

Differential Fronto-Parietal Activation Depending on Force Used in a Precision Grip Task: An fMRI Study

H. HENRIK EHRSSON,^{1,2} ANDERS FAGERGREN,¹ AND HANS FORSSBERG¹

¹Motor Control Laboratory, Department of Woman and Child Health and ²Division of Human Brain Research, Department of Neuroscience, Karolinska Institutet, 171 77 Stockholm, Sweden

Received 13 October 2000; accepted in final form 9 February 2001

Ehrsson, H. Henrik, Anders Fagergren, and Hans Forssberg. Differential fronto-parietal activation depending on force used in a precision grip task: an fMRI study. *J Neurophysiol* 85: 2613–2623, 2001. Recent functional magnetic resonance imaging (fMRI) studies suggest that the control of fingertip forces between the index finger and the thumb (precision grips) is dependent on bilateral frontal and parietal regions in addition to the primary motor cortex contralateral to the grasping hand. Here we use fMRI to examine the hypothesis that some of the areas of the brain associated with precision grips are more strongly engaged when subjects generate small grip forces than when they employ large grip forces. Subjects grasped a stationary object using a precision grip and employed a small force (3.8 N) that was representative of the forces that are typically used when manipulating small objects with precision grips in everyday situations or a large force (16.6 N) that represents a somewhat excessive force compared with normal everyday usage. Both force conditions involved the generation of time-variant static and dynamic grip forces under isometric conditions guided by auditory and tactile cues. The main finding was that we observed stronger activity in the bilateral cortex lining the inferior part of the precentral sulcus (area 44/ventral premotor cortex), the rostral cingulate motor area, and the right intraparietal cortex when subjects applied a small force in comparison to when they generated a larger force. This observation suggests that secondary sensorimotor related areas in the frontal and parietal lobes play an important role in the control of fine precision grip forces in the range typically used for the manipulation of small objects.

INTRODUCTION

The precision grip between the tips of the thumb and the index finger has developed in primates for the manipulation of small and delicate objects (Napier 1961). It requires independent finger movements (Lawrence and Kuypers 1968; Passingham et al. 1983; Porter and Lemon 1993) and a sophisticated control of the small fingertip forces applied to the surface of the object (Johansson 1996; Johansson and Westling 1984). An illustrative example of this control is when picking a raspberry—too much force will crush the raspberry, too little and it will slip away.

The precision grip configuration is highly dependent on cortical control (Passingham 1993; Porter and Lemon 1993). In a recent functional magnetic resonance imaging (fMRI) study, we examined the cortical areas activated when healthy subjects used a precision grip to apply well-controlled time-variant grip

forces to a fixed object under isometric conditions (Ehrsson et al. 2000). This precision grip task was associated with bilateral activity in a set of frontal and parietal areas in addition to the primary motor cortex (M1). Several of these areas, i.e., the bilateral ventral premotor cortex (PMV, also engaging area 44), the rostral cingulate motor area (CMAr), the supramarginal cortex, the ventral lateral prefrontal cortex, and the right intraparietal cortex, were either recruited exclusively or showed augmented activity when the subjects used the precision grip as opposed to when they used a palmar power grasp to perform a similar manipulative task. These differences could reflect differences in the hand posture or higher demands imposed when controlling small forces at the fingertip-object interface.

In the present study, we examined whether the cortical control of small precision grip forces differs from the control of large forces when the same grasp is used. In particular, we test the hypothesis that some of the cortical regions associated with precision grips would be more active during the employment of small fingertip forces than when generating large grip forces. This hypothesis is grounded on single-cell recordings in non-human primates that have demonstrated that a larger number of corticospinal neurons modulate their discharge rate for forces in the small force range than for larger forces (Evarts et al. 1983; Hepp-Reymond et al. 1978) and that some populations of neurons in frontal motor areas [M1, PMV, and primary somatosensory cortex (S1)] increase their rate of firing as the precision grip force is decreased (i.e., there is a negative correlation with force) (Hepp-Reymond 1988; Hepp-Reymond et al. 1994; Maier et al. 1993; Wannier et al. 1991). There are also studies in humans that indicate that the control of fine precision grip forces is dependent on cortical mechanisms that can be impaired during various neurological conditions (e.g., cerebral palsy, focal dystonia, stroke, attention deficit/hyperactivity disorder) (Eliasson et al. 1992; Hermsdörfer and Mai 1996; Odergren et al. 1996; Pereira et al. 2000).

We used fMRI to measure the cortical activity when healthy subjects performed a precision grip task fulfilling one of two force conditions: a small grip force (3.8 N), representative of the forces that are typically used when manipulating small objects with precision grips in everyday situations (comparable to lifting a cup of coffee), or a large grip force (16.6 N) that

Present address and address for reprint requests: H. H. Ehrsson, Neurophysiology Unit, Dept. of Women and Child Health, Astrid Lindgren Hospital, 171 76 Stockholm, Sweden (E-mail: Henrik.Ehrsson@neuro.ki.se).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

represents a somewhat excessive force in this respect (comparable to lifting a 1.5-l soda bottle).

METHODS

Subjects

Six healthy male subjects (21–28 yr) participated in the study. They were all naive with regard to the specific purposes of the experiments. All subjects were right-handed (Oldfield 1971) and all had given their informed consent. The Ethical Committee of the Karolinska Hospital had approved the study.

General procedure and task

The subjects performed a precision grip task with two force conditions. A baseline condition in which the hand was relaxed was also included. The subjects rested comfortably in a supine position on the bed in the magnetic resonance (MR) scanner. The room was dark, and the subjects were instructed to keep their eyes closed. All subjects wore headphones to reduce noise and to present auditory cues. The extended right arm was oriented parallel to the trunk and supported up to the radial side of the hand to minimize movement (Fig. 1B). The subjects grasped a nonmagnetic immovable test object between the pulps of the thumb and the index finger (Fig. 1A). The test object had flat parallel contact surfaces 30 mm apart (covered with sandpaper; grit size, 180). Optometric transducers in the object allowed measurements of the grip forces normal (perpendicular) to the contact surfaces. The grip force was represented as the mean of the normal forces measured at the two grasp surfaces (400 samples/s). The data were stored and analyzed using the SC/ZOOM data-acquisition system (Physiology Section, IMB, University of Umeå, Sweden).

To perform the precision-grip task, the subjects applied forces normal to the contact surfaces (grip force) cyclically, following the pace of a metronome that generated click sounds at 0.67 Hz. They increased the force, then maintained the grip force until the next click of the metronome (this interval is referred to as the static plateau period), at which point they first released the grip force completely and then immediately started to increase it again (thereby performing a complete force cycle). When they reached the force of 2 N (*small* force condition) or 16 N (*large* force condition), they received a brief weak vibrotactile pulse delivered tangentially to the contact surfaces (of 10-ms duration and with a force of less than 0.5 N). The subjects then applied a self-selected static grip force slightly above this force threshold. They were asked to reproduce the same force across the force cycles and not to generate forces that greatly exceeded the force threshold. Figure 1, C and D, illustrates the grip force profiles together with the auditory and tactile cues for the grip task for the two forces. During the baseline condition (*baseline*), the subjects held the thumb and index finger in weak contact with the contact surfaces almost without applying any grip force. They received the tactile pulses and heard the metronome sound (0.67 Hz) through the headphones exactly as they had in the grip task.

We selected the lower force level so that it would be representative of the small forces that are typically used when manipulating small objects with precision grips in everyday situations. The level of the larger force was chosen to represent a somewhat excessive precision grip force in this respect. A constraint for the large force level was that it had to be employed without muscular fatigue, general effort, or impaired performance. Pilot experiments showed that a target force of 16 N was appropriate.

Before the scanning commenced, the subjects practiced the grip task at both force levels for 15 min until they produced the requested grip force profiles. After the training, the subjects were able to keep up a conversation while performing the task, which suggests that it had been well learned.

