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RAPID PUBLICATION

Functional Imaging of Human Motor Cortex at High Magnetic Field

SEONG-GI KIM, JAMES ASHE, APOSTOLOS P. GEORGOPOULOS, HELLMUT MERKLE, JUTTA M. ELLERMANN, RAVI S. MENON, SEIJI OGAWA, AND KÂMIL UĞURBIL
Center for Magnetic Resonance Research, University of Minnesota Medical School, Minneapolis, Minnesota 55455; Brain Sciences Center, Veterans Affairs Medical Center, Minneapolis, Minnesota 55417; and Biological Computation Research Department, AT&T Bell Labs, Murray Hill, New Jersey 07974

SUMMARY AND CONCLUSIONS

1. We used conventional gradient echo magnetic resonance imaging (MRI) at high field strength (4 Tesla) to functionally image the right motor cortex in six normal human subjects during the performance of a sequence of self-paced thumb to digit oppositions with the left hand (contralateral task), the right hand (ipsilateral task), and both hands (bilateral task).

2. A localized increase in activity in the lateral motor cortex was observed in all subjects during the task. The area of activation was similar in the contralateral and bilateral tasks but 20 times smaller in the ipsilateral task. The intensity of activation was 2.3 times greater in the contralateral than the ipsilateral task.

INTRODUCTION

From the time that the stimulation experiments of Fritsch and Hitzig (1870) and the clinical deductions of Hughlins Jackson (1882) established that the motor cortex was concerned with movements, investigators have devised a variety of methods to elucidate its function, including electrical stimulation, recording the electrical activity of single cells, positron emission tomography (PET), and magnetic resonance imaging (MRI).

The measurement of regional cerebral blood flow initially with radioactive Xenon (Roland et al. 1980a,b) and subsequently by using PET (Fox and Raichle 1986; Roland et al. 1982) has been valuable in elucidating the "where" rather than the "how" of motor function. Early studies (Roland et al. 1980a,b) demonstrated increased blood flow in the contralateral primary motor and somatosensory cortex during simple voluntary movements. For complex sequences of movements, increased activity was observed bilaterally in the supplementary motor area and the lateral premotor cortex. Studies have attempted to determine the motor areas involved in self-initiated and reaction time movements (Deiber et al. 1991) and to investigate the control of proximal and distal arm movements (Colebatch et al. 1991). Because of the relatively low signal changes with PET, data are averaged within subjects and between subjects.

MRI has recently been used to examine human cortical function, noninvasively and without the use of exogenous contrast agents (Bandettini et al. 1992; Kwong et al. 1992; Ogawa et al. 1992). The basis for this technique is that deoxyhemoglobin acts as an endogenous paramagnetic contrast agent (Ogawa et al. 1990b; Turner et al. 1991) and therefore changes in its local concentration lead to alterations in the T_2^* weighted magnetic resonance image signal (Ogawa et al. 1990a,c; Thulborn et al. 1982). Neural activation within the cerebral cortex leads to a large increase in blood flow without an increase of similar magnitude in oxygen extraction (Fox and Raichle 1986), which in turn causes a decrease in the capillary and venous deoxyhemoglobin concentrations producing an increase in the T_2^* weighted magnetic resonance signal. The technique has been successfully applied to functionally image the human visual cortex at high magnetic field of 4 Tesla (4 T) (Ogawa et al. 1992) and both visual (Kwong et al. 1992) and motor cortex (Bandettini et al. 1992) at low magnetic field strength of 1.5 Tesla (1.5 T).

In this study we used high magnetic field strength (4 T), which gives higher signal-to-noise ratio and better spatial resolution to functionally image the human motor cortex.

METHODS

Subjects

Six healthy human volunteers participated in these experiments. Five of the subjects were right-handed, and one (*subject 6*) was ambidextrous. Handedness was quantitatively assessed by using the Edinburgh Inventory (Oldfield 1971). They were recruited from the academic environment of the University of Minnesota Medical School.

Task

Subjects were instructed to make repetitive opposition movements of the thumb and each of the remaining four fingers while exerting moderate pressure at each contact. The time to start and stop the movements was indicated to the subjects through a speaker. There were three sets of movements in an experiment ("experimental conditions"): movements with the right (ipsilateral task), left (contralateral task), and both hands (bilateral task).

Magnetic resonance imaging

All MRI experiments were performed on a 4 T whole-body system (Sisco, Sunnyvale, CA and Siemens, Erlangen, Germany) with actively shielded gradient coil. The home-built MR rf antenna used an anatomically fitted parallel two-loop surface coil (14×18 cm^2). The experiments were approved by the institutional review board of the University of Minnesota Medical School. Rf power deposition was kept below the FDA specific absorption rate guidelines.

