensure that there were no significant differences between conditions being combined. Neither main effects of condition nor interactions between Condition and Region even approached significance for any of the dependent variables. When calculating t-values for each voxel, the first trials of the two repetitive tapping conditions were combined to calculate t-values for the first "trial" of the simple condition, and the second trials of the two repetitive

conditions were combined to calculate t-values for the repetition of the simple condition. Data for the two sequential tapping conditions were treated similarly when calculating t-values for the complex "trials."

It is not clear on either theoretical or empirical grounds what is the most appropriate dependent variable to use in such analyses. Consequently, we conducted analyses using three different dependent measures. *First* was the average percent signal change from baseline to task of all voxels within the anatomically defined region ("P"). This has the advantage of being free from any arbitrarily selected activation threshold. It has the significant disadvantage, however, of including data from many voxels within each region that do not include tissue activated during the task but which contribute significant variance to the analysis. *Second* was the number of voxels with $t > 2$ for both task repetitions ("N," a constant t-threshold was used since all relevant comparisons were within sessions rather than across sessions as in the reproducibility study). This has the advantages of eliminating noise and of providing an index of the volume of significant activation. In the three subjects in whom one trial was dropped due to excessive movement, the t value for the remaining trial of that condition was required to be >3 for a voxel to be considered active. *Third* was the summed percent signal change of all voxels above threshold ("S"). This has the advantage of combining in a single variable data from changes in both volume and intensity of activation. The last two variables have the disadvantages of subjecting the data to a somewhat arbitrary thresholding, and of excluding potentially relevant information from areas of less intense signal change.

RESULTS

I. Reproducibility

Images showing voxels above threshold in the superior slice from each test session are presented in Figure 1. Close inspection of sulcal markings showed excellent session to session reproducibility of image slice selection. Similar reproducibility of task-related activation was also apparent. A clear region of activation was always evident in the same segment of the left hemisphere MA. In 5 of the 9 sessions, 100% of the peak-activated-voxels were within this area. In the remaining sessions corresponding values were: 80, 50, 22 and 13%. In the latter two sessions, areas of activation equal or stronger than those in the primary motor area were evident elsewhere in the brain. Interestingly, most prominent among these areas were the right PMA, left SMA and left SPA, all components of the motor activation system (see above and below). Percent signal change for the cluster of activated voxels

in the MA ranged from 1.2 to 3.0% across sessions, with values for 8 sessions between 1.2 and 1.8% (mean \pm s.d., 1.5 ± 0.2).

II. Effects of Varying Force of Movement

The initial overall ANOVAs yielded main effects of force that were significant for the dependent measure N [$F(1, 9) = 6.24, p = .03$ e.g., figure 2D] and approached significance for S [$F(1, 9) = 4.11, p = .07$]. The main effects of force did not approach significance for P ($F = .00$). The mean increase in N across all subjects as force of movement increased was 63%. The mean increase in S was 84%, indicating that while the most significant effect of increasing force of movement was to increase the volume of tissue showing clear task-related activation (i.e., N), there was also evidence of some increase in the intensity of activation. Interactions between force and brain region were not significant for any of the dependent measures.

III. Effects of Varying Rate of Movement

The initial overall ANOVAs failed to reveal any main effects of rate. However, the interaction between rate and brain region approached significance for P [$F(9, 81) = 1.78, p = .085$]. Comparison of the two tapping rates in each region individually failed to identify any in which activation differences between the rates were statistically significant. Inspection of mean changes in each region, however, indicated that the trend for an interaction between rate and region resulted from the fact that only the left MA showed a substantial increase in activity with increased rate (e.g., figure 2E), while small decreases were evident in other regions. Pair-wise comparisons indicated that change in activity with increased rate in the left LMA differed from change in the left SMA ($p = .002$), the right PMA ($p = .01$), the right SMA ($p = .05$), the right SPA ($p = .06$) and the left SMA ($p = .08$).

IV. Effects of Increasing Movement Complexity

The initial overall ANOVAs revealed main effects of complexity for N [$F(1, 5) = 183, p = .0001$, Fig. 2F] and for S [$F(1, 5) = 22.9, p = .005$], but not for P. N increased 111% with the sequential as compared to the repetitive movements. The increase in S (125%) paralleled the increase in N, indicating that the primary effect of requiring more complex sequential movements was to increase the number of voxels with t-values above threshold, rather than increasing the signal from already active tissue.