After the scanning, we measured the grip-force during maximal

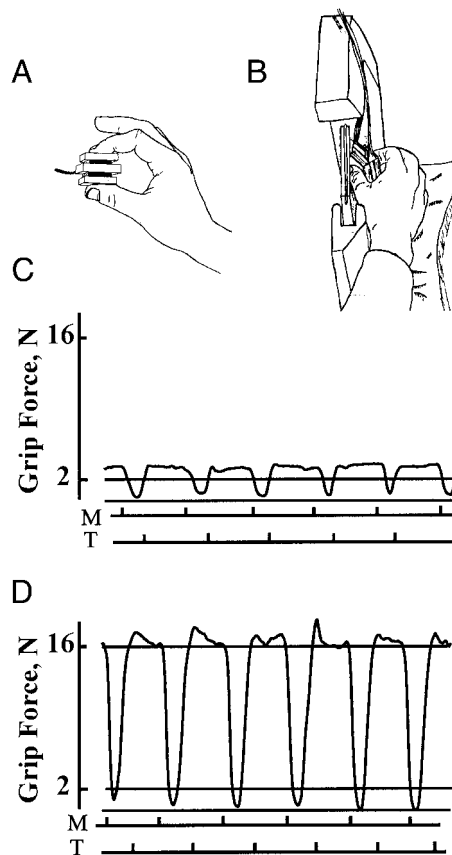


FIG. 1. The precision grip task. The same posture of the hand was adopted in all conditions (A); a small handle was grasped between the pulps of the index finger and the thumb with the arm being supported up to the radial side of the hand so that force could be generated practically without movement of the digits, wrist, or arm (B). C and D: a representative force recording from 1 subject while he performed the precision grip task in the small force condition (C) and in the large force condition (D). Note that the same time course of grip forces was generated in both conditions, only the force was different. In the task (for both force levels), a weak brief vibration was delivered through the handle to signal that the force of 2 N (in small) or 16 N (in large) had been reached (T). The subjects then applied a self-selected static grip force slightly above this force threshold. The pace of the force cycles followed metronome beats (M). For details, see METHODS.

voluntary contraction (MVC) as the subjects grasped a standard dynamometer (cylindrical handle, 30-mm diam) with a precision-grip (Nordenskiöld and Grimby 1993). A surface EMG (Myo115-electrodes with in-built 2000X preamplifiers, Liberty Technology, Hopkinton, MA) was recorded in four subjects while they performed the precision-grip task at the two force levels outside the MR scanner. We recorded from the right biceps-brachii and deltoideus to check for possible recruitment of proximal muscles of the arm, and the left 1DI and AbPB to check for nonvoluntary synergistic movements of the nonparticipating hand.

Kinetic analysis

The force data were analyzed using the ZOOM software (Department of Physiology, University of Umeå). Force cycles in which the subjects did not generate the requested time course for the forces were defined as incorrect. We analyzed the mean grip force and the variability of the grip force during the static plateaus of each grip cycle (mean \pm SD for data pooled across subjects; see Fig. 1, C and D). The static plateau was defined as the period between the peak grip force after the dynamic force increase to the beginning of the force relax-

ation (defined as the local minima of the 2nd derivative of the grip force).

To measure the accuracy of the force generation, we analyzed the variability of the plateau grip force across force cycles (SD of the grip force for data pooled across subjects). To compare variability of the grip force in the two force conditions, we determined the coefficient of variation (i.e., the ratio SD/mean).

Brain imaging

fMRI was conducted on a 1.5 T scanner (Signa Horizon Echospeed, General Electric Medical Systems) equipped with a head-coil. We collected gradient-echo, echo-planar (EPI) T2*-weighted image volumes with blood oxygenation level-dependent (BOLD) contrast (Kwong et al. 1992; Ogawa et al. 1992). The scanning parameters were: echo time (TE) = 50 ms; field of view (FOV) = 22 cm; matrix size = 64×64 ; pixel size = 3.4×3.4 mm, and flip angle = 90° . Twenty contiguous axial slices of 3.4-mm thickness were collected in each volume. We selected slices from the dorsal surface of the brain to cover the frontal and parietal lobes. The cerebellum, brain stem, and part of the basal ganglia were outside the field of view. A plastic bite bar restricted head movements. A high resolution, three-dimensional gradient echo T1-weighted anatomical image volume of the whole brain was collected (3D-SPGR).

Functional-image volumes were collected in six separate runs, and for each run, a total of 104 volumes was collected. During each run, volumes were acquired continuously every 5000 ms (TR = 5 s) while the subjects performed the grip task or relaxed with the hand (baseline condition). The grip task was performed in periods of 25 s (5 volumes being collected in this time) alternated with baseline periods of 25 s. During each grip period, the subjects performed one force condition, and across periods, the two force conditions alternated. During each force condition an equal number of volumes was collected. To allow for T1 equilibration effects, four volumes were recorded immediately before each run; these were neither stored nor analyzed.

Data analysis and image processing

We used the publicly available software SPM-96 to analyze the functional images (Wellcome Dept. Cognitive Neurology, London, <http://www.fil.ion.ucl.ac.uk/spm>). The volumes were realigned, co-registered to each individual anatomical T1-weighted image (3D-SPGR) and normalized to the stereotactic coordinate system of Talaraich and Tournoux (1988) using the Montreal Neurological Institute (MNI) template brain (Friston et al. 1995a). Then the images were spatially smoothed with an isotropic Gaussian filter of 8 mm full width at half-maximum (FWHM) and temporally smoothed with a Gaussian kernel with a FWHM of 2.83 s. To increase the sensitivity of the analysis and detect activity that was present across the subjects, we analyzed the functional images from the six subjects as a group (fixed effect model). We estimated the task specific effects using the general linear model (GLM) with a delayed boxcar wave form at each voxel (Friston et al. 1995b,c; Worsley and Friston 1995). The fMRI data corresponding to each run were modeled with regressors for the conditions and the mean value using the standard model implemented in SPM-96. A high-pass filter (cutoff frequency, 0.005 Hz) was used to remove low-frequency drifts and fluctuations of the signal, and proportional scaling was applied to eliminate the effects of global changes in the signal (Holms et al. 1997). The significance of the condition specific effects was assessed using Z statistics for every voxel from the brain, and these sets of Z values were used to create statistical images. Linear contrasts between the different conditions were used to create these statistical images; these were arbitrarily thresholded at a Z value of 3.09. From these statistical images (known as activation maps), we report peaks (or local maxima) of activity that, when corrected for multiple comparisons for the whole brain volume, corresponded to $P < 0.05$ on the basis on a test of peak height (Friston

et al. 1995c). All clusters that are shown in the figures and described in the text were also significant on the basis of a test for the extent of the cluster (Poline et al. 1997). To localize activity that reflected the generation of the precision grip task at both force levels we defined the contrast (small – baseline + large – baseline). This tests the main effect of the precision grip task. We also examined the contrasts (small – baseline) and (large – baseline). To localize changes in activity that specifically reflected whether a small or large force was applied, we used the contrasts (small – large) and (large – small), respectively. For the brain regions that showed a force specific activation (i.e., activity detected when we contrasted the 2 force conditions), we only report voxels that were active when the force condition was compared with the baseline condition (at $Z > 3.09$ at each voxel). By this mean, we focused on brain areas that showed stronger activity while the hand was grasping than when it was relaxed. This excluded the possibility that differences between the tasks merely reflected different degrees of deactivation.

To exclude the possibility that the results obtained in the group analysis (fixed effects model) were biased by one or two subjects only exhibiting very strong effects (Friston et al. 1999), we examined the activation patterns of each individual subject in a descriptive analysis (reported in Table 2). We probed for increases in BOLD contrast signals close to (within a sphere of 12-mm radius; corresponding to the FWHM of the smoothness of the statistical images as determined using SPM96) or at the location of the most relevant peak activations from the group analysis. We concluded that the results obtained in the group analysis were representative of the observations made for individual subjects (see RESULTS).

Anatomical definitions and localizations

The anatomical localizations of the activations were related to the major gyri and sulci that were identifiable from an average image generated from normalized T2*-weighted images from each of the six subjects.

We used the terminology of Roland and Zilles (1996b) for the functional areas of the cortical motor system, and we used the European Computerized Human Brain Data Base (ECHBD; Div. Human Brain Research, Stockholm) (Roland and Zilles 1996a) to define the location and extent of M1, S1, area 45, and area 44 in the standard anatomical space. Arbitrary criteria were used for PMV, dorsal premotor cortex (PMD), supplementary motor area (SMA), and the cingulate motor areas (CMAs). The ECHBD is a digital three-dimensional brain atlas in which representations of microstructurally defined cytoarchitectural areas from 10 postmortem brains are available in the standard anatomical format. The methods used for the anatomical delineation (Amunts et al. 1999; Geyer et al. 1996, 1999), spatial transformations (Geyer et al. 2000; Schormann and Zilles 1998), and generation of population maps of these cytoarchitectural areas have been described in detail elsewhere (Roland and Zilles 1998; Roland et al. 1997) (SPM was used to match the ECHBD to the MNI space). M1 was defined as the voxels where at least 3 of 10 post mortem brains (30% population map) had their area 4a or 4p; S1 was defined as the 30% population maps of areas 3a, 3b or 1 (we do not differentiate between different cytoarchitectural areas within M1 or S1 because of the limited effective resolution of the statistical images from the group analysis). Areas 44 and 45 were also defined as the 30% population maps of these areas. By the SMA, we mean the cortex rostral to area 4a on the medial side of the hemisphere above the cingulate sulcus. The rostral border of the SMA was defined to be in the vertical plane at $y = +16$ (Buser and Bancaud 1967; Roland and Zilles 1996b). Activations located in the SMA posterior to $y = 0$ probably correspond to the classical SMA (or SMA-proper) (Picard and Strick 1996; Roland and Zilles 1996b). The lateral premotor cortex, divided into a dorsal (PMD) and a ventral (PMV) portion, is located rostral to lateral area 4a (Geyer et al. 1996; Roland and Zilles 1996b). The rostral border of the PMD is not known. The PMV was defined as the cortex

posterior to area 44 and anterior to area 4a, i.e., the tentative location of the ventral part of area 6. The border between the PMD and the PMV was defined as a horizontal plane at $z = +45$. The CMAs refer to the cortex lining the cingulate sulcus. Their preliminary parcellation into a rostral part (CMAr) and a caudal part (CMAc) were described in Roland and Zilles (1996b).