To locate the motor cortex (i.e., precentral gyrus), multislice, axial T_1 weighted images were acquired by using refocused fast low-angle shot (FLASH) imaging technique (Haase et al. 1986) based on a magnetization prepared rapid gradient recalled echo

sequence [echo time (TE) = 8 ms, repetition time (TR) = 13 ms, and 0.5-cm slice thickness] with 128 phase-encoding steps segmented in four blocks of 32 interleaved steps. An adiabatic inversion pulse followed by a delay of 1.2 s was used to generate T_1 weighted precontrast images in which white matter signal is enhanced. An oblique plane between axial and sagittal planes was defined along the central sulcus for T_2^* weighted images; in the oblique plane, the motor cortex and somatic sensory cortex were located anterior and posterior to the central sulcus, respectively. In this study, the right hemisphere was used for all studies. Data were collected as single slices. Consecutive single-slice gradient echo oblique images were acquired with a two-scan average by using a T_2^* weighted refocused FLASH pulse sequence; typically 15 control, 10 task, and 15 recovery images were collected. Typical acquisition parameters for T_2^* weighted imaging were TE = 35 ms, TR = 53 ms, inter-scan delay = 2 s, and total acquisition time = 2 × 5.4 s. 128 complex points in readout domain and 64-phase encoding steps were recorded in a 16 × 13 cm^2 field of view (FOV), i.e., in-plane pixel resolution 1.3 × 2.0 mm^2 with 1.2-cm slice thickness. The acquired data were zero-filled to 256 × 256 then Fourier-transformed. All subsequent analysis, including the functional maps, used 256 × 256 pixel points in a 16 × 13 cm^2 FOV.

Data analysis

A percent change (PC) map of the signal intensity due to activation was calculated as follows. The difference between averaged baseline and averaged task-induced image intensities was calculated and normalized by the corresponding baseline image intensity on a pixel-by-pixel basis. The baseline image intensity was obtained by averaging the premovement and recovery images. The Student's t test was used to compare the baseline and movement-related image intensity at a probability level of $P < 0.0001$; only pixels with such a statistically significant activation were shown in the PC map. The PC map was overlaid on a T_1 weighted anatomic image to locate the activation site. We located the maximum intensity change in the precentral gyrus of the PC map. Then an iso-contour area was demarcated around the point so that all points within this area had a change of >13.5% of the maximum change. This value was used because, in a normal distribution, ~95% of the points would be included within such an iso-contour area. Finally, the pixel PC values from all these areas were pooled and an average PC intensity per pixel was computed. The time course of the image intensity in the activated area was obtained by integrating image intensity of the activated pixels and dividing by the number of pixels. For each image, we calculated the area of activation as well as the distance from the midline to the location of the point of maximum activation. Standard statistical analyses (Snedecor and Cochran 1980) were used to analyze the data.

RESULTS

General

A localized activation in the lateral part of the motor cortex was observed in all subjects. A PC map is shown (see Journal cover), and examples of the time course of the activation in three subjects are shown in Fig. 1. There was a brisk increase in signal intensity during the task. In general, the rise time of the activation from the background level was within the time resolution of image acquisition employed in this study (10.8 s). Three experimental variables