The interaction between complexity and brain region was significant for N [$F(9, 45) = 3.7, p = .002$, Fig. 3] and for S [$F(9, 45) = 3.1, p = .005$], but not for P. As seen in figure 3, all areas except for the left MA and the right SMA showed at least a trend toward

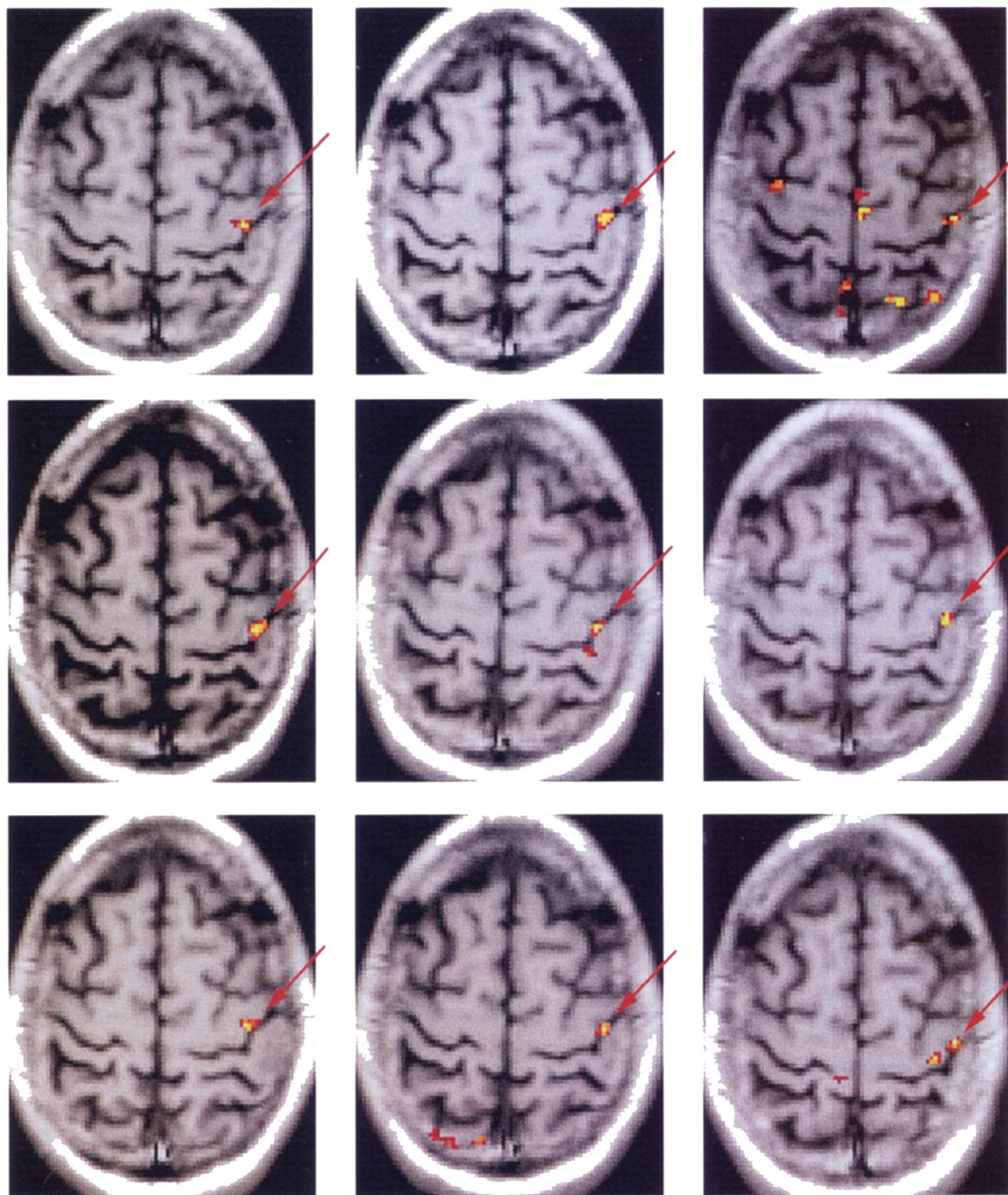
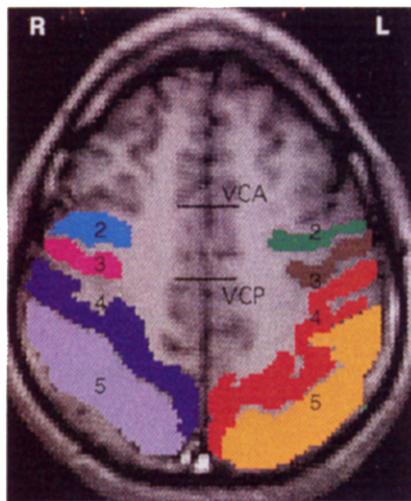