RESULTS

Behavioral performance

In more than 99% of the force cycles, all subjects performed the precision-grip task according to the instructions at both force levels (small and large). There was no difference in the number of correct force cycles between the force conditions.

In the small force condition, the mean grip force during the plateau phase was 3.81 ± 0.28 N (mean \pm SD for data pooled across subjects). In the large force condition, it was 16.6 ± 1.21 N.

For both conditions of the grip task, the variability of the grip force during the static plateau period across force cycles was relatively low, which indicates regular and consistent performance of both tasks. There was no difference in the

coefficient of variation (SD/mean) of the plateau grip force across force cycles in the two conditions (7.3% in both force conditions). Thus the accuracy of the force production was similar for the two force levels.

The mean of the maximal voluntary contraction (total grip force MVC) was 73 N (range: 58–96 N) for the precision grip. Thus the force production was performed in the lower 40% range of the MVC. The surface EMG showed no consistent activity in the proximal muscles of the right arm (biceps and deltoideus) or in the first dorsal interosseous muscle (1DI) or abductor pollicis brevis muscle (AbPB) muscles of the left hand during any of the tasks.

Brain activations

PRECISION GRIP TASK VERSUS BASELINE CONDITION. The regions of the brain with stronger activity when the subjects performed the precision grip task at both force levels (main effect of the precision grip task) compared with the baseline condition (large – baseline + small – baseline) are shown in Table 1 and Fig. 2. The cerebellum, the brain stem, and the lower parts of the basal ganglia and thalamus were outside the field of view.

TABLE 1. Precision grip task versus baseline (main effect)

| Anatomical Region (functional/cytoarchitectural area) | Talarach Coordinates (Montreal Neurological Institute) | | | | | |
|---|--|-----|----|--------------|------------------|------------------|
| | x | y | z | Peak Z score | Small – Baseline | Large – Baseline |
| Small – Baseline + Large – Baseline | | | | | | |
| Left hemisphere | | | | | | |
| Left central sulcus, M1/S1 | –36 | –20 | 48 | 9.75 | 9.07 | 9.77 |
| Superior frontal gyrus, SMA* | 0 | 0 | 48 | 9.09 | 8.92 | 8.62 |
| Left inferior part of the precentral gyrus, PMV | –64 | 0 | 16 | 8.13 | 7.92 | 7.39 |
| Left lateral parietal operculum | –48 | –32 | 20 | 8.02 | 7.01 | 8.00 |
| Left putamen | –24 | 0 | 8 | 7.95 | 7.69 | 7.24 |
| Left thalamus | –16 | –16 | 12 | 7.86 | 7.13 | 7.45 |
| Left inferior frontal gyrus | –36 | 16 | 8 | 7.63 | 7.45 | 6.94 |
| Left intraparietal sulcus | –40 | –40 | 36 | 7.02 | 5.86 | 5.87 |
| Left insular cortex | –40 | –4 | 16 | 6.83 | 3.55† | 7.18 |
| Left cingulate sulcus, CMAc | –12 | –20 | 40 | 5.93 | 3.20† | 6.83 |
| Left inferior frontal gyrus | –52 | 40 | 20 | 5.73 | 5.81 | 4.89 |
| Left intraparietal sulcus | –32 | –60 | 40 | 5.58 | 4.20† | 4.76 |
| Left inferior frontal sulcus | –48 | 52 | 12 | 5.33 | 6.51 | <3.01† |
| Left precuneus | –12 | –68 | 36 | 5.15 | 4.01† | 4.25† |
| Right hemisphere | | | | | | |
| Right supramarginal gyrus | 64 | –36 | 36 | 8.40 | 7.90 | 8.08 |
| Right inferior part of the precentral sulcus, PMV | 56 | 4 | 8 | 8.38 | 7.89 | 8.03 |
| Right precentral sulcus, PMV | 56 | 0 | 40 | 8.33 | 8.02 | 7.84 |
| Right supramarginal gyrus | 56 | –36 | 32 | 8.32 | 8.04 | 7.73 |
| Right putamen | 24 | 4 | 8 | 8.22 | 7.96 | 7.53 |
| Right inferior part of the precentral sulcus, PMV | 40 | 0 | 32 | 8.14 | 8.21 | 6.79 |
| Right supramarginal gyrus | 40 | –40 | 36 | 8.04 | 7.75 | 7.27 |
| Right inferior frontal sulcus | 44 | 32 | 24 | 8.01 | 8.04 | 6.51 |
| Right putamen | 28 | 16 | 4 | 7.69 | 7.58 | 5.95 |
| Right intraparietal sulcus | 48 | –52 | 52 | 7.37 | 7.58 | 4.25† |
| Right inferior frontal gyrus | 32 | 40 | 16 | 7.05 | 6.71 | 5.05 |
| Right parietal operculum | 44 | –40 | 16 | 6.82 | 4.84 | 6.32 |
| Right intraparietal sulcus | 28 | –68 | 40 | 4.94 | 4.51 | 4.20† |
| Right superior parietal gyrus | 36 | –64 | 60 | 4.37 | 3.13† | 3.26† |

Significant increases in the blood-oxygen-level-dependent (BOLD) contrast signal ($P < 0.05$, corrected for multiple comparisons) when we contrasted the precision grip task (both force conditions) with the baseline condition. For the areas we detected in this analysis, we also report the activity detected when contrasting each force condition with the baseline condition ($Z > 3.09$). Anatomical locations were related to the mean standardized MR image. MI and SI, primary motor and somatosensory cortex; SMA, supplementary motor area; PMV, ventral premotor cortex; CMAc, caudal cingulate motor area. *The activation was located on the ventral part of the superior frontal gyrus. †This voxel did not, after a correction for the multiple comparisons in the whole brain, reach the significance criterion of $P < 0.05$ ($Z > 4.35$) based on a test for peak height. (It did however belong to a cluster that was significant at $P < 0.05$ corrected for multiple comparisons based on a test for extent of the activation.) We report the activity in this voxel to show the correspondence with the results obtained in the other comparisons.

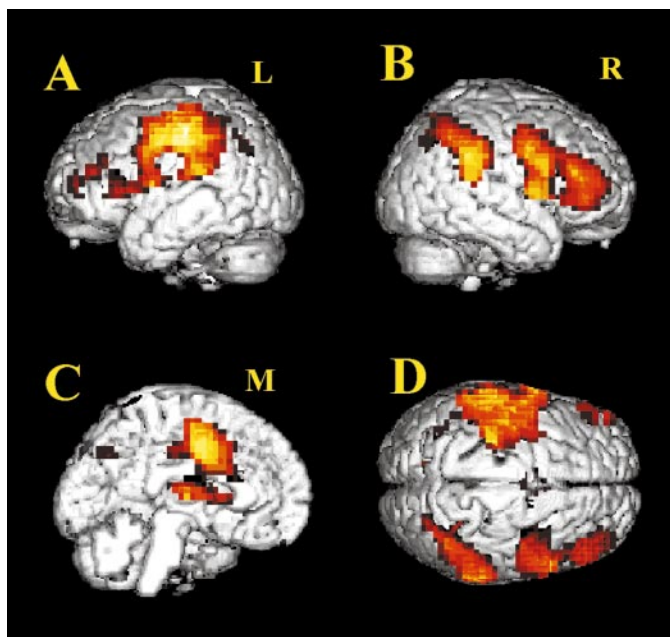


FIG. 2. The main effect of the precision grip task (small – baseline + large – baseline). The regions of the brain that revealed significantly increased blood oxygenation level-dependent (BOLD) contrast signals ($P < 0.05$ corrected for multiple comparisons) when the precision grip task (for both force conditions) was compared with the baseline condition are shown. The activations are superimposed on a 3-dimensional reconstruction of a template brain (Montreal Neurological Institute, MNI). *A*: the left hemisphere; *B*: the right hemisphere; *C*: the left medial wall; and *D*: the top view. The cerebellum was outside the field of view. See RESULTS and Table 1 for details.

The precision-grip task was associated with activity in a set of sensorimotor related regions: the contralateral M1 and S1, and bilateral PMV, area 44, PMD, SMA, and the CMAs. In the SMA, the cluster of activated voxels extended from $y = -14$ mm to $y = +16$ mm in the standard anatomical space (MNI). In the cingulate sulcus, the cluster of active voxels extended from $y = -24$ mm to $y = +20$ mm in standard space, i.e., both the CMAr and the CMAc were engaged (Roland and Zilles 1996b). In the bilateral PMD, the activity extended into the superior part of the precentral sulcus and the posterior part of the middle frontal gyrus (to $y = +6$ mm in standard space).