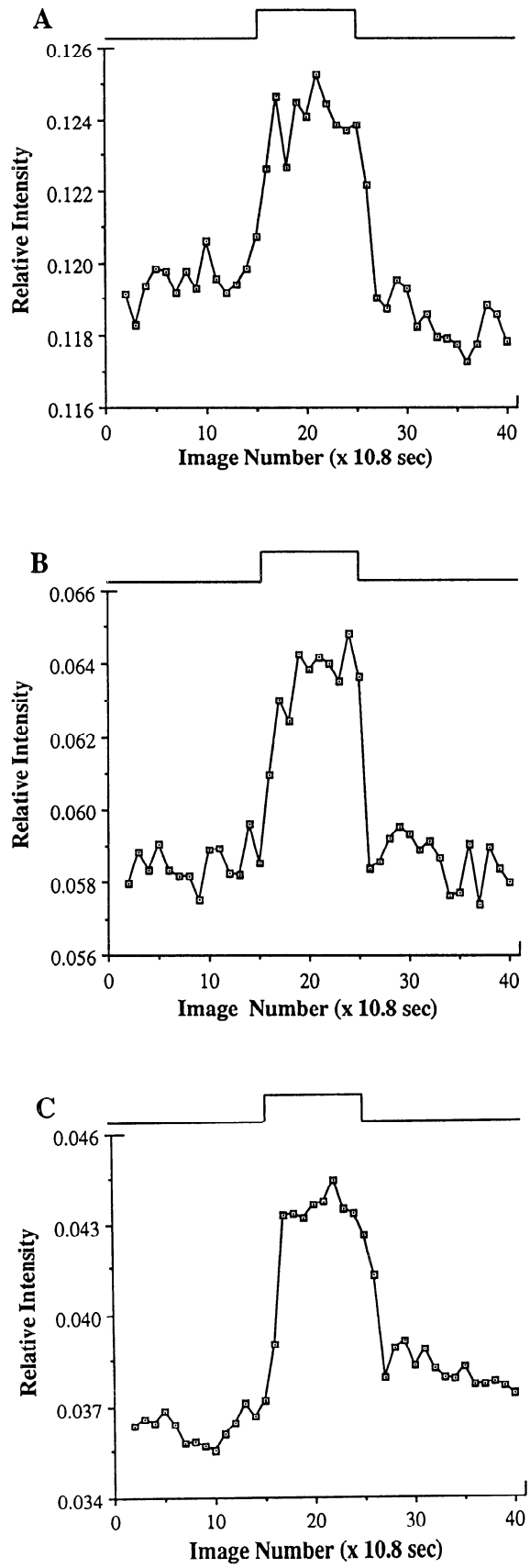

FIG. 1. Time course of image intensity before, during, and after contralateral finger movements in three subjects (2, 4, and 3) represented respectively in A, B, and C. Top trace in each time course indicates task onset.

were analyzed quantitatively: surface area, intensity, and localization of the activation.

Surface area of activation

The surface area of activation in the right motor cortex for each one of the six subjects and each of the three conditions (contralateral, ipsilateral, and bilateral tasks) is shown in Table 1. Statistical analyses were made on log-transformed data because we were interested in proportional rather than absolute comparisons. The area of activation was similar in the contralateral and the bilateral tasks (t-test, not significant) but was 20 times smaller in the ipsilateral task (t-test, $P < 0.0001$ and $P < 0.006$ for contralateral versus ipsilateral, and bilateral vs. ipsilateral comparisons, respectively). In the ambidextrous subject the activation in the ipsilateral task was much higher than that observed in the right-handed subjects and was only two times smaller than the contralateral or bilateral activation.

Intensity of activation

Within subject comparisons were carried out for each pair of conditions as follows. Each area of activation consisted of a number of pixels that were contained within the iso-intensity contour area within the precentral gyrus (see METHODS). The mean and SD of the intensity of activation per pixel for each subject and condition are given in Table 2. Pairwise statistical comparisons in all subjects showed the following *1*) activation was higher in the contralateral rather than the ipsilateral task, *2*) activation was higher when both hands moved than when only one hand moved, and *3*) all pairwise comparisons were statistically significant (t-test, $P < 0.001$). These effects were observed in all subjects.

Relation between surface area and mean intensity of activation

There was a small positive correlation ($r = 0.236$, $n = 14$) between the surface area and the mean intensity of activation; however, it was not statistically significant. The apparent independence between these two variables allows the testing of the null hypothesis that two particular conditions have equal means for both variables. This hypothesis was tested by computing Hotelling's T^2 multivariate statistic. It was found that the contralateral vs. ipsilateral, and the ipsilateral vs. bilateral tasks differed significantly ($P = 0.0006$ and 0.0011, respectively), but the contralateral did not differ from the bilateral task ($P = 0.9$).

TABLE 1. *Surface area (cm^2) of activation of the right motor cortex for each subject and condition*

Subjects (RH)	Left Hand (contralateral)	Right Hand (ipsilateral)	Both Hands (bilateral)
1	0.835	0.022	1.209
2	1.631	—	1.328
3	0.720	0.152	—
4	1.409	0.032	—
5	1.276	0.032	—
Mean	1.174	0.060	1.269
N	5	4	2
AMB			
6	1.073	0.498	1.209

RH, denotes right-handed subjects; AMB, one ambidextrous subject.