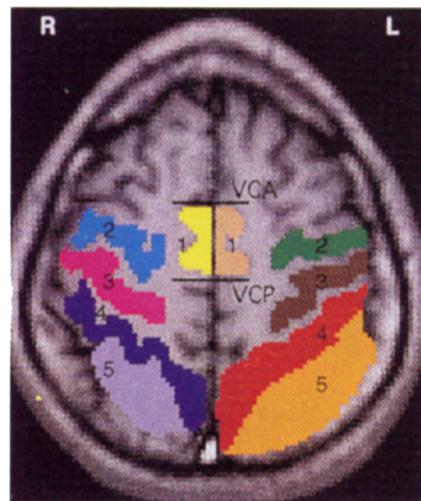
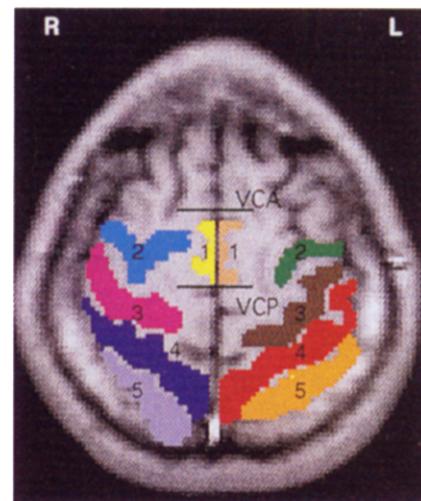
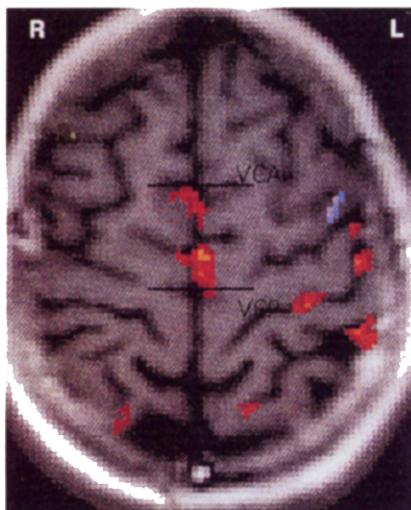
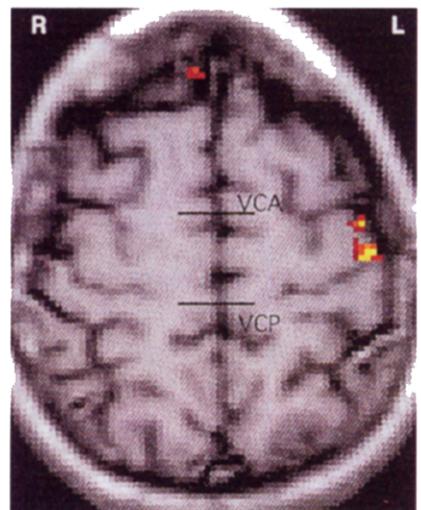
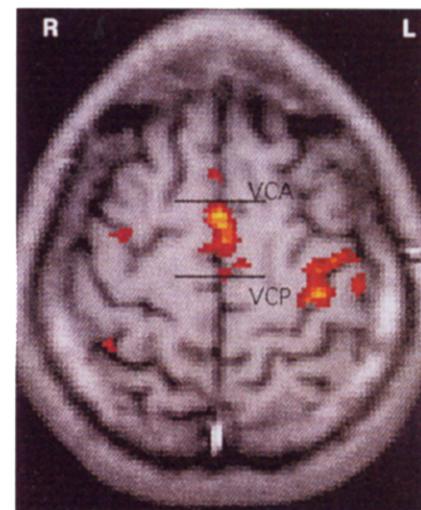
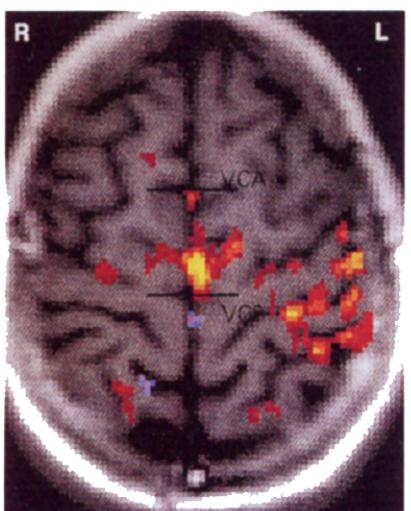
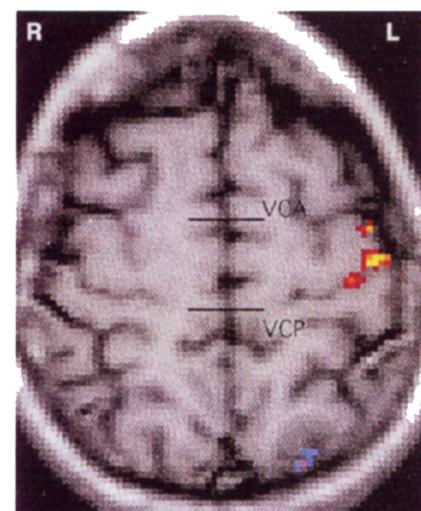
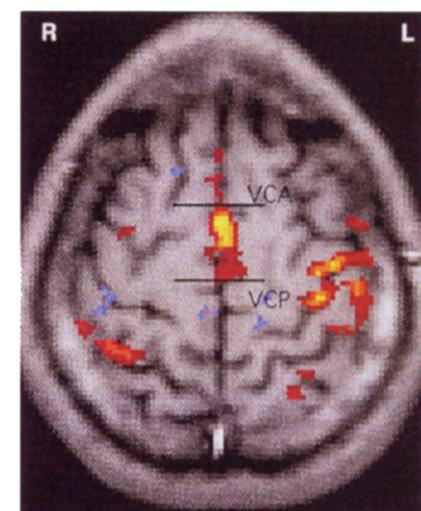