More ventrally, extensive bilateral activity was present in the PMV and area 44. The activations extended from the precentral gyrus over the inferior part of the precentral sulcus into pars opercularis and pars triangularis of the inferior frontal gyrus. In addition, activity was found bilaterally in the ventral part of the lateral prefrontal cortex (rostral to area 45).

In the parietal lobe, we observed peaks of activations in the bilateral parietal operculum (PO), in anterior- and posterior parts of the bilateral intraparietal cortex (the clusters of active voxels extending into the supramarginal cortex in both hemispheres), in the right supramarginal cortex, and in the left precuneus.

The contrasts (large – baseline) and (small – baseline) were also inspected (Table 1 and Fig. 3). These analyses showed that the precision grip task activated practically the same set of frontal and parietal areas irrespective of the force level (consistent with the activation maps obtained by examining the main effect of the grip task).

SMALL FORCE VERSUS LARGE FORCE. The regions that displayed significantly stronger BOLD contrast signals when the subjects used the small precision grip force in comparison with when they generated the large force (small – large) are shown in Table 2 and Fig. 4 ($P < 0.05$ corrected for multiple comparisons).

Local peaks of activity were located bilaterally in the cortex lining the inferior part of the precentral sulcus (PMV/area 44). In the left hemisphere, the peak of the activation was located in area 44 (as suggested by the cytoarchitectural population maps, see METHODS), although some of the voxels in the cluster also extended into the PMV (the cluster extended from $y = +8$ to $y = +16$ in the standard space). In the right hemisphere, there were two clusters: one with a peak activation in area 44 (the

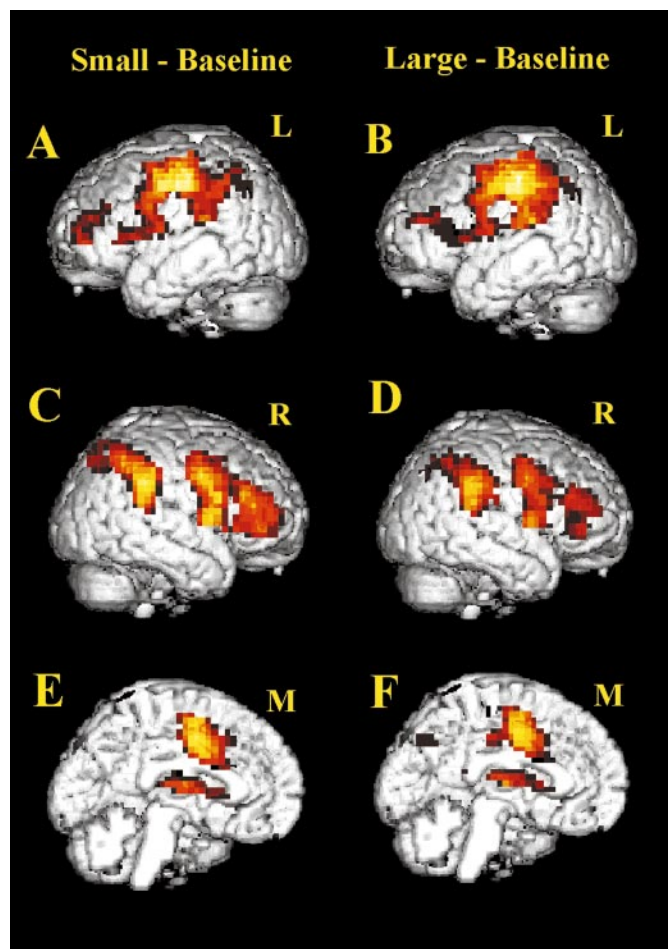


FIG. 3. Brain regions that were significantly activated during the small force condition (left, *A*, *C*, and *E*) and the large force condition (right, *B*, *D*, and *F*) in comparison with the baseline condition ($P < 0.05$ after correction for multiple comparisons). Both force conditions were associated with very similar activation patterns in the frontal and parietal lobes (the same areas as were detected in the main effect analysis, see Fig. 2 and Table 1). *A* and *B* (the left hemisphere) and *C* and *D* (the right hemisphere): the bilateral activations of the dorsal and ventral premotor cortex (PMD and PMV), parietal operculum (PO), posterior parietal regions (intraparietal cortex and supramarginal cortex), and the ventral prefrontal cortex for both force conditions. The clusters of active voxels overlapped with area 44 and 45 on both hemispheres. *E* and *F* (the medial wall): the activation of supplementary motor area (SMA), rostral cingulate motor area (CMAr), and the thalamus (represented on the medial wall on this 3-dimensional reconstruction) during both conditions. A stronger activation in caudal CMA (CMAc) was seen when the larger forces were generated. The cerebellum was outside the field of view. See Table 1 for details.

TABLE 2. Force-related activations

| Anatomical Region (functional/cytoarchitectural area) | Talarach Coordinates (MNI) | | | BOLD Signal Increase Relative Baseline | | Peak Z Score | No. of Subjects With Activation |
|---|----------------------------|-----|----|--|---------------|--------------|---------------------------------|
| | X | Y | Z | Large | Small | | |
| Small versus large | | | | | | | |
| Left inferior part of the precentral sulcus, area 44 ^a | -64 | 12 | 28 | 0.14 ± 0.022 | 0.27 ± 0.022 | 5.06 | 5/6 |
| Cingulate sulcus, CMAR | 0 | 16 | 32 | 0.054 ± 0.019 | 0.21 ± 0.019 | 4.97 | 5/6 ^d |
| Right intraparietal sulcus | 52 | -44 | 48 | 0.22 ± 0.029 | 0.48 ± 0.031 | 4.90 | 5/6 |
| Right inferior part of the precentral sulcus (posterior bank), PMV ^b | 48 | 4 | 28 | 0.19 ± 0.018 | 0.36 ± 0.019 | 4.86 | 5/6 ^e |
| Right inferior part of the precentral sulcus, area 44 ^c | 64 | 12 | 12 | 0.052 ± 0.031 | 0.33 ± 0.031 | 4.50 | 6/6 |
| Large versus small | | | | | | | |
| Left central sulcus, M1 ^e | -40 | -24 | 52 | 0.80 ± 0.019 | 0.35 ± 0.018 | 8.53 | 6/6 |
| Left lateral parietal operculum | -52 | -24 | 16 | 0.23 ± 0.017 | 0.066 ± 0.017 | 5.17 | 6/6 |
| Right lateral parietal operculum | 52 | -24 | 32 | 0.14 ± 0.015 | — | 4.78 | 5/6 ^f |

Significant increases in the BOLD contrast signal ($P < 0.05$, corrected for multiple comparisons). $Z > 4.35$ corresponds to $P < 0.05$ corrected, $Z > 4.90$ to $P < 0.01$ corrected, and $Z > 5.51$ to $P < 0.001$ corrected. The increase in adjusted BOLD contrast signals in both grip tasks as compared to the baseline condition is given (expressed as means ± SE in percentages; signals smaller than 0.05% are not reported). Finally, we report the number of individual subjects (of the 6 studied) that showed a peak activation of $Z > 1.66$ (corresponding to $P < 0.05$ without a correction for multiple comparisons) located at, or close to each focus detected in the group analysis (see METHODS for details). ^a The peak activation was located in area 44 (population map of 10 brain, see METHODS for details). ^b The peak activation located just posterior to area 44, i.e., in the PMV. (Only 1 of the 10 postmortem brains had area 44 located here.) The cluster of active voxels extended into area 44. ^c The peak activation was located in area 44 (population map of 10 brains, see METHODS for details). The cluster of active voxels extended into area PMV. ^d The sixth subject showed an activation on the medial wall; the ventral part of the superior frontal gyrus 12 mm superior and 8 mm rostral to the foci detected in the group analysis. ^e The sixth subject showed a right-sided PMV activation; it was located 17 mm from the foci detected in the group analysis. ^f The large cluster extended from $y = -44$ to $y = -4$ in the standard anatomical space. ^f The sixth subject did show an activation in the right PO, though it was located 13 mm inferior to the foci detected in the group analysis.

activation extended from $y = +8$ to $y = +32$ mm in the standard space) and one located in a more dorsal position, with the peak of the activation in the PMV (the activation extended from $y = 0$ to $y = +12$ in the standard space).

There were also small force specific activations of the right intraparietal cortex and the CMAR. The activation of the cortex lining the intraparietal sulcus (IPS) was centered on the lateral bank of the anterior part of the sulcus (the cluster extended medially into the sulcus and laterally into the supramarginal gyrus). The cluster of active voxels extended from $y = -64$ mm to $y = -40$ mm in standard anatomical space. The cingulate (CMAR) activation extended from $y = +4$ mm to $y = +18$, and from $z = +28$ to $z = +52$ mm in the standard space (with some voxels located in the anterior part of SMA).