TABLE 2. *Intensity of activation per pixel (percent increase over the background) for each subject and condition*

Subject		Left Hand (contralateral)	Right Hand (ipsilateral)	Both Hands (bilateral)
1	Mean	5.050	2.756	6.789*
	SD	1.801	0.888	2.366*
	N	263	7	1,143*
2	Mean	4.160		4.912†
	SD	1.651		2.100†
	N	334		544†
3	Mean	21.589	5.410	
	SD	12.600	1.630	
	N	227	48	
4	Mean	8.537	4.607	
	SD	2.580	0.693	
	N	444	10	
5	Mean	5.712	3.139	
	SD	2.100	0.875	
	N	402	10	
6	Mean	11.171	8.946	14.044‡
	SD	3.890	4.430	6.899‡
	N	293	136	2,237‡

N, number of pixels in the iso-intensity area. [Number of activated pixels was calculated from the 256 × 256 functional map (see METHODS).] *Pooled data from three experiments. †Pooled data from two experiments. ‡Pooled data from six experiments.

Localization of activation

All areas of activation were within the precentral gyrus. The anteroposterior coordinate of the maximum for this activation could not be easily determined due to variations in the cortical slice from subject to subject. However, a distance from the midline could be reliably calculated. This distance for each subject and condition is given in Table 3. The mean distances were very similar between conditions and did not differ significantly (t-test).

TABLE 3. *Distance (cm) from the midline to the maximum activation for each subject and condition*

Subject	Left	Right	Both
1	4.27	4.33	4.13
2	3.41		3.82
3	3.38	3.49	
4	3.41	3.31	
5	3.04	2.40	
6	3.76	3.33	3.46
Mean	3.55	3.37	3.80
SD	0.422	0.686	0.335
N	6	5	3

The distance from the midline was measured as the perpendicular distance from the maximal activation to the interhemispheric fissure.

DISCUSSION

Methodological considerations

The exact physiological mechanism of T_2^* weighted image signal changes has not yet been quantitatively determined. However, it is recognized that susceptibility changes are closely related to blood flow, venous blood volume, and blood oxygen consumption rate. Based on PET studies during somatosensory stimulation, Fox and Raichle (1986) reported that blood flow in the somatosensory cortex increased by 29%, whereas oxygen consumption increased only 5%. The mismatch between blood flow and oxygen consumption changes leads to an increased concentration of oxygenated blood and a concomitant decrease in deoxyhemoglobin. The change in the deoxyhemoglobin level is related to the T_2^* signal changes seen with MR. This relation however, is complicated, and depends on several parameters including blood volume, magnetic field strength, diffusion distance and echo time. If we assume on the basis of PET data, that a particular activation leads to 29% blood flow increase, 5% oxygen extraction increase, and 7% blood volume increase (Fox and Raichle 1986) in the presence of normal hematologic parameters, then we would expect about a 3% increase in MR signal by using a 35 ms echo time (Ogawa et al. 1992). The magnitude of signal change in this study and in Ogawa et al. (1992) suggests a much greater increase in blood flow with motor tasks than that predicted on the basis of studies using PET, or a greater cerebral blood volume than assumed in these calculations.

Gradient echo images at 1.5 T magnetic field have been used to study functional changes in the motor cortex associated with finger movement (Bandettini et al. 1992; Kwong et al. 1992). These studies showed that the signal intensity changes associated with the tasks were from 2 to 4%, the task-induced signal-to-noise ratio was typically 2:1, and the spatial in-plane resolution was $\geq$3 mm with 26-mm slice thickness (Bandettini et al. 1992). Under high magnetic field strength (4 T) the signal changes detected in gradient echo images secondary to neuronal activation will be amplified, as the magnetic susceptibility induced alterations in $1/T_2^*$ contain both linear and quadratic terms with respect to magnetic field strength (Menon et al. 1992). This has already been demonstrated in the visual cortex using 4 T (Ogawa et al. 1992) in which the signal changes were 3 to 6 times greater than those seen at low field strength (Kwong et al. 1992). The average signal increase in the motor cortex at 4 T is 2–4 times greater and the signal-to-noise ratio (see Fig. 1) is better than that at 1.5 T (Bandettini et al. 1992; Kwong et al. 1992). Moreover the high spatial resolution afforded by 4 T (1.3 $\times$ 2.0 mm) allows for a close correlation between the functional maps and the anatomic detail seen in the T_1 weighted MRI, in contrast to the low resolution areas seen with 1.5 T images. Although the temporal resolution (2–3 s) with 1.5 T echo planar imaging (EPI) is better than in the current study, the addition of EPI and the use of single scan imaging should significantly improve our results.

Functional MRI is noninvasive and offers several advantages over conventional PET studies: the magnitude of signal change within a subject is sufficient to render intersubject averaging unnecessary, and the location of the stimulus-induced change in activation can easily be identified anatomically (see Journal cover and Fig. 1).