Fig. 1. Activation (t-maps associated with repetitive index tapping in a single subject imaged on nine different days over a six week period.

an increase in activation as complexity increased. However, when both of these regions are removed from the analyses the interaction between region and

complexity remained significant ($p = .001$), indicating that there were significant differences among the remaining regions in the extent of complexity-related

A. ROI ($z=44$)B. ROI ($z=51$)C. ROI ($z=58$)D1. Easy ($z=53$)E1. Slow ($z=51$)F1. Repetitive ($z=58$)D2. Hard ($z=53$)E2. Fast ($z=51$)F2. Sequential ($z=58$)

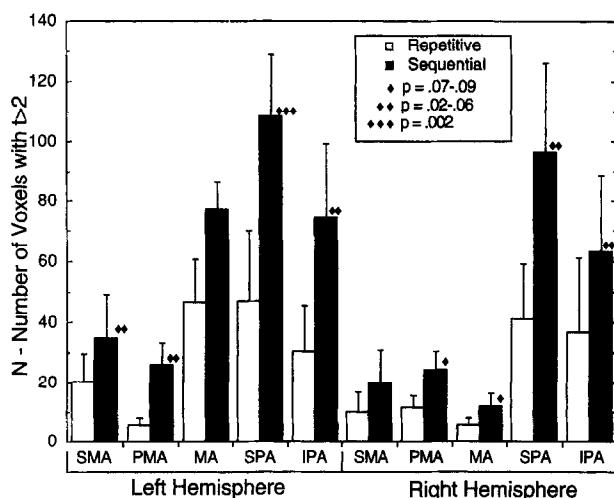


Fig. 3. Number of voxels with $t > 2$ for each of the 10 ROIs with repetitive and sequential finger movements. P-values indicate significance level of t-tests comparing repetitive and sequential conditions in each region individually. Bars represent standard error.

activity increases. Pair-wise comparisons among these regions indicated that the LSPA showed a significantly greater increase in activity than did the left SMA ($p = .01$), the left PMA ($p = .02$), the right PMA ($p = .01$), the right MA ($p = .005$) and the right IPA ($p = .05$). The left IPA showed marginally greater changes than the right PMA ($p = .07$) and the right MA ($p = .04$), and the right SPA showed marginally greater changes than right PMA ($p = .06$) and the right MA ($p = .02$).