The results of the complementary analyses of the fMRI data from the individual subjects confirmed the results obtained in the group analysis: we detected increases in activity at the location of each of the peak activations obtained in group analysis in at least five out of the six subjects (see Table 2 and METHODS). Furthermore the general activation pattern—with increases in activity in bilateral fronto-parietal areas when the subjects applied the small grip forces—was observed for all subjects.

LARGE VERSUS SMALL. The regions of the brain that exhibited significantly stronger BOLD contrast signals when subjects applied the large force in comparison with when they employed the small force are indicated in Table 2 and Fig. 5 (large – small) ($P < 0.05$ corrected for multiple comparisons). The left M1 and S1 showed such force specific activations with a maximum of activity in the depth of the central sulcus. The active voxels of this cluster extended rostrally into the PMD and posteriorly into the anterior part of the intraparietal sulcus (the cluster extended from $y = -44$ to $y = -4$ in the standard anatomical space). We also recorded positive force-related effects bilaterally into the PO. In addition, there were two areas

with weaker increases in activity located on the medial wall of the frontal lobe: one in the most ventral part of the superior frontal gyrus (SMA; $x = -16$, $y = -8$, $z = 48$; $Z = 3.89$, $P < 0.25$ after correcting for multiple comparisons) and one in the cingulate sulcus (CMAR; $x = -8$, $y = -24$, $z = 40$; $Z = 3.94$, $P < 0.25$ after a correction for multiple comparisons). The difference in the activity in these areas did not attain the statistical criterion of $P < 0.05$ after a correction for multiple comparison in the whole brain space ($P < 0.25$ corrected). Nevertheless we report this finding to show the correspondence with a previous study (Dettmers et al. 1995).

The activations detected in the group analysis were representative of the pattern of activity observed in at least five of the six individual subjects (Table 2).

DISCUSSION

The most important finding of the present study is that several sensory and motor related fronto-parietal areas were more strongly activated when a small precision grip force was applied to a stationary object than when a larger force was used. This result suggests that the bilateral cortex lining the inferior part of the precentral sulcus (area 44/PMV), CMAR, and the cortex lining the right intraparietal sulcus are involved in the control of small fingertip forces in the range typically used in manipulation.

Precision grip task

All subjects produced accurate force trajectories in the grip task at both force levels. The subjects had their eyes closed and did not move the digits. Thus the task used in the present study tests isometric fingertip force control guided by somatosensory feedback. The subjects had to control both the amplitude of the fingertip forces and the temporal sequence to produce proper cycles. The rhythm was paced by the metronome, and tactile

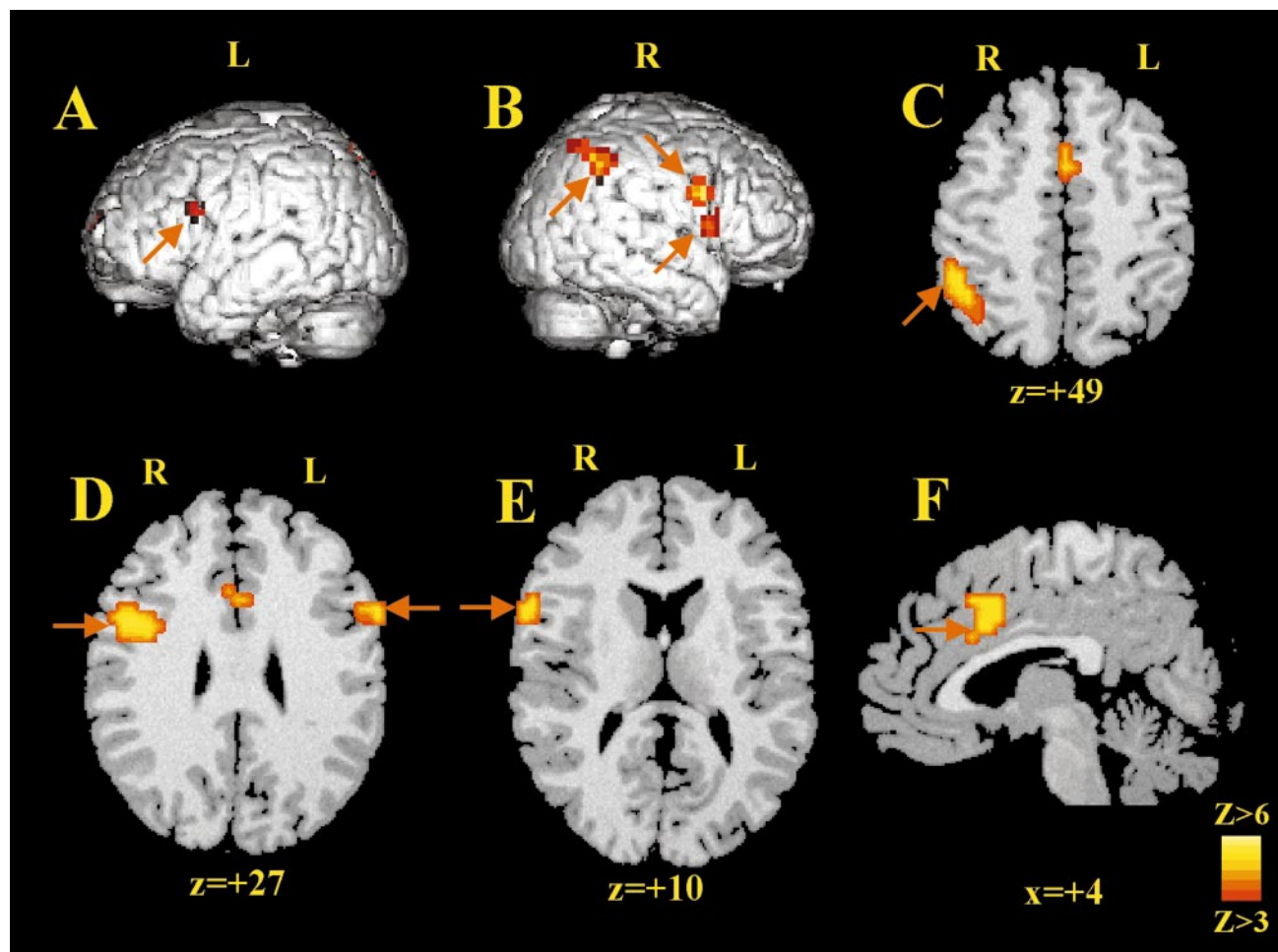


FIG. 4. Brain regions with significant increased BOLD contrast signals when the subjects applied small fingertip forces as compared with large forces (small – large; $P < 0.05$ corrected for multiple comparisons). The activations are superimposed on a 3-dimensional reconstruction (A and B) or 2-dimensional slices (C–F) of the template brain (MNI). →, point to the peak (local maxima) of the activations. A: the activation of the cortex lining the inferior part of the left precentral sulcus (area 44). B: the 2 right-sided activations located in the inferior part of the precentral sulcus (area 44/PMV) and the activation of the right intraparietal cortex. C: the right intraparietal activation and the CMAr activation (on this slice some active voxels of the cluster are engaging the anterior part of SMA). D: the bilateral activation of the inferior part of the precentral sulcus (area 44/PMV) and the CMAr. E: a more ventral activation of the cortex lining the same sulcus on the right side (area 44). F: the CMAr activation as seen from a sagittal view through the midline. For the definition of area 44 and PMV in the standard space, see METHODS, and for details of the activations, see Table 2.

signals from a brief vibration of the object provided feed back when the requested minimum force was reached. The same sensory cues were presented to the subjects at both force levels and in the baseline condition. Thus putative neuronal responses associated with these sensory signals were probably eliminated by comparing the two force conditions. Another possible confounding factor could have been increased recruitment of proximal muscles (shoulder, neck) when the larger force was applied. However, there was no consistent muscle activity of proximal muscles. Another issue relates to whether one of the force conditions was more difficult to perform and thus required more attention. We find no support for this concern because the grip task was well trained before the scanning (both force conditions), the subjects produced the requested force-trajectories at both force levels, and the variability of the grip forces in relation to the mean grip force (the coefficient of variation of the static plateau force) was similar during the two force conditions (7.3%).

Brain regions with stronger activity when generating the small precision grip force

Our results showing increased cortical activity in frontoparietal areas suggest that the control of small precision grip forces is dependent on distributed cortical areas that are more active during small than large grip forces. Support for this finding in humans comes from recordings of neurons in the monkey motor cortex. These studies showed that several M1 neurons tend to code for low forces in a limited range, while relatively few neurons are found to be recruited specifically at high force levels (Cheney and Fetz 1980; Evarts et al. 1983; Hepp-Reymond et al. 1978). Furthermore Hepp-Reymond et al. (1978) showed that during precision grips a larger number of cortical motor neurons had a positive correlation between discharge rate and grip force at low forces, than the forces were larger. Finally, during precision grips, some populations of neurons in M1, S1, and PMV show activity that is negatively correlated with force (Hepp-Reymond et al. 1994; Maier et al.