The results obtained serve to confirm the validity of the methods used. There was consistency among the subjects with respect to activation in the task, including the timing, surface area and mediolateral localization of the area of activation. Moreover, the within subject pairwise comparisons were also remarkably consistent among subjects. We discuss these findings separately below.

Area of activation

The area of motor cortex activated in the task was small compared with a rather large area of the motor cortex from which hand movements can be elicited by electrical stimulation based on published studies (Kwan et al. 1978; Leyton and Sherrington 1917; Penfield and Boldrey 1937; Waters et al. 1990). Recent work using electrical microstimulation has shown that muscles are multiply represented in the motor cortex (Gould et al. 1986; Kwan et al. 1978; Waters et al. 1990). However, even early studies had shown a great deal of instability in the responses to electrical stimulation (Graham Brown and Sherrington 1912; Leyton and Sherrington 1917): the responses elicited from stimulation of a particular point could be facilitated, extinguished, or changed. Therefore, it is important to know the extent of activation of the motor cortex, under conditions of physiological performance. Indeed, the results of the present study showed that this area is relatively small. This finding could reflect the limited repertoire of movements performed in our task, even though these movements involved all the fingers and therefore engaged many muscles. This explanation would support Hughlins Jackson's view (Jackson 1882) summarized succinctly by Walshe (1943), namely that "the cortex represents performances and not performing parts." This idea is also supported by the fact that motor cortical damage in patients with stroke leads to impairment of movements rather than paralysis of specific muscles; in some cases the muscular strength may be normal but there is a loss of dexterity because of the inability to perform particular movements or combinations of movements.

Ipsilateral representation

There is anatomic evidence that ~10–15% of fibers in the lateral cortical spinal tracts of humans (Nyberg-Hansen and Rinvik 1963) and monkeys (Glees and Cole 1952; Yakovlev and Rakic 1966) are uncrossed. The ipsilateral pathway seems to be of functional significance. In a simple motor task involving distal muscles Tanji et al. (1988) documented changes in ~8% of ipsilateral precentral cortical neurons. The responses were identical to those of movement related neurons on the contralateral side. By using a relatively uncontrolled movement, Evarts (1966) documented ipsilateral changes of similar magnitude. Aizawa et al. (1990) identified an area of the motor cortex from which ipsilateral in addition to contralateral digit muscle activity was elicited by using intracortical microstimulation. Following lesions of *area 4* in the monkey Glees and Cole (1952)

noted a quantifiable decrease in grip strength on the ipsilateral side, though this returned to normal levels within a few weeks. Brodal (1973) in describing symptoms associated with his own stroke noted impairment of hand writing on the side ipsilateral to the lesion. A decrease in muscle strength (Colebatch and Gadevia 1989) and impairment of complex movements (Jones et al. 1989) on the ipsilateral side has been documented in patients with hemiplegia. Finally ipsilateral pathways are involved in the functional recovery after lesions of the motor cortex (Passingham et al. 1983; Twitchell 1951) or the pyramidal tract (Chapman and Wisendanger 1982; Hepp-Reymond et al. 1974; Kucera and Wisendanger 1985).

Early PET studies (Roland et al. 1980a,b) failed to show any increase in activity in the ipsilateral motor cortex. A more recent PET study on patients with hemiplegia documented an increase in ipsilateral activation when movements were performed with the affected hand; no ipsilateral increase was found during movements of the normal side (Chollet et al. 1991). Colebatch et al. (1991), using PET, described an increase in the activity of ipsilateral sensorimotor cortex while normal subjects moved the shoulder but not during hand movements. We have documented that ipsilateral activation occurs in the motor cortex during distal hand movements although it is 20 times less than that observed with contralateral hand movements. It is possible that this increase in activity was related to inadvertent movement by the subject on the contralateral side. This is not likely given the consistency of the finding and the explicit instructions to all subjects to move only the body parts involved in the task. Moreover, the observation that in an ambidextrous subject the area of activation ipsilaterally was much greater, in fact only 2.3 times smaller than the contralateral activation, suggests that ipsilateral activation does occur and that it may actually vary with the degree of use of the corresponding hand. This is consistent with recent data in the monkey, which showed an expansion of the cortical area from which distal forelimb movements could be elicited by microstimulation, following training of the animal in a task that involved hand and finger manipulations (Milliken et al. 1992).

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Address for reprint requests: S.-G. Kim, Center for Magnetic Resonance Research, University of Minnesota Medical School, Minneapolis, MN 55455.

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