V. Laterality in the Motor System

The MAs were the only component of the motor system to show consistently and significantly lateralized activation. For example, N was higher in the left than right MA collapsed across repetitive and sequential movements at $p = .0005$, and collapsed across the different rate and force levels at $p = .03$. The SMAs showed greater activation on the left than the right collapsed across the repetitive and sequential movement conditions ($p = .02$), and although asymmetry was in the same direction in all conditions of the rate and force study, the difference here did not approach significance.

DISCUSSION

Repeated study of the same subject indicates that when task parameters are closely controlled, fMRI is a reliable and sensitive method for measuring task-related activation of the human cortical motor system. In nine different sessions activation was detected in virtually the same 8 mm strip of the MA contralateral to the moving fingers. The task-related percent signal increase was similarly consistent, with the standard deviation only 13% of the mean over eight sessions. In one session, however, the percent signal increase was twice the mean of the other eight sessions, and in two sessions activation was noted in cortical motor areas other than the contralateral MA which was equal to or greater than that in the contralateral MA. Given the high level of reproducibility evident in the data set as a whole, it is likely that the changes observed were true physiological changes, and that this study provides evidence of the sensitivity of fMRI to real changes in the way the brain may perform even a very simple task on different occasions. Similar variability is also evident among different individuals doing the same task. For example, the subject illustrated in panels E1 and E2 of Figure 2 failed to show significant SMA activation with slow or fast repetitive movements while the subjects illustrated in panels D1 and F1 both did.

Systematic variation of three basic aspects of movement—rate, force and complexity—led to distinct patterns of increased activity in the cortical motor system. Increasing the rate of tapping was associated with increased activity only in the contralateral MA. This apparently localized motor system response to the increased functional demand associated with increased movement rate contrasted sharply with the generalized and distributed increase in activity associated with increased force and complexity of movement. These last two responses differed from one another in that there was evidence that activity in some component areas was selectively enhanced beyond the generalized increase in activity in association with increased complexity, while no such localized effects were apparent with increased force of movement. With increased complexity of movement, the contralateral SPA, and to a lesser extent the contralateral IPA and the ipsilateral SPA showed greater increases in activity than did other regions.

Fig. 2. Regions of interest (ROI, A-C) and changes in brain activation (D-F) during right-handed tasks of varying resistance (D1-D2, t-map), rate (E1-E2, percent difference map), and complexity (F1-F2, t-map). Numbers in parenthesis indicate slice position along vertical axis (z) of Talairach coordinate system. VCA and VCP refer to lines vertical to anterior commissure and posterior commissure, respectively. Motor system areas are demarcated by color and denoted by numbers: 1-supplementary motor area, 2-premotor area, 3-primary motor sensory area, 4-superior parietal area, and 5-inferior parietal area. R is subject's right hemisphere; L is left hemisphere. In D-F, red-yellow indicates voxels with $t \geq 2$ and blue-purple voxels with $t \leq -2$. Yellow and purple indicate larger absolute values of t. Figures A-C and F1-F2 are from one subject, D1-D2 from a second subject, and E1-E2 from a third subject.

These data add to the existing literature characterizing the response of cortical motor areas to different functional demands. Most significantly, they demonstrate distributed, multi-component increases in activity with two different types of functional demands, thus illustrating integrated, systemic response properties of the cortical motor areas. These integrated responses seemed for the most part to transcend hemispheric boundaries, despite the fact that all movements were unimanual. Only the MAs, and to a lesser extent the SMAs, showed lateralized activation. Within the context of system-wide activation responses, there was also evidence of specialized activation of particular areas. Parietal areas, particularly the SPA, appeared to be selectively activated as the complexity of movements increased. This observation is consistent with the aggregate results of several previous studies, some of which showed SPA activation with relatively complex movements (Dieber et al, 1991; Grafton et al, 1992b), while others using less complex tasks failed to find SPA activation (Fox et al, 1985; Remy et al, 1994).