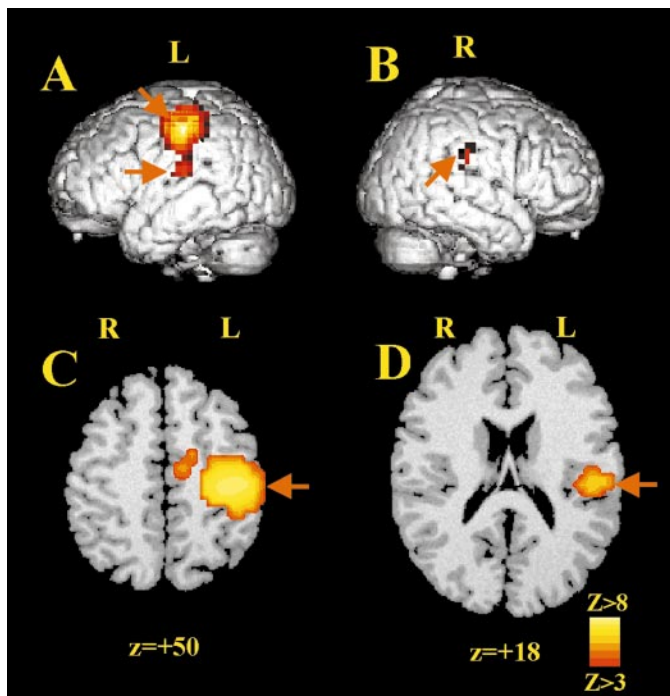


FIG. 5. Brain regions with a positive relationship between the precision grip force and the BOLD contrast signals. Areas that showed significantly stronger BOLD contrast signals ($P < 0.05$ corrected for multiple comparisons) when the subjects generated the large precision grip forces in comparison to when they employed the small force amplitudes are highlighted (large – small). The significant activations are indicated with \rightarrow (pointing to the peak of the activations; $P < 0.05$ corrected for multiple comparisons). The activations are superimposed on a 3-dimensional reconstruction (A and B) and horizontal slices (C and D) of the template brain (MNI). A: the activation of the primary sensorimotor cortex (M1 and S1) and the PO of the left hemisphere (note that the PO activation is represented on the lateral surface of the brain on this 3-dimensional reconstruction). B: the right PO activation. For the horizontal slices (C and D), the Talaraich coordinates are indicated. C: the strong force related effects that were observed in M1 and S1, and a weaker activation of the cortex on the medial wall of the frontal lobe (ventral part of the SMA; nonsignificant, $P < 0.25$ after a correction for multiple comparisons). D: the significant activation of the left PO. For details, see Table 2.

1993; Wannier et al. 1991). Hence, our fMRI results obtained in human subjects together with the single-cell recordings in monkeys suggest that the cortical representation of small precision grip forces involves strong activity of distributed populations of neurons in the frontal and parietal lobes.

Another argument supporting increased neural activity when small forces are applied can be raised from an ecological approach. The small force (3.8 N) used in the present experiments is within the normal range of the precision grip, while the large force (16.6 N) (comparable to lifting a 1.5-l soda bottle) exceeds this range. Thus a speculative possibility is that frequent use of finger forces within this smaller force range will exert an “ecological pressure” to develop a rich neural representation in this range (Nudo et al. 1996; Sanes and Donoghue 2000).

The increases in activity while generating small grip forces could also reflect an additional recruitment of sensorimotor control mechanisms due to a more sophisticated control of small forces during hand-object interaction. When humans grasp objects with a fine precision grip, both the direction and amplitude of the force vectors applied to the surface of the object have to be well controlled (Johansson and Westling

1984), while the grasp automatically becomes more stable when large forces are applied (the friction increases). The somatosensory signals from the fingertips may also play a more important role when applying fine forces than large forces. Indeed if the fingertips are anesthetized, subjects lose their ability to conduct fine manipulation and start to use excessive grip forces (Johansson and Westling 1984; Roland and Ladegaard-Pedersen 1977). Furthermore neurons in the monkey primary motor cortex responded more strongly when a somatosensory stimulus was applied during the performance of fine finger movements than when the same stimulus was applied during a more forceful movement (Fromm and Evarts 1977). This indicates increased processing (central gain control) of the somatosensory signals in sensorimotor areas during fine force control.

Brain areas

PMV/AREA 44. Previous positron emission tomography (PET) and fMRI studies suggest that the cortex on the inferior part of the precentral gyrus and the cortex lining the inferior precentral sulcus (PMV/area 44 region) are active when healthy subjects use their right hand to manipulate objects (Binkofski et al. 1999; Ehrsson et al. 2000; Kawashima et al. 1998; Seitz et al. 1991). The pattern of activations in these studies could reflect the movement of the digits, the hand posture, or the fingertip force control. Therefore it is interesting that we could show here that the bilateral cortex lining the inferior part of the precentral sulcus was specifically activated in association with the control of small isometric forces applied between the fingertips. In general terms, these results are consistent with recent anatomical and electrophysiological studies in non-human primates (Gentilucci et al. 1988; Kurata 1989; Preuss et al. 1996), which show multiple representations of the distal forelimb in the PMV region (parts of which might be homologous with human area 44 according to some researchers) (e.g., Rizzolatti and Arbib 1998), and that neurons in the rostral PMV region (area F5) are active during specific grip tasks, e.g., while grasping small objects with a precision grip (Rizzolatti et al. 1988).

ROSTRAL CINGULATE MOTOR AREA (CMAR). Electrophysiological and anatomical studies in non-human primates (Dum and Strick 1991; He et al. 1995; Shima et al. 1991) and functional imaging studies in humans (Grafton et al. 1993; Jahanshahi et al. 1995; Kawashima et al. 1996; Larsson et al. 1996; Picard and Strick 1996) suggest the existence of motor representations of the hand in the cortex lining the cingulate sulcus rostral to the anterior commissure line in standard anatomical space (Talaraich and Tournoux 1988). The present CMAR activation specific for the small grip forces seemed to engage this “hand section” of this area (the cluster of active voxels extended from $y = +4$ to $y = +18$ in the standard anatomical space). Thus this observation suggests that the CMAR could be especially involved in force control during fine-skilled precision grip actions. More speculatively, the activity could also reflect a suppression of the motor output to keep the low force level (Krams et al. 1998).

INTRAPARIETAL CORTEX. The human posterior parietal cortex (PPC) has been regarded as a multimodal association area involved in a variety of cognitive functions. However, experiments in primates suggested that the PPC is involved in

higher-order sensorimotor integration during the planning and execution of goal-directed actions (Andersen et al. 1997; Mountcastle et al. 1975). Multiple parallel parietofrontal circuits connect the posterior parietal lobe with the frontal motor areas (Rizzolatti et al. 1998). The present study demonstrates that the activity increased in an anterior section of the cortex lining the right IPS when subjects employed a small precision grip force to the object. The same section of the right intraparietal cortex (as determined from the Talaraich coordinates) was also more active during isometric force production with a precision grip (right hand), than during a power grasp (Ehrsson et al. 2000). It also showed stronger activity when objects with complex rather than simple shapes were explored by hand (using either hand) (Binkofski et al. 1999). Thus the present study adds to these previous observations in that it indicates that the right anterior intraparietal cortex is involved in somatosensorimotor integration required for the control of fine fingertip forces during object manipulation.

Neurons of the anterior part of the intraparietal sulcus in monkeys are activated by preshaping of the hand for a grasp or by contact with objects (Murata et al. 2000; Sakata et al. 1995; Taira et al. 1990). Thus in general terms our results fit with these observations. However, one should bear in mind that the homology relation between the posterior parietal cortex of non-human primates and humans is largely unknown (Eidelberg and Galaburda 1984; Milner 1997).

Brain regions with stronger activity when generating the large precision grip force

We expected that contralateral M1 and S1 would show stronger activation when the subjects applied the large precision grip force in comparison to when they employed the small force (Dettmers et al. 1995, 1996; Kinoshita et al. 2000; Thickbroom et al. 1998; Wexler et al. 1997). And indeed, the contralateral M1 and S1 and the bilateral PO did show such positive force related effects. The increased BOLD signals in the M1 presumably reflect an increased overall synaptic activity in this area caused by increased firing of corticospinal neurons and other neuronal elements. In man, the S1 and PO is activated by tactile stimuli applied to the contralateral hand (Burton et al. 1997; Disbrow et al. 2000; Ledberg et al. 1995). Thus the activation of these areas could reflect increased somatosensory feedback arising from increased compression of the densely innervated pulp of the fingertips in conjunction with increased tension of the tendons.

Conclusions

There are several implications for the novel finding of increased fronto-parietal activity when subjects employ small precision grip forces. First, it demonstrates that the sensorimotor control mechanisms associated with the generation of small fingertip forces is dependent on distributed cortical regions in both hemispheres in addition to the contralateral M1. Second, it suggests that the relationship between muscular force and the general pattern of human brain activity is more complex than has previously been described (Dettmers et al. 1995, 1996; Kinoshita et al. 2000; Thickbroom et al. 1998; Wexler et al. 1997). Finally, it suggests that the brain activity during object manipulation does not merely reflect the grasp configuration

used (e.g., precision or power grasp), but that the activation in some areas is increased when small forces are applied at the fingertip-object interface.

The authors especially thank Dr. Göran Westling (Dept. Physiology, Umeå University) for technical development of the MR-grip instrument and the optical transducers. We are also grateful for the cytoarchitectural data provided by Dr. Stefan Geyer, Dr. Katrin Amunts, and Prof. Karl Zilles (Dept. of Neuroanatomy and C. and O. Vogt Institute for Brain Research, University of Düsseldorf, Düsseldorf, Germany). We thank T. Jonsson (MR Center, Karolinska Institute) and G. Ehrsson for technical assistance. Finally, we appreciate valuable discussions with Prof. Per Roland (Dept. Neuroscience, Karolinska Institutet) and Prof. Roland Johansson (Dept. Physiology, Umeå University).

This work was supported by Axel and Margaret Ax:son Johnson's foundation and the Swedish Medical Research Council (Project 5925). H. H. Ehrsson was supported by Stiftelsen Sunnerdahls Handikapp Fond, Stiftelsen Frimurarna Barnhuset, and Sällskapet Barnavård.

REFERENCES

- AMUNTS K, SCHLEICHER A, BURGEL U, MOHLBERG H, UYLINGS HBM, AND ZILLES K. Broca's region revisited: cytoarchitecture and intersubject variability. *J Comp Neurol* 412: 319–341, 1999.
- ANDERSEN RA, SNYDER LH, BRADLEY DC, AND XING J. Multimodal representation of space in the posterior parietal cortex and its use in planning movements. *Annu Rev Neurosci* 20: 303–330, 1997.
- BINKOFSKI F, BUCCINO G, POSSE S, SEITZ RJ, RIZZOLATTI G, AND FREUND H-J. A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study. *Eur J Neurosci* 11: 3276–3286, 1999.
- BURTON H, MACLEOD AM, VIDEEN TO, AND RAICHLER ME. Multiple foci in parietal and frontal cortex activated by rubbing embossed grating patterns across fingerpads: a positron emission tomography study in humans. *Cereb Cortex* 7: 3–17, 1997.
- BUSER P AND BANCAUD J. Bases techniques et methodologiques de exploration fonctionnelle stereotaxique de telencephale. In: *Atlas Stereotaxique de Telencephale*, edited by Talaraich J. Paris: Masson et cie. 1967, p. 251–318.
- CHENEY PD AND FETZ EE. Functional classes of primate corticomotoneuronal cells and their relation to active force. *J Neurophysiol* 44: 773–791, 1980.
- DETTMERS C, CONNELLY A, STEPHAN KM, TURNER R, FRISTON KJ, FRACKOWIAK RS, AND GADIAN DG. Quantitative comparison of functional magnetic resonance imaging with positron emission tomography using a force-related paradigm. *Neuroimage* 4: 201–209, 1996.
- DETTMERS C, FINK GR, LEMON RN, STEPHAN KM, PASSINGHAM RE, SILBERSWEIG D, HOLMES A, RIDDING MC, BROOKS DJ, AND FRACKOWIAK RS. Relation between cerebral activity and force in the motor areas of the human brain. *J Neurophysiol* 74: 802–815, 1995.
- DISBROW E, ROBERTS T, AND KRUBITZER L. Somatotopic organization of cortical fields in the lateral sulcus of homo sapiens: evidence for SII and PV. *J Comp Neurol* 418: 1–21, 2000.
- DUM RP AND STRICK PL. The origin of corticospinal projections from the premotor areas in the frontal lobe. *J Neurosci* 11: 667–689, 1991.
- EHRSSON HH, FAGERGREN A, JONSSON T, WESTLING G, JOHANSSON RS, AND FORSSBERG H. Cortical activity in precision versus power grip tasks: an fMRI study. *J Neurophysiol* 83: 528–536, 2000.
- EIDELBERG D AND GALABURDA AM. Inferior parietal lobule. Divergent architectonic asymmetries in the human brain. *Arch Neurol* 41: 843–852, 1984.
- ELIASSON AC, GORDON AM, AND FORSSBERG H. Impaired anticipatory control of isometric forces during grasping by children with cerebral palsy. *Dev Med Child Neurol* 34: 216–225, 1992.
- EVARTS EV, FROMM C, KROLLER J, AND JENNINGS VA. Motor cortex control of finely graded forces. *J Neurophysiol* 49: 1199–1215, 1983.
- FRISTON KJ, ASHBURNER J, FRITH CD, POLINE JB, HEATHER JD, AND FRACKOWIAK RS. Spatial registration and normalization of images. *Hum Brain Map* 2: 165–189, 1995a.
- FRISTON KJ, HOLMES AP, POLINE JB, GRASBY PJ, WILLIAMS SC, FRACKOWIAK RS, AND TURNER R. Analysis of fMRI time-series revisited (see comments). *Neuroimage* 2: 45–53, 1995b.
- FRISTON KJ, HOLMES AP, AND WORSLEY KJ. How many subjects constitute a study? *Neuroimage* 10: 1–5, 1999.
- FRISTON KJ, HOLMES A, WORSLEY KJ, POLINE JB, FRITH CD, AND FRACKOWIAK RS. Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Map* 2: 189–210, 1995c.