Activity in the contralateral MA appeared to be particularly sensitive to increases in the rate of movement, as has also been noted in two other studies (Schlaug et al, 1995; Sadato et al, 1996). Both studies also noted increases in SMA activity across the lower range of rates studied; increases in activity as tapping increased from 15 to 30 taps/minute in one study with activity unchanging or decreasing from 30 to 240 taps/minute (Sadato et al, 1996) and increases from 60 to 120 taps/minute with activity unchanging from 120 to 180 taps/minute in the other (Schlaug et al, 1995). Neither study made direct comparisons of the magnitude of rate-dependent changes in the SMA and MA, but nonetheless their data suggest that the absence of rate-dependent changes in the SMA in the present study may have to do with the particular rates compared.

The increase in activation throughout the cortical motor system observed as the force of movement increased also replicates a recent PET study (Dettmers et al, 1995). In that study activation was recorded as subjects tapped at a rate of 60 taps/minute at five different force levels. Blood flow was significantly correlated with force level in areas within the left and right MAs, the left PMA, left SMA and left SPA. It is not clear from either the previous or the present study what the relationship is between this widely distributed cortical response and possible activation of new muscle groups. In the present study the wrist and arm were immobilized in an effort to limit movement to the same muscle group at both force levels. In addition the high force level was individually set to be well below each subject's maximum potential so as to minimize need for additional muscle groups. In the previous PET

study, the researchers were explicitly interested in the cortical systems associated with the natural production of finger movements of different force, and consequently made no effort to stabilize the wrist or arm. Subsequent to the imaging studies, however, EMG was recorded from distal and proximal muscles on both upper extremities, as subjects tapped as they had during the scans. These recordings indicated that at force levels 40% or 60% of maximum capability, activity increased in the proximal arm muscles bilaterally (biceps, deltoid, pectoralis). Thus, increased activation in some brain areas might reflect increased numbers of active muscle groups, while increased activation of other regions might reflect processes involved in integrating multiple muscle groups. Alternatively, spreading cortical activation in the service of increasing the force of movement generated by distal contralateral musculature, might excite projections to other muscles that are not demanded by the force requirements. In any case, it is not possible from either study to draw conclusions about the cortical correlates of increasing the force of contraction by a fixed set of muscles.

Of the three dependent measures used in the statistical analyses, N, the number of voxels showing significant activation, was the most sensitive to the experimental manipulation of movement difficulty. Changes in S, the sum of percent signal increase in clearly activated voxels, simply paralleled changes in N. P, the percent signal change in the entire anatomically defined regions of interest also proved less sensitive than N. This is probably because only approximately 10% of voxels in each area showed clear task-related activation, and this index therefore has a relatively low signal to noise ratio. The sensitivity of this variable may be decreased further by the presence of voxels showing task-related decrease in signal, which, while of potential interest, serve in this context to decrease net signal increase. From the practical point of view, these observations demonstrate the value of using some threshold cut-off to eliminate voxels not showing task-related signal changes before doing region-based quantitative analyses. From the theoretical point of view, significant changes in N and essentially parallel changes in S suggest that the primary response to increasing task demands may be activation of cells that had shown little or no task-related activity at lower levels of task demand, rather than further increasing the activity of tissue already active. Recruitment of new tissue to meet increased functional demand would be consistent with single cell recording data which suggest that networks of cells constitute functional units in a probabilistic rather than dedicated fashion, and can represent the same information or function with different cells at different times (e.g., John, 1972). Activation maps of

individual subjects clearly show the spread of activation as task demands increased, and suggest that, within the anatomic resolution of our method, newly activated areas are usually contiguous with already active areas. Examination of data from individual subjects also suggests interindividual variability in cortical motor system response to the same functional demands.

The major limitation of the present project is that it assessed only two levels of difficulty along each task dimension. It is not clear, therefore, whether the system response changes in character as well as intensity at other points along a given dimension of task difficulty. This shortcoming is most evident in evaluation of rate effects, since only two relatively slow rates were compared. In addition, although findings were statistically reliable, study groups were relatively small, especially in the study of complexity. Careful efforts were made to limit hand and arm movement, but without EMG recording it is not possible to determine the extent of activation of new muscles in more demanding conditions. Finally, the scope of the project was limited to dominant hand function by dextrals and did not consider cingulate, cerebellar or subcortical motor areas. Studies of sinistrals, of non-dominant hand use, of other body movements and of clinical populations will all provide important information about possible system configurations. Consideration of other motor areas will be essential for fuller understanding of the system as a whole.

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