- FROMM C AND EVARTS EV. Relation of motor cortex neurons to precisely controlled and ballistic movements. *Neurosci Lett* 5: 259–265, 1977.
- GENTILUCCI M, FOGASSI L, LUPPINO G, MATELLI M, CAMARDA R, AND RIZZOLATTI G. Functional organization of inferior area 6 in the macaque monkey. I. Somatotopy and the control of proximal movements. *Exp Brain Res* 71: 475–490, 1988.
- GEYER S, LEDBERG A, SCHLEICHER A, KINOMURA S, SCHORMANN T, BURGEL U, KLINGBERG T, LARSSON J, ZILLES K, AND ROLAND PE. Two different areas within the primary motor cortex of man. *Nature* 382: 805–807, 1996.
- GEYER S, SCHLEICHER A, AND ZILLES K. Areas 3a, 3b, and 1 of human primary somatosensory cortex. I. Microstructural organization and interindividual variability. *Neuroimage* 10: 63–83, 1999.
- GEYER S, SCHORMANN T, MOHLBERG H, AND ZILLES K. Areas 3a, 3b, and 1 of human primary somatosensory cortex. II. Spatial normalization to standard anatomical space. *Neuroimage* 11: 684–696, 2000.
- GRAFTON ST, WOODS RP, AND MAZZIOTTA JC. Within-arm somatotopy in human motor areas determined by positron emission tomography imaging of cerebral blood flow. *Exp Brain Res* 95: 172–176, 1993.
- HE SQ, DUM RP, AND STRICK PL. Topographic organization of corticospinal projections from the frontal lobe: motor areas on the medial surface of the hemisphere. *J Neurosci* 15: 3284–3306, 1995.
- HEPP-REYMOND MC. Functional organization of motor cortex and its participation in voluntary movements. In: *Comparative Primate Biology*, edited by Seklis HD and Erwin J. New York: Liss, 1988, p. 501–624.
- HEPP-REYMOND MC, HUSLER EJ, MAIER MA, AND QI HX. Force-related neuronal activity in two regions of the primate ventral premotor cortex. *Can J Physiol Pharmacol* 72: 571–579, 1994.
- HEPP-REYMOND MC, WYSS UR, AND ANNER R. Neuronal coding of static force in the primate motor cortex. *J Physiol (Paris)* 74: 287–291, 1978.
- HERMSDÖRFER J AND MAI N. Disturbed grip-force control following cerebral lesions. *J Hand Ther* 9: 33–40, 1996.
- HOLMES A, JOSEPHS O, BUCHEL C, AND FRISTON KJ. Statistical modeling of low frequency confounds in fMRI. *Neuroimage* 5: 480–480, 1997.
- JAHANSHAHI M, JENKINS IH, BROWN RG, MARSDEN CD, PASSINGHAM RE, AND BROOKS DJ. Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects (see comments). *Brain* 118: 913–933, 1995.
- JOHANSSON RS. Sensory control of dexterous manipulation. In: *Hand and Brain*, edited by Wing AM, Haggard P, and Flanagan JR. New York: Academic, 1996, p. 381–412.
- JOHANSSON RS AND WESTLING G. Roles of glabrous skin receptors and sensorimotor memory in automatic control of precision grip when lifting rougher or more slippery objects. *Exp Brain Res* 56: 550–564, 1984.
- KAWASHIMA R, ITOH H, ONO S, SATOH K, FURUMOTO S, GOTOH KOYAMA M, YOSHIOKA S, TAKAHASHI T, TAKAHASHI K, YANAGISAWA T, AND FUKUDA H. Changes in regional cerebral blood flow during self-paced arm and finger movements. A PET study. *Brain Res* 716: 141–148, 1996.
- KAWASHIMA R, MATSUMURA M, SADATO N, NAITO E, WAKI A, NAKAMURA S, MATSUNAMI K, FUKUDA H, AND YONEKURA Y. Regional cerebral blood flow changes in human brain related to ipsilateral and contralateral complex hand movements—a PET study. *Eur J Neurosci* 10: 2254–2260, 1998.
- KINOSHITA H, OKU N, HASHIKAWA K, AND NISHIMURA T. Functional brain areas used for the lifting of objects using a precision grip: a PET study. *Brain Res* 857: 119–130, 2000.
- KRAMS M, RUSHWORTH MF, DEIBER MP, FRACKOWIAK RS, AND PASSINGHAM RE. The preparation, execution and suppression of copied movements in the human brain. *Exp Brain Res* 120: 386–398, 1998.
- KURATA K. Distribution of neurons with set- and movement-related activity before hand and foot movements in the premotor cortex of rhesus monkeys. *Exp Brain Res* 77: 245–256, 1989.
- KWONG KK, BELLIVEAU JW, CHESLER DA, GOLDBERG IE, WEISSKOFF RM, PONCELET BP, KENNEDY DN, HOPPEL BE, COHEN MS, AND TURNER R. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci USA* 89: 5675–5679, 1992.
- LARSSON J, GULYAS B, AND ROLAND PE. Cortical representation of self-paced finger movement. *Neuroreport* 7: 463–468, 1996.
- LAWRENCE DG AND KUYPERS HG. The functional organization of the motor system in the monkey. I. The effects of bilateral pyramidal lesions. *Brain* 91: 1–14, 1968.
- LEDBERG A, O'SULLIVAN BT, KINOMURA S, AND ROLAND PE. Somatosensory activations of the parietal operculum of man. A PET study. *Eur J Neurosci* 7: 1934–1941, 1995.
- MAIER MA, BENNETT KM, HEPP-REYMOND MC, AND LEMON RN. Contribution of the monkey corticomotoneuronal system to the control of force in precision grip. *J Neurophysiol* 69: 772–785, 1993.
- MILNER AD. Neglect, extinction and the cortical streams of visual processing. In: *Parietal Lobe Contributions to Orientation in 3D Space*, edited by Their P and Karnath H-O. Heidelberg: Springer-Verlag, 1997, p. 3–22.
- MOUNTCASTLE VB, LYNCH JC, GEORGIOPOULOS A, SAKATA H, AND ACUNA C. Posterior parietal association cortex of the monkey: command functions for operations within extrapersonal space. *J Neurophysiol* 38: 871–908, 1975.
- MURATA A, GALLESE V, LUPPINO G, KASEDA M, AND SAKATA H. Selectivity for the shape, size, and orientation of objects for grasping in neurons of monkey parietal area AIP. *J Neurophysiol* 83: 2580–2601, 2000.
- NAPIER JRJ. Prehensibility and opposability in the hands of primates. *Symp Zool Soc Lond* 5: 115–132, 1961.
- NORDENSKIÖLD UM AND GRIMBY G. Grip force in patients with rheumatoid arthritis and fibromyalgia and in healthy subjects. A study with the Grippit instrument. *Scand J Rheumatol* 22: 14–19, 1993.
- NUDO RJ, MILLIKEN GW, JENKINS WM, AND MERZENICH MM. Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *J Neurosci* 16: 785–807, 1996.
- ODERGREN T, IWASAKI N, BORG J, AND FORSSBERG H. Impaired sensory-motor integration during grasping in writer's cramp. *Brain* 119: 569–583, 1996.
- OGAWA S, TANK DW, MENON R, ELLERMANN JM, KIM SG, MERKLE H, AND UGURBIL K. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proc Natl Acad Sci USA* 89: 5951–5955, 1992.
- OLDFIELD RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9: 97–113, 1971.
- PASSINGHAM RE. *The Frontal Lobes and Voluntary Action*. Oxford, UK: Oxford Press, 1993.
- PASSINGHAM RE, PERRY VH, AND WILKINSON F. The long-term effects of removal of sensorimotor cortex in infant and adult rhesus monkeys. *Brain* 106: 675–705, 1983.
- PEREIRA HS, ELIASSON AC, AND FORSSBERG H. Detrimental neural control of precision grip lifts in children with ADHD. *Dev Med Child Neurol* 42: 545–553, 2000.
- PICARD N AND STRICK PL. Motor areas of the medial wall: a review of their location and functional activation. *Cereb Cortex* 6: 342–353, 1996.
- POLINE JB, WORSLEY KJ, EVANS AC, AND FRISTON KJ. Combining spatial extent and peak intensity to test for activations in functional imaging. *Neuroimage* 5: 83–96, 1997.
- PORTER R AND LEMON RN. *Corticospinal Function and Voluntary Movement*. New York: Oxford, 1993.
- PREUSS TM, STEPNIWSKA I, AND KAAS JH. Movement representation in the dorsal and ventral premotor areas of owl monkeys: a microstimulation study (published erratum appears in *J Comp Neurol* 377: 611, 1997). *J Comp Neurol* 371: 649–676, 1996.
- RIZZOLATTI G AND ARBIB MA. Language within our grasp. *Trends Neurosci* 21: 188–194, 1998.
- RIZZOLATTI G, CAMARDA R, FOGASSI L, GENTILUCCI M, LUPPINO G, AND MATELLI M. Functional organization of inferior area 6 in the macaque monkey. II. Area F5 and the control of distal movements. *Exp Brain Res* 71: 491–507, 1988.
- RIZZOLATTI G, LUPPINO G, AND MATELLI M. The organization of the cortical motor system: new concepts. *Electroencephalogr Clin Neurophysiol* 106: 283–296, 1998.
- ROLAND PE, GEYER S, AMUNTS K, SCHORMANN T, SCHLEICHER A, MALIKOVIC A, AND ZILLES K. Cytoarchitectural maps of the human brain in standard anatomical space. *Hum Brain Map* 5: 222–227, 1997.
- ROLAND PE AND LADEGAARD-PEDERSEN H. A quantitative analysis of sensations of tension and of kinaesthesia in man. Evidence for a peripherally originating muscular sense and for a sense of effort. *Brain* 100: 671–692, 1977.
- ROLAND PE AND ZILLES K. The developing European computerized human brain database for all imaging modalities. *Neuroimage* 4: 39–47, 1996a.
- ROLAND PE AND ZILLES K. Functions and structures of the motor cortices in humans. *Curr Opin Neurobiol* 6: 773–781, 1996b.
- ROLAND PE AND ZILLES K. Structural divisions and functional fields in the human cereb cortex. *Brain Res Brain Res Rev* 26: 87–105, 1998.
- SAKATA H, TAIRA M, MURATA A, AND MINE S. Neural mechanisms of visual guidance of hand action in the parietal cortex of the monkey. *Cereb Cortex* 5: 429–438, 1995.

- SANES JN AND DONOGHUE JP. Plasticity and primary motor cortex. *Annu Rev Neurosci* 23: 393–415, 2000.
- SCHORMANN T AND ZILLES K. Three-dimensional linear and nonlinear transformations: an integration of light microscopical and MRI data. *Hum Brain Map* 6: 339–347, 1998.
- SEITZ RJ, ROLAND PE, BOHM C, GREITZ T, AND STONE-ELANDER S. Somatosensory discrimination of shape: tactile exploration and cerebral activation. *Eur J Neurosci* 3: 481–492, 1991.
- SHIMA K, AYA K, MUSHIAKE H, INASE M, AIZAWA H, AND TANJI J. Two movement-related foci in the primate cingulate cortex observed in signal-triggered and self-paced forelimb movements. *J Neurophysiol* 65: 188–202, 1991.
- TAIRA M, MINE S, GEORGIOPOULOS AP, MURATA A, AND SAKATA H. Parietal cortex neurons of the monkey related to the visual guidance of hand movement. *Exp Brain Res* 83: 29–36, 1990.
- TALARAICH J AND TOURNOUX P. *Co-planar Stereotaxic Atlas of the Human Brain*. Stuttgart: Thieme, 1988.
- THICKBROOM GW, PHILLIPS BA, MORRIS I, BYRNES ML, AND MASTAGLIA FL. Isometric force-related activity in sensorimotor cortex measured with functional MRI. *Exp Brain Res* 121: 59–64, 1998.
- WANNIER TM, MAIER MA, AND HEPP-REYMOND MC. Contrasting properties of monkey somatosensory and motor cortex neurons activated during the control of force in precision grip. *J Neurophysiol* 65: 572–589, 1991.
- WEXLER BE, FULBRIGHT RK, LACADIE CM, SKUDLARSKI P, KELZ MB, CONSTABLE RT, AND GORE JC. An fMRI study of the human cortical motor system response to increasing functional demands. *Magnet Resonance Imag* 15: 385–396, 1997.
- WORSLEY KJ AND FRISTON KJ. Analysis of fMRI time-series revisited—again [comment]. *Neuroimage* 2: 173–181, 1